DEPARTMENT OF HEALTH AND HUMAN SERVICES **Public Health Service**

Center for Drug Evaluation and Research
Office of Training and Communication
Freedom of Information Staff HFD-205
5600 Fishers Lane 12 B 05
Rockville, Maryland 20857

June 12, 1998

In Response Refer to File : F98-06282

FD&C Reports Inc.
Christine Lee
5550 Friendship Blvd.
Chevy Chase, MD 20851

Dear Ms. Lee;

This is in response to your request of mARCH 3, 1998, in which you requested the approval package for NDA 50722(S002) and NDA 50723 (S001). Your request was received in the Center for Drug Evaluation and Research on March 5, 1998.

The documents you have requested are enclosed. "In order to help reduce processing time and costs, certain material has been deleted from the record(s) furnished to you because a preliminary review of the record(s) indicated that the deleted information is not required to be publicly disclosed. If, however, you desire to review the deleted material, please make an additional request at the following address:

Food and Drug Administration
Freedom of Information Staff, HFI-35
5600 Fishers Lane
Rockville, MD 20857

Should the Agency then deny this information, you would have the right to appeal such denial. Any letter of denial will explain how to make this appeal." SMG 2460.7(3)

This concludes the response for the Center for Drug Evaluation and Research.

Charges of $68.20 (Search $14.50, Review $43.50, Reproduction $10.20, Computer time $0.00) will be included in a monthly invoice. **DO NOT SEND ANY PAYMENT UNTIL YOU RECEIVE AN INVOICE.**

If there are any problems with this response, please notify us <u>in writing</u> of your specific problem(s). Please reference the above file number.

Sincerely,

J. Santford Williams, R.Ph.

J. Santford Williams, R.Ph.
Freedom of Information Officer
Office of Training and Communications
Freedom of Information Staff, HFD-205
Direct Line (301)827-3456

Enclosure:

102 pages, approval package for NDA 50722(S002) and NDA 50723(S001)

CDER FOI CONTROL RECORD

Contrl No.: F98-06282
Requestor: C LEE
FDC REPORTS INC
5550 FRIENDSHIP BLVD STE ONE
CHEVY CHASE MD 20815

Request Date:
FDA Recd Date: 04-MAR-1998
CDER Recd Date: 05-MAR-1998
Due Date: 01-APR-1998

Request Type: NEWS/ED.

CDER Subject:
ROCHE - CELLCEPT RVW DOCS 2/11/98

----- FDA FOI Routing Offices -----

Office		Date Assigned	Status
HFD205	CENTER DRUG EVALUATION &	04-MAR-1998	PA PENDING ACTION

----- CDER FOI Routing Offices -----

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

DOCUMENT REQUEST

IN REPLY REFER TO:

1. NAME OF REQUESTER: Christine Lee

2. FIRM NAME AND ADDRESS

F-D-C Reports, Inc.
5550 Friendship Blvd.
Chevy Chase, MD 20815

3. TELEPHONE: (301) 657-9830

4. DATE: 3-3-98

COMPLETE THE FOLLOWING AS FULLY AS POSSIBLE

5. DESCRIPTION OF MATERIAL REQUESTED	NUMBER OF PAGES
Review documents for the Feb. 11, 1998 supplemental approval	A530
of Roche's CellCept for use in heart transplant	
patients	
98-6282	
TOTAL	

RECEIVED
MAR 4 1998
FDA FOI STAFF (HFI-35)

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CDER FOI CONTROL RECORD

Contrl No.: F98-06282
Requestor: C LEE
FDC REPORTS INC
5550 FRIENDSHIP BLVD STE ONE
CHEVY CHASE MD 20815

Request Date:
FDA Recd Date: 04-MAR-1998
CDER Recd Date: 05-MAR-1998
Due Date: 01-APR-1998

Request Type: NEWS/ED.

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ROCHE - CELLCEPT RVW DOCS 2/11/98

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RR590	06-MAR-1998	

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NEW
N50-922 S-002
N50-923 S-001

AP 2-11-98

CDER FOI CONTROL RECORD

Contrl No.: F98-06282
Requestor: C LEE
FDC REPORTS INC
5550 FRIENDSHIP BLVD STE ONE
CHEVY CHASE MD 20815

Request Date:
FDA Recd Date: 04-MAR-1998
CDER Recd Date: 05-MAR-1998
Due Date: 01-APR-1998

Request Type: NEWS/ED.

CDER Subject:
ROCHE - CELLCEPT RVW DOCS 2/11/98

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HFD205	CENTER DRUG EVALUATION &	04-MAR-1998	PA PENDING ACTION

----- CDER FOI Routing Offices -----

Office	Date Referred	Action Taken
~~530~~	~~05-MAR-1998~~ nothing 3/6/98	
~~RR550~~	~~06-MAR-1998~~	
RR 20	11-March-98	

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NEW
N50-922 S-002
N50-923 S-001

AP 2-11-98

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 050722/S002 AND 050723/S001

Trade Name: CELLCEPT 500 MG TABLETS AND 250 MG CAPSULES

Generic Name: MYCOPHENOLATE MOFETIL

Sponsor: SYNTEX(U.S.A.) INC.

Approval Date: 2/11/98

INDICATION(s): PROVIDES FOR A NEW INDICATION FOR THE PROPHYLAXIS OF ORGAN REJECTION IN PATIENTS RECEIVING ALLGENEIC CARDIAC TRANSPLANTS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 050722/S002 and 050723/S001

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	Included	Pending Completion	Not Prepared	Not Required
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Tenative Approval Letter				X
Approvable Letter				X
Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI				X
Pharmacology Review(s)	X			
Statistical Review(s)	X			
Microbiology Review(s)	X			
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)				X
Administrative Document(s)/ Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 050722/S002 AND 050723/S001

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-722/S-002
NDA 50-723/S-001

CERTIFIED MAIL
RETURN RECEIPT

FEB 11 1998

Syntex (U.S.A.) Inc.
Attention: Carmen Rodriguez, M.Sc.
3401 Hillview Avenue
Palo Alto, CA 94304

Dear Ms. Rodriguez:

We acknowledge your supplemental new drug applications dated July 31, 1997 (accepted for filing on August 14, 1997) and February 10, 1998, received August 1, 1997 and February 11, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CellCept, (mycophenolate mofetil), 500 mg tablets and 250 mg capsules.

We acknowledge receipt of your submissions dated August 13, 1997, October 8, 1997, December 5, 1997(2), December 11, 1997, December 17, 1997, December 23, 1997, January 6, 1998, January 27, 1998, January 29, 1998, February 5, 1998, and February 9, 1998.

These supplemental applications provide for a new indication for the prophylaxis of organ rejection in patients receiving allogeneic cardiac transplants.

We have completed the review of these supplemental applications including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submissions dated February 9, 1998 and February 10, 1998 with the revisions listed below.

Accordingly, the supplemental applications are approved effective on the date of this letter. As discussed by telephone on February 11, 1998 between Ms. Chris Conroy of Roche and Ms. Lisa Hubbard of this Division, the revisions are as follows:

1. The term "MMF" should be replaced with the word "CellCept" throughout the clinical trials section of the label.

2. The word "should" will be replaced with the word "may" in the sentence "CellCept should be used for cardiac transplant patients with severe chronic renal impairment if the potential benefits outweigh the potential risks." throughout the label.

These revisions are terms of the supplemental NDA approval.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDAs 50-722/S-002, 50-723/S-001. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Lisa Hubbard, R.Ph., Regulatory Management Officer, at (301) 827-2335.

Sincerely yours,

/S/

Mark J. Goldberger, M.D., MPH
Director
Division of Special Pathogens and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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cc:
Original NDAs 50-722, 50-723
HFD-590/Div. files
HFD-590/CSO/L.Hubbard /S/
HFD-590/TL/MMann
HFD-590/MO/JKorvick /S/ 2/12/98
HFD-590/Chem/NSchmuff /S/ 2/12/98
HFD-590/Chem/MSeggel /S/ 2/12/98
HFD-590/PharmTL/KHastings /S/ 2/12/98
HFD-590/Pharm/SKunder /S/ 2/12/98
HFD-725/StatTL/PFlyer /S/ 2/12/98
HFD-725/Stat/MElashoff
HFD-880/TLBiopharm/FAjayi
HFD-880/Biopharm/Kumi
HFD-002/ORM (with labeling)
HFD-104/Office Director
HFD-101/L.Carter
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling) - for all NDAs and supplements for adverse reaction changes.
HFD-560/OTC (with labeling - for OTC Drug Products Only)
HFI-20/Press Office (with labeling)
HFD-021/ACS (with labeling)

Drafted by: lh/February 11, 1998/50722ap
Initialed by:
final:

APPROVAL (AP)

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 050722/S002 AND 050723/S001

MEDICAL REVIEW(S)

Date submitted:	7/31/1997
Date received:	8/1/1997
Advisory Committee:	1/14/1998
Regulatory Action:	2/11/1998
Review completed:	2/11/1998
Final Written review:	5/26/1998
Reviewer:	Joyce Korvick, M.D.
Drug name:	CellCept®, Mycophenolate mofetil
Sponsor:	Syntex (USA) Inc. 3401 Hillview Avenue Palo Alto, CA. 94304
Dosage Formulation/ Route of Administration:	250 mg Capsules, for oral administration 500 mg Tables, for oral administration
Drug Classification:	Antibiotic, (immunosuppressant)
Proposed Indication:	Prophylaxis of transplant rejection in patients receiving allogenic heart transplants.

APPEARS THIS WAY
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IX. APPENDIX A 26

I. INTRODUCTION

A. Materials Reviewed

Overview: vol. 2 of 329

Protocols and amendments: vols. 20.1-20.5

Efficacy Review:

1.) MYCS 1864 study report and line listings; vols. 27-50
2.) SAS files were supplied by the company were reviewed by the statistical reviewer with advice and consultation with the medical reviewer.
3.) Integrated Summary of Efficacy: vol. 26

Safety Review:

1.) Line Listings: vols. 207-209
2.) CD ROM Case Report forms for death and serious adverse events.
3.) Access database supplied by the applicant for Adverse Events line listings
4.) Proposed revisions to the label report (Dec 23, 1997), pancreatitis and other infections.
5.) Death and Adverse Event Summaries: vols. 207-209
6.) Backgrounder and Slides for the Advisory Committee: vol. 1 and 2
7.) Integrated Summary of Safety including 3-year renal safety update: Dec. 5, 1997 vols. 1-2.

B. Pharmacokinetics:

Primary Reviewer: Kofi Kumi, Ph.D.

Subsequent to the approval of the 250 mg capsule of CellCept, the 500 mg tablet was approved.

. For additional information, please refer to the clinical pharmacology review.

C. Pharm/Toxicology:

Primary Reviewer; Kenneth Hastings, Ph.D.

There were no new toxicology issues raised by this application.

D. Chemistry:

Primary Reviewer; Mark Seggel, Ph.D.

An Environmental Assessment was necessary with this application because of the expansion of the patient population. No other issues were noted in the chemistry review.

E. Statistical Review:

Primary Reviewer; Michael Elashoff, Ph.D.

Please see primary review for statistical details of efficacy review.

II. BACKGROUND

Roche Pharmaceuticals (Syntex (USA) Inc.) submitted New Drug Application 50-722/S-002 for CellCept® on July 31,1997. As of that filing date, only Sandimmune and Neoral were labeled for prophylaxis against organ rejection in patients receiving allogeneic cardiac transplantation in the U.S. CellCept® was previously approved for the prophylaxis of organ rejection in patients receiving allogeneic renal transplantation, on May 3, 1995.

CellCept is available for oral use as a 250 mg capsule or 500 mg tablet, and is to be used concomitantly with cyclosporine and steroids at a dose of 1 gram twice per day.

This application consisted of one large, prospective, randomized, double-blind, controlled clinical trial (MYCS 1864), and five small non-randomized studies 1754, 1812, 2108, 1803, 2400). Study MYCS 1864 was considered central to the evaluation of CellCept for the cardiac indication. The smaller studies did not contribute to the overall evaluation of efficacy of CellCept and were not commented upon further in this review.

FDA agreed with the applicant that one large, well controlled study may provide enough evidence for the cardiac indication, given the similar mechanisms of rejection for cardiac and renal transplants, and CellCept's efficacy in the prevention of "treatment failure" at 6 months for renal transplants. This agreement was finalized through two pre-NDA meetings. During the first meeting, (held in February, 1997) one year results were presented to the FDA. In late April of 1997, Roche contacted the FDA requesting an additional meeting to receive further clarification of the Agency's view of the study outcomes. This meeting was held in July of 1997 and included one member of the FDA advisory committee and an additional government consultant. Based on the discussion in this meeting, Roche agreed to submit a marketing application for the cardiac indication.

Mycophenolate mofetil (CellCept) is an anti-lymphocyte agent which is rapidly absorbed following oral administration and hydrolyzed to form mycophenolic acid, which is the active metabolite. Mycophenolic acid is a potent, selective, non-competitive and reversible inhibitor of inosine monophosphate dehydrogenase, and therefore inhibits the *de novo* pathway of guanosine nucleotide synthesis without incorporation into DNA. Thus, CellCept has a potent cytostatic effect on lymphocytes, which are dependent for their proliferation on *de novo* synthesis of purines. Additionally, Mycophenolic acid suppresses the antibody formation by B-lymphocytes.

III. CARDIAC TRANSPLANTATION INDICATION

A. STUDY MYCS 1864: STUDY DESIGN

This prospective, double-blind, active-control study for the prevention of acute cardiac allograft rejection was initiated in 1994, prior to the original approval of CellCept. The study design was similar to that of the renal transplant trials, in which a 6-month acute rejection endpoint and a 12 month patient and graft survival endpoint were utilized. Azathioprine is not approved for cardiac transplant.

Key study design elements included:

- Double-blind, randomized controlled study
- Azathioprine control arm
- 3 g/day dose of CellCept
- Routine endomyocardial biopsies
- Angiography and IV ultrasound
- Extensive follow-up for death/retransplantation, malignancies and CVD through 3 years for all patients
- Standardized histologic typing for graft rejections
- **Primary endpoints:** (1) biopsy proven acute rejection with hemodynamic compromise (superiority) at 6-months while providing (2) equivalent patient and graft survival at one year.

Treatment Regimens:
CELLCEPT: CellCept 3 g/day, Steroids, Cyclosporine
AZATHIOPRINE: Azathioprine 1.5-3 mg/kg/day according to each center's regimen, Steroids, Cyclosporine

Medical Officer Comment:
This study is the largest, randomized, double-blind comparative study which has been performed in cardiac transplant recipients. The applicant chose to continue the 3 g/day dose of CellCept in the cardiac study even after the approval, in renal transplant recipients, of the 2 g/day dose and not the 3 g/day dose. It was felt that cardiac transplant patients may need more intensive immunosuppressive therapy than renal transplants.

Previously, the standard outcome measure for transplantation studies had been the one year survival endpoint. The standardization of the histologic grading of acute rejection is evolving, and the clinical correlation to the histologic grade is not exact. Historical data regarding the efficacy of azathioprine were available at the one-year time point.

1. Active Control: Historical Perspective

The standard therapy for prevention of cardiac allograft rejection in the majority of U.S. and non-U.S. transplantation centers is currently triple immunosuppressive therapy with azathioprine, cyclosporine and steroids in combination. The applicant stated that because azathioprine is the community standard, and none of the investigators felt that they could enroll the study if it was not utilized, azathioprine, cyclosporine and steroids were selected as the active control therapy against which the combination of CellCept®, cyclosporine and steroids was compared. The dose of azathioprine selected. was somewhat higher than that used in the renal transplantation trials,

The applicant reviewed the literature, and presented the one year survival results for several large observational studies. Of interest was the comparison of two drug therapy (cyclosporine and steroids) compared to a regimen containing azathioprine, cyclosporine and steroids. Survival at one year ranged from for double therapy (cyclosporine and steroids without azathioprine compared to for triple drug regimens.

Medical Officer Comment:
The adoption of azathioprine/cyclosporine/steroid triple combination therapy has evolved not so much as a result of controlled clinical trials, but as a result of empirical therapy which, along with improved donor matching and surgical techniques, has improved outcomes over time. As pointed out by the applicant, care must be utilized in making comparisons between studies presented by the applicant, due to the use of non-concurrent, historical comparisons. Transplantation technology, tissue-typing, reduction in cold-ischemic time and a host of other factors have also contributed to the improved clinical outcome of patients over the past 15 years. We would concur with the applicant qualitatively, that azathioprine contributes to the activity of the regimen; however, it is more difficult to quantify the effect. Because of these concerns, the study was originally designed to demonstrate superiority of the CellCept combination over the active control for the prevention of 6-month acute rejection while demonstrating equivalent patient and graft survival at one year. Equivalence to azathioprine with respect to the 1-year graft/patient survival rate could potentially form the basis of an approval even in the absence of demonstrated superiority at six months.

2. Study Endpoints:

During the study the primary outcome measures evolved. Originally, the primary endpoint was "need to treat rejection". In December of 1994 the applicant requested a 3-year endpoint of prevention of coronary allograft vasculopathy be considered the primary endpoint and adjusted the sample size to 300 patients. In May of 1996 the primary endpoint was changed to that which was finally used in the intent-to-treat analysis. This was due to the fact that a change in practice to the use of more quantitative definition of coronary vascular disease and a subsequently higher rate of allograft coronary vascular

disease, and the number of patients discontinuing early would make the 3-year endpoint very difficult to evaluate.

The final endpoints to be used in the primary analysis of the data were agreed upon prior to unblinding of the data. These were 1.) acute biopsy proven rejection with hemodynamic compromise, and 2.) patient and graft survival at 1 year. Hemodynamic compromise was prospectively defined as any one of the following: inotropic support, ejection fraction less than 30%, pulmonary capillary wedge pressure greater than 20 mm or increased by 25%, cardiac index less than 2.0 or decreased by 25%, new S3 gallop, fractional shortening less than 20% or decreased by 25%, pulmonary artery oxygen saturation less than 60 % or decreased by 25%, or other.

Medical Officer Comment:

The six month endpoint was to be tested for superiority and the one-year endpoint was designed to test for equivalence. Given that the historic data for azathioprine were available for the 1-year survival endpoint and that it was a community standard, it was felt the demonstration of equivalence was acceptable to demonstrate efficacy. The 6-month endpoint was required in order to demonstrate superiority to azathioprine and not equivalence since no historical data supporting the activity of azathioprine were available for this endpoint.

3. Planned Analysis

The primary analysis was to include all patients randomized. The co-primary endpoint of 6 month rejection with hemodynamic compromise was to be analyzed by the Cochran-Mantel-Haenszel (CMH) test, stratifying by center. An alpha-level of 0.05 would be used to test for the superiority of CellCept. Equivalency for the co-primary endpoint of 12 month graft and patient survival was to be based on a 95% confidence interval on the difference in proportions of subjects having an event in the first 12 months. If the lower bound of the Confidence Interval (CI) was within the range ± 10% then equivalence could be concluded.

4. Randomization and Enrollment

A total of 650 patients were randomized into the study at the time of transplantation. Of these, 11% never received study drug due to the fact that they could not take oral medications for the first 5 days following transplantation. The applicant considered the "treated" subgroup as the appropriate group upon which to base the primary analysis. There were 28 centers enrolling patients in the US and abroad.

Table 1: Distribution of Patients

	CellCept	Azathioprine	TOTAL
Randomized	327	323	650
Untreated	38	34	72
Treated	289	289	578

(source: vol. 26, fig 1)

Medical Officer Comment:
The untreated group patients were excluded in a blinded manner based upon a decision to withdraw patients unable to receive oral study medication by day 5. The number of deaths in the untreated CellCept group was larger than those untreated but assigned to azathioprine (61% [23/38] vs. 47%[16/34], CellCept and azathioprine respectively). This unexpected event may have favored CellCept in the treated analysis.

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5. Demographics and Baseline Characteristics

Patients randomized into the study were an average of 52 years of age, predominantly male (83%), and Caucasian (87%).

Baseline characteristics were well matched across treatment groups, except for a slight imbalance in donor/recipient CMV serologic status and an imbalance in mean cold ischemic time (3.0 h for azathioprine vs. 3.7 h for CellCept).

Medical Officer Comment:
The treatment groups were well balanced by demography. The demographic and baseline characteristics among patients in this study are similar to those of the United Network for Organ Sharing (UNOS) heart transplantation registry. Thus, the study results may be generalizable to that population.

The imbalance in cold ischemic time may favor the azathioprine arm.

6. Results

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a. Survival:

The patient and graft survival were presented according to the intent-to-treat and the treated analysis. In addition to calculating the CI, the applicant presented a test of significance upon which they wished to claim superiority.

Table 2. Applicant's analysis of 1 year death or retransplantation rates.

Analysis	Azathioprine	CellCept	Difference	95% CI
Intent-to-Treat	15.2% (49/323)	12.8% (42/327)	2.6%	-2.5% to 5.1%
Treated	11.4% (33/289)	6.2% (18/289)	5.3%	0.9% to 9.7%

See applicants background document for a description of the weighting scheme
(source: vol. 26, tables 9 and 10).

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ON ORIGINAL

Medical Officer Comment:
Please see the FDA statistical review for details of the statistical issues surrounding equivalence. The FDA favored the intent-to-treat analysis, and in addition performed a

sensitivity analysis of the "treated patient" analysis. It was determined that the one year survival outcome for the treated subgroup was not robust, in that one or two failures in the CellCept arm would extend the lower limit below zero. As a result of this analysis and discussions of the Advisory Committee, FDA believes that the applicant has demonstrated that CellCept is at least as good as azathioprine for the prevention of graft loss or death at one year. Superiority was not demonstrated.

The applicant has agreed to submit the data base when all of the patients reach the 2-year follow-up date.

b. Rejection:

As described in the applicant's summary of efficacy, attempts to define a clinically meaningful 6-month endpoint evolved over the course of the trial. FDA originally recommended the use of 1-year graft and patient survival as the primary endpoint. The applicant indicated that the one year graft and patient survival included non-rejection events, against which CellCept could not be expected to have an effect. Therefore, the applicant suggested the inclusion of a 6-month endpoint which would discribe the anti-rejection activity of CellCept.

Medical Officer Comment:
The clinical significance of biopsy-proven rejection in heart transplantation varies with the histologic grade of severity. The standardization of histological staging is still in evolution, and the clinical importance of the lower grades of rejection is still uncertain. Thus, it was felt by FDA that evaluation of a 6-month rejection endpoint in heart transplantation should also include a direct measure of clinical outcome. Histology without clinical signs or symptoms of rejection would be an incomplete measure. The final 6-month endpoint of biopsy proven rejection plus hemodynamic compromise was agreed upon with the applicant prior to unblinding the study data. These data were prospectively collected on the case report forms from the beginning of the study. Another definition of the 6-month endpoint was proposed by the applicant after examination of the data. This will be discussed below.

The results of the six month endpoint, agreed upon prior to unblinding the data are listed in the table below.

Table 3. Six-month Rejection and Hemodynamic Compromise

	Intent-to-Treat	Treated
CellCept	37% (120/327)	32% (92/289)
Azathioprine	38% (121/323)	35% (100/289)
Difference	1%	3%
p-value	0.75	0.34

(source: vol. 26, table 7 and 8)

There were no statistically significant differences for this endpoint in either the treated or intent-to-treat populations. The applicant discussed this with the Steering Committee (including site investigators), who were no longer blind to the data. Because the rate of rejection was higher than the projected rate, the committee members suggested the applicant "tighten" the definition of hemodynamic compromise. The criteria for severe hemodynamic compromise were a subset of the original criteria for hemodynamic compromise (inotropic support, ejection fraction, and fractional shortening). The results are listed below.

Table 4. Rejection at Six Months with Severe Hemodynamic Compromise

	Intent-to-Treat	Treated
CellCept	18% (59/327)	11% (33/289)
Azathioprine	20 % (65/323)	17% (50/289)
Difference	2%	6%
p-value	0.49	0.04

(source: vol. 26, table 7 and 8)

Medical Officer Comment:
While the secondary analysis presented above is interesting and may provide additional insight into the clinical definition of hemodynamic compromise, when adjusted for multiple comparisons the p-value is not longer significant.

Additional secondary endpoint analyses were presented by the applicant regarding various measures of rejection. These included comparisons of Biopsy Proven Rejection (BPR) grade ≥ 2, BPR grade ≥ 3, BPR and treatment with pulse immunosuppression, BRP or presumed rejection treated with pulse immunosuppression, BRP or presumed rejection treated with OKT3 or antithymocyte globulin (ATG). These analyses were presented for both the intent-to-treat population and the "treated". The applicant did point to one analysis in the treated population (Biopsy Proven or presumed rejection treated with pulse immunosuppression) which was associated with an unadjusted p-value of 0.025.

Medical Officer Comment:
The favored analysis did not achieve a statistically significant difference when adjusted for multiple comparisons. None of the other secondary endpoints were statistically significant.

IV. CARDIAC TRANSPLANTATION SAFETY DATA BASE

All patients who received at least one dose of study medication (684 patients with 395 receiving CellCept) in six cardiac allograft transpant studies were included in the supplementary Integrated Safety Summary (ISS) for CellCept. In addition the applicant supplied results from patients enrolled in two 3-year Azathioprine-controlled studies for prevention of acute rejection in renal allograft recipients (pooled ICM 1866 and IICR 023

data). These two renal studies were pivotal in the original licensing application for CellCept and include 992 patients, 666 of which received CellCept. The dose of CellCept used in the renal studies was either 2 g or 3 g daily.

In brief, the results of the ISS for cardiac transplant studies revealed:

1. Numerically fewer deaths among patients who were treated with CellCept at any time post-transplantation.

2. Similar safety profiles, in general, for CellCept and azathioprine when used for the prevention of acute rejection in cardiac transplant patients.

3. Patients taking CellCept had a higher incidence of Adverse Events, including those involving the digestive system, than those taking azathioprine.

4. Opportunistic infections were more frequent in cardiac transplant patients treated with CellCept than azathioprine.

5. Malignancies occurred at the same incidence in patients with CellCept or azathioprine.

6. Safety data in the 3-year follow-up database for renal transplant patients did not reveal any new or unexpected safety hazard.

Only one of the six cardiac transplantation studies presented by the applicant was controlled (MYCS 1864). Adverse events in the uncontrolled studies were similar in nature to those in the comparative trial. This safety review focused on the specific Adverse Events encountered in study MYCS 1864.

A. STUDY 1864 (CARDIAC TRANSPLANTATION)

There were 289 patients in each treatment arm who received at least one dose of study drug. The safety data base includes only these patients. The duration of treatment for these patients includes one dose to multiple doses over the course of up to 2.5 years in some cases (Table 5). The proportion of patients who received at least 1 year of study drug therapy was 65% for CellCept and 55% for azathioprine.

Table 5. Duration of Treatment in Study MYCS 1864.

Duration of Treatment	CellCept 3 g/day N = 289	AZA 1.5-3 mg/kg/d N=289
≤1 year	30.4%	40.1%
>1 - 2 years	65.1%	55.4%
>2 - 3years	4.5%	4.5%

(Source: Table 9, vol. 207)

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The average daily dose of CellCept during the entire study period was 2.69 g/day compared to 1.89 mg/kg/day of azathioprine. These doses were slightly higher during the first six months of the study, 2.74 g/day and 1.96 mg/kg/day, for CellCept and azathioprine respectively.

1. Overall Adverse Events

In general the adverse event profile was similar to that observed in the renal transplant experience. (For a list of Adverse Events which occurred $\geq$ 10% frequency during the study please refer to the Appendix A.) Patients were followed while they were receiving study medication and for 14 days after discontinuation of study medication.

Medical Officer Comment:

The following comments are made by body system and include comparisons with the renal data found in the label from the original approval based on one year data.

In the category "Body as Whole" the frequency of the events were generally greater in the cardiac study than in the renal studies. This may be in part due to the more extensive and rigorous types of procedures the cardiac transplant patients undergo and the somewhat higher doses of immunosuppressants used for cardiac transplant rejection treatment and prophylaxis. In the cardiac transplant study, the most striking difference in frequencies between treatment groups in this category was for infection (25.6% CellCept versus 19.4% azathioprine). This will be discussed in a later section.

For the Category "Hemic and Lymphatic", again the rates in the cardiac transplant recipients were higher than in the renal. This may in part be due to the post-transplantation physiology, as the rates were similar between the CellCept and azathioprine treatment groups. Adverse events in this category with the greatest difference in rates include leukopenia (30.4% vs 39.1%), ecchymosis (40.5% vs 35.6%), and leukocytosis (40.5% vs 35.6%) respectively for CellCept and azathioprine.

The "Digestive" category again revealed frequencies which were higher when compared to the renal transplant experience, but the profile was similar. Adverse events having the largest difference when compared to azathioprine in the cardiac transplant studies included diarrhea (44.6% vs 33.9%), and nausea (52.6% vs 47.4%).

As would be expected for a group of cardiac transplant recipients, there were more adverse events in the "Cardiovascular" category than in seen in the renal transplant experience. In addition to hypertension, hypotension, "cardiovascular disorder", tachycardia, arrythmia, bradycardia, pericardial effusion, and heart failure were seen at frequencies greater than 10%. Generally the frequencies were similar between the two treatment arms.

The "Respiratory System" category also included more types of adverse events in the cardiac than the renal which occurred at a frequency of ≥ 10%, including lung disorder, sinusitis, rhinitis, pleural effusion, asthma, pneumonia. The rates were similar between treatment groups in the cardiac studies.

"Urogenital System" category had similar types of adverse events to that of the renal transplant experience, however the frequencies were lower in the cardiac experience. The frequencies between the treatment groups in the cardiac study were similar.

In the "Metabolic and Nutritional" Category similar events were seen except for hypophosphatemia which was seen in renal and not cardiac transplant studies at a rate of ≥ 10%. Additional events occurred in the cardiac transplant experience including increased creatinine and BUN, increased lactic dehydrogenase, bilirubinemia, hypervolemia, generalized edema, hyperuricemia, SGOT increased, hypomagnesemia, acidosis, weight gain, SGPT increased, hyponatremia, hyperlipemia. The rates were similar among the two treatment groups with the largest numeric difference being for peripheral edema (59.5% CellCept vs. 51.2%). Hyperglycemia was seen more frequently in the azathioprine group (30.1%) compared to CellCept (23.5%). Hypervolemia was seen more frequently in the azathioprine group (17.6%) compared to the CellCept group (13.5%).

For the "Nervous System" category, the rate of the most frequently occurring events were higher in the cardiac transplant experience than the renal. The frequency of events in the two treatment arms was similar in the cardiac studies. The largest numeric difference was seen for insomnia, 40.8% for CellCept and 37.7% for azathioprine. Additional events occurring at a rate of ≥ 10% in the cardiac experience included anxiety, paresthesia, hypertonia, depression, agitation, somnolence, confusion, nervousness.

Amblyopia was reported in 14.9% of the patients on CellCept and 6.6% of the patients receiving azathioprine in the cardiac studies. In most cases the verbatim term was blurred vision.

In Summary, the profile of the Adverse Events seen in the cardiac transplant trial was similar to that of the renal trials, except where the influence of the side effects of the specific organ transplanted are seen, e.g., more frequent renal side effects in the renal transplant recipients and more cardio-pulmonary events seen in the cardiac trials. The overall frequency of adverse events was somewhat higher for the cardiac transplant recipients than that in the renal transplant recipients. This may be due to the more intense immunosuppresive regimens received by the cardiac patients, and the more extensive surgery. In addition, it should be recognized that cross study comparisons should be made with caution. Additional labeling changes due to review of the phase four experience in renal transplantation will be considered below.

2. Serious Adverse Events

Serious Adverse events which occurred in the cardiac transplant study are listed below. Severe neutropenia, defined as an absolute neutrophil count < 500 /uL on-study (for any length of time) or within 15 days of discontinuing study drug, occurred in 2.8% of patients in the CellCept arm and zero percent in the azathioprine arm. The other events were similar between treatment arms and occurred at rates less than 15.6%.

Table 6. Medically Serious Adverse Events (MCS 1864)

	MMF 3 g/day N = 289	AZA 1.5-3 mg/kg/d N=289
Premature Termination Due to AE, Intercurrent Illness or Lab Abnormality	14.5%	15.6%
Death	8.0%	14.5%
Severe Hepatitis	5.5%	4.2%
Malignancy*	2.8%	4.2%
Severe Neutropenia	2.8%	0%
GI Bleeding	1.7%	1.7%
GI Perforation	0.3%	0.7%
Severe Thrombocytopenia	0%	0.3%

* Excludes squamous cell skin carcinoma and basal cell skin carcinoma. (Source: Table 13, Vol. 207)

Similar findings were observed in the pooled cardiac data base for the uncontrolled studies, except for gastrointestinal bleeding which was 7.1% (7 of 98 patients). The applicant suggested the reason for a slightly greater incidence was that these patients were in studies which included treatments for acute rejection, that there was a greater duration of treatment, and that there was a greater requirement for pulse immunosuppressive therapy. None of the patients in the pooled, uncontrolled cardiac studies had a gastrointestinal perforation.

Medical Officer Comment:

Review of Appendix 1, volume 208, reveals 8 patients listed as Serious Medical Events of Neutropenia (6 on CellCept, 2 on azathioprine). All of them were reported to have survived at least 1 year. Thus, while more serious neutropenia events were seen in the CellCept arm than the azathioprine arm, these events were not fatal. Similarly from the same appendix 16 patients receiving CellCept had serious hepatitis compared to 12 receiving azathioprine. The death rates among those with serious hepatitis were similar (6/16 [38%] in the CellCept group, 6/12 [50%] in the azathioprine group). Several of these cases also had concomitant CMV infections. These results indicate that while serious events did occur, the outcomes were similar among the two treatment groups.

3. Withdrawal due to Adverse Events

Adverse events leading to premature withdrawal in Study MYCS 1864 were similar between both treatment groups. The rates are displayed below for the individual causes according to the number of patients who experienced at least one event.

Table 7. Adverse Events Leading to Premature Withdrawal from Study Drug

Body System	CellCept (3 g/day) N=289	Azathioprine N=289
Any Body System	42 (14.5%)	45 (15.6%)
Hematopoetic and Lymphatic System	15 (5.2%)	19 (6.6%)
Digestive System	17 (5.9%)	13 (4.5%)
Body As A Whole	5 (1.7%)	8 (2.8%)
Respiratory System	2 (0.7%)	7 (2.4%)
Metabolic and Nutritional Disorders	2 (0.7%)	5 (1.7%)
Nervous System	3 (1.0%)	3 (1.0%)
Urogenital System	1 (0.3%)	3 (1.0%)
Cardiovascular System	1 (0.3%)	2 (0.7%)
Skin and Appendages	0	1 (0.3%)

(Source: vol. 207, table 21)

The categories with the highest frequencies of adverse events leading to premature withdrawal included the digestive system and the hematopoetic and lymphatic system. Nausea was the most frequent event in the digestive category (3 patients on CellCept and 4 on azathioprine). The most frequent event in the hematologic category was leukopenia 3.5% (10 patients) and 4.5% (13 patients) respectively for CellCept and azathioprine.

Medical Officer Comment:
Note that the rates were slightly higher for the azathioprine group.

4. Opportunistic Infections

Information regarding the following infections was collected in the data base: cytomegalovirus (CMV), herpes zoster virus, herpes simplex virus, Candida, Pneumoncystis carinii, Aspergillus/Mucor, Cryptococcus, and Listeria monocytogenes. CMV was further divided into there categories: CMV viremia/syndrome; CMV tissue invasion; and CMV infection. The designation of CMV infection refers to the presence of CMV in body fluids excluding blood in the absence of evidence of CMV disease.

The overall incidence of opportunistic infection was 53.3% with CellCept compared to 43.6% with azathioprine. The most frequent infection in the CellCept group was Herpes simplex 60 (20.8%) vs 42 (14.5%) in the azathioprine group (please see final approved label for complete listing). The frequencies of the remaining infections were similar between treatment groups.

Medical Officer Comment:
It is of interest to note that the rate of specific opportunistic infections was similar between the cardiac and renal transplant experience. Herpes simplex was seen in 20% of the patients on CellCept 3 g/day and 19.0% of patients on azathioprine in the renal transplantation studies. Death rates due to infection were similar in both treatment arms in the cardiac transplantation study (details discussed in Section 6: Deaths). ..

5. Malignancies:

Malignancies were diagnosed at a similar frequency in both treatment arms. The types of malignancies are listed below. Note the malignancies reported below occurred anytime while on study drug or 14 days after discontinuation of study drug. The majority of patients had between one and 2 years of therapy (Table 5).

Table 8. Malignancies in Cardiac Allograft Transplantation Study MYCS 1864

	CellCept 3 g/day N=289	Azathioprine 1.5-3 mg/kg/day N=289
Number of patients with 1 or more malignancies	**20 (6.9%)**	**20 (6.9%)**
Nonmelanoma Skin Malignancy	**12 (4.2%)**	**8 (2.8%)**
Basal Cell Carcinoma	7 (2.4%)	5 (1.7%)
Squamous cell carcinoma	6 (2.1%)	3 (1.0%)
Other Malignancy	**6 (2.1%)**	**6 (2.1%)**
Kaposi Sarcoma	2 (0.7%)	2 (0.7%)
Adenocarcinoma/Prostate	1 (0.3%) ..	1 (0.3%)
Renal cell Carcinoma	1 (0.3%)	1 (0.3%)
Adenocarcinoma-Lung	0 (0%)	1 (0.3%)
Adenocarcinoma/Pancreas	1 (0.3%)	0 (0%)
Gastric Carcinoma	1 (0.3%)	0 (0%)
Squamous cell carcinoma/Lung	0 (0%)	1 (0.3%)
Lymphoma/lymphoproliferative Disease (Lymphoma)	**2 (0.7%)**	**6 (2.1%)**

(Source: Table 19 vol. 207)

Equal numbers of malignancies were diagnosed in both treatment groups. Of the nonmelanoma skin malignancy all were either basal or squamous cell carcinomas.

Medical Officer Comment:
A similar rate of lymphoma/lymphoproliferative disease was seen in the renal trials. The one year renal transplant rate for was 1.2% (4 patients) CellCept 3 g/day and 0.3% (1 patient) for azathioprine, and the three year rate was 1.8% (6 patients) CellCept 3 g/day and 0.6% (2 patients) for azathioprine . It is known that the risk for Non-Hodgkins Lymphoma is the highest in the firs year after transplantation, then the incidence falls and remains at a relatively constant rate of The rates reported above are in this relative range.

Non-melanoma skin malignancies have been reported in renal transplant patients at rates of 20% at 5 years in Australia to 10% in 10 years in the Netherlands. The rates seen in this study support recommended changes in the warning section of the approved label regarding limiting exposure to sunlight and UV light through the use of protective clothing and sunscreen with a light protection factor.

It will be of interest to review the incidence, as well as the types of malignancies reported at 3 years in the cardiac transplant recipients, who may receive a higher amount of immunosuppression than the renal transplant patients.

6. Deaths

The incidence of death (on-study and post-termination) at any time following transplantation for patients who received at least one dose of study medication was 8.0% (23/289) in the CellCept group and 14.5% (42/289) in the azathioprine group. The applicant has recategorized 11 of the causes of death from the category "other", and one from "cerebrovascular event". These changes were a result of additional information submitted to the applicant after the "data" lock. The following table represents causes of death after the reclassification.

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Table 9. Causes of Death Occurring Any Time Post-transplant in Cardiac Allograft Transplantation Study MYCS 1864

CAUSES OF DEATH	Azathioprine 1.5-3 mg/kg/day N = 289	Cellcept 3 gm/day N = 289
TOTAL DEATHS	42	23
Cardiovascular Event	11 (3.8%)	9 (3.1%)
Accident/Trauma/Surgery	0	1 (0.3%)
Cancer	2 (0.7%)	2 (0.7%)
Infection/Sepsis	14 (4.8%)	6 (2.1%)
Pulmonary Embolism	2 (0.7%)	1 (0.3%)
Suicide	0	1 (0.3%)
Cerebrovascular event	1 (0.3%)	0
Allograft Rejection	10 (3.5%)	2 (0.7%)
OTHER:	2 (0.7%)	1 (0.3%)
Unknown-suspect tamponade	0	1 (0.3%)
Unknown-sudden death	1 (0.3%)	0
Acute renal failure	1 (0.3%)	0

(Source: vol. 208, appendix 40)

There were more deaths in the azathioprine arm at any time post-transplant than in the CellCept arm. More deaths attributed to cardiovascular events, infection/sepsis and allograft rejection occurred in the azathioprine arm.

Medical Officer Comment:
The line listings and textual comments provided by the applicant in appendix 41 vol. 208 were reviewed. According to this data, the further clarification and reclassification of causes of death appears to be appropriate. Only 4 cases had completely unknown causes at the time of the data lock. It is of interest to note that four of the cases were due to acute allograft rejection and one to chronic allograft rejection. For the remaining deaths, case report forms and patient summaries were reviewed. The cause of death assignments were appropriate, given the data presented by the applicant.

7. Laboratory Abnormalities

The applicant provided laboratory summaries for selected tests by time periods on study medication (first 30 days on treatment, days 31- 180 on treatment, days 181-365 on treatment, and > 365 days on treatment). The laboratory results listed were for the following: minimum absolute neutrophil count (ANC), minimum platelet count, minimum hemoglobin, maximum serum creatinine, maximum total bilirubin, maximum alkaline phosphatase, maximum SGOT (AST), and maximum SGPT (ALT).

Absolute Neutrophil Counts (ANC) results of < 750 cells/uL at any time during therapy occurred in 10 patients on CellCept and 4 patients on azathioprine. These events occurred most frequently during the 31-180 day time period. Beyond one year few patients exhibited ANC < 1300/uL.

The frequency of low platelet count (< 100,000/uL) was highest during the first 30 days of treatment (14.6% for CellCept vs. 12.2% for azathioprine). Beyond 30 days, the incidence of "low platelet" count was for both treatment groups. Only one extremely low (<25,000/uL) value occurred in this study in the azathioprine treatment group.

The majority of patients had minimum hemoglobin concentrations reported greater than 8 g/dL in the first 30 days of treatment (93% for CellCept vs. 91% for azathioprine). In both groups minimum hemoglobin levels improved with time, similarly in both groups. 13.4% in the CellCept group and 14.3% in the azathioprine group, had minimum hemoglobin levels < 11 g/dL after one year of treatment. No patients who were treated with CellCept had minimum hemoglobin measurements below 6.5 g/dL, compared to three who received azathioprine.

The majority of patients in both treatment groups had maximum serum creatinine concentrations , during the first 30 days of treatment (66 for CellCept vs. 67 for azathioprine). The proportion of patients with this creatinine concentration increased in the period between 31 and 180 days of treatment in both groups (83% for CellCept vs. 77% for azathioprine), and stabilized at this level. For the extreme maximum creatinine measured in the first 30 days of treatment, there were 15 % in the CellCept group and 12% in the azathioprine group, decreasing in frequency over

time. At greater than 1-year of treatment creatinine levels > 2.5 mg/dL occurred in 8% of the patients treated with CellCept and 14% treated with azathioprine.

Maximum alkaline phosphatase levels were most frequently in the
in the first 30 days of therapy (73% for CellCept vs. 68% for azathioprine). Values of > 1,000 U/L were not seen in either group. Approximately 60% of patients in each treatment group had maximum alkaline phosphatase in this range at greater than 1 year of treatment.

Maximum bilirubin most frequently occurred at levels of
during the initial 30 days (58% for CellCept and 67% for azathioprine). These frequencies decreased over time to 16% vs. 35% for CellCept and azathioprine respectively. The proportion of patients having maximum bilirubin values below 1.2 mg/dL was 84% vs. 66% for CellCept and azathioprine respectively.

Approximately 20% of patients in each treatment group had maximum SGOT $\leq$ 60 U/L during the first 30 days of treatment. These frequencies improved so that patients who were treated for greater than one year had SGOT levels in this range for 98% of the patients in both arms. Only one patient on the CellCept arm had an SGOT of $\geq$ 400 U/L at > 1-year. The pattern for maximum SGPT was similar to SGOT and comparable between treatment groups.

Medical Officer Comment:
Laboratory values reports of selected chemistries did not reveal evidence for progressive nephrotoxicity or hepatotoxicity with CellCept. The highest incidence of ANC < 1300 occurred during days 31-180 of treatment and remained fairly stable thereafter for both treatment groups; ANC less than 1300 /uL was more common with CellCept. The majority of patients had elevated serum creatinine concentrations during the initial 30 days. At greater than 365 days of treatment, about twice as many azathioprine patients as CellCept had serum creatinine concentrations > 2.5 mg/dL. It is noted that study drug was adjusted downward for toxicities of grade 2 or higher and withheld at the physician's discretion for toxicities greater than grade 3.

Analysis of adverse events and toxicities for race and gender were performed, and profiles were similar to those for the overall AEs. It should be noted that the majority of the patients were male (83%) and Caucasian (87%).

8. Outcome of Pregnancies
No patients in study MYCS 1864 reported having conceived a child while on study drug or for three months after completion of study. However there have been pregnancies recorded in other studies. There were are a total 19 pregnancies reported in studies where patients were treated with CellCept since the original NDA for renal transplantation was submitted. The results of these pregnancies included 7 normal

births, 6 spontaneous abortions/miscarriages (3 occurred during 3 twin pregnancies), one intrauterine death, one congenital adrenal hyperplasia, one birth with hand and foot deformities where the parent had a history of syndactyly, and three terminations. Only two of these pregnancies were in patients who received cardiac transplantation, the remainder were renal transplant recipients.

Medical Officer Comment:

The frequency of miscarriage (6/19, or 36%) is higher than in the safety database included in the original new drug application (1/12, or 8%). Events in the original database included 8 normal births, one terminated, one miscarriage, one congenital adrenal hyperplasia, one undeveloped diaphragm and possible heart disease.

Other databases reporting outcomes of pregnancies for renal and cardiac patients treated with cyclosporine/steroids and azathioprine report rates of miscarriage from 12-18%. If one combines the information available in the original NDA and in this efficacy supplement, the overall rate of miscarriages in reported pregnancies is 22% (7/31).

CellCept is currently labeled as a Category C drug, and the applicant has an active pregnancy registry.

B. 3 YEAR FOLLOW-UP RENAL TRANSPLANTATION SAFETY DATABASE

Three year safety data from renal transplantation studies has been previously submitted to the NDA. In the current submission the applicant compared the safety profile in renal transplantation studies (ICM 1866 and IICR 023) with that in heart transplantation in the Integrated Safety Summary. Both renal studies were combined in a single data base due to similarities in the study designs: azathioprine control arm and two separate doses of CellCept (2 gm and 3 gm per day). Two aspects of these comparisons are of interest in the in the review of safety for cardiac transplantation: 1.) comparison of the 3 g/day safety profile at one year in heart transplant recipients with the one-year profile in kidney transplant recipients (both 2 and 3 g/day doses); (2.) long-term follow-up safety data (3 year) profile, particularly including malignancy and infection. The latter was of interest since the heart transplantation study utilized a higher daily dose of CellCept than was recommended for the renal transplant recipient (2 g/day).

Serious adverse events at 1 and 3 years are displayed for the renal transplant recipients below.

Table 10. Medically Serious Adverse Events in Renal Transplantation Studies (ICM 1866 and IICR 023) at 1 and 3 Years of Follow-up.

	CellCept 2g/day 1-year	CellCept 2g/day 3-year	CellCept 3g/day 1-year	CellCept 3g/day 3-year	AZA 1-year	AZA 3-years
Number Pts	336	336	330	330	326	326
Premature DC due to AE, illness or lab	40 (12%)	53 (16%)	52 (16%)	69(21%)	43 (13%)	58 (18%)
Death	17 (5%)	25 (7%)	21 (6%)	38 (12%)	17 (5%)	37 (11%)
GI Bleeding	8 (2%)	10 (3%)	12 (4%)	16 (5%)	4 (1%)	5 (2%)
Malignancy	6 (2%)	9 (3%)	11 (3%)	20 (6%)	8 (3%)	18 (6%)
Severe Neutropenia	2 (1%)	3 (1%)	7 (2%)	7 (2%)	2 (1%)	2 (1%)
GI Perforation	1 (0.5%)	1 (0.5%)	3 (1%)	4 (1%)	1 (0.3%)	4 (1%)
Severe Thrombocyto-penia	0	1 (0.5%)	2 (1%)	3 (1%)	1 (0.3%)	1 (0.3%)
Severe Hepatitis	0	1 (0.5%)	1 (0.3%)	2 (1%)	4 (1%)	1 (0.3%)

(Source: vol. 207, table 14 and 15)

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Medical Officer Comment:

The one-year incidence of severe adverse events in the cardiac transplantation study is similar to that of the renal transplantation studies. The incidence of serious malignancy was 2.8% in the cardiac transplantation study for CellCept, this was similar to that of the 3 g/dose rate in the renal transplantation studies. Note that the rates increased somewhat in the three year comparison. It was of interest to note that the increased rate of serious malignancy was similar for the azathioprine and the CellCept 3 g/day (an increase of 2 times).

The Overall malignancy rates for the pooled renal studies are displayed in the following table.

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Table 11. Malignancies at 1 and 3 years in the Renal Transplant Studies

	CellCept 2g/day 1-year	CellCept 2g/day 3-year	CellCept 3g/day 1-year	CellCept 3g/day 3-year	AZA 1-year	AZA 3-year
# of patients with 1 or more malignancies	23 (6.8%)	40 (11.9%)	21 (6.4%)	37 (11.2%)	16 (4.9%)	43 (13.2%)
Nonmelanoma skin	17 (5.1%)	32 (9.5%)	10 (3.0%)	17 (5.2%)	8 (2.5%)	30 (9.2%)
other malignancies	3 (0.9%)	7 (2.1%)	8 (2.4%)	15 (4.5%)	7 (2.1%)	16 (4.9%)
Lymphoma/lympho-proliferative	3 (0.9%)	3 (0.9%)	4 (1.2%)	6 (1.8%)	1 (0.3%)	2 (0.6%)

(Source: vol. 207 table 20)

Medical Officer Comment:
Again there was an increase in the frequency of malignancies over time in all of the treatment groups. Much of this increase is due to nonmelanoma skin malignancy. The lymphoproliferative malignancies remained at a low level.

It is important to note that dosage adjustment was permitted in the studies. In the renal data base 33% of the patients had been treated with CellCept for more than 3 years. The mean daily dose of CellCept was 1.78 g/day for the 2 g cohort and 2.60 g/day for the 3 g cohort. Thus, 3 year malignancy rates reflect continuing exposure to doses of CellCept that are near the target dose for both treatment dosages.

Infections were found in 46.7% of patients with CellCept 2 g/day, 47.6% with CellCept 3 g/day and 46.0% with azathioprine in the renal transplant studies at the 1-year data cut. This increased somewhat at 3 years for all groups. Both CellCept 2 g/day and azathioprine groups had infection rates of 51% at 3 years compared to 53.9% in the CellCept 3 g/day group. The distribution of pathogens was similar to that in the cardiac studies.

Medical Officer Comment:
Long term follow up is needed in the cardiac transplant population in order to fully evaluate the benefit and risk profile in transplant recipients. Malignancies, specifically nonmelanoma skin, and infections are related to the degree and duration of immunosuppression. Adequate recommendations for precautions intended to minimize the occurrence of skin malignancies have been included in the WARNINGS section of the proposed revised package insert.

At three years following renal transplantation, there was no evidence to suggest that CellCept was any worse than azathioprine with respect to rates of malignancy or infection.

VI. SUMMARY COMMENTS STUDY MYCS1864

Study MYCS1864 met one of two study goals. It demonstrated equivalence of CellCept with respect one-year patient and graft survival to azathioprine. This result was obtained in combination with cyclosporine and prednisone. The applicant failed to demonstrate superiority with respect to the six-month endpoint (biopsy proven rejection with

hemodynamic compromise). Long-term follow-up for patient and graft survival, malignancy and opportunistic infection is ongoing.

The safety profile was similar to that seen in the renal transplant studies. Laboratory values reports of selected chemistries did not reveal evidence for progressive nephrotoxicity or hepatotoxicity with CellCept. Lymphoproliferative disease or lymphoma developed in approximately 1% of patients receiving CellCept, which was comparable to the renal transplantation experience and that of the azathioprine control group. Pancreatitis will be added to the label as a rare event. Finally, cases of fatal infection/sepsis occurred in less than 2% of patients receiving CellCept.

V. ADVISORY COMMITTEE RECOMMENDATIONS

An FDA Advisory Committee Meeting was held on January 14, 1998, to discuss the interpretation of the clinical study (MYCS 1864) for cardiac transplantation and the possible extension of the label for the use of CellCept in the cardiac transplant population.

The committee agreed that CellCept was safe and effective for the prevention of acute rejection of cardiac allograft transplants. In addition, strong recommendations were given to the FDA that equivalence had been demonstrated and not superiority, and as such, superiority should in no way be inferred in the label.

Regarding choice of endpoint for future studies, the committee strongly recommended the use of 1-year patient and graft survival with further long-term follow-up. While potentially useful, the six month rejection endpoints, were not shown to be clinically meaningful in this study. Further refinements of a six month biopsy proven rejection endpoint may be explored in future studies, but it is not clear how reliable a clinical outcome measure they would ultimately prove to be.

VI. LABEL (See Revised "Package Insert" included in approval package)

Changes made to the current label approved for renal transplantation, concerned the pharmacokinetics in cardiac patients, the clinical study section report of the study results, the safety information from the cardiac trial, addition of the cardiac indication, recommendation of the 3 g/day dose, nonmelanoma skin malignancy, and pancreatits. The study results section reported intent-to-treat and treated results for the two co-primary endpoints. As per the advisory committee's recommendation, no claim of superiority was made, rather equivalence to azathioprine at 12 months was allowed in the label.

VII. RECOMMENDATIONS:

The single, double-blind, controlled study (MYCS 1864) submitted in support of CellCept for the prevention of acute cardiac allograft rejection in addition to the previously submitted renal studies (Study 022, 1866, 023) meet the regulatory requirements for approval of this indication. Pursuant to 21 CRF 314.105 (a) the study performed was an adequate and well-controlled investigation and established that 3 g/day dose of CellCept is at least as effective for the prevention of cardiac allograft rejection as the established community standard against which it was compared (azathioprine). CellCept is recommended for approval for this indication.

Recommend Approval of NDA 50-722/s-002: prevention of acute cardiac allograft rejection (250 mg Capsules).

Recommend Approval of NDA 50-723/s-001: prevention of acute cardiac allograft rejection (500 mg Tablets).

Medical Reviewer:

Joyce Korvick, M.D. /S/ 5/26/98

Concurrence:

/S/

Director/HFD-590: Goldberger, M.

Team Leader: Cavaille-Coll, M. (edit 3-31-98, 5-26-98) /S/ 5.27.98

APPENDIX

Adverse Events Listed in Label ≥ 10%

	CellCept 3 g/day (n=289)	Azathioprine 1.5 to 3 mg/kg/day (n=289)
Body as a Whole		
Pain	75.8%	74.7%
Abdominal pain	33.9	33.2
Fever	47.4	46.4
Headache	54.3	51.9
Infection	25.6	19.4
Sepsis	18.7	18.7
Asthenia	43.3	36.3
Chest pain	26.3	26.0
Back pain	34.6	28.4
Accidental injury	19.0	14.9
Chills	11.4	11.4
Hemic and Lymphatic		
Anemia	42.9	43.9
Leukopenia	30.4	39.1
Thrombocytopenia	23.5	27.0
Hypochromic anemia	24.6	23.5
Leukocytosis	40.5	35.6
Ecchymosis	16.6	8.0
Urogenital		
Urinary tract infection	13.1	11.8
Kidney function abnormal	21.8	26.3
Oliguria	14.2	12.8
Cardiovascular		
Hypertension	77.5	72.3
Hypotension	32.5	36.0
Cardiovascular disorder	25.6	24.2
Tachycardia	20.1	18.0
Arrhythmia	19.0	18.7
Bradycardia	17.3	17.3
Pericardial effusion	15.9	13.5
Heart failure	11.8	8.7
Metabolic and Nutritional		
Peripheral edema	64.0	53.3
Hypercholesteremia	41.2	38.4
Edema	26.6	25.6
Hypokalemia	31.8	25.6

Hyperkalemia	14.5	19.7
Hyperglycemia	46.7	52.6
Creatinine increased	39.4	36.0
BUN increased	34.6	32.5
Lactic dehydrogenase increased	23.2	17.0
Bilirubinemia	18.0	21.8
Hypervolemia	16.6	22.8
Generalized edema	18.0	20.1
Hyperuricemia	16.3	17.6
SGOT increased	17.3	15.6
Hypomagnesemia	18.3	12.8
Acidosis	14.2	16.6
Weight gain	15.6	15.2
SGPT increased	15.6	12.5
Hyponatremia	11.4	11.8
Hyperlipemia	10.7	9.3
Digestive		
Diarrhea	45.3	34.3
Constipation	41.2	37.7
Nausea	54.0	54.3
Dyspepsia	18.7	19.4
Vomiting	33.9	28.4
Nausea and vomiting	11.1	7.6
Oral moniliasis	11.4	11.8
Flatulence	13.8	15.6
Respiratory		
Infection	37.0	35.3
Dyspnea	36.7	36.3
Cough increased	31.1	25.6
Pharyngitis	18.3	13.5
Lung disorder	30.1	29.1
Sinusitis	26.0	19.0
Rhinitis	19.0	15.6
Pleural effusion	17.0	13.8
Asthma	11.1	11.4
Pneumonia	10.7	10.4
Skin and Appendages		
Acne	12.1	9.3
Rash	22.1	18.0
Skin disorder	12.5	8.7
Nervous System		
Tremor	24.2	23.9
Insomnia	40.8	37.7

Dizziness	28.7	27.7
Anxiety	28.4	23.9
Paresthesia	20.8	18.0
Hypertonia	15.6	14.5
Depression	15.6	12.5
Agitation	13.1	12.8
Somnolence	11.1	10.4
Confusion	13.5	7.6
Nervousness	11.4	9.0
Musculoskeletal System		
Leg Cramps	16.6	15.6
Myasthenia	12.5	9.7
Myalgia	12.5	9.3
Special Senses		
Amblyopia	14.9	6.6
Endocrine System	12.1	12.8

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 050722/S002 AND 050723/S001

CHEMISTRY REVIEW(S)

SUPPLEMENTAL NDA CHEMIST'S REVIEW	1. ORGANIZATION HFD-590	2. NDA NUMBER 50-723

3. NAME AND ADDRESS OF APPLICANT *(City and State)*	4. AF NUMBER	
Syntex (U.S.A.) Inc. 3401 Hillview Avenue Palo Alto, CA 94304	5. DOCUMENT(S) NUMBER(S) SLR-001	DATE(S) 2/10/98

6. NAME OF DRUG	7. NONPROPRIETARY NAME
CellCept	mycophenolate mofetil

8. SUPPLEMENT(S) PROVIDES FOR:	9. AMENDMENTS AND OTHER *(Reports, etc.)* DATES
the use of mycophenolate mofetil for the prophylaxis of organ rejection in patients receiving allogeneic cardiac transplants.	

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF(S)
Immunosuppressant	|X| Rx | | OTC	N50-722/SE1-002

13. DOSAGE FORM(S)	14. POTENCY(IES)
Tablet	500-mg

15. CHEMICAL NAME	16. MEMORANDA
See current package insert	

17. COMMENTS

CellCept (mycophenolate capsules, 250 mg) NDA 50-722 was originally approved on May 3, 1995, for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants. On June 19, 1997, a 500-mg tablet was approved for this indication under N50-723.

A supplemental application (N50-722/SE1-002) providing for the prophylaxis of organ rejection in patients receiving allogeneic cardiac transplants with CellCept was submitted on July 31, 1997. The current labeling supplement was submitted to cover the use of the tablet formulation in the new indication. There are no chemistry, manufacturing and controls changes associated with the new indication.

In N50-722/SE1-002, the applicant initially claimed a categorical exclusion from the environmental assessment requirements as provided for by 21 CFR 25.24(c)(2). However, since the supplement provides for "different indications than were previously in effect", the supplement does not meet those exclusion criteria. Nevertheless, at our request the applicant has applied for a categorical exclusion under regulations promulgated in the Federal Register on July 29, 1997.

18. CONCLUSIONS AND RECOMMENDATIONS

Labeling supplement N50-7232/SLR-001 is approvable from the chemistry, manufacturing and controls perspective.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Mark R. Seggel	/S/	2/11/98

20. CONCURRENCE: HFD-590/NSchmuff /S/ 2/10/98

DISTRIBUTION							
	X	Original Jacket	X	MSeggel	X	MCavailleColl
	X	Division File	X	NSchmuff	X	LHubbard
			X	HFD-830/CChen		

SUPPLEMENTAL NDA CHEMIST'S REVIEW	1. ORGANIZATION HFD-590	2. NDA NUMBER 50-722

3. NAME AND ADDRESS OF APPLICANT *(City and State)*	4. AF NUMBER	
Syntex (U.S.A.) Inc. 3401 Hillview Avenue Palo Alto, CA 94304	5. DOCUMENT(S) NUMBER(S) SE1-002	DATE(S) 7/31/97

6. NAME OF DRUG	7. NONPROPRIETARY NAME
CellCept	mycophenolate mofetil

8. SUPPLEMENT(S) PROVIDES FOR:	9. AMENDMENTS AND OTHER *(Reports, etc.)* DATES
the use of mycophenolate mofetil for the prophylaxis of organ rejection in patients receiving allogeneic cardiac transplants.	BC 1/6/98 (re: EA)

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF(S)
Immunosppressant	|X| Rx | | OTC	N50-723/SLR-001, 2/10/98

13. DOSAGE FORM(S)	14. POTENCY(IES)
Capsule	250-mg

15. CHEMICAL NAME	16. MEMORANDA
See current package insert	

17. COMMENTS

CellCept (mycophenolate capsules, 250 mg) was originally approved on May 3, 1995, for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants. A 500-mg tablet was approved on June 19, 1997, for this indication (N50-723).

This supplemental application provides for the prophylaxis of organ rejection in patients receiving allogeneic cardiac transplants with CellCept. There are no chemistry, manufacturing and controls changes associated with the new indication.

The applicant originally claimed a categorical exclusion from the environmental assessment requirements as provided for by 21 CFR 25.24(c)(2). However, since the supplement provides for "different indications than were previously in effect", the supplement does not meet those exclusion criteria. Nevertheless, at our request the applicant has applied for a categorical exclusion under regulations promulgated in the Federal Register on July 29, 1997.

18. CONCLUSIONS AND RECOMMENDATIONS

Efficacy supplement SE1-002 is approvable from the chemistry, manufacturing and controls perspective.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Mark R. Seggel	/S/	2/11/98

20. CONCURRENCE: HFD-590/NSchmuff /S/ 2/16/98

DISTRIBUTION							
	X	Original Jacket	X	MSeggel	X	MCavailleColl
	X	Division File	X	NSchmuff	X	LHubbard
			X	HFD-830/CChen		

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 050722/S002 AND 050723/S001

PHARMACOLOGY REVIEW(S)

FEB 10 1998

PHARMACOLOGIST'S REVIEW

NDA# 50-722/S-002
DATE SUBMITTED: 23 December 1997
DATE RECEIVED: 29 December 1997
DATE ASSIGNED: 29 December 1997
DATE REVIEW COMPLETED: 10 February 1998
SPONSOR: Roche
DRUG: CellCept (mycophenolate mofetil)
HFD-590

APPEARS THIS WAY
ON ORIGINAL

RELATED DOCUMENTS: none
INDICATION: Cardiac transplantation

REVIEW AND CONCLUSIONS

The product, CellCept (mycophenolate mofetil), is an approved drug. No pharmacology/toxicology information was included in this submission. No regulatory action is indicated

/S/

Steven C. Kunder, Ph.D.
Reviewing Pharmacologist

APPEARS THIS WAY
ON ORIGINAL

concurrences:
HFD-590/ADir/RAlbrecht
HFD-590/SPharm/KHastings /S/ 2/10/98
Steven C. Kunder/Pharm/

disk:
HFD-590/KHastings

cc:
HFD-590 (original)
HFD-590 Division file
HFD-340
HFD-590/LHubbard
HFD-590/JKorvick
HFD-590/SLard
HFD-590/MSeggel
HFD-345/

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 050722/S002 AND 050723/S001

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA#:	50,722/S-002, 50-723/S-001
APPLICANT:	Syntex USA, Inc.
NAME OF DRUG:	Cellcept (mycophenolate mofetil)
INDICATION:	Prophylaxis of transplant rejection and increased patient and graft survival in patients receiving allogenic cardiac transplants.
DOCUMENTS REVIEWED:	sNDA
MEDICAL INPUT:	Joyce Korvick, M.D.

1. Summary

Cellcept was previously approved for use in kidney transplant patients, this application is a supplemental NDA to add cardiac transplant patients to the indication. One efficacy trial, study MYCS 1864, was submitted.

2. Study MYCS 1864

Study MYCS 1864 is a randomized, multi-center, double-blind trial started in 1994 and still ongoing. The study will eventually provide 3 year follow-up data. The first twelve months of data for all subjects was submitted in the sNDA. Subjects were randomized at the time of transplant to either oral MMF or oral AZA. Subjects were to be started on the oral study drug within 5 days after transplantation.

2.1 Endpoints

The definition of the primary endpoint was changed several times following initiation of the study. Shown here is a history of these changes, made prior to unblinding.

Initial:	Biopsy-proven acute rejection at 6 months
Changed to:	Coronary artery vasculopathy at 36 months
Final (co-primary):	Biopsy-proven acute rejection with hemodynamic compromise at 6 months
Final (co-primary):	Graft failure (death/retransplantation) at 12 months

Hemodynamic compromise (HDC) was defined as any of the following: inotropic support, ejection fraction less than 30%, pulmonary capillary wedge pressure greater than 20 mm or increased by 25%, cardiac index less than 2.0 or decreased by 25%, new S3 gallop, fractional shortening less than 20% or decreased by 25%, pulmonary artery oxygen saturation less than 60% or decreased by 25%, or other.

Secondary endpoints included modified definitions of rejection, such as rejections of greater than grade 2 or rejections that required treatment. These will be discussed in greater detail in section 3.5.

2.2 Planned Analysis

The protocol specified that the primary analysis would include all patients randomized. The co-primary endpoint of 6 month rejection with HDC was to be analyzed by the CMH test, stratifying by center. An alpha level of .05 would be used to test for the superiority of MMF. Equivalence for the co-primary endpoint of 12 month graft survival was to be based on a 95% confidence interval on the difference in proportions of subjects having an event in the first 12 months. The applicant proposed in the protocol that if the lower bound of the CI was within the range ±10% then equivalence could be concluded (it should be noted that the applicant was advised that no formal definition of equivalence has been established in this setting). The difference in proportions and the corresponding CI was to be weighted by center. No interim analysis was planned prior to the analysis of the 12 month efficacy results.

3. Applicant Analysis

This section summarizes the applicant's analysis of the study.

3.1 Enrollment

Table 1 summarizes the patient disposition. A total of 11% of subjects did not receive treatment. The sponsor submitted results for the complete set of 650 patients as well as for the treated subset. In the NDA, the treated subset was considered primary. Subjects were randomized in 28 centers, with centers enrolling between 4 and 57 subjects. The median center size was 19 subjects.

Table 1: Patient Disposition

	Treatment		
	MMF	AZA	Total
Randomized	327	323	650
Untreated	38	34	72
Treated	289	289	578

3.2 Demographics

Subjects were primarily Caucasian (86%) and male (84%), with a mean age of 52 years. The treatment groups were well balanced with respect to these demographic characteristics. No difference between the treatment groups was noted in any of the baseline disease variables in either the "all randomized" group of patients or in the treated group of patients.

3.3 Survival

As noted in Section 2.2, the study was designed to demonstrate equivalence of the two treatments with respect to 12 month survival. Table 2 shows the results for this endpoint. The sponsor used the lower bound of the confidence interval on the difference in survival rates to assess equivalence. Note that the sponsor used a center-adjusted method to calculate the survival difference and associated confidence interval. The lower limits of 0.9% and -2.5% were within the protocol-defined range of equivalence (–10% to 10%).

Table 2: Death/Retransplantation

	ITT	Treated
MMF	87.2%	93.8%

AZA	84.8%	88.6%
Difference	2.6%	5.3%
95% CI	-2.5% to 7.6%	.9% to 9.7%
p-value	.402	.037

The sponsor also performed a Cochran-Mantel-Haentsel test for the 12 month survival rates, yielding a p-value of .03. A logrank test comparing time-to-death yielded a p-value of .03 as well. The sponsor concluded in the Integrated Summary of Efficacy that:

Equivalence of MMF to AZA was the prospectively set hypothesis to assess the co-primary endpoint of graft failure (death or retransplantation). By the protocol's definition of equivalence, MMF was found to be equivalent to AZA. However, MMF was statistically and clinically superior to AZA as demonstrated by a 45% reduction in mortality at one year (11% versus 6%) as well as by a statistically significant earlier time to death in the AZA group.

3.4 Rejection

The study was designed to demonstrate superiority of MMF to AZA with respect to rejection with hemodynamic compromise (HDC).

Table 3: Rejection + HDC

	ITT	Treated
MMF	37%	32%
AZA	38%	35%
Difference	1%	3%
p-value	.75	.34

After the rejection + HDC analysis was performed, the applicant derived a new endpoint: rejection with severe HDC (SHDC). The applicant claimed that the definition of rejection plus HDC "resulted in almost twice the rate of such acute rejections in the control group (31%) than had been anticipated at the time of the selection of the endpoint (14%)." The criteria for SHDC were a subset of 3 of the 8 HDC criteria (inotropic support, ejection fraction, and fractional shortening). The results for this new endpoint are shown in Table 4.

Table 4: Rejection + SHDC

	ITT	Treated
MMF	18%	11%
AZA	20%	17%
Difference	2%	6%
p-value	.49	.044

The applicant, focusing on the p-value of .044, stated that they had demonstrated statistical superiority of MMF over AZA.

The applicant also looked at the one-year survival rates for subjects with and without a prior rejection + SHDC event. It was noted that, while 12 of the 38 AZA subjects who had the event died by one year, none of the 19 MMF patients who had the event died at one year.

3.5 Secondary Rejection Endpoints

The applicant analyzed several other definitions of rejection, as shown in Table 5.

Table 5: Secondary Rejection Endpoints

	All Patients				Treated Patients			
	MMF	AZA	Diff	p	MMF	AZA	Diff	p
BPR*	95%	97%	2%	.39	95%	97%	2%	.21
BPR Grade≥2	68%	70%	3%	.50	65%	69%	4%	.31
BPR Grade ≥3	49%	55%	6%	.12	45%	53%	8%	.054
BPR + trt PI	67%	72%	5%	.15	64%	71%	7%	.057
BPR/P + trt PI	69%	75%	6%	.12	66%	74%	8%	.025
BPR/P + trt O/A	21%	24%	2%	.43	15%	21%	6%	.060

*BPR = Biopsy-Proven Rejection of Grade 1 or greater, BPR/P = Biopsy-Proven/Presumed Rejection, trt PI = treated with pulse immunosuppressives, trt O/A = treated with OKT3 or ATG

The applicant attributed statistical significance to p-values less than .05. The applicant also claimed an overall pattern in these data, namely that the more "severe" the rejection the larger the advantage for MMF.

3.6 Conclusions

The applicant concluded:

Treatment with MMF offers an advantage over standard therapy with AZA in preventing acute rejection during the first 6 months following cardiac transplantation. The efficacy of MMF appears more pronounced in preventing severe rejection.

4. Reviewer Comments

4.1 Continuity Correction

The applicant did not incorporate the continuity correction in their analyses. Including the continuity correction would result in p-values higher than the applicant's by about .01. In the context of the other issues raised in this section, however, the effect is negligible.

4.2 All Patients vs. Treated Patients Analysis

The protocol stated that:

All patients randomized in the study will be included in the inferential analyses on the basis of intent-to-treat. Additional analyses of efficacy variables may be performed using data from patients receiving at least one dose of study medication.

It is clear from this statement that the primary analysis would be the ITT analysis with all patients, and the treated analysis would be viewed as secondary. The applicant elected not to modify the primary ITT analysis prior to unblinding the study when it was known that 11% of patients failed to receive study drug. However in the NDA, the applicant has emphasized the results of the treated analysis rather than the ITT analysis. Since the change in focus occurred after the data were unblinded and analyzed, there is concern that the treated group analysis was emphasized because of the more favorable results.

The treated analysis is not necessarily flawed. Since the decision to administer study drug was presumably made in a double-blind fashion, the randomization still supports statistical tests. In addition,

the treated analysis is a clinically relevant analysis. However, performing several analyses gives multiple chances to win, and thus the p-values for analyses other than ITT should not be taken at face value. The ITT analysis must still be viewed as primary, and p-values in the treated analysis should be adjusted to reflect the multiple comparisons. This adjustment means that p-values in the treated analysis should be multiplied by a number a little less than 2[1]. For example, a p-value in the treated subgroup of about .05 should be viewed like a p-value resulting from a single analysis of about . This will apply both to the 6 month rejection analysis and to the 12 month analysis.

4.3 Survival

The other co-primary endpoint was 12 month survival. The applicant proposed to demonstrate equivalence for this endpoint. The protocol proposed that equivalence be based on the lower bound of a 95% CI on the difference in survival rates between MMF and AZA. The applicant proposed that equivalence be defined as the lower bound of this confidence interval being greater than -10%.

Table 2 showed the survival results for this study. In the ITT analysis the observed difference was 2.6% with a LCB of -2.5%. On the basis of this result, MMF has been demonstrated to be no worse than AZA. However, the applicant has emphasized the result in the treated subgroup over the ITT result. Recall that the applicant elected to keep the primary analysis as ITT analysis prior to unblinding. The change in emphasis occurred after the more favorable result in the treated analysis was known. However, even with this change in emphasis to the treated subgroup, the conclusion is unchanged. The treated results fell within the protocol definition of equivalence. Based on the rule proposed in the protocol, the MMF arm would have to be 10% better to conclude superiority, however, the MMF arm in the treated analysis did not meet this goal. Therefore, based on the applicant's pre-specified rule, superiority has not been demonstrated.

The applicant has focused on the fact that the LCB in the treated analysis was greater than 0% with a p-value less than .05. However, several points can be made regarding this claim. First, the primary hypothesis was equivalence and not superiority. An equivalence design allows efficacy to be demonstrated even when the experimental arm is somewhat worse than the control. Conversely, if the experimental arm is a little better than the control, the claim of superiority does not follow automatically. This means that only a compelling result would support a claim of superiority. However, for several methods of analysis, had there been one less death in the AZA arm or one more in the MMF arm the LCB would be less than 0% and the p-value would be above .05. Additionally, there is the concern over p-values from the treated analysis discussed earlier, namely that the treated results may have been emphasized due to the more favorable results. The protocol specified ITT results clearly showed equivalence and not superiority. Observed p-values in the treated group in the range are more like p-values of Thus, these considerations lead one to conclude that the treated result, while suggestive, does not demonstrate superiority of MMF for one year survival.

To summarize the survival results, the study has demonstrated equivalence. However, superiority has not been established. There is a suggestion from the observed survival difference that MMF might provide some advantage, and this can be revisited when longer term follow-up has been completed.

[1] A simulation study was conducted to determine an appropriate adjustment factor. The simulation study found that an adjustment factor of 1.8 to 1.9 was necessary to maintain the overall Type I error rate at 5%. The appropriate number is a little less than 2 (a Bonferroni adjustment) due to the fact that the analyses are correlated.

4.4 AZA Efficacy

To put the survival results into perspective, this section briefly summarizes the data supporting the efficacy of AZA on survival. The historical data supporting the effect of AZA on 12 month survival come from several published epidemiological studies. The two large studies the applicant submitted are the Opeltz and the Shumway studies. Both indicated a survival advantage at 1 year of about 4 percent. In interpreting these findings, one must keep in mind that the results are confounded by time. This confounding results from the fact that the studies looked at heart transplants occurring over a several year period. During this time period the frequency of triple therapy has increased while at the same time survival has improved for other reasons not related to triple therapy. Studies such as these cannot separate these two contributions to increased survival. Thus the value of 4% may be an upper bound on the survival advantage of AZA. Both studies also indicated that the benefit of AZA may be limited to the first year of treatment, with no additional benefit accruing after the first year.

And finally, no historical data were presented for the effect of AZA on 6 month rejection.

4.5 Rejection

The 6 month primary rejection endpoint was composed of biopsy-proven rejection accompanied by hemodynamic compromise. Death also counted as an event in this analysis. This table shows the observed results. The results indicated no significant difference between the arms in either the ITT analysis or in the treated subgroup.

After the trial was unblinded and these data were analyzed, the applicant, in conjunction with a steering committee, decided on a new endpoint definition. One of the stated reasons for this change was that the event rates of rejection +HDC were about 33%, which was felt to be too high compared to the expected when the endpoint was chosen. The new endpoint was called SHDC. Again though, analogous to the ITT vs. Treated discussion, the applicant chose not to change the definition of the primary endpoint in the protocol prior to unblinding and analyzing the data. One must therefore view skeptically the results for this new endpoint. In addition there was already a protocol defined SHDC definition, that, while not specified as an endpoint, was used to manage patients. The protocol definition of SHDC (inotropic support plus any one of the other HDC criteria) differs from the new SHDC endpoint. As Table 6 shows, no significant difference was seen between the arms for the protocol SHDC definition in either analysis.

Table 6: Rejection + protocol SHDC

	ITT	Treated
MMF	15%	9%
AZA	16%	11%
Difference	1%	3%
p-value	.83	.31

Recall, one of the main justifications for the new endpoint was that the more restrictive definition resulted in event rates closer to the expected However, as the table indicates, the rates for the protocol definition of SHDC were also in the range And, this definition was felt to be clinically relevant as evidenced by its use in the clinical management of patients.

To summarize the rejection endpoints, it is helpful to break them into several groups. The first is the primary endpoint. Since it was the designated as the primary analysis, the finding of no difference between the arms must be given the highest weight in the overall assessment of rejection. The next group

is the endpoints with modified definitions of HDC: the new and the protocol SHDC definitions. Only the new SHDC definition in the treated subgroup had a p-value less than .05, and any type of post-hoc multiple comparisons adjustment would inflate the p-value to well above .05. As an additional analysis, Dr. Korvick suggested an analysis of the endpoint biopsy-proven rejection + inotropic support, which was felt to be the most serious of the components of hemodynamic compromise. That endpoint showed no significant difference either (all patients p-value = .826, treated p-value = .12). The next group of rejection endpoints is composed of the secondary rejection endpoints from the protocol. None of these were significant in either the ITT or treated analysis, even if one does not apply any multiple comparison adjustments either for the fact that there were two sets of subjects or for the fact that multiple endpoints were analyzed. The applicant discussed two other endpoints. The first is the endpoint biopsy-proven rejection of grade 3 which was not in the protocol and the second is biopsy proven or presumed rejection with immunosuppressive treatment which was in the protocol under the heading of variables that would only be looked at descriptively.

Again, one must place the p-values in the context of the entire analysis. Most or all of these analyses are clinically relevant definitions of rejection. But, since so many analyses were done, even a non-conservative multiple comparison adjustment would raise even the smallest p-value they report to well above .10. Overall, none of the planned (primary or secondary) rejection analyses yielded a significant difference in either the ITT analysis or the treated subgroup even without multiple comparisons adjustments. None of the unplanned rejection endpoints are significant if one takes the multiple comparisons into account. The smallest p-values were for unplanned endpoints in the secondary treated analysis.

And as a final point, since these endpoint definitions are closely related and statistically correlated, consistency of results in favor of one treatment or the other is to be expected. Thus the fact that MMF showed a small numeric advantage for several similar rejection definitions does not compensate for the fact that none of the endpoints demonstrated superiority on its own. In summary, on the basis of this trial the applicant did not meet the goal of demonstrating superiority of MMF over AZA with respect to 6-month rejection. The two arms appeared to have similar efficacy for this endpoint, however, no information regarding the efficacy of AZA for any definition of 6 month rejection has been presented. Thus, the meaning of similar efficacy for this endpoint is uncertain.

5. Conclusions

In conclusion, the applicant met one of the two goals of the study. The applicant has demonstrated equivalence for the 12 month survival endpoint. There is a suggestion from the observed survival difference that MMF might provide some advantage, but this result is subject to enough uncertainty that a claim superiority is not justified.

The applicant failed to demonstrate superiority for 6 month rejection. It appeared that the two arms had similar response rates for this endpoint. However, the import of this finding is uncertain since AZA has not been shown to be effective for 6 month rejection.

/S/

Michael Elashoff, Ph.D.

Concur: Dr. Flyer /S/ 2/12/98

cc:
Archival NDA# 50,722
HFD-590/Ms. Hubbard
HFD-590/Dr. Korvick
HFD-590/Dr. Goldberger
HFD-104/Ms. Sage (via Teamlinks)
HFD-725/Dr. Elashoff
HFD-725/Dr. Flyer
HFD-725/Dr. Huque
HFD-725/Ms. Shores
This review contains 8 pages

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 050722/S002 AND 050723/S001

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

NDA: 50,722/S-002
50,723/S-001

Submission Dates: 7/31/97, 8/13/97, 12/23/97

Generic Name, Strength and Formulation: Mycophenolate Mofetil 250 mg Capsules and 500 mg Tablets

Brand Name: Cellcept(R)

Date Assigned: 8/7/97

APPEARS THIS WAY
ON ORIGINAL

Applicant: Roche (Syntex USA, Inc)

Final Review: 2/2/98

Submission Code: P

Reviewer: Kofi A. Kumi, Ph.D.

Individual data are on file in the Division of Pharmaceutical Evaluation 3.

SYNOPSIS

The applicant submitted an efficacy supplement for Mycophenolate Mofetil (MMF, Cellcept(R)) to be used for the prophylaxis of organ rejection in cardiac transplantation. MMF is approved (NDA 50,722) for use in the prevention of acute allograft rejection following renal transplantation. In this application, the sponsor submitted one pivotal efficacy study (MYCS 1864) in which the pharmacokinetics of MMF in a subgroup of the cardiac transplant patients were evaluated. Three pilot studies that evaluated the pharmacokinetics of MMF in cardiac patients were submitted as supportive studies. MMF is the morpholino-ethyl ester pro-drug for mycophenlic acid (MPA). MMF is hydrolyzed to 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). The absorption, distribution, metabolism and excretion of MMF in healthy and renal transplant patients were described in NDA 50,722 review and are cross-referenced in this review. In renal transplant patients, AUC and Cmax were found to be about 50% lower in the immediate post transplant period ($\leq$ 40 days) compared to stable renal transplant period ($\geq$ 3months) or in healthy patients. The dosage form used in the pivotal efficacy and pharmacokinetic studies is the approved 250 mg capsule formulation.

In the pivotal clinical study, the pharmacokinetics were evaluated in a subgroup of cardiac transplant patients on day 1, 5, day before discharge (about day 7) and at 6 months post transplantation. The mean AUC, Cmax and Tmax of MPA after administration of MMF 1.5 gm two times a day (BID) are summarized in the following table

Mean MPA Plasma Pharmacokinetics Parameters

PK Parameter	Day 1	Day 5	Day of Discharge	≥ 6 months
	Mean ± SD (n) MPA			
Cmax (μg/mL)	11.6 ±7.45 (17)	13.3 ±7.80 (10)	11.51 ± 6.76 (11)	20.0 ±9.35 (52)
AUC(0-4h) (μg*h/mL)	21.7 ±9.65 (17)	29.1 ±11.0 (8)	23.9 ± 13.2 (10)	34.7 ± 12.9 (46)
AUC(0-12h) (μg*h/mL)	36.7 ±11.9 (16)	NC	43.3 ± 20.8 (9)	54.1 ± 20.4 (49)#
Tmax (h)	2.02 ±1.83 (17)	1.58 ±1.00 (10)	1.77 ± 1.32 (11)	1.12 ± 0.66 (52)

NC= Not computed; Day 1= Day 1 of receiving MMF 1.5 gm BID after transplant; Day5 = Day 5 of receiving MMF 1.5 gm BID after transplant; Day of Discharge = Day before discharge from hospital (about day 7), receiving MMF 1.5 gm BID.
# Estimated from data collected over 4 hours

There was a trend towards an increase in Cmax and AUC of MPA when the early (day of discharge, about 7 days) and late (> 6 months) are compared; mean AUC and Cmax of MPA were approximately 20% and 45%, respectively, lower for the early compared to the late transplant period. Because of significantly fewer early than late transplant patients with PK parameters, it is not clear whether this a significant observation. However, the same trend was observed in the renal transplant patients. Steady state conditions appeared to be reached by day 14 (probably sooner) of dosing 1.5 gm MMF twice a day.

Concentration-Effect (PK/PD) Relationship: The results from the logistic regression analyses performed on data from a subgroup of patients in the pivotal study (MYCS 1864) indicated that, there was no significant difference in the concentrations of the early transplant patients who experienced Biopsy Proven Rejection (BPR) and those who did not experience BPR. However, the mean AUC of MPA of the 6 patients who did not experience BPR was lower than the 3 patients who experienced BPR. For the late transplant patients, again, there was no significant correlation between AUC of MPA and the probability of BPR. In the renal transplant application, there was a suggestion of higher frequency of rejection associated with lower MPA concentrations. There is inconclusive evidence in the pivotal cardiac study to provide such an observation. The concentration effect relationship should be further explored in future studies. A visual evaluation of the concentration observed after an adverse event episode did not indicate a relationship between the occurrence of adverse events and MPA concentration.

Cardiac vs Renal Transplant Patients: Pharmacokinetics: A summary of the pharmacokinetics obtained from the pivotal pharmacokinetic studies (MYCS 1864 and MYCc 1866) for cardiac and renal transplant patients administered 1.5 gm MMF are provided in the following tables

Pharmacokinetic Parameters of MPA after Administration of MMF 1.5 gm BID

Parameter	Cardiac Transplants (Study MYCS 1864)			Renal Transplants (Study MYCc 1866)		
	MPA Mean ± SD (n)					
	Day 1	Last Day	≥ 6 months	Day 1	Last Day	≥ 3 months
Tmax (hr)	2.02 ± 1.83 (17)	1.77 ± 1.32 (11)	1.12 ± 0.66 (52)	3.22 ± 3.78 (29)	1.86 ± 2.46 (20)	0.90 ± 0.24#
Cmax (μg/mL)	11.6 ± 7.45 (17)	11.51 ± 6.76 (11)	20.0 ± 9.35 (52)	6.09 ± 5.47 (29)	11.7 ± 8.62 (20)	29.7 ± 14.2 (20)
AUC (μg*hr/mL)	36.7 ± 11.9 (16)	43.3 ± 20.8 (9)	54.1 ± 20.4 (49)	20.8 ± 12.6 (29)	35.9 ± 16.5 (20)	52.1 ± 17.7 (20)

Last Day: Day Before Discharge, #pooled data from package insert (n=23)

Pharmacokinetic Parameters of MPAG after Administration of 1.5 gm MMF BID

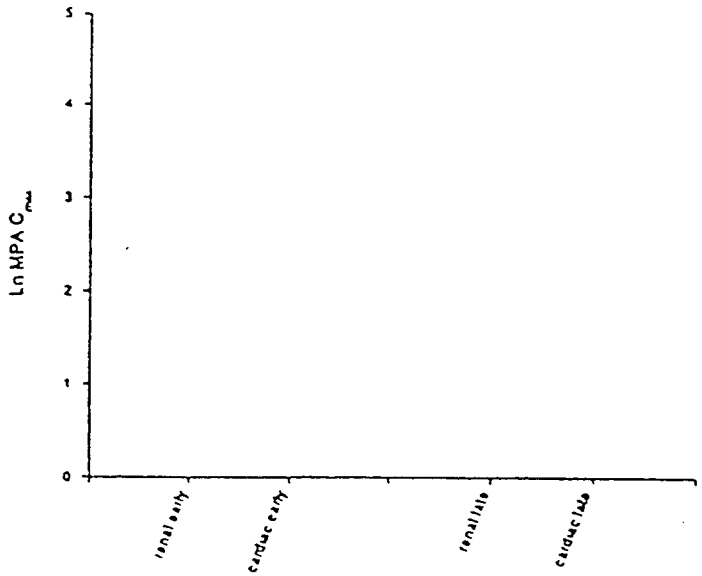
Parameter	Cardiac Transplants (Study MYCS 1864)			Renal Transplants (Study MYCc 1866)		
	MPAG (MPA EQ.) Mean ± SD (n)					
	Day 1	Last Day	≥ 6 months	Day 1	Last Day	≥ 3 months
Tmax (hr)	5.78 ± 3.26 (17)	4.54 ± 4.25 (11)	2.52 ± 1.18 (54)	7.1 ± 4.33 (29)	2.50 ± 1.23 (20)	NA
Cmax (μg/mL)	50.0 ± 15.7 (17)	94.1 ± 34.7 (11)	104 ± 34 (54)	29.0 ± 18.9 (29)	99.6 ± 45.4 (20)	NA
AUC (μg*hr/mL)	423 ± 137 (17)	963 ± 525 (9)	NC	229 ± 142 (29)	890 ± 341 (20)	NA

Last Day: Day Before Discharge, NC = not calculated, NA = not available

The pharmacokinetics of MPA and MPAG after administration of 1.5 gm of MMF twice a day to renal and cardiac transplant patients appear to be similar. Cmax and AUC in both patient groups increase after 3 or 6 months of administration when compared to the early post transplant period. A box plot (figure on next page) of pooled data from renal patients and the cardiac patients who received 1.5 gm of MMF also indicated that the pharmacokinetics of MPA appear to be similar. However, because of the differences in the number of patients, definite conclusions can not be made.

Drug Interaction: No new drug interactions studies were submitted in this application. Drug interaction studies submitted to the NDA 50,722 are cross referenced in this application. There was no significant interaction observed when MMF and cyclosporine A were coadministered.

Gender: There are no significant gender differences in the pharmacokinetics of MPA after administration of MMF.



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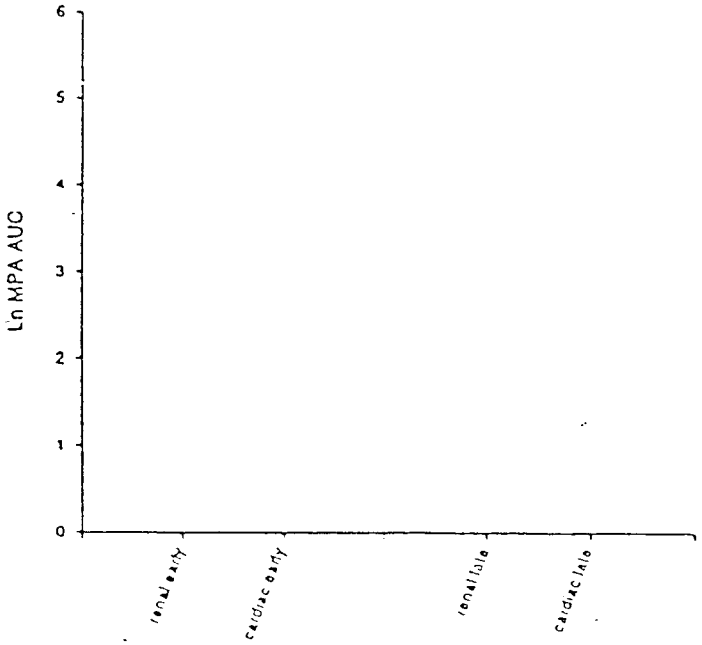

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As shown, the pharmacokinetics of MMF as evidenced by MPA AUC_{0-12} and C_{max} are comparable in renal and cardiac transplantation; both parameters increase with time.

Proposed Indication (From Draft Package Insert): Cellcept is indicated for the prophylaxis of organ rejection and increased graft patient survival in patients receiving allogeneic cardiac transplants. Cellcept should be used concomitantly with cyclosporine and corticosteroids.

LABELING COMMENTS

Please eliminate the final sentence in the paragraph beginning on line 115. This sentence should be replaced with the following sentence:

The Cmax and AUC of MPA in early transplant patients (<40 days posttransplant) are approximately lower respectively as compared to healthy volunteers or to stable renal and cardiac transplant patients.

COMMENTS

It was evident from the advisory meeting for this application that it is difficult to determine biopsy proven rejection in cardiac patients. This may have contributed to the difficulty in demonstrating concentration effect relationships in cardiac patients. Therefore, the sponsor is encouraged to explore alternative ways of evaluating whether there is a relationship between concentration of MPA and effect in cardiac patients.

There is insufficient information in this application to evaluate if the pharmacokinetics are different in different ethnic groups. As recommended in the original application, the applicant should explore whether there are ethnic differences in the pharmacokinetics of MMF. Also, it is recommended that the sponsor evaluate the pharmacokinetics in pediatric patients.

RECOMMENDATION

The pharmacokinetic studies submitted to the Human Pharmacokinetics and Bioavailability section of NDA 50,722 (SE1-002) to fulfill sections 320 and 201.5 of 21 CFR are acceptable and support a recommendation for approval.

/S/

2/3/98

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

/S/

Concurrence: 2/3/98

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

APPEARS THIS WAY
ON ORIGINAL

NDA 50,722 SE1-002 (original)

CC HFD-590 Division Files
/MO/JKorvick
/PM/LHubbard

HFD-340 /Viswanathan

HFD-880 /TLDPEIII/FAjayi
/DPEIII/KKumi
/DPEIII Drug Files ✓

CDR /BMurphy ✓

file:WP6.1/data/kumiwp/cellcept/cardiac/overall
Draft 1: 1/12/98
Draft 2: 1/30/98

REVIEW

BACKGROUND:

The application was submitted to request approval of Mycophenolate Mofetil for the prophylaxis of organ rejection in cardiac transplantation. MMF (Cellcept) is approved for use in the prevention of acute allograft rejection following renal transplantation. MMF is used in combination with corticosteroid and cyclosporine. The pharmacokinetic data for MMF was derived from 4 studies; one pivotal and 3 pilot studies. The formulation used in the pivotal studies was the approved 250 mg capsules. A 500 mg tablet which is bioequivalent to the capsule is also approved.

MMF is the morpholino-ethyl ester pro-drug for mycophenlic 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 cardiac allografts in a variety of species. Five uncontrolled pilot studies demonstrated benefit in the prevention of acute rejection and treatment of refractory acute rejection in cardiac transplant patients. From the previous 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 peak 6-12 hours 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 (≥ 3months) or in healthy patients.

OVERVIEW OF PHARMACOKINETIC STUDIES

Pivotal Study

Study MYCS 1864: Randomized, Double-Blind Comparative Study of Mycophenolate Mofetil or Azathioprine Each in Combination with Cyclosporine and Corticosteroids for the Assessment of Rejection, Graft and Patient Survival in Cardiac Allograft Recipients: Pharmacokinetics Report (Volumes 5 and 10 page 1)

Introduction: Mycophenolate Mofetil (MMF) is an anti-lymphocyte agent currently approved for prophylaxis of organ rejection in patients receiving allogeneic renal transplants. The applicant is pursuing an indication for the use of MMF to prevent organ rejection in cardiac transplant patients. MMF is a prodrug which undergoes first pass metabolism in the liver to mycophenolic acid (MPA), an active metabolite which further gets glucuronidated to an inactive metabolite (MPAG). In a subset of patients in this comparative safety and efficacy study, the pharmacokinetics of MMF in both early and late cardiac transplant patients were evaluated. This report summarizes the findings of the pharmacokinetics evaluation.

Objectives: The objective of the pharmacokinetics portion of the study was to characterize the pharmacokinetics of MPA and MPAG in the early transplants period or at a time 6 months or more following transplantation

Design: This was a multi center, double-blind, randomized, controlled study in 650 primary cardiac transplant recipients. Patients received MMF 1.5 gm orally twice daily or azathioprine (according to local center practice) plus matching placebo. Six hundred fifty patients were enrolled, 323 randomized to AZA and 327 to MMF. The patients were on maintenance immunosuppressive therapy with cyclosporine and corticosteroid. Intravenous cyclosporine could be administered on the day of transplantation and thereafter until oral cyclosporine could be tolerated. Oral cyclosporine dosing was adjusted to maintain trough levels that reflect a standard assay range at each center; the mean values at 6 months for AZA and MMF arms were 1.12 ± 0.03 and 1.13 ± 0.03 μg/mL, respectively. Immediately before transplantation, patients could receive up to 1 g methylprednisolone IV and then up to 500 mg methyl prednisolone IV 12 hours later. Additional IV corticosteroids could be administered for up to 3 days. In a subset of patients, blood samples (5 mL) were collected for full pharmacokinetics (PK) profile on day 1 and the day before discharge at 0, 0.5, 1, 1.5, 2, 4, 8 and 12 hour postdose; a mini-profile was collected on day 5 (0, 0.5, 1 and 4h post dose). Predose samples were collected days 7 and 9. Blood samples (0, 20, 40, 60, 75, 90 mins, 2 and 4 hours post morning dose) were collected for determination of PK profile after long term (at least 6 months) dosing of MMF.

Data Analysis: The following pharmacokinetics parameters of MPA and MPAG (expressed as MPA equivalent units) were computed for days 1 and the day before discharge (about day 7) data: Cmax, Tmax and AUC(0-12h). AUC(0-4) was computed for days 1, 5 and day before discharge. For greater than 6 month, the concentrations at 6, 8 and 12 hours were estimated by a validated algorithm (APPENDIX). AUC(0-12) was then calculated using the observed and estimated concentrations by the linear trapezoidal rule. The algorithm was validated by comparing AUC(0-12) calculated with the estimated AUC(0-12h) on the day of discharge (APPENDIX). In an effort to determine the relationship between concentrations and selected adverse event episodes, blood samples were collected after selected episodes of adverse events. To evaluate if pharmacokinetics-pharmacodynamic relationship exist between AUC of MPA and clinical outcome, a logistic regression analysis was performed to describe the probability of rejection as a function of either AUC or ln(AUC) of MPA.

Results: Seventeen and 55 patients provided early and late pharmacokinetics data, respectively. The mean age for the patients who provided early and late data were 47.5 and 52.4 years, respectively. The mean pharmacokinetics parameters of MPA after administration of MMF 1.5 gm two times a day (BID) are summarized in the following table.

Mean MPA Plasma Pharmacokinetics Parameters

PK Parameter	Day 1	Day 5	Day before Discharge	≥ 6 months
	Mean ± SD (n) MPA			
Cmax (μg/mL)	11.6 ±7.45 (17)	13.3 ±7.80 (10)	11.51 ± 6.76 (11)	20.0 ±9.35 (52)
AUC(0-4h) (μg*h/mL)	21.7 ±9.65 (17)	29.1 ±11.0 (8)	23.9 ± 13.2 (10)	34.7 ± 12.9 (46)
AUC(0-12h) (μg*h/mL)	36.7 ±11.9 (16)	NC	43.3 ± 20.8 (9)	54.1 ±20.4 (49)#
Tmax (h)	2.02 ±1.83 (17)	1.58 ±1.00 (10)	1.77 ± 1.32 (11)	1.12 ± 0.66 (52)

NC= Not computed; Day 1= Day 1 of receiving MMF 1.5 gm BID after transplant; Day5 = Day 5 of receiving MMF 1.5 gm BID after transplant; Day of Discharge = Day before discharge from hospital (about day 7), receiving MMF 1.5 gm BID.
# Estimated from data collected over 4 hours

There was no significant difference in MPA pharmacokinetics parameters from day 1 up to the time of discharge. There was a trend towards an increase in Cmax and AUC of MPA when MMF was administered over a longer period of time; however, because the number of patients with PK parameters taken after 6 months were significantly higher than those with PK parameters between day 1 and day before discharge, definite conclusion can not be deduced on the difference in concentrations observed between early and late periods post transplantation. There is no significant difference in the PK parameters during the period post transplantation.

Mean MPAG Plasma Pharmacokinetics Parameters

PK Parameter	Day 1	Day 5	Day before Discharge	≥ 6 months
	Mean ± SD (n) MPAG			
Cmax(μg/mL)	50.0 ± 15.7 (17)	113 ± 34.3 (10)	94.1 ± 34.7 (11)	104 ± 34 (54)
AUC(0-4h) (μg*h/mL)	102 ± 54.0 (17)	442 ± 153 (8)	344 ± 189 (10)	361 ± 189 (48)
AUC(0-12h) (μg*h/mL)	423 ± 137 (17)	NC	963 ± 525 (9)	NC
Tmax (h)	5.78 ± 3.26 (17)	2.58 ± 1.45 (10)	4.54 ± 4.25 (11)	2.52 ± 1.18 (54)

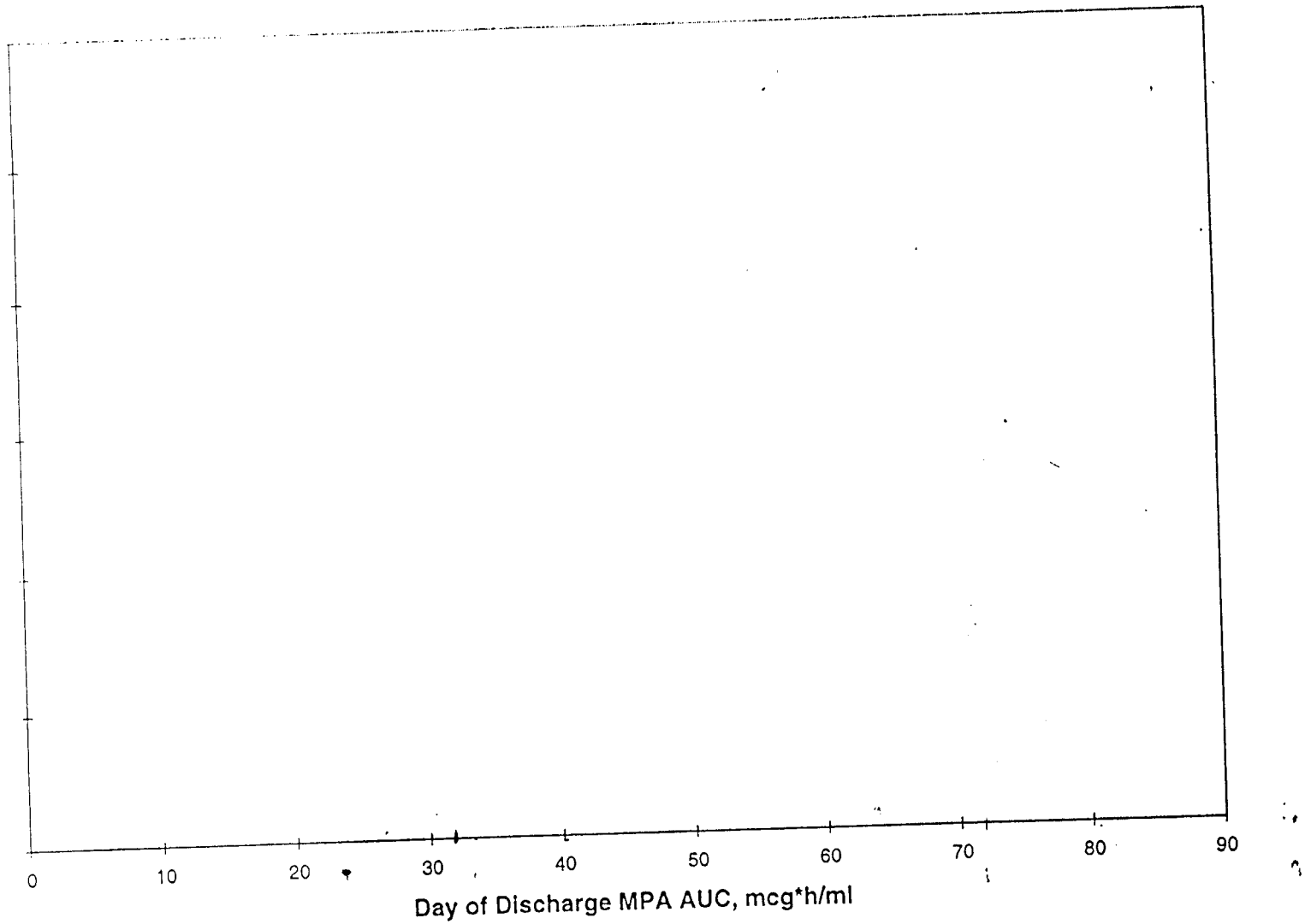
NC= Not computed; Day 1= Day 1 of receiving MMF 1.5 gm BID after transplant; Day5 = Day 5 of receiving MMF 1.5 gm BID after transplant; Day of Discharge = Day before discharge from hospital (about day 7), receiving MMF 1.5 gm BID.

Cmax and AUC of MPAG was significantly different on day 1 from day before discharge; there is about a 3-fold increase in AUC of MPAG when day 1 is compared to day before discharge. Day before discharge AUC and Cmax of MPAG were similar to that observed after 6 months.

Pharmacokinetics-Pharmacodynamic Relationship: Blood samples were collected following rejection or selected adverse events. Adverse events were grouped into categories: hematological infection, opportunistic infection, malignance, gastrointestinal, rejection and other. MPA and MPAG concentration data were plotted by category versus time; data was overlaid on reference curves prepared from the > 6 month data showing the 50th, 90th and 95th centiles. Also, in the MMF group, for the subset of patients for which AUC of MPA data were available, a logistic regression analysis to describe the probability of rejection as a function of either AUC or ln (AUC) of MPA was conducted. Pharmacokinetics data were available from a subset of patients (n=9) in which 12 hour profile was performed on the day before discharge and in a subset of patients (n=49) in which an abbreviated pharmacokinetics profile had been performed 6 months or later following transplantation. The logistic regression analysis was evaluated with the help of Dr. He Sun, Pharmacometrics Node for DPE3.

The results from the logistic regression analysis for the early transplant patients did not demonstrate a significant difference in concentrations of patients who experienced Biopsy Proven Rejection (BPR) and those who did not experience BPR. However, the mean AUC of MPA of the 6 patients who did not experience BPR was lower than the 3 patients who experienced BPR (Table on following page). For the late transplant patients, again, there was no significant relationship between AUC of MPA and the occurrence of BPR. In the renal transplant application, there was a suggestion of higher frequency of rejection associated with lower MPA concentrations. There is inconclusive evidence in the pivotal cardiac study to provide such a suggestion. The sponsor speculated that a correlation between AUC of MPA and the occurrence of BPR was not demonstrated in these patients possibly because the end point of BPR may not be amenable to establishing concentration effect relationship in cardiac transplant patients. The sponsor stated that evaluating BPR in cardiac transplants is much more difficult than in renal

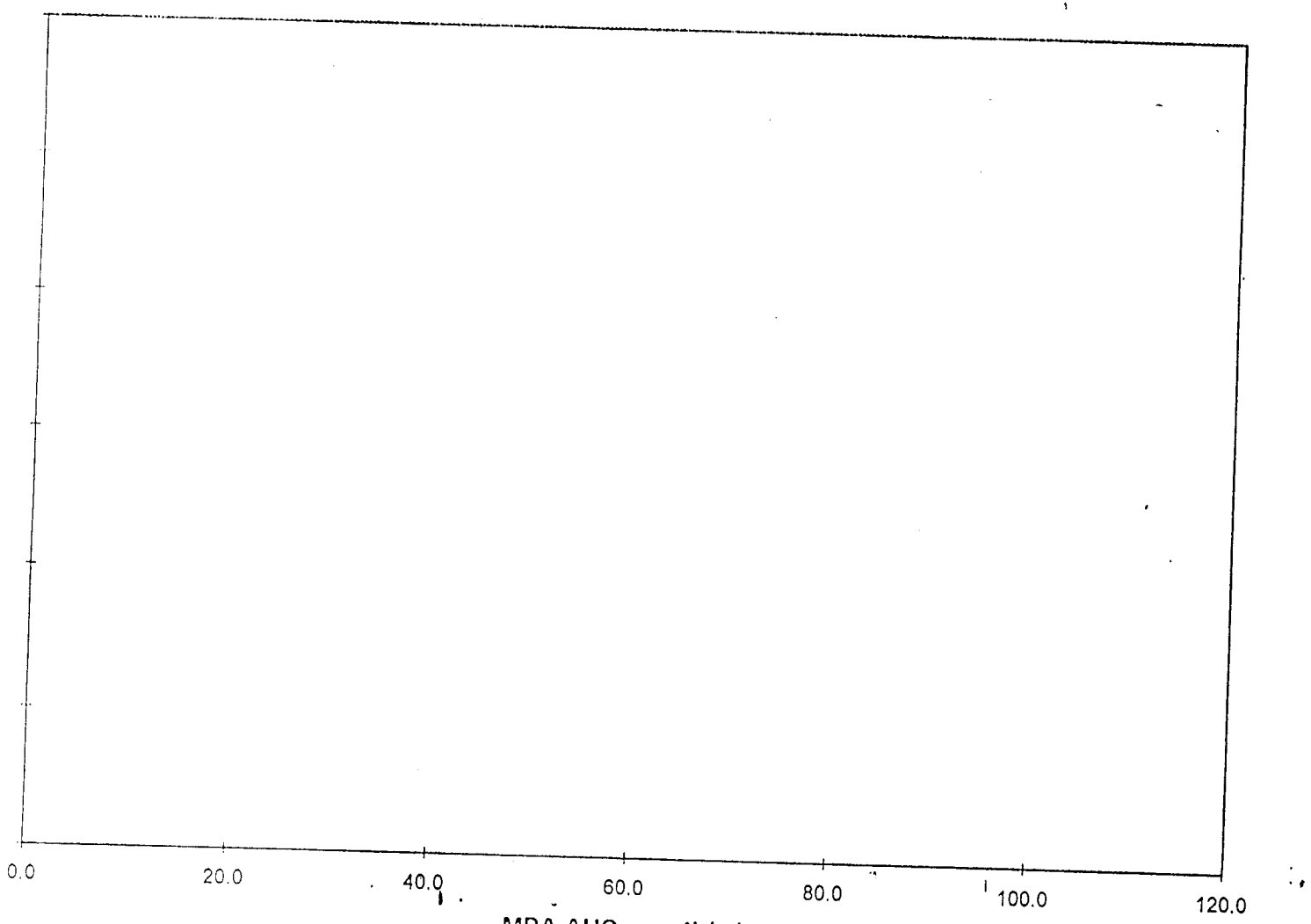
Fig 28A: Appendix H Data - BPR (IIIA or greater)



BPR: Biopsy Proven Rejection

te

Fig 28B: Appendix O Data - BPR (IIIA or greater)



(Late 6months or greater

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TABLE 1 : Patients Included in PK/PD Analysis (Appendix H Data)

Patients Experiencing ISHLT Biopsy Grade IIIA or Greater		
Patient Number	MPA AUC (mcg•h/ml)	Num. Days Post Tx
-----	85.4	8
-----	28.8	12
-----	51.7	6
Mean	55.3	8.67
Std Dev	28.5	3.06
% CV	51.5	35.3
Min		
Max		
N	3	3

Patients NOT Experiencing ISHLT Biopsy Grade IIIA or Greater		
Patient Number	MPA AUC (mcg•h/ml)	Num. Days Post Tx
-----	23.4	16
-----	58.0	13
-----	42.1	15
-----	18.1	11
-----	50.2	9
-----	32.3	17
Mean	37.4	13.5
Std Dev	15.5	3.08
% CV	41.5	22.8
Min		
Max		
N	6	6

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Notes:

1. Biopsy had to occur less than 181 days following transplantation
2. Num. Days Post Tx is the number of days post transplant when the pharmacokinetic profile was obtained.
3. Profile was to be taken on day of discharge following transplantation.
4. Patient numbers are obscured until the study is completely unblinded.

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TABLE 2 : Patients Included in PK/PD Analysis (Appendix O Data)

Patients Experiencing ISHLT Biopsy Grade IIIA or Greater		
Patient Number	MPA AUC (mcg•h/ml)	Num. Days Post Tx
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Mean	58.2	334.
Std Dev	18.2	92.2
% CV	31.2	27.7
Min		
Max		
N	26	26

Patients NOT Experiencing ISHLT Biopsy Grade IIIA or Greater		
Patient Number	MPA AUC (mcg•h/ml)	Num. Days Post Tx
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Mean	49.5	358.
Std Dev	22.2	108.
% CV	44.8	30.1
Min		
Max		
N	23	23

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Notes:

1. Biopsy had to occur less than 181 days following transplantation
2. Num. Days Post Tx is the number of days post transplant when the pharmacokinetic profile was obtained.
3. Patient numbers are obscured until the study is completely unblinded.

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Table 3 : Univariate Logistic Regression Results

							Whole Model			
Comparison	F/N	Intercept	Coef.	S.E.	L-R Chi^2	p-value	-log likelihood	RSquare (U)	L-R Chi^2	p-value
App. H, MPA AUC	3/9	3.01	-0.05	0.04	1.71	0.1914	0.853	0.1490	1.71	0.1914
App. H, ln(MPA AUC)	3/9	8.42	-2.07	1.92	1.45	0.2291	0.723	0.1262	1.45	0.2291
App. O, MPA AUC	26/49	1.11	-0.02	0.02	2.36	0.1247	1.179	0.0348	2.36	0.1247
App. O, ln(MPA AUC)	26/49	5.37	-1.40	0.80	3.42	0.0642	1.712	0.0505	3.42	0.0642

transplant patients. A relationship between MPA concentration and the occurrence of the commonly observed adverse events could not be established in this population (APPENDIX). The concentration of MPA was not determined at the same time after each adverse event which may have contributed inadequate evaluation of the relationship of concentration to adverse events was not possible. Also, it is not clear how much of the observed adverse events were due to cyclosporine administration. The relationship between concentration of MPA and BPR and adverse events should be explored further if further studies are conducted.

Conclusion: The pharmacokinetics of MPA in cardiac transplant patients are similar to that observed in renal transplant patients. MPA and MPAG concentrations were lower during the early period of cardiac transplant compared to that observed after 6 months of therapy. There was a trend towards accumulation of both MPA and MPAG after multiple dosing of MMF; however, MPAG accumulation was much more pronounced than that observed for MPA. Pharmacokinetics-Pharmacodynamic relationship could not be established for AUC of MPA and BPR (ISHLT grade 3 or better). No evidence of a relationship between MPA concentration and the occurrence of commonly observed adverse events could be demonstrated.

Supportive Studies

Study MYCc2108 (P180180): An Open Label, Safety, Dose-Finding, and Pharmacokinetic Pilot Study of Mycophenolate Mofetil in Combination with Cyclosporine and Corticosteroids in Cardiac Allograft Recipients: Pharmacokinetics Report (Volume 21 page 1).

Introduction: Mycophenolate Mofetil (MMF) is approved for use in the prevention of rejection of renal transplant. This phase II pilot study was to evaluate the safety and the maximum tolerable dose (MTD) in cardiac allograft recipients. MMF was an adjunctive immunosuppressant.

Objective: The primary objectives were: 1) To evaluate the safety and tolerability and to determine the maximum tolerated dose of MMF in combination with cyclosporine and corticosteroids in cardiac allograft recipients experiencing acute cellular rejection 2) To evaluate the safety and tolerability and to determine the MTD of MMF administered in the early postoperative period through 6 months post transplant in combination with cyclosporine and corticosteroids, in cardiac allograft recipients 3) To obtain pharmacokinetic data for MMF in cardiac allograft recipients when administered in combination with cyclosporine and corticosteroids.

Design: This was a single center, open label, dose escalating study in two patient groups: Group A patients received MMF within 48 hours of biopsy-proven International Society for Heart Transplant (ISHT) grade IIB or II acute rejection; Group A patients began participating in the study between 81 and 1054 days following transplantation. Group B patients received MMF within 48 hours following transplantation. The first 5 patients enrolled in group A started at dose of 2 gm BID and subsequent enrollment to higher doses occurred only when the earlier patients

had received at least 14 days of therapy. The dose was to be increased until 2 or more patients experience toxicities as outlined in the protocol. In group B, the first 6 patients started at 1.5 gm BID. Dose increments were the same as group A. Predose mycophenolic acid (MPA) and mycophenolic acid glucuronide (MPAG) concentrations were determined on days 7 and 14, full 12-hour pharmacokinetic profiles were obtained on Days 1 and 21 and once during the Month 3. The sampling times were 0 (predose), 0.5, 1, 1.5, 2, 4, 8 and 12 hours after MMF administration. MPA and MPAG concentrations were determined by an The quantitation limits of the methods were 0.4 µg/mL for MPA and MPAG. The formulation and batch numbers of MMF used in the study were 61443-051 and 61443-00-1964, respectively.

Data Analysis: The following pharmacokinetic parameters for MPA and MPAG (MPA equivalents) were calculated: Cmax, Tmax, Cmin (computed as the mean of the predose and the end of dosing interval concentrations), Cmax/Cmin, Cave, Cmax/Cave, AUC(0-12).

Results: The maximum dose studied was 5 g/day due to development of leukopenia. Ten patients enrolled in group A and 12 in group B of the study. All patients who enrolled and participated in the study were included in safety, efficacy and pharmacokinetic analyses. The mean ±SD age and weight were 50.6 ± 11.0 years and 79.7±15.5 kg, respectively.
Plasma MPA and MPAG concentrations were highly variable. Steady state conditions appeared to have been reached by day 14 of daily dosing of MMF. The mean pharmacokinetic parameters are provided in the APPENDIX. Between day comparison of AUC and Cmax of MPA in group A are provided in the following tables.

MMF Dose	Mean ±SD MPA AUC (µg*hr/mL) (n)		
	Day of Treatment		
	Day1	Day21	Month 3
4 g/day (2g BID)	87.5 ±48.9 (5)	65.9 ±7.85 (4)	87.1 ±30.8 (4)
5 g/day (2.5g BID)	71.8 ±7.13 (5)	94.1±24.0 (5)	66.0 ±7.88 (2)

MMF Dose	Mean ± SD MPA Cmax (µg/mL) (n)		
	Day of Treatment		
	Day 1	Day 21	Month 3
4 g/day (2 g BID)	34.6±18.4 (5)	23.8 ±8.01 (4)	32.7 ± 19.5 (4)
5 g/day (2.5 g BID)	29.3 ±6.27 (5)	26.7 ±10.2 (5)	26.3 ± 11.5 (2)

There was no consistent trend in both AUC and Cmax within a given dose between the days studied. No significant differences in AUC and Cmax were detected during the therapy. It must be noted that this was a pilot study and the number of patients in each group was small.

MMF Dose	Mean ±SD MPAG AUC (μg*hr/mL) (n)		
	Day of Treatment		
	Day1	Day 21	Month 3
4 g/day (2g BID)	590 ± 226 (5)	1177 ±405 (4)	1048 ±303 (4)
5 g/day (2.5g BID)	664 ±166 (5)	1623 ± 129 (5)	1327 ± 115 (2)

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MMF Dose	Mean ± SD MPAG Cmax (μg/mL) (n)		
	Day of Treatment		
	Day 1	Day 21	Month 3
4 g/day (2 g BID)	74.0 ±25.8 (5)	133 ± 30.0 (4)	122 ± 37.8 (4)
5 g/day (2.5 g BID)	78.7 ± 11.8 (5)	187 ± 25 (5)	170 ± 65.5 (2)

There is about a 2-fold accumulation in MPAG after multiple dosing of MMF; however, this not expected to have clinical significance.

Between day comparison of AUC and Cmax of MPA in group B are provided in the following tables:

MMF Dose	Mean ±SD MPA AUC (μg*hr/mL) (n)		
	Day of Treatment		
	Day 1	Day 21	Month 3
3g/day (1.5 g BID)	42.5±13.1 (6)	44.7±11.5 (5)	62.2±21.3 (5)
4 g/day (2 g BID)	31.3±10.7 (6)	42.7±15.4 (5)	48.5 ±13.5 (5)

MMF Dose	Mean ±SD MPA Cmax (μg/mL) (n)		
	Day of Treatment		
	Day 1	Day 21	Month 3
3g/day (1.5 g BID)	11.3±9.53 (6)	15.3±2.69 (5)	23.3±8.34 (5)
4 g/day (2 g BID)	7.09±5.59 (6)	14.2±9.19 (5)	15.9 ±4.84 (5)

There was no statistically significant difference in AUC and Cmax of MPA among the various days studied. However, it appeared that in these patients (group B), there was a trend towards an increase in both AUC and Cmax of MPA by month 3 of MMF administration. Individual patient data generally showed a trend towards an increase in Cmax and AUC of MPA by month 3 of MMF administration, even though in a few patients the concentration remained the same or decreased. The same trend was not clearly obvious when day 1 and 21 data were compared.

MMF Dose	Mean ±SD MPAG AUC (μg*hr/mL) (n)		
	Day of Treatment		
	Day 1	Day 21	Month 3
3g/day (1.5 g BID)	237 ±80.3 (6)	634 ± 94.1 (5)	894 ± 271 (5)
4 g/day (2 g BID)	227 ± 66.9 (6)	657 ± 243 (5)	859 ±310 (5)

MMF Dose	Mean ±SD MPAG Cmax (μg/mL) (n)		
	Day of Treatment		
	Day 1	Day 21	Month 3
3g/day (1.5 g BID)	29.0 ± 8.54 (6)	74.0 ± 17.0 (4)	106 ± 26.2 (5)
4 g/day (2 g BID)	29.2 ±11.5 (6)	81.4 ± 26.6 (5)	99.9 ± 37.1 (5)

There is significant accumulation of AUC and Cmax of MPAG after multiple dosing. This may not be of clinical significance.

When the dose for the groups are normalized to 2000 mg, the AUC of MPA for Group A patients appeared to be greater than that seen in the post transplant period for the days 1 and 21 of the group B patients; however, by month 3 the AUC appeared to be similar (APPENDIX).

None of the patients were reported to have lost their graft during the study. Overall, the investigator reported that at the doses studied, some MMF patients showed resolution of acute cellular rejection and that no benefit was noted with respect to prevention of rejection.

Conclusion: The pharmacokinetics of MMF appeared to be different during the first three weeks of therapy in patients who had acute episodes of rejection (Group A) prior to starting MMF from those who received MMF within 48 hours of transplant (Group B). This difference appeared to be due to the fact that Group A patients received MMF ; post transplant (late transplant period) compared to within 2 days (early transplant period) for the Group B patients. The plasma concentrations appeared to be smaller during the first three weeks compared to at 3 month of therapy in group B patients. This is consistent with what is reported for renal transplant patients. Doses up to 5 g/day were reasonably tolerated according to the investigator's report. However, higher doses were associated with the development of leukopenia which resulted in the termination of the study. The maximum dose reasonably tolerated in this study was 5 g/day.

Study ICM 1754 (CL 6783): An Open-Label, Pilot, Dose-Finding, Safety and Efficacy Study of Mycophenolate Mofetil for Treatment of Cardiac Allograft Recipients: Pharmacokinetics Report (Volume 17 page 1)

Introduction: This pilot study was designed to evaluate the efficacy and safety of MMF in patients whose cardiac allograft was undergoing mild acute cellular rejection or who were at high risk of rejection as their corticosteroid dosage was being reduced.

Objective: To evaluate the safety and efficacy of MMF in cardiac transplant patients also receiving cyclosporine and prednisone for 1) the treatment of mild acute cellular rejection with doses ranging from 500 mg to 3 gm per day 2) To evaluate the safety and efficacy of two dose levels (500 mg and 1 gm per day) of MMF in the prevention of rejection in patients also receiving cyclosporine and prednisone 3) To evaluate the pharmacokinetics of MMF in patients undergoing cardiac transplantation 4) To monitor for the occurrence of adverse events and opportunistic infections in patients being treated with MMF also receiving cyclosporine and prednisone.

Study Design: This was a single center, open-label study in which 39 patients (ages 20 to 65 years) were enrolled. There were two groups of cardiac patients: Group A patients had biopsy-confirmed evidence of mild (Grade 3) acute cellular rejection of their cardiac allograft and Group B patients were those at high risk of rejection during a planned, phased reduction in the dose of corticosteroids during the first 4 postoperative months. In Group A, 9 patients each were enrolled in the 1 gm/day and 2 gm/day subgroups and 6 patients each in the 500 mg/day and 2 gm/day subgroups. In Group B, 6 patients each were enrolled 500 mg/day and 3 were enrolled in the 1 gm/day subgroup. This was an ascending dose finding study, hence patients were enrolled sequentially at higher dose levels. MMF was begun within 48 hours of entry biopsy and was given for 56 days. Plasma samples for full pharmacokinetic profiles were obtained on Days 1 and 28 of dosing. (1hr postdose) and (predose) values were obtained on Days 14, 42 and 56. MPA and MPAG in plasma were quantitated The quantitation limit of this method for MPA and MPAG was 0.4 and 0.355 μg/mL, respectively.

Data Analysis: The following pharmacokinetic parameters were computed for MPA and MPAG on day 28: Cmax, AUC, Tmax, Cave, Cmin (calculated as the average of the 0 and 24 hour plasma concentration for the once daily regimen or the average of the 0 and 12-hour plasma concentration for the BID regimen) and fluctuation percent defined as 100 x (Cmax-Cmin)/Cave. On day 1, Cmax, AUC, Tmax were computed.

Results: Cmax, AUC and Tmax of MPA and MPAG for Group A patients are contained in the following tables; additional pharmacokinetic parameters are provided in the APPENDIX.

MPA Pharmacokinetic Parameters on Day 1

Parameter	500 mg QD	1 gm QD	1 gm BID	1.5 gm BID
	Mean ±SD (n) Day 1			
Tmax (hr)	1.25 ± 0.61 (6)	3.72 ± 7.62 (9)	2.50 ± 3.86 (8)	2.00 ± 1.27 (6)
Cmax (μg/mL)	7.40 ± 3.11 (6)	22.06 ± 15.61 (9)	11.80 ± 7.85 (8)	10.08 ± 9.85 (6)
AUC (μg*hr/mL)#	17.86 ± 3.92 (6)	48.85 ± 19.21 (8)	29.29 ± 21.05 (8)	28.32 ± 10.63 (6)

AUC's are 24 hour for QD patients and 12 hour for BID patients

MPA Pharmacokinetic Parameters on Day 28

Parameter	500 mg QD	1 gm QD	1 gm BID	1.5 gm BID
	Mean ±SD (n) Day 28			
Tmax (hr)	1.50 ± 0.58 (4)	3.88 ± 8.15 (8)	1.29 ± 1.22 (7)	3.00 ± 1.41 (5)
Cmax (μg/mL)	7.04 ± 5.00 (4)	18.82 ± 7.51 (8)	8.52 ± 4.81 (7)	5.83 ± 2.27 (5)
AUC (μg*hr/mL)#	21.15 ± 7.37 (4)	49.36 ± 18.49 (8)	37.43 ± 15.98 (7)	28.93 ± 5.30 (5)

AUC's are 24 hour for QD patients and 12 hour for BID patients

The mean Cmax for MPA on day 1 for the 1gm/day was about 2-fold higher than that for the 1gm BID regimen but Cmax occurred at a later time for the 1 gm/day when compared to 1 gm BID dosing regimen. The mean AUC computed after 1 gm BID dosing is similar to that after 1.5 gm BID. This is unexpected and the reason for this observation is not clear. The AUC(0-24) for the 500 mg/day and the 1 gm/day dose groups appeared to increase proportionally with dose on day 28 but a similar trend was not observed between the other dose groups. The mean Cmax after daily dosing of 1.5 gm BID for 28 days is lower than that observed after 1 gm BID dosing. This is unexpected since and the reasons are not clear. Multiple dosing for 28 days does not appear to result in any significant accumulation which is unexpected since Cellcept has terminal elimination half life of about 17 hours. A few patients in the 1.5 gm BID dosing group had lower than expected plasma concentration time profiles which may explain the inconsistency in the AUC and Cmax for this dose group. The pharmacokinetic data was highly variable and too few patients to make adequate inferences from this pilot study.

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MPAG Pharmacokinetic Parameters on Day 1

Parameter	500 mg QD	1 gm QD	1 gm BID	1.5 gm BID
	Mean ±SD (n) Day 1			
Tmax (hr)	2.83 ± 1.33 (6)	5.78 ± 6.89 (9)	3.06 ± 1.02 (8)	5.83 ± 2.56 (6)
Cmax (μg/mL)	18.35 ± 7.10 (6)	36.42 ± 6.48 (9)	34.56 ± 10.24 (8)	36.22 ± 6.32 (5)
AUC (μg*hr/mL)#	269.9 ± 102.7 (6)	512.5 ± 163.8 (8)	264.9 ± 95.18 (8)	324.9 ± 49.71 (5)

AUC's are 24 hour for QD patients and 12 hour for BID patients

MPAG Pharmacokinetic Parameters on Day 28

Parameter	500 mg QD	1 gm QD	1 gm BID	1.5 gm BID
	Mean ±SD (n) Day 28			
Tmax (hr)	2.50 ± 1.00 (4)	3.01 ± 1.06 (8)	4.14 ± 3.67 (7)	5.20 ± 3.90 (5)
Cmax (μg/mL)	32.28 ± 11.74 (4)	54.71 ± 21.06 (8)	49.57 ± 15.45 (7)	74.00 ± 10.31 (5)
AUC (μg*hr/mL)#	486.3 ± 185.9 (4)	722.80 ± 370.40 (8)	469.9 ± 127.10 (7)	646.50 ± 184.8 (5)

AUC's are 24 hour for QD patients and 12 hour for BID patients

The AUC(0-24) of MPAG for the 500 mg/d and the 1 gm/d also appeared to increase proportionally with dose. However, similar trend was not observed between the other dose groups. There is a trend toward accumulation of MPAG after dosing for 28 days.

Trough concentrations were not taken between days 1 and 14 of dosing hence it is difficult to precisely estimate when steady state was reached in these patients. However, based on trough concentrations obtained after day 14, it appears steady was reached by day 14 of dosing.

Enrollment in Group B was terminated prematurely to concentrate on the Group A patients when it appeared that MMF might be efficacious in preventing graft rejection. Hence, there is too few patients in Group B to make any inferences. The pharmacokinetic parameters from the small group of patients enrolled in the 500 and 1 gm/day in this study are provided in the APPENDIX.

Conclusion: There was considerable variability and too few patients in some dosing groups to make definite conclusions from the pharmacokinetic data. However, there appeared to be a trend towards MPAG accumulation upon multiple dosing, but it may not be of clinical significance. It appears that steady state conditions are reached by day 14 (probably sooner) of multiple dosing.

Study ICM 1812 (CL 6818): An Open-Label, Pilot, Pharmacokinetic, Safety and Efficacy Study of Mycophenolate Mofetil for Treatment of Refractory Cellular Allograft Rejection: Pharmacokinetic Report (Volume 11 page 1).

Introduction: This was one of the initial phase II studies to evaluate the use of MMF as an immunosprressive agent to prevent advanced acute rejection following solid organ transplantation. This study included renal, cardiac, and hepatic allograft recipients with biopsy-proven refractory acute cellular rejection, who had recurrent rejection or rejection unresponsive to steroids and OKT3 or ALG or who were unable to tolerate further treatment with these agents. This review focuses on the pharmacokinetics in cardiac transplant patients.

Objectives: The primary objectives were to evaluate the following: 1) The effect of treatment on the course of rejection 2) The safety and tolerability of MMF when administered with baseline levels of cyclosporine and prednisone 3) The effect of treatment on graft and patient survival over the 56-day treatment period and 4) The pharmacokinetics of MMF when administered with baseline levels of cyclosporine and prednisone.

The secondary objectives were to evaluate 1) The effect of administration of MMF in combination with cyclosporine and prednisone for the prevention of further rejection episodes and 2) The occurrence of opportunistic infections during treatment.

Study Design: This was a 56-day, multi center, open-label study that enrolled 158 patients that met the entry criteria as specified by the protocol. Concomitant treatments with cyclosporine and prednisone were permitted. The original protocol allowed a MMF starting dose of 1 g twice daily (BID) with an increase to 1.5 gm BID on Day 5 or later if there is inadequate therapeutic response. Amendment to the protocol allowed MMF starting dose of 1.5 gm BID with an increase to 1.75 gm BID on Day 5 or later if there is no or inadequate therapeutic response or no severe adverse events attributed to MMF for patients who weighed 40 kg or more. Most patients in the study were started on MMF 1.5 gm BID. Trough blood concentrations of cyclosporine were obtained and recorded weekly. Full 12-hour pharmacokinetic profiles for MMF were determined on days 1 and 28; and peak and trough sampling on Days 3, 7, 14 and 21. Patients who completed the initial 28-days of treatment with MMF with clinical and histologic evidence of complete or partial resolution of rejection and without severe MMF-related adverse events, were allowed to receive MMF for an additional 28 days. Pharmacokinetic evaluation was not conducted during the second 28-day treatment. Each patient received 1, 1.5, 1.75 gm of MMF BID, 30 mins before breakfast and 12 hours later.

Pharmacokinetic Data Analysis: The following pharmacokinetic parameters for MPA and MPAG were computed as appropriate: Tmax, Cmax, AUC(0-12), Cave (AUC(0-12)/12), Cmin (morning predose sample), Cmax/Cmin, Cmax/Cave and Percent Fluctuation (100 x (Cmax-Cmin)/Cave)

Results: Thirty-seven out of the 158 patients who enrolled were cardiac allograft recipients; Ten of the cardiac patients did not complete the study. The mean MPA pharmacokinetic parameters for the 1gm and 1.5 gm BID dosing groups for the cardiac patients are provided below. The pharmacokinetic parameters for the other groups are provided in the APPENDIX.

Mean±SD MPA Pharmacokinetic Parameters for Cardiac Transplant Patients

Pharmacokinetic Parameters	1 gm BID		1.5 gm BID	
	Day 1 (n=7)	Day 28 (n=3)	Day 1	Day 28
Tmax (hr)	1.01 ± 0.49	3.17 ± 4.20	NA	2.28 ± 3.22 (n=5)
Cmax (μg/mL)	9.46 ± 7.01	9.06 ± 8.24	NA	10.86 ± 4.54 (n=5)
AUC (μg*hr/mL)	21.29 ± 10.01	35.53 ± 13.76	NA	41.70 ± 6.15 (n=3)

NA: Insufficient data for computation

Mean±SD MPAG Pharmacokinetic Parameters for Cardiac Transplant Patients

Pharmacokinetic Parameters	1 gm BID		1.5 gm BID	
	Day 1 (n=7)	Day 28 (n=3)	Day 1	Day 28
Tmax (hr)	4.33 ± 3.51	5.33 ±2.31	NA	3.38 ± 2.76 (n=5)
Cmax (μg/mL)	32.64 ± 19.45	55.02 ± 22.68	NA	108.6 ± 52.70 (n=5)
AUC (μg*hr/mL)	250.6 ± 107.8	531.6 ± 241.0	NA	1281 ± 369.2 (n=3)

NA: Insufficient data for computation

When the pharmacokinetic data for Day 1 were compared with those for Day 28 for the 1 gm BID group, a small degree of accumulation was observed (mean AUC increased from 21.3 to 35.5-μg*h/mL) after multiple dosing which is unexpected since MPA has a terminal elimination half-life of about 17 hours. There was a trend towards an increase in Cmax and AUC after multiple dosing with an increase in dose, but this does not appear to be proportional to dose. However, there is insufficient information from this study to determine whether MPA pharmacokinetics in cardiac patients are linear or non linear. Trough MPA plasma concentrations suggest that steady state may be achieved by Day 14 of dosing.

The mean MPA and MPAG pharmacokinetic parameters computed for renal transplant patients are contained in the following tables.

Mean±SD MPA Pharmacokinetic Parameters for Renal Transplant Patients

Pharmacokinetic Parameters	1 gm BID		1.5 gm BID	
	Day 1	Day 28	Day 1	Day 28
Tmax (hr)	1.69 ± 1.19 (n=8)	1 (n=2)	3.98 (n=1)	3.25 ± 4.33 (n=6)
Cmax (μg/mL)	8.28 ± 8.06 (n=8)	16.66 (n=2)	1.94 (n=1)	12.67 ± 8.54 (n=6)
AUC (μg*hr/mL)	17.11 ± 8.08 (n=9)	32.96 (n=1)	14.43 (n=1)	53.90 ± 33.54 (n=5)

Mean±SD MPAG Pharmacokinetic Parameters for Renal Transplant Patients

Pharmacokinetic Parameters	1 gm BID		1.5 gm BID	
	Day 1	Day 28	Day 1	Day 28
Tmax (hr)	4.79 ± 3.65 (n=8)	2.03 (n=2)	8.00 (n=1)	4.01 ±2.18 (n=6)
Cmax (μg/mL)	26.56 ± 9.24 (n=8)	114.4 (n=2)	38.34 (n=1)	90.85 ± 50.70 (n=6)
AUC (μg*hr/mL)	214.3 ± 88.33 (n=9)	1066 (n=1)	256.1 (n=1)	703.2 ± 218.2 (n=5)

When the pharmacokinetic data for Day 1 were compared with those for Day 28 for the 1 and 1.5 gm BID dose groups in the renal transplant patients, there appeared to be an increase in both Cmax and AUC of MPA after multiple dosing for 28 days.

However, because of too few patients in some of the dosing groups, inferences could not be made. Similarly, because of the large variability and too few patients, no trends could be made from the MPAG data except for the 1 gm BID group in which mean Cmax and AUC doubled. Again, it must be emphasized that there were too few patients in some groups and large variability in the data to warrant concrete inferences from these observations. Trough concentrations suggest steady state concentrations are achieved by day 14 of dosing (APPENDIX) but because of the variability in the data and too few predose concentrations, it is difficult to precisely estimate when steady state was achieved in these patients. It is therefore feasible that steady state conditions may have been achieved earlier than day 14 of dosing. In the hepatic patients, because of the variability in the data and number of patients, no trend could be deduced from the pharmacokinetic data.

In general, Cmax and AUC of MPA increased little or moderately after multiple doses and steady state appeared to be achieved by day 14 of dosing. However, Cmax and AUC of MPAG showed a greater degree of accumulation after multiple doses. Because of the variability in the pharmacokinetic data and too few patients in some dose groups, quantitative and definite conclusions could not be drawn. Comparison between different patient groups was difficult and tenuous because of the variability in the number of patients in each group and the variability in the data. However, an evaluation of the 1 gm BID dose group data on day 1 (APPENDIX) may suggest that there is no difference in the pharmacokinetic data for the different patient groups. Because this was the first MMF study for the treatment of acute allograft rejection and the severity of the medical conditions, the investigators reported a lot of protocol violations resulting in considerable variability in the data and few evaluable patients available in some dosing groups. This made the data tenuous and difficult to interpretate.

Conclusion: There was a trend towards an increase in AUC and Cmax of both MPA and MPAG after multiple dosing in cardiac patients. Steady state appears to have been reached by day 14 of dosing. There was considerable variability in the pharmacokinetic data to allow adequate comparison between different patient groups and doses. Most patients in the study received 1.5 gm BID dosing regimen.

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APPLICATION NUMBER: 050722/S002 and 050723/S001

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

Roche

Supplemental NDA 50-722
CellCept® (mycophenolate mofetil capsules) 250 mg

Certification Statement for Generic Drug Enforcement Act of 1992

On behalf of Syntex (U.S.A.) Inc., Roche Global Development has made a diligent effort to insure that no person debarred under section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act has provided any services in connection with this application. Relying on this effort, Roche certifies that it did not and will not use in any capacity the services of any person debarred under Section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this application.

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Patent Information

Mycophenolate mofetil is the subject of U.S. patents 4,753,935 and 4,786,637. The following documents provide information about these patents, including patent certification.

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PATENT INFORMATION

CellCept™ (mycophenolate mofetil) 250 mg Capsules
NDA 20-513

Syntex Laboratories, Inc. submits the following patent information, as required by Section 505(b) of the Federal Food, Drug, and Cosmetic Act, as amended, and in compliance with 21 CFR 314.53(c) (draft of July 10, 1989).

The following patents are relevant to this New Drug Application:

Patent No. 4,753,935;	expires June 28, 2005;	drug, drug product;
Patent No. 4,786,637;	expires November 22, 2005;	method of use.

The owner of the patents is:

Syntex (U.S.A.) Inc.
3401 Hillview Avenue
P.O. Box 10850
Palo Alto, California 94303

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE EXTENDING PATENT TERM UNDER 35 U.S.C. § 156

PATENT NO.	:	4,753,935
ISSUED	:	June 28, 1988
INVENTOR(S)	:	Peter H. Nelson et al.
PATENT OWNER	:	Syntex (U.S.A.) Inc.

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This is to certify that there has been presented to the

COMMISSIONER OF PATENTS AND TRADEMARKS

an application under 35 U.S.C. § 156 for an extension of the patent term. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

824 days

from the date of expiration of the original patent term, January 30, 2007, with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).

I have caused the seal of the Patent and Trademark Office to be affixed this 23rd day of September 1996.

Bruce A. Lehman

Bruce A. Lehman
Assistant Secretary of Commerce and
Commissioner of Patents and Trademarks

PATENT CERTIFICATION

CellCept™ (mycophenolate mofetil) 250 mg Capsules
NDA 20-513

Syntex Laboratories, Inc. submits the following patent certification, as required by Section 505(b) of the Federal Food, Drug, and Cosmetic Act, as amended, and in compliance with 21 CFR 314.53(c) (draft of July 10, 1989).

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The undersigned certifies that the drug and/or the formulation or composition of CellCept™ (mycophenolate mofetil) 250 mg Capsules is claimed by U.S. Patent No. 4,753,935. This product is the subject of this application for which approval is being sought.

The undersigned certifies that U.S. Patent No. 4,786,637 covers the use of CellCept™ (mycophenolate mofetil) 250 mg Capsules that is the subject of this application for which approval is being sought: namely, adjunctive therapy for prophylaxis of rejection and treatment of refractory rejection in renal allograft recipients.

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Alan M. Krubiner

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EXCLUSIVITY SUMMARY for NDA # 50-722 SUPPL # 002
NDA# 50-723 SUPPL #001
Trade Name CellCept Generic Name mycophenolate mofetil
Applicant Name Syntex (U.S.A.) Inc HFD- 590

Approval Date February 11, 1998

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?
   YES /___/ NO /__x_/

   b) Is it an effectiveness supplement?

   YES /__x_/ NO /___/

   If yes, what type? (SE1, SE2, etc.) SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /_x__/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /___/ NO /__x_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /_x__/

APPEARS THIS WAY
ON ORIGINAL

If yes, NDA # _____ Drug Name_____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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ON ORIGINAL

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /__x_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

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PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_x__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 50-722 _____

NDA # 50-723 _____

APPEARS THIS WAY
ON ORIGINAL

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

APPEARS THIS WAY
ON ORIGINAL

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

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PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_x__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_x__/ NO /___/

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ON ORIGINAL

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_x__/

APPEARS THIS WAY ON ORIGINAL

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

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If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /__x_/

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If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # MYCS 1864 _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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ON ORIGINAL

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /__x_/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

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b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /_x__/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

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c) If the answers to ... ion in the application or sup... estigations listed in #2(c), les...

Investigation ...

Investigation ...

Investiga... ...

4. To be eligible for exclu... must also have been conducted or ...nducted or sponsored by" the appl... ...on, 1) the applicant was the spo... ...e Agency, or 2) the applicant (or ...rt for the study. Ordinarily, ...f the cost of the study.

a) For each i... ...estigation was ... ...71 as the sponso...

Investigat...

IND #

Investigati...

IND # ____

(b) For eac... ...icant was not iden... ...plicant's predecesso...

Investigation ...

YES /___/ Ex...

BEST POSSIBLE COPY

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_x__/

If yes, explain: _____

_____

_____

_____

/S/ _____ 2/10/98

Signature Date

Title: Acting SCSO HFD-590

/S/ _____ 2/19/98

Signature of Division Director Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 50-722 Supplement # S-002 Circle one: SE1

HFD-590 Trade and generic names/dosage form: CellCept® (mycophenolate mofetil) tablets and capsules
Action: AP
Applicant Syntex (U.S. A.) Inc. Therapeutic Class Immunosuppression
Indication(s) previously approved: prophylaxis of organ rejection in patients receiving allogeneic renal transplants,

Pediatric information in labeling of approved indication(s) is adequate x inadequate__

Indication in this application : prophylaxis of organ rejection in patients receiving allogeneic cardiac transplants

__ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

__ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

__X__ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

__ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

__ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

x__ c. The applicant has committed to doing such studies as will be required.
- x__ (1) Studies are ongoing, (for renal)
- __ (2) Protocols were submitted and approved.
- __ (3) Protocols were submitted and are under review.
- __ (4) If no protocol has been submitted, attach memo describing status of discussions.

__ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

__ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

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ON ORIGINAL

XX 5. **If none of the above apply**, attach an explanation, as necessary.

Signature of Preparer and Title /S/ Date: February 11, 1998
Lisa M. Hubbard, R. Ph., Senior Regulatory Management Officer

cc: Orig NDA/PLA/PMA # 50-722, 50-723
HFD-590 /Div File
NDA/PLA Action Package
HFD-006/ SOImstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

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NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 2/11/98)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE CONFERENCE WITH INDUSTRY

DATE: January 8, 1998

TO: Christine Conroy, Pharm.D.

ADDRESS: Christine Conroy, Pharm.D.
Roche Global Development-Palo Alto
3401 Hillview Avenue
Palo Alto, CA 94394-1397

FROM: Mary Dempsey, FDA Project Manager

NDA: 50-722/S-002

SUBJECT: Statistical Issues

FDA Attendees:

Mike Elashoff, Statistician
Paul Flyer, Statistician
Mary Dempsey, Project Manager

Sponsor Attendees:

Richard Mamelok, M.D., Medical Monitor
Mandee Rees, M.S., Director, Statistics
David Ipe, M.S., Statistician
Chris Conroy, Sr. Regulatory Project Manager

The purpose of this telecon was to revisit the statistical issues that were addressed at the January 5th, 1998 telecon.

Dr. Elashoff explained to Roche the rationale for his statistical analysis of the data. He detailed the Robustness issue and clarified the statistical techniques employed to arrive at the P value. Dr. Elashoff also placed the P value in perspective with the claims of superiority.

N 50-722/S-002

Roche concurred that they were very close to agreement with the techniques and findings of Dr. Elashoff's statistical analysis.

The Agency and Roche are going to telecon tomorrow, January 9th, 1998, to further prepare for the upcoming Advisory Committee Meeting.

If you have any additional questions concerning your application, please contact Mary Dempsey, Project Manager at 301-827-2335.

Signature minutes preparer: /S/ /S/ Date: 01-09-98
Conference Chair (or designated signatory) Date:

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N 50-722

CC:
HFD-725/Stat/MElashoff
cc:
Division File
NDA 50-722
HFD-590/MO/JKorvick
HFD-590/MO/MCavaille'-Coll
HFD-590/Act.TL/LHubbard
HFD-725/Stat/MElashoff
~~HFD-725/Act.TL/AChakravarty~~
HFD-590/PM/MDempsey

HFD-725/Stat TL/Fly 1/31

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE CONFERENCE WITH INDUSTRY

DATE: December 12, 1997

TO: Christine Conroy, Pharm.D.

ADDRESS: Roche Global Development
3401 Hillview Avenue, A3-330
Palo Alto, CA 94304
Telephone 650-855-5894
Fax 650-852-1861

FROM: Mary Dempsey, Project Manager

NDA: **50-722/S-002**

SUBJECT: Hemodynamic Compromise

FDA Attendees: Mike Elashoff, Ph.D., Statistician
Mary Dempsey, Project Manager

Roche Attendees: Richard Mamelok, M.D., Medical Monitor
Mandee Rees, M.S., Director, Statistics
David Ipe, M.S., Statistician
Patrick Macbeath, Statistics
Christine Conroy, Pharm.D., Sr. Regulatory Manager

Dr. Elashoff requested that Roche clarify the definition of hemodynamic compromise. He referred to the definition as it was outlined in the Protocol and that it was different from the definition that was being used in the Data Set.

Roche's response was that the Data Set definition is made up of eight variables including a category for 'inotropic support' and a category for 'other'. Roche stated that during a meeting with the Division on March 19, 1997, they discussed the criteria that would be used to assess hemodynamic compromise (as part of a 6-month rejection endpoint).

Roche further explained that during this meeting, the final endpoint change for study 1864 was discussed and the definition of hemodynamic compromise was presented. The minutes and overheads from this meeting were filed to IND 33,872/S-404 dated May 5, 1996. 'Inotropic support' was included in the definition of hemodynamic compromise at this time. See attached copy of the definition of hemodynamic compromise.

Signature minutes preparer: /S/ Date: 01/09/98

Conference Chair (or designated signatory) /S/ Date:

NDA 50-722/S-002

Concurrence:
HFD-590/ActTL/PM/LHubbard

cc:
NDA 50-722
Division File
HFD-590/MO/MCavaille'-Coll
HFD-590/MO/JKorvick /S/
HFD-725/Stat/PFlyer
HFD-725/Stat/MElashoff
HFD-590/ActTL/PM/LHubbard /S/
HFD-590/PM/MDempsey

Address: V:\DSPIDP\Dempsey\N50-722\tel010998

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Public Health Service
Food and Drug Administration
Rockville MD 20857

Hubbard 590

Memorandum of Industry Telephone Conference

Date: 20 November 1997

NDA: 50-722, SE-1, S-002

APPEARS THIS WAY ON ORIGINAL

Drug: CellCept

Sponsor: Syntex U.S.A.

Chair: Joyce Korvick, M.D.

Facilitator/Recorder: Lisa M. Hubbard, R.Ph /S/

APPEARS THIS WAY ON ORIGINAL

Sponsor Chair: Chris Conroy

FDA Participants:
Joyce Korvick, M.D., Medical Officer,
Mike Elashoff, Ph.D., Statistician
Lisa Hubbard, R.Ph., Regulatory Management Officer

External Participants:
Dr. Richard Mamelock
Dr. David Ipe
Ms. Mandy Rees
Ms. Chris Conroy

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Purpose/Objectives:
1. To clarify the FDA request for a dataset requested 17 November 1997.
2. To clarify the FDA request for an argument related to Azathioprine activity
3. To clarify the FDA request for information related to pancreatitis

Discussion Points:

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1. A dataset to investigate the six-month co-primary endpoint
2. Azathioprine activity in cardiac transplant patients
3. Overview of pancreatitis in patients receiving CellCept

Decisions reached:

Public Health Service
Food and Drug Administration
Rockville MD 20857

Unresolved Issues

1. Roche will determine whether or not they will submit a request to alter the goal date for this application by the end of the month.
2. FDA will determine the final representatives of the Advisory Committee by the end of the month.

Action Items

1. **Roche will submit an additional statistical dataset as described above.**
2. **Roche will submit an argument related to Azathioprine activity as described above.**
3. **Roche will submit a summary with respect to pancreatitis as described above.**
4. **Roche will confirm availability for a telephone conference tentatively scheduled for December 8, 1997.**
5. **Roche will confirm Dr. Miller's availability for the Advisory Committee meeting in early December.**
5. **FDA will determine the final Advisory Committee participants by early December.**

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APPEARS THIS WAY
ON ORIGINAL

Roche Global Development
3401 Hillview Avenue
Palo Alto, CA 94304-1397

DATE: December 18, 1997

TO: Nancy Sager — **PHONE:** 301 594 5629
Office of Pharmaceutical Science, FDA — **FAX:** 301 827 2772

FROM: Dr. Sabine Geisel — **PHONE:** + 1 415 855 5923
Drug Regulatory Affairs — **FAX:** + 1 415 852 1861

RE: Environmental Assessment Report - Application for Categorical Exclusion for
CellCept - cardiac indication (NDA 50-722/S002)
CellCept Intravenous (NDA 50-758)
CellCept Oral Suspension (NDA 50-759)

CC: Dr. Mark Seggel, CDER

APPEARS THIS WAY
ON ORIGINAL

Message

Dear Nancy,

As discussed in our teleconference yesterday please find attached a memo with our current production estimates for mycophenolate mofetil and the calculation of the Expected Introduction Concentration (EIC).

Our proposed wording for application for Categorical Exclusion is:
"Herewith we apply for a categorical exclusion for submitting an environmental assessment report for NDA 50-722/S002
We state that we are in compliance with the categorical exclusion criteria according to §25.31(b) and to our knowledge no extraordinary circumstances exist."

We would appreciate getting your comments on the rationale to support the request for Categorical Exclusion as well as on the proposed wording for the actual application. We would also like to get your advice about the feasibility to submit one application for categorical exclusion for all three NDAs together or if it would be more appropriate to have a separate application for each NDA.

Thank you very much for your assistance.

Best regards

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ON ORIGINAL

Sabine Geisel, Ph.D.
Regulatory Program Manager

Attachment

Syntex EH&S Center
Memorandum

December 18, 1997

Re: Status on Need for Environmental Assessments for Mycophenolate Mofetil Based on Current Production Estimates

Based on current Mycophenolate Mofetil market projections and production estimates for the year 2002, the expected peak production year within the next five years, the production volume in the United States for the year 2002 is estimated to be This estimate includes all indications and formulations expected to be approved by the year 2002 in the Cellcept program, i.e. renal, cardiac, capsules, tablets, oral suspension, and sterile lyophilized powder for intravenous infusion.

Mycophenolate Mofetil is excreted as the pharmacologically inactive compound MPAG (a glucuronide conjugate of mycophenolic acid). In vivo studies suggest that MPAG may then be hydrolyzed to mycophenolic acid (MPA). MPAG is also expected to be hydrolyzed to MPA upon discharge into the environment. Therefore, MPA can be considered as the major metabolite of Mycophenolate Mofetil in the environment. Based on this, the expected environmental introduction concentration is calculated for MPA rather than for mycophenolate mofetil or MPAG.

The Expected Introduction Concentration (EIC) of Mycophenolic Acid is then calculated from the estimated production volume as follows:

As the EIC for MPA is (for an estimated production volume of a Request for Categorical Exemption from an Environmental Assessment may be submitted.

NDA 50722

Cell Cept

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-722

Syntex Laboratories, Inc.
Attention: Daniel Zabrowski, Ph.D.
Drug Regulatory Affairs
3401 Hillview Avenue
Palo Alto, CA 94303

MAY - 3 1995

Dear Dr. Zabrowski:

Please refer to your November 10, 1994 new drug application submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for CellCept® (mycophenolate mofetil) 250 mg Capsules.

We acknowledge receipt of your amendments dated:

November 11, 1994
November 14, 1994
November 15, 1994
November 18, 1994
November 21, 1994 (2)
December [illegible]94
December 6, 1994
December 12, 1994 (2)
December 15, 1994
December 16, 1994
December 20, 1994
December 21, 1994
December 23, 1994 (3)
January 4, 1995 (2)
January 6, 1995 (2)
January 9, 1995
January 10, 1995
January 18, 1995
January 25, 1995 (2)
January 30, 1995
February 6, 1995 (3)
February 7, 1995
February 9, 1995
February 11, 1995
February 13, 1995 (2)
February 20, 1995
March 2, 1995
March 6, 1995 (4)
March 7, 1995
March 9, 1995
March 10, 1995 (2)
March 14, 1995
March 15, 1995
March 16, 1995
March 17, 1995 (3)
March 21, 1995 (4)
March 22, 1995
March 23, 1995 (3)
April 3, 1995
April 6, 1995 (2)
April 11, 1995
April 12, 1995
April 13, 1995
April 19, 1995
April 25, 1995
April 28, 1995 (2)

This new drug application provides for (1) the prophylaxis of organ rejection in patients receiving allogeneic renal transplants

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use in the prophylaxis of organ rejection in patients receiving allogenic renal transplants as recommended in the April 28, 1995 draft labeling. Accordingly, the application is approved effective on the date of this letter.

We have the following recommendations that pertain to post-marketing studies for the prophylaxis indication:

1. Please further explore the pharmacokinetics of mycophenolate mofetil in black patients. If the pharmacokinetics in this group is substantially different compared to Caucasians, then additional studies of efficacy should be undertaken in this population.

2. Please continue current studies in pediatric populations. In addition, studies which would further characterize the pharmacokinetics of mycophenolate mofetil and its metabolites after the administration of I.V. and oral formulations, as well as activity of MPA from these formulations, should be undertaken in the pediatric populations.

3. Please further explore the pharmacokinetics of mycophenolate mofetil and its metabolites in patients with alcoholic cirrhosis and in patients with other hepatic diseases.

4. You should consider conducting treatment-strategy type studies (e.g., starting with three grams per day and permitting the option of decreasing the dose to two grams per day, at least in some patients).

Pursuant to 21 CFR 314.125(b)(5), there is lack of substantial evidence consisting of adequate and well-controlled investigations establishing that CellCept is effective for the treatment in patients who have received allogenic renal transplants.

Based on the limited amount of data to support CellCept for the treatment of an additional clinical trial(s) will need to be conducted to support this indication. If you decide to pursue this indication further, we are available to meet with you to discuss the design of this clinical trial.

The final printed labeling (FPL) must be identical to the April 28, 1995 draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit twenty copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 50-722. Approval of this labeling by FDA is not required before it is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and
Communications, HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any deficiencies that may occur.

Please submit one market package of the drug when it is available.

Under section 736(a)(1)(B)(ii) of the Prescription Drug User Fee Act of 1992, this letter triggers the remaining 50% of the fee assessed for this application. You will receive an invoice for the amount due within the next month. Payment will be due within 30 days of the date of the invoice.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Matthew J. Tarosky, R.Ph., Regulatory Management Officer, at (301) 443-9553.

Sincerely yours,

David W. Feigal, Jr., M.D., M.P.H.
Acting Deputy Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

DIVISION OF SYNTEX (U.S.A.) INC.
3401 HILLVIEW AVENUE, P.O. BOX 10850
PALO ALTO, CALIFORNIA 94303

SYNTEX

HUMAN PHARMACEUTICAL REGULATORY AFFAIRS

April 28, 1995

Division of Antiviral Drug Products (HFD-530)
Center for Drug Evaluation and Research
Food and Drug Administration
Nicholson Research Center - Room 221
5516 Nicholson Lane
Kensington, Maryland 20895

SUBJECT:

CELLCEPT® (Mycophenolate Mofetil) - Oral Capsule

Dear Reviewers:

Enclosed please find the final version of the label as discussed with Mr. Tarosky today. It incorporates all agreed upon changes as outlined in the April 13, 1995, version of the label and the agreed upon text of today for the hepatic insufficiency section of the label in the Pharmacokinetic section (i.e., the change of the word "ideologies" to "etiologies" in the fax of April 28, 1995).

We greatly appreciate the continuing support the Agency has provided us in the development program and throughout the review for mycophenolate mofetil. Please feel free to contact me at (415) 354-7245 if you have any questions.

Sincerely,

Carol C. Grundfest
Regulatory Program Director

Desk Copy: Mr. Matthew Tarosky (by fax)

CellCept®

(mycophenolate mofetil capsules)

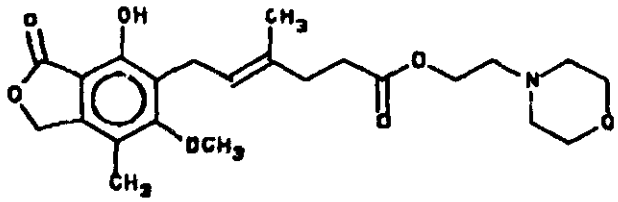
WARNING

Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. Only physicians experienced in immunosuppressive therapy and management of renal transplant patients should use CellCept®. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

DESCRIPTION

CellCept (mycophenolate mofetil) is the 2-morpholinoethyl ester of mycophenolic acid (MPA), an immunosuppressive agent.

The chemical name for mycophenolate mofetil is 2-morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate. It has an empirical formula of $C_{23}H_{31}NO_7$, a molecular weight of 433.50, and the following structural formula:



CellCept is available for oral administration as capsules containing 250 mg of mycophenolate mofetil. Inactive ingredients include croscarmellose sodium, magnesium stearate, povidone (K-90) and pregelatinized starch. The capsule shells contain black iron oxide, FD&C blue #2, gelatin, red iron oxide, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and yellow iron oxide.

Mycophenolate mofetil is a white to off-white crystalline powder. It is slightly soluble in water (43 µg/mL at pH 7.4); the solubility increases in acidic medium (4.27 mg/mL at pH 3.6). It is freely soluble in acetone, soluble in methanol, and sparingly soluble in ethanol. The apparent partition coefficient in 1-octanol/water (pH 7.4) buffer solution is 238. The pKa values for mycophenolate mofetil are 5.6 for the morpholino group and 8.5 for the phenolic group.

CLINICAL PHARMACOLOGY

Mechanism of Action

Mycophenolate mofetil has been demonstrated in experimental animal models to prolong the survival of allogeneic transplants (kidney, heart, liver, intestine, limb, small bowel, pancreatic islets, and bone marrow). Mycophenolate mofetil has also been shown to reverse ongoing acute rejection in the canine renal and rat cardiac allograft models. Mycophenolate mofetil also inhibited proliferative arteriopathy in experimental models of aortic and heart allografts in rats, as well as in primate cardiac xenografts. Mycophenolate mofetil was used alone or in combination with other immunosuppressive agents in these studies. Mycophenolate mofetil has been demonstrated to inhibit immunologically-mediated inflammatory responses in animal models and to inhibit tumor development and prolong survival in murine tumor transplant models.

Mycophenolate mofetil is rapidly absorbed following oral administration and hydrolyzed to form MPA, which is the active metabolite. MPA is a potent, selective, uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), and therefore inhibits the *de novo* pathway of guanosine nucleotide synthesis without incorporation into DNA. Because T- and B-lymphocytes are critically dependent for their proliferation on *de novo* synthesis of purines whereas other cell types can utilize salvage pathways, MPA has potent cytostatic effects on lymphocytes. MPA inhibits proliferative responses of T- and B-lymphocytes to both mitogenic and allospecific stimulation. Addition of guanosine or deoxyguanosine reverses the cytostatic effects of MPA on lymphocytes. MPA also suppresses antibody formation by B-lymphocytes. MPA prevents the glycosylation of lymphocyte and monocyte glycoproteins that are involved in intercellular adhesion to endothelial cells and may inhibit recruitment of leukocytes into sites of inflammation and graft rejection. Mycophenolate mofetil did not inhibit early events in the activation of human peripheral blood mononuclear cells, such as the production of interleukin-1 (IL-1) and interleukin-2 (IL-2), but did block the coupling of these events to DNA synthesis and proliferation.

Pharmacokinetics

Following oral administration, mycophenolate mofetil undergoes rapid and extensive absorption and complete presystemic metabolism to MPA, the active metabolite. MPA is metabolized to form the phenolic glucuronide of MPA (MPAG) which is not pharmacologically active. Mycophenolate mofetil is not measurable systemically in plasma following oral administration.

Absorption: In 12 healthy volunteers, the mean absolute bioavailability of oral mycophenolate mofetil relative to IV mycophenolate mofetil (based on MPA AUC) was 94%. The area under the plasma-concentration time curve (AUC) for MPA appears to increase in a dose-proportional fashion in renal transplant patients receiving multiple doses of mycophenolate mofetil up to a daily dose of 3 g (see table below on pharmacokinetic parameters in renal transplant patients).

Immediately post-transplant (<40 days), mean AUC and Cmax are approximately 50% lower in renal transplant patients than that observed in healthy volunteers or in stable renal transplant patients.

Food (27 g fat, 650 calories) had no effect on the extent of absorption (MPA AUC) of mycophenolate mofetil when administered at doses of 1.5 g b.i.d. to renal transplant patients. However, MPA Cmax was decreased by 40% in the presence of food. (See DOSAGE AND ADMINISTRATION.)

Distribution: The mean (±SD) apparent volume of distribution of MPA in twelve healthy volunteers is approximately 3.6 (±1.5) and 4.0 (±1.2) L/kg following IV and oral administration, respectively. MPA, at clinically relevant concentrations, is 97% bound to plasma albumin. MPAG is 82% bound to plasma albumin at MPAG concentration ranges that are normally seen in stable renal transplant patients; however, at higher MPAG concentrations (observed in patients with renal impairment or delayed graft function), the binding of MPA may be reduced as a result of competition between MPAG and MPA for protein binding. Mean blood to plasma ratio of radioactivity concentrations was approximately 0.6 indicating that MPA and MPAG do not extensively distribute into the cellular fractions of blood.

In vitro studies to evaluate the effect of other agents on the binding of MPA to human serum albumin (HSA) or plasma proteins showed that salicylate (at 25 mg/dL with HSA) and MPAG (at ≥460 µg/mL with plasma proteins) increased the free fraction of MPA. At concentrations that exceeded what is encountered clinically, cyclosporine, digoxin, naproxen, prednisone, propranolol, tacrolimus, theophylline, tolbutamide, and warfarin did not increase the free fraction of MPA. MPA at concentrations as high as 100 µg/mL had little effect on the binding of warfarin, digoxin or propranolol, but decreased the binding of theophylline from 53% to 45% and phenytoin from 90% to 87%.

Metabolism: Mycophenolate mofetil undergoes complete presystemic metabolism to MPA, the active metabolite. MPA is metabolized principally by glucuronyl transferase to form the phenolic glucuronide of MPA (MPAG) which is not pharmacologically active. The following metabolites of the 2-hydroxyethyl-morpholino moiety are also recovered in the urine following

oral administration of mycophenolate mofetil to healthy subjects: N-(2-carboxymethyl)-morpholine, N-(2-hydroxyethyl)-morpholine, and the N-oxide of N-(2-hydroxyethyl)-morpholine.

Secondary peaks in the plasma MPA concentration-time profile are usually observed 6-12 hours post-dose. The coadministration of cholestyramine (4 g t.i.d.) resulted in approximately a 40% decrease in the MPA AUC (largely as a consequence of lower concentrations in the terminal portion of the profile). These observations suggest that enterohepatic recirculation contributes to MPA plasma concentrations.

Increased plasma concentrations of mycophenolate mofetil metabolites (MPA 50% increase and MPAG about 3-6 fold increase) are observed in patients with renal insufficiency. (See CLINICAL PHARMACOLOGY: Special Populations.)

Excretion: Negligible amount of drug is excreted as MPA (<1% of dose) in the urine. Orally administered radiolabeled mycophenolate mofetil resulted in complete recovery of the administered dose; with 93% of the administered dose recovered in the urine and 6% recovered in feces. Most (about 87%) of the administered dose is excreted in the urine as MPAG. MPA and MPAG are usually not removed by hemodialysis. However, at high MPAG plasma concentrations (>100 µg/mL), small amounts of MPAG are removed.

Mean (±SD) apparent half-life and plasma clearance of MPA are 17.9 (±6.5) hours and 193 (±48) mL/min following oral administration and 16.6 (±5.8) hours and 177 (±31) mL/min following IV administration, respectively.

Pharmacokinetics in Healthy Volunteers and Renal Transplant Patients: Shown below are the mean (±SD) pharmacokinetic parameters for MPA following the administration of oral mycophenolate mofetil given as single doses to healthy volunteers and multiple doses to renal transplant patients. As noted below, MPA AUC and Cmax in early transplant patients (<40 days post-transplant) are approximately 50% lower as compared to healthy volunteers or to stable renal transplant patients.

PHARMACOKINETIC PARAMETERS FOR MPA
[mean (±SD)]
FOLLOWING ADMINISTRATION OF MYCOPHENOLATE MOFETIL
TO HEALTHY VOLUNTEERS (SINGLE DOSE)
AND
RENAL TRANSPLANT PATIENTS (MULTIPLE DOSES)

Healthy Volunteers (no. of subjects)	Dose	Tmax (h)	Cmax (µg/mL)	Total AUC (µg·h/mL)
(n=129) * (n=117)	1 g	0.80 (±0.36)	24.5 (±9.5)	63.9 * (±16.2)
Time After Renal Transplantation (no. of patients)	**Dose**	**Tmax (h)**	**Cmax (µg/mL)**	**Interdosing Interval AUC_{0-12} (µg·h/mL)**
Early (<40 days) (n=25)	1 g b.i.d.	1.31 (±0.78)	8.16 (±4.50)	27.3 (±10.9)
Early (<40 days) (n=27)	1.5 g b.i.d.	1.21 (±0.81)	13.5 (±8.18)	38.4 (±15.4)
Late (>3 months) (n=23)	1.5 g b.i.d.	0.90 (±0.24)	24.1 (±12.1)	65.3 (±35.4)

Special Populations

Shown below are the mean (±SD) pharmacokinetic parameters for MPA following the administration of oral mycophenolate mofetil given as single doses to subjects with renal and hepatic impairment.

PHARMACOKINETIC PARAMETERS FOR MPA
[*mean* (±SD)]
FOLLOWING SINGLE DOSES OF MYCOPHENOLATE MOFETIL
CAPSULES IN CHRONIC RENAL AND HEPATIC IMPAIRMENT

Renal Impairment (no. of patients)	Dose	T_{max} (h)	C_{max} (µg/mL)	AUC_{0-12} (µg·h/mL)
Healthy Volunteers GFR >80 mL/min/1.73m² (n=6)	1 g	0.75 (±0.27)	25.3 (±7.99)	45.0 (±22.6)
Mild Renal Impairment GFR 50-80 mL/min/1.73m² (n=6)	1 g	0.75 (±0.27)	26.0 (±3.62)	59.9 (±12.9)
Moderate Renal Impairment GFR 25-49 mL/min/1.73m² (n=6)	1 g	0.75 (±0.27)	19.0 (±13.2)	52.9 (±25.5)
Severe Renal Impairment GFR <25 mL/min/1.73m² (n=7)	1 g	1.00 (±0.41)	16.3 (±10.8)	78.6 (±46.4)
Hepatic Impairment (no. of patients)	**Dose**	**T_{max} (h)**	**C_{max} (µg/mL)**	**AUC_{0-12} (µg·h/mL)**
Healthy Volunteers (n=5)	1 g	0.63 (±0.14)	24.3 (±5.73)	29.0 (±5.78)
Alcoholic cirrhosis (n=18)	1 g	0.85 (±0.58)	22.4 (±10.1)	29.8 (±10.7)

Renal Insufficiency: In a single-dose study (6 volunteers per group), plasma MPA AUCs observed in volunteers with severe chronic renal impairment [glomerular filtration rate (GFR) <25 mL/min/1.73 m²] were about 75% higher relative to those observed in healthy volunteers (GFR >80 mL/min/1.73 m²). In addition, the single dose plasma MPAG AUC was 3-6 fold higher in volunteers with severe renal impairment than in volunteers with mild renal impairment or healthy volunteers, consistent with the known renal elimination of MPAG. Multiple dosing of mycophenolate mofetil in patients with severe chronic renal impairment has not been studied. No data are available on the safety of long-term exposure to this level of MPAG. (See PRECAUTIONS: General and DOSAGE AND ADMINISTRATION.)

In patients with delayed graft function post-transplant, mean MPA AUC_{0-12} was comparable to that seen in post-transplant patients without delayed graft function. Mean plasma MPAG

AUC_{0-12} was 2-3 fold higher than in post-transplant patients without delayed graft function. (See PRECAUTIONS: General and DOSAGE AND ADMINISTRATION.)

The pharmacokinetics of mycophenolate mofetil are not altered by hemodialysis. Hemodialysis usually does not remove MPA or MPAG. At high concentrations of MPAG (>100 µg/mL), hemodialysis removes only small amounts of MPAG.

Hepatic Insufficiency: In a single dose (1 g) study of 18 volunteers with alcoholic cirrhosis and 6 healthy volunteers, hepatic MPA glucuronidation processes appeared to be relatively unaffected by hepatic parenchymal disease when pharmacokinetic parameters of healthy volunteers and alcoholic cirrhosis patients within this study were compared. However, it should be noted that for unexplained reasons, the healthy volunteers in this study had about a 50% lower AUC as compared to healthy volunteers in other studies, thus making comparisons between volunteers with alcoholic cirrhosis and healthy volunteers difficult. Effects of hepatic disease on this process probably depend on the particular disease. Hepatic disease with other etiologies may show a different effect.

Pediatrics: Very limited pharmacokinetic data are available for pediatric renal transplant recipients. Data on these patients collected on day 21 post-transplant are presented in the table below:

PHARMACOKINETIC PARAMETERS FOR MPA
[mean ± (SD)]
FOLLOWING MULTIPLE ORAL DOSES OF
MYCOPHENOLATE MOFETIL IN PEDIATRIC RENAL
TRANSPLANT PATIENTS

Age Range	Dose	Tmax (h)	Cmax (µg/mL)	AUC_{0-12} (µg•h/mL)
≥ 3 mo to < 6 yr (Mean = 2.75) (n=4)	15 mg/kg b.i.d.	1.25 (±0.87)	3.70 (±2.08)	13.6 (±6.69)
≥ 6 yr to < 12 yr (Mean =9.0) (n=4)	15 mg/kg b.i.d.	0.50 (±0.00)	13.5 (±4.48)	23.4 (±2.84)
≥ 12 yr to 18 yr (Mean = 15.6) (n=5)	15 mg/kg b.i.d.	0.50 (±0.00)	13.2 (±6.86)	30.0 (±8.34)
≥ 12 yr to 18 yr (Mean = 14.0) (n=7)	23 mg/kg b.i.d.	1.14 (±0.80)	10.6 (±9.59)	28.3 (±12.8)

Gender: Data obtained from several studies were pooled to look at any gender related differences in the pharmacokinetics of MPA (data were adjusted to 1 g dose). Mean (±SD) MPA AUC_{0-12} for males (n=79) was 32.0 (±14.5) and for females (n=41) was 36.5 (±18.8) µg•h/mL while mean (±SD) MPA Cmax was 9.96 (±6.19) in the males and 10.6 (±5.64) µg/mL in the females. These differences are not of clinical significance.

Clinical Studies

The safety and efficacy of CellCept in combination with corticosteroids and cyclosporine for the prevention of organ rejection following allogeneic renal transplants were assessed in three randomized, double-blind, multicenter trials.

These studies compared two dose levels of CellCept (1.0 g b.i.d. and 1.5 g b.i.d.) with azathioprine (2 studies) or placebo (1 study) when administered in combination with cyclosporine (Sandimmune®) and corticosteroids to prevent acute rejection episodes. One

study also included antithymocyte globulin (ATGAM®) induction therapy. The three studies are described by geographic location of the investigational sites. One study was conducted in the USA at 14 sites, one study was conducted in Europe at 20 sites, and one study was conducted in Europe, Canada, and Australia at a total of 21 sites.

The primary efficacy endpoint was the proportion of patients in each treatment group who experienced treatment failure within the first six months after transplantation (defined as biopsy-proven acute rejection on treatment or the occurrence of death, graft loss or early termination from the study for any reason without prior biopsy-proven rejection). CellCept, when administered with antithymocyte globulin (ATGAM®) induction (one study) and with cyclosporine and corticosteroids (all three studies), was compared to the following three therapeutic regimens: (1) antithymocyte globulin (ATGAM®) induction/azathioprine/ cyclosporine/corticosteroids, (2) azathioprine/cyclosporine/corticosteroids, and (3) cyclosporine/corticosteroids.

CellCept, in combination with corticosteroids and cyclosporine reduced (statistically significant at the <0.05 level) the incidence of treatment failure within the first 6 months following transplantation. The following tables summarize the results of these studies. These tables show (1) the proportion of patients experiencing treatment failure, (2) the proportion of patients who experienced biopsy-proven acute rejection on treatment, and (3) early termination, for any reason other than graft loss or death, without a prior biopsy-proven acute rejection episode. Patients who prematurely discontinued treatment were followed for the occurrence of death or graft loss, and the cumulative incidence of graft loss and patient death are summarized separately. Patients who prematurely discontinued treatment were not followed for the occurrence of acute rejection after termination. More patients discontinued receiving CellCept (without prior biopsy-proven rejection, death or graft loss) than discontinued in the control groups, with the highest rate in the CellCept 3 g/day group. Therefore, the acute rejection rates may be underestimates, particularly in the CellCept 3 g/day group.

Incidence of Treatment Failure (Biopsy-Proven Rejection or Early Termination for Any Reason)

USA Study (n=499 patients)	CellCept 2 g/day (n=167 patients)	CellCept 3 g/day (n=166 patients)	Azathioprine 1-2 mg/kg/day (n=166 patients)
All treatment failures	31.1%	31.3%	47.6%
Early termination without prior acute rejection*	9.6%	12.7%	6.0%
Biopsy-proven rejection episode on treatment	19.8%	17.5%	38.0%

Europe/ Canada/ Australia Study (n=503 patients)	CellCept 2 g/day (n=173 patients)	CellCept 3 g/day (n=164 patients)	Azathioprine 100-150 mg/day (n=166 patients)
All treatment failures	38.2%	34.8%	50.0%
Early termination without prior acute rejection*	13.9%	15.2%	10.2%
Biopsy-proven rejection episode on treatment	19.7%	15.9%	35.5%

Europe Study (n=491 patients)	CellCept 2 g/day (n=165 patients)	CellCept 3 g/day (n=160 patients)	Placebo (n=166 patients)
All treatment failures	30.3%	38.8%	58.0%
Early termination without prior acute rejection*	11.5%	22.5%	7.2%
Biopsy-proven rejection episode on treatment	17.0%	13.8%	46.4%

* Does not include death and graft loss as reason for early termination.

Cumulative incidence of twelve-month graft loss and patient death are presented below. No advantage of CellCept with respect to graft loss and patient death was established. Numerically, patients receiving CellCept 2 g/day and 3 g/day experienced a better outcome

than controls in all three studies; patients receiving CellCept 2 g/day experienced a better outcome than CellCept 3 g/day in two of the three studies. Patients in all treatment groups who terminated treatment early were found to have a poor outcome with respect to graft loss and patient death at one year.

Cumulative Incidence of Combined Graft Loss and Patient Death at 12 Months

Study	CellCept 2 g/day	CellCept 3 g/day	Control (Azathioprine or Placebo)
USA	8.5%	11.5%	12.2%
Europe/ Canada/ Australia	11.7%	11.0%	13.6%
Europe	8.5%	10.0%	11.5%

INDICATIONS AND USAGE

CellCept is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants. CellCept should be used concomitantly with cyclosporine and corticosteroids.

CONTRAINDICATIONS

Allergic reactions to CellCept have been observed; therefore, CellCept is contraindicated in patients with a hypersensitivity to mycophenolate mofetil, mycophenolic acid or any component of the drug product.

WARNINGS

(See boxed WARNING.)

Patients receiving immunosuppressive regimens involving combinations of drugs, including CellCept, as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. Oversuppression of the immune system can also increase susceptibility to infection. CellCept has been administered in combination with the following agents in clinical trials: antithymocyte globulin (ATGAM®), OKT3 (Orthoclone OKT® 3), cyclosporine (Sandimmune®), and corticosteroids. The efficacy and safety of the use of CellCept in combination with other immunosuppressive agents have not been determined.

Lymphoproliferative disease or lymphoma developed in patients receiving CellCept with other immunosuppressive agents in approximately 1% of patients in the controlled studies of prevention of rejection. (See ADVERSE REACTIONS.)

Adverse effects on fetal development (including malformations) occurred when pregnant rats and rabbits were dosed during organogenesis. These responses occurred at doses lower than those associated with maternal toxicity, and at doses below the recommended clinical dose. There are no adequate and well-controlled studies in pregnant women. However, as CellCept has been shown to have teratogenic effects in animals, it may cause fetal harm when administered to a pregnant woman. Therefore, CellCept should not be used in pregnant women unless the potential benefit justifies the potential risk to the fetus.

Women of childbearing potential should have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 1 week prior to beginning therapy. It is recommended that CellCept therapy should not be initiated by the physician until a report of a negative pregnancy test has been obtained.

Effective contraception must be used before beginning CellCept therapy, during therapy, and for 6 weeks following discontinuation of therapy, even where there has been a history of infertility, unless due to hysterectomy. Two reliable forms of contraception must be used simultaneously unless abstinence is the chosen method. If pregnancy does occur during treatment, the physician and patient should discuss the desirability of continuing the pregnancy. (See PRECAUTIONS: Pregnancy and Information for Patients.)

In the three controlled studies for prevention of rejection, similar rates of fatal infections/sepsis (<2%) occurred in patients while receiving CellCept or control therapy in combination with other immunosuppressive agents. (See ADVERSE REACTIONS.)

Up to 2.0% of patients receiving CellCept for prevention of rejection developed severe neutropenia [absolute neutrophil count (ANC) < 0.5 x $10^3/\mu L$]. (See ADVERSE REACTIONS.) Patients receiving CellCept should be monitored for neutropenia. (See PRECAUTIONS: Laboratory Tests.) The development of neutropenia may be related to CellCept itself, concomitant medications, viral infections, or some combination of these causes. If neutropenia develops (ANC <1.3 x $10^3/\mu L$), dosing with CellCept should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately. (See DOSAGE AND ADMINISTRATION.) Neutropenia has been observed most frequently in the period from 31 to 180 days post-transplant in patients treated for prevention of rejection.

PRECAUTIONS

General

Gastrointestinal tract hemorrhage has been observed in approximately 3% of patients treated with CellCept. Gastrointestinal tract perforations have rarely been observed. Most patients receiving CellCept were also receiving other drugs known to be associated with these complications. Patients with active peptic ulcer disease were excluded from enrollment in studies with mycophenolate mofetil. Because CellCept has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, hemorrhage, and perforation, CellCept should be administered with caution in patients with active serious digestive system disease.

Subjects with severe chronic renal impairment (GFR <25 mL/min/1.73 m^2) who have received single doses of CellCept showed higher plasma MPA and MPAG AUCs relative to subjects with lesser degrees of renal impairment or normal healthy volunteers. No data are available on the safety of long-term exposure to these levels of MPAG. Doses of CellCept greater than 1 g administered twice a day should be avoided and they should be carefully observed. (See CLINICAL PHARMACOLOGY: Pharmacokinetics and DOSAGE AND ADMINISTRATION.)

In patients with delayed graft function post-transplant, mean MPA AUC_{0-12} was comparable, but MPAG AUC_{0-12} was 2-3 fold higher, compared to that seen in post-transplant patients without delayed graft function. In the three controlled studies of prevention of rejection, there were 298 of 1,483 patients (20%) with delayed graft function. Although patients with delayed graft function have a higher incidence of certain adverse events (anemia, thrombocytopenia, hyperkalemia) than patients without delayed graft function, these events were not more frequent in patients receiving CellCept than azathioprine or placebo. No dose adjustment is recommended for these patients, however, they should be carefully observed. (See CLINICAL PHARMACOLOGY: Pharmacokinetics and DOSAGE AND ADMINISTRATION.)

It is recommended that CellCept not be administered concomitantly with azathioprine because such concomitant administration has not been studied clinically.

In view of the significant reduction in the AUC of MPA by cholestyramine, caution should be used in the concomitant administration of CellCept with drugs that interfere with enterohepatic recirculation because of the potential to reduce the efficacy of CellCept. (See PRECAUTIONS: Drug Interactions.)

Information for Patients

Patients should be informed of the need for repeated appropriate laboratory tests while they are receiving CellCept. Patients should be given complete dosage instructions and informed of the increased risk of lymphoproliferative disease and certain other malignancies. Women of childbearing potential should be instructed of the potential risks during pregnancy, and that they should use effective contraception before beginning CellCept therapy, during therapy and

for 6 weeks after CellCept has been stopped. (See WARNINGS and PRECAUTIONS: Pregnancy.)

Laboratory Tests

Complete blood counts should be performed weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year. (See WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION.)

Drug Interactions

Drug interaction studies with mycophenolate mofetil have been conducted with acyclovir, antacids, cholestyramine, cyclosporine, ganciclovir, oral contraceptives, and trimethoprim/sulfamethoxazole. Drug interaction studies have not been conducted with other drugs that may be commonly administered to renal transplant patients. CellCept has not been administered concomitantly with azathioprine.

acyclovir: Coadministration of mycophenolate mofetil (1 g) and acyclovir (800 mg) to twelve healthy volunteers resulted in no significant change in MPA AUC and Cmax. However, MPAG and acyclovir plasma AUCs were increased 10.6% and 21.9%, respectively. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are acyclovir concentrations, the potential exists for the two drugs to compete for tubular secretion further increasing the concentrations of both drugs.

antacids with magnesium and aluminum hydroxides: Absorption of a single dose of mycophenolate mofetil (2.0 g) was decreased when administered to ten rheumatoid arthritis patients also taking Maalox® TC (10 mL q.i.d.). The Cmax and AUC_{0-24} for MPA were 33% and 17% lower, respectively, than when mycophenolate mofetil was administered alone under fasting conditions. CellCept may be administered to patients who are also taking antacids containing magnesium and aluminum hydroxides; however, it is recommended that CellCept and the antacid not be administered simultaneously.

cholestyramine: Following single-dose administration of 1.5 g mycophenolate mofetil to twelve healthy volunteers pretreated with 4 g t.i.d. of cholestyramine for 4 days, MPA AUC decreased approximately 40%. This decrease is consistent with interruption of enterohepatic recirculation which may be due to binding of recirculating MPAG with cholestyramine in the intestine. CellCept is not recommended to be given with cholestyramine or other agents that may interfere with enterohepatic recirculation.

cyclosporine: Cyclosporine (Sandimmune®) pharmacokinetics (at doses of 275 to 415 mg/day) were unaffected by single and multiple doses of 1.5 g b.i.d. of mycophenolate mofetil in ten stable renal transplant patients. The mean (±SD) AUC_{0-12} and Cmax of cyclosporine after 14 days of multiple doses of mycophenolate mofetil were 3290 (±822) ng•h/mL and 753 (±161) ng/mL, respectively, compared to 3245 (±1088) ng•h/mL and 700 (±246) ng/mL, respectively, one week before administration of mycophenolate mofetil. The effect of cyclosporine on mycophenolate mofetil pharmacokinetics could not be evaluated in this study, however, the plasma concentrations of MPA were similar to that for healthy volunteers.

ganciclovir: Following single-dose administration to twelve stable renal transplant patients, no pharmacokinetic interaction was observed between mycophenolate mofetil (1.5 g) and IV ganciclovir (5 mg/kg). Mean (±SD) ganciclovir AUC and Cmax (n=10) were 54.3 (±19.0) µg•h/mL and 11.5 (±1.8) µg/mL, respectively after coadministration of the two drugs, compared to 51.0 (±17.0) µg•h/mL and 10.6 (±2.0) µg/mL, respectively after administration of IV ganciclovir alone. The mean (±SD) AUC and Cmax of MPA (n=12) after coadministration were 80.9 (±21.6) µg•h/mL and 27.8 (±13.9) µg/mL, respectively compared to values of 80.3 (±16.4) µg•h/mL and 30.9 (±11.2) µg/mL, respectively after administration of mycophenolate mofetil alone. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are ganciclovir concentrations, the potential exists for the two drugs to compete for tubular secretion and thus further increases in concentrations of both drug may occur.

oral contraceptives: Following single-dose administration to fifteen healthy women, no pharmacokinetic interaction was observed between mycophenolate mofetil (1.0 g) and two tablets of Ortho-Novum® 7/7/7 (1 mg norethindrone [NET] and 35 µg estradiol ethinyl [EE]).

This single-dose study suggests the lack of a gross pharmacokinetic interaction, but cannot exclude the possibility of changes in the pharmacokinetics of the oral contraceptive under long term dosing conditions with CellCept which might adversely affect the efficacy of the oral contraceptive.

trimethoprim/sulfamethoxazole: Following single dose administration of mycophenolate mofetil (1.5 g) to twelve healthy male volunteers on day 8 of a 10 day course of Bactrim® DS (trimethoprim 160 mg/sulfamethoxazole 800 mg) administered b.i.d., no effect on the bioavailability of MPA was observed. The mean (±SD) AUC and Cmax of MPA after concomitant administration were 75.2 (±19.8) µg•h/mL and 34.0 (±6.6) µg/mL, respectively compared to 79.2 (±27.9) and 34.2 (±10.7), respectively after administration of mycophenolate mofetil alone.

other interactions: The measured value for renal clearance of MPAG indicates removal occurs by renal tubular secretion as well as glomerular filtration. Consistent with this, coadministration of probenecid, a known inhibitor of tubular secretion, with mycophenolate mofetil in monkeys results in a 3-fold increase in plasma MPAG AUC and a 2-fold increase in plasma MPA AUC. Thus, other drugs known to undergo renal tubular secretion may compete with MPAG and thereby raise plasma concentrations of MPAG or the other drug undergoing tubular secretion.

Drugs that alter the gastrointestinal flora may interact with mycophenolate mofetil by disrupting enterohepatic recirculation. Interference of MPAG hydrolysis may lead to less MPA available for absorption.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week oral carcinogenicity study in mice, mycophenolate mofetil in daily doses up to 180 mg/kg was not tumorigenic. The highest dose tested was 0.5 times the recommended clinical dose (2 g/day) when corrected for differences in body surface area (BSA). In a 104-week oral carcinogenicity study in rats, mycophenolate mofetil in daily doses up to 15 mg/kg was not tumorigenic. The highest dose was 0.08 times the recommended clinical dose when corrected for BSA. While these animal doses were lower than those given to patients, they

were maximal in those species and were considered adequate to evaluate the potential for human risk. (See WARNINGS.)

Mycophenolate mofetil was not genotoxic, with or without metabolic activation, in several assays: the bacterial mutation assay, the yeast mitotic gene conversion assay, the mouse micronucleus aberration assay, or the Chinese hamster ovary cell (CHO) chromosomal aberration assay.

Mycophenolate mofetil had no effect on fertility of male rats at oral doses up to 20 mg/kg/day. This dose represents 0.1 times the recommended clinical dose when corrected for BSA. In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg/kg/day caused malformations (principally of the head and eyes) in the first generation offspring in the absence of maternal toxicity. This dose was 0.02 times the recommended clinical dose when corrected for BSA. No effects on fertility or reproductive parameters were evident in the dams or in the subsequent generation.

Pregnancy: Category C

In teratology studies in rats and rabbits, fetal resorptions and malformations occurred in rats at 6 mg/kg/day and in rabbits at 90 mg/kg/day, in the absence of maternal toxicity. These levels are equivalent to 0.03-0.92 times the recommended clinical dose on a BSA basis. In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg/kg/day caused malformations (principally of the head and eyes) in the first generation offspring in the absence of maternal toxicity. This dose was 0.02 times the recommended clinical dose when corrected for BSA.

There are no adequate and well-controlled studies in pregnant women. CellCept should not be used in pregnant women unless the potential benefit justifies the potential risk to the fetus. Effective contraception must be used before beginning CellCept therapy, during therapy and for 6 weeks after CellCept has been stopped. (See WARNINGS, PRECAUTIONS: Information for Patients.)

Nursing Mothers

Studies in rats treated with mycophenolate mofetil have shown mycophenolic acid to be excreted in milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from mycophenolate mofetil, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Patients

Safety and effectiveness in pediatric patients have not been established. Very limited pharmacokinetic data are available in pediatric patients. (See CLINICAL PHARMACOLOGY: Pharmacokinetics.)

ADVERSE REACTIONS

The principal adverse reactions associated with the administration of CellCept include diarrhea, leukopenia, sepsis and vomiting, and there is evidence of a higher frequency of certain types of infections.

The incidence of adverse events for CellCept was determined in three randomized comparative double-blind trials in prevention of rejection in renal transplant patients. Because of the lower overall reporting of events in the European placebo-controlled, prevention of rejection study, these data were not combined with the other two active-controlled prevention trials, but are instead presented separately.

Safety data are summarized below for all patients in the double-blind prevention studies while receiving treatment; approximately 53% of these patients have been treated for more than 1 year. Adverse events that were reported in ≥10% of patients in either CellCept treatment group are presented below for the two active-controlled studies combined (USA and Europe/Canada/Australia) and for the one European placebo-controlled study. Opportunistic infections are summarized separately.

Adverse Events in Prevention of Renal Allograft Rejection

USA Study Combined with Europe/Canada/Australia Study

	CellCept 2 g/day (n=336)	CellCept 3 g/day (n=330)	Azathioprine 1-2 mg/kg/day or 100-150 mg/day (n=326)
Body as a Whole			
Pain	33.0%	31.2%	32.2%
Abdominal pain	24.7	27.6	23.0
Fever	21.4	23.3	23.3
Headache	21.1	16.1	21.2
Infection	18.2	20.9	19.9
Sepsis	17.6	19.7	15.6
Asthenia	13.7	16.1	19.9
Chest pain	13.4	13.3	14.7
Back pain	11.6	12.1	14.1
Hemic and Lymphatic			
Anemia	25.6	25.8	23.6
Leukopenia	23.2	34.5	24.8
Thrombocytopenia	10.1	8.2	13.2
Hypochromic anemia	7.4	11.5	9.2
Leukocytosis	7.1	10.9	7.4
Urogenital			
Urinary tract infection	37.2	37.0	33.7
Hematuria	14.0	12.1	11.3
Kidney tubular necrosis	6.3	10.0	5.8
Cardiovascular			
Hypertension	32.4	28.2	33.2
Metabolic and Nutritional			
Peripheral edema	28.6	27.0	28.2
Hypercholesteremia	12.8	8.5	11.3
Hypophosphatemia	12.5	15.8	11.7
Edema	12.2	11.8	13.5
Hypokalemia	10.1	10.0	8.3
Hyperkalemia	8.9	10.3	16.9
Hyperglycemia	8.6	12.4	15.0
Digestive			
Diarrhea	31.0	36.1	20.9
Constipation	22.9	18.5	22.4
Nausea	19.9	23.6	24.5
Dyspepsia	17.6	13.6	13.8
Vomiting	12.5	13.6	9.2
Nausea and vomiting	10.4	9.7	10.7
Oral moniliasis	10.1	12.1	11.3

		USA Study Combined with Europe/Canada/Australia Study		
		CellCept 2 g/day (n=336)	CellCept 3 g/day (n=330)	Azathioprine 1-2 mg/kg/day or 100-150 mg/day (n=326)
	Respiratory			
	Infection	22.0%	23.9%	19.6%
	Dyspnea	15.5	17.3	16.6
	Cough increased	15.5	13.3	15.0
	Pharyngitis	9.5	11.2	3.0
	Skin and Appendages			
	Acne	10.1	9.7	6.4
	Rash	7.7	6.4	10.4
	Nervous System			
	Tremor	11.0	11.8	12.3
	Insomnia	8.9	11.8	10.4
	Dizziness	5.7	11.2	11.0
		Europe Study		
		CellCept 2 g/day (n=165)	CellCept 3 g/day (n=160)	Placebo (n=166)
	Body as a Whole			
	Sepsis	21.8%	17.5%	13.9%
	Infection	12.7	15.6	13.3
	Abdominal pain	12.1	11.9	11.4
	Hemic and Lymphatic			
	Leukopenia	11.5	16.3	4.2
	Urogenital			
	Urinary tract infection	45.5	44.4	37.3
	Urinary tract disorder	6.7	10.6	4.2
	Cardiovascular			
	Hypertension	17.6	16.9	19.3
	Digestive			
	Diarrhea	16.4	18.8	13.9
	Respiratory			
	Infection	15.8	13.1	9.0
	Bronchitis	8.5	11.9	8.4
	Pneumonia	3.6	10.6	10.8

The above data demonstrate that in three controlled trials for prevention of rejection, patients receiving 2 g per day of CellCept had an overall better safety profile than did patients receiving 3 g per day of CellCept. Sepsis, which was generally CMV viremia, was slightly more common in patients treated with CellCept, with an incidence of 18-22%, compared to 16% in patients receiving azathioprine and 14% in patients receiving placebo. In the digestive system, diarrhea was most clearly increased in patients receiving CellCept, with an incidence of up 36%, compared to 21% for patients receiving azathioprine and 14% for patients receiving placebo.

The incidence of malignancies among the 1,483 patients enrolled in controlled trials for the prevention of rejection who were followed for ≥1 year was similar to the incidence reported in the literature for renal allograft recipients. There was a slight increase in the incidence of lymphoproliferative disease in the CellCept treatment groups compared to the placebo and azathioprine groups. (See WARNINGS.) The following table summarizes the incidence of malignancies observed in the prevention of rejection trials.

Malignancies Observed in Prevention of Renal Rejection Trials

	CellCept 2 g/day (n=501)	CellCept 3 g/day (n=490)	Placebo (n=166)	Azathioprine 1-2 mg/kg/day or 100-150 mg/day (n=326)
Lymphoma/lympho-proliferative disease	0.6%	1.0%	0.0%	0.3%
Non-melanoma skin carcinoma	4.0	1.6	0.0	2.4
Other malignancy	0.8	1.4	1.8	1.8

Up to 2.0% of patients receiving CellCept for prevention of rejection have developed severe neutropenia [absolute neutrophil count (ANC) < 0.5 x $10^3/\mu L$]. (See WARNINGS, PRECAUTIONS: Laboratory Tests, and DOSAGE AND ADMINISTRATION.)

The following tables show the incidence of opportunistic infections that occurred in the transplant population in the prevention of rejection trials:

Opportunistic Infections in Prevention of Renal Rejection Trials

USA Study Combined with Europe/Canada/Australia Study

	CellCept 2 g/day (n=336)	CellCept 3 g/day (n=330)	Azathioprine 1-2 mg/kg/day or 100-150 mg/day (n=326)
Herpes simplex	16.7%	20.0%	19.0%
CMV			
viremia/syndrome	13.4	12.4	13.8
tissue invasive disease	8.3	11.5	6.1
Herpes zoster	6.0	7.6	5.8
Candida			
fungemia/disseminated	0.6	0.6	0.3
tissue invasive	0.6	0.6	0.3
Aspergillus/Mucor invasive disease	0.3	0.9	0.3
Pneumocystis carinii	0.3	0.0	1.2

Europe Study

	CellCept 2 g/day (n=165)	CellCept 3 g/day (n=160)	Placebo (n=166)
Herpes simplex	15.2%	12.5%	6.0%
CMV			
viremia/syndrome	15.2	15.0	13.3
tissue invasive disease	3.6	7.5	2.4
Herpes zoster	6.7	6.9	2.4
Candida			
fungemia/disseminated	0.0	0.6	0.0
tissue invasive	0.0	0.6	0.0
Pneumocystis carinii	0.0		2.4

In the three controlled studies for prevention of rejection, similar rates of fatal infections/sepsis (<2%) occurred in patients while receiving CellCept or control therapy in combination with other immunosuppressive agents. (See WARNINGS.)

The following adverse events, not mentioned in any of the tables above, were reported with ≥3% incidence in patients treated with CellCept: BODY AS A WHOLE: abdomen enlarged, accidental injury, chills and fever, cyst, face edema, flu syndrome, hemorrhage, hernia, malaise, pelvic pain; HEMIC AND LYMPHATIC: ecchymosis, polycythemia; UROGENITAL: albuminuria, dysuria, hydronephrosis, impotence, pain, pyelonephritis, urinary frequency, urinary tract disorder; CARDIOVASCULAR: angina pectoris, atrial fibrillation, cardiovascular disorder, hypotension, palpitation, peripheral vascular disorder, postural hypotension, tachycardia, thrombosis, vasodilatation; METABOLIC AND NUTRITIONAL: acidosis, alkaline phosphatase increased, creatinine increased, dehydration, gamma glutamyl transpeptidase increased, hypercalcemia, hyperlipemia, hyperuricemia, hypervolemia, hypocalcemia, hypoglycemia, hypoproteinemia, lactic dehydrogenase increased, SGOT increased, SGPT increased, weight gain; DIGESTIVE: anorexia, esophagitis, flatulence, gastritis, gastroenteritis, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, gum hyperplasia, hepatitis, ileus, infection, liver function tests abnormal, mouth ulceration, rectal disorder; RESPIRATORY: asthma, lung disorder, lung edema, pleural effusion, rhinitis, sinusitis; SKIN AND APPENDAGES: alopecia, fungal dermatitis, hirsutism, pruritis, skin benign neoplasm, skin disorder, skin hypertrophy, skin ulcer, sweating; NERVOUS: anxiety, depression, hypertonia, paresthesia, somnolence; ENDOCRINE: diabetes mellitus, parathyroid disorder; MUSCULO-SKELETAL: arthralgia, joint disorder, leg cramps, myalgia, myasthenia; SPECIAL SENSES: amblyopia, cataract (not specified), conjunctivitis.

OVERDOSAGE

There has been no reported experience of overdosage of mycophenolate mofetil in humans. The highest dose administered to renal transplant patients has been 4 g per day. In limited experience with cardiac and hepatic transplant patients, the highest doses used were 4 g or 5 g per day. At doses of 4 g or 5 g per day, there appears to be a higher rate, compared to the use of 3 g per day or less, of gastrointestinal intolerance (nausea, vomiting, and/or diarrhea).

and occasional hematologic abnormalities, principally neutropenia, leading to a need to reduce or discontinue dosing.

In acute oral toxicity studies, no deaths occurred in adult mice at doses up to 4000 mg/kg or in adult monkeys at doses up to 1000 mg/kg; these were the highest doses of mycophenolate mofetil tested in these species. These doses represent 11 times the recommended clinical dose when corrected for BSA. In adult rats, deaths occurred after single oral doses of 500 mg/kg of mycophenolate mofetil. The dose represents approximately 3 times the recommended clinical dose when corrected for BSA.

MPA and MPAG are usually not removed by hemodialysis. However, at high MPAG plasma concentrations (>100 µg/mL), small amounts of MPAG are removed. By increasing excretion of the drug, MPA can be removed by bile acid sequestrants, such as cholestyramine.

DOSAGE AND ADMINISTRATION

The initial dose of CellCept should be given within 72 hours following transplantation. A dose of 1.0 g administered twice a day (daily dose of 2 g) is recommended for use in combination with corticosteroids and cyclosporine in renal transplant patients. Although a dose of 1.5 g administered twice daily (daily dose of 3 g) was used in clinical trials and was shown to be safe and effective, no efficacy advantage could be established. Patients receiving 2 g per day of CellCept demonstrated an overall better safety profile than did patients receiving 3 g per day of CellCept. Food had no effect on MPA AUC, but has been shown to decrease MPA Cmax by 40%. It is recommended that CellCept be administered on an empty stomach.

Dosage Adjustments

In patients with severe chronic renal impairment (GFR <25 mL/min/1.73m^2) outside of the immediate post-transplant period, doses of CellCept greater than 1 g administered twice a day should be avoided. These patients should also be carefully observed. No dose adjustments are needed in patients experiencing delayed graft function post-operatively. (See CLINICAL PHARMACOLOGY: Pharmacokinetics and PRECAUTIONS: General.)

If neutropenia develops (ANC <1.3 x $10^3/\mu L$), dosing with CellCept should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately. (See WARNINGS, ADVERSE REACTIONS, and PRECAUTIONS: Laboratory Tests.)

HANDLING AND DISPOSAL

Because mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits, CellCept capsules should not be opened or crushed. Avoid inhalation or direct contact with skin or mucous membranes of the powder contained in CellCept capsules. If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water.

HOW SUPPLIED

CellCept capsules are blue/brown, two-piece hard gelatin capsules, printed in black with "CellCept 250" on the blue cap and "Roche" on the brown body. Supplied in the following presentations:

NDC Number	Size
NDC 0033-2920-42	Bottle of 100
NDC 0033-2920-62	Bottle of 500
NDC 0033-2920-53	Unit of dose; 10 count blister pack
	Box of 100 (package of 10 packs)

Storage

Store at 15 - 30° C (59 - 86° F).

CAUTION:

Federal (USA) law prohibits dispensing without a prescription.

Manufactured by Syntex Puerto Rico, Inc.
Humacao, Puerto Rico 00791
for Hoffmann-La Roche Inc., Nutley, New Jersey 07110-1199

 APRIL 1995

EXCLUSIVITY SUMMARY FOR NDA # 50722 SUPPL #_____

Trade Name CellCept Generic Name mycophenolate mofetil

Applicant Name Syntex (Roche) HFD # 530

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /X/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /___/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /___/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /X/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

FIVE (5)

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use?

YES /___/ NO /X/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion?

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

Signature
Title: Project Manager

4-5-95
Date

Signature of
Division Director

4.22.95
Date

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

Date: April 20, 1995

To: David W. Feigal, M.D., M.P.H.
Acting Deputy, Office of Drug Evaluation II

From: Donna J. Freeman, M.D.
Deputy Director, Division of Antiviral Drug Products

Subject: NDA 50-722
CellCept (Mycophenolate Mofetil)
Syntex Laboratories, Inc.

This memorandum accompanies the reviews and related materials for NDAs 50-722 for CellCept (Mycophenolate mofetil) 250 mg capsule I concur with the consensus of the reviewers that NDA 50-722, the capsule formulation, should be approved for the indication of prophylaxis of organ rejection in patients receiving allogeneic renal transplants, to be used concomitantly with cyclosporine and corticosteroids.

The IND for mycophenolate mofetil was transferred from the Oncology group, HFD-150, to the Division of Antiviral Drug Products in February, 1992. The NDA applications were submitted November 11, 1994, and were considered acceptable for filing following a review team meeting on January 1, 1995. The Transplantation Subcommittee of the Antivirals Advisory Committee met on March 30, 1995, and recommended approval for the indication noted above. Several issues arose during the review of these applications and are summarized below.

For the field of transplantation medicine in general, CellCept represents a notable advance in that it is an effective immunosuppressive agent that does not have significant concomitant nephrotoxicity, an adverse side effect that complicates the use of other agents. In addition, Syntex has succeeded in conducting three double-blind, controlled trials, one of them placebo-controlled, to generate the data needed to support this application. Follow up for patient and graft survival out to 12 months was obtained on all patients in these protocols. This is a notable accomplishment in the field of transplantation and therapeutic immunosuppression. Many sponsors have claimed that blinded, controlled studies simply could not be done, but Syntex has demonstrated that such high quality studies can be completed and has set a standard in the field for other sponsors to emulate. Finally, the principle that information on 12 month patient and graft survival is critical for evaluation of immunosuppressive therapies has been supported in the review of this product and in the discussion of the Advisory Committee. While the primary efficacy endpoint of assessing the incidence of acute rejection in the six month period following transplantation was acceptable, the full 12 month data was required as a safety consideration.

Several issues await further resolution in proposed phase 4 post-marketing studies. These include determining whether there are advantages, particularly in some populations, to initiating treatment at a higher dose then reducing the dose for maintenance therapy. Further information is also needed on use in pediatric populations, as well as in black populations.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Antiviral Drug Products

DATE:Mon, Apr 17, 1995

301-443-9560 (phone)
301-443-9292 (fax)

TO: Donna Freeman MD

FROM: Mark J Goldberger MD MPH MJG

SUBJECT: NDA 50-722 and _ CellCept Capsules

The major issues with the two NDAs submitted for CellCept brand of Mycophenolate mofetil (MMF) have been well described in the pre-clinical reviews and the combined medical statistical review. There are a few areas which may deserve additional comment:

Prevention of Rejection

There is agreement that the three adequate and well-controlled studies submitted by Syntex have met the statutory requirement for safety and efficacy. Although Syntex has requested that their product labeling include a recommendation for both MMF doses studied we do not believe that they have identified a group who would benefit from the three gram dose. We believe that given the low drug levels observed in the immediate post transplant an appropriate phase IV study would be a treatment strategy approach allowing subjects to begin at three grams with subsequent dose reduction. One of the three clinical trials enrolled a meaningful number of black patients. In that trial there was suggestive evidence that drug levels are lower in this patient group and failures higher. This must be explored in phase IV studies.

The clinical trials for prevention of rejection used a six month endpoint based on proportion of patients who experienced a biopsy proven rejection. Due to a lack of follow-up data on patients who discontinued study drug prematurely, a treatment failure endpoint which included AEs and other events was also used. The use of this endpoint did not change the overall conclusions of the study but this issue needs to be kept in mind in light of the lower observed rate of acute rejections in

the three vs. the two gram dose of MMF, premature discontinuation rates were higher in the former (see the combined medical-statistical review for a discussion of this point). The importance of the six month acute rejection endpoint derives from other data in which rejections within the first six months after transplant predicted the risk of death and graft loss at one year and beyond. Analyses performed by both the FDA and the applicant confirmed such a relationship in these trials although the relationship appeared weaker in the FDA analyses. This issue will need to be addressed by longer term follow of patients from these trials as well as in future studies for this indication.

Alternative Dosing Form

The applicant conducted all their clinical trials with the capsule formulation.

cc:
HFD-530:
Original NDA
Division File
Deputy Director/Freeman
Chem/Boring
Micro/O'Hanian

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # Trade (generic) names CellCept (mycophenolate mofetil) Capsules

Check any of the following that apply and explain, as necessary, on the next page:

___ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

___ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(C) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

___ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

___ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate).

_X_ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children.

_X_ a. The applicant has committed to doing such studies as will be required.

_X_ (1) Studies are ongoing.
___ (2) Protocols have been submitted and approved.
___ (3) Protocols have been submitted and are under review.
___ (4) If no protocol has been submitted, on the next page explain the status of discussions.

___ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

___ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

Syntex, the sponsor, submitted protocol ID 2190, entitled "An Open-Label, Dose-Ranging Pharmacokinetics, Safety, and Tolerance Study of IV Followed by Oral Mycophenolate Mofetil in the Prevention of Rejection in Pediatric Renal and Hepatic Allograft Recipients," on February 22, 1994. The ongoing study includes an I.V. and oral dosage form which can be utilized by pediatric patients. Preliminary data from this study is summarized in the Pediatric subsection of the Pharmacokinetics subsection of the CLINICAL PHARMACOLOGY section of the label. This limited information is following multiple doses of mycophenolate mofetil (on day 21 post-transplant). A phase IV recommendation is to conduct studies in pediatric populations.

Signature of Preparer

4-13-95
Date

cc: Orig NDA
HFD-530/Div File
NDA Action Package

DRAFT.

Apr 28, 1995

MYCOPHENOLATE MOFETIL (CELLCEPT®)

Joint Biostatistical/Medical Review

(NDA #50,722

1 MYCOPHENOLATE MOFETIL (CELLCEPT®)

1.1 Joint Medical/Biostatistical Review

1.1.1 NDA # 50,722;

1.1.2 Submitted: November 9, 1994

1.1.3 Review Completed: April 14, 1995

1.2 Drug Name:

1.2.1 Generic name: Mycophenolate mofetil

1.2.2 Proposed trade name: CellCept ®

1.2.3 Chemical name: 2-(4-morpholino)ethyl-(E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate

1.3 Sponsor: Syntex Laboratories, Inc.

1.4 Pharmacologic Category: Antibiotic

1.5 Proposed Indications: Prevention of acute rejection in renal allograft recipients

1.6 Dosage Form and Route of Administration:

NDA # 50,722: CellCept® Capsules (250 mg) Oral Route

1.7 Related Drugs: New Molecular Entity

1.8 Related Reviews: Clinical Pharmacology and Biopharmaceuticals, Chemistry Manufacturing and Controls, Preclinical Pharmacology and Toxicology.

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3 MATERIAL REVIEWED:

3.1 Prophylaxis Indication:

Overview: vols 1.2, 1.3

Protocols and amendments: vols 1.462, 1.497, 1.552

Efficacy Review: a) vols

b) SAS files supplied by the company which included data related to the primary efficacy endpoint.

Safety Review:

a) vols: 1.460-1.463; 1.495-1.49[illegible]; 1.550-1.551; 1.808-1.813.
b) 1 year patient and graft survival: vol 1 (12/15/94)
c) Deaths Summaries: reviewed for all patients.
d) 1 year safety update: vols 7/56-10/56 (2/6/95)
e) Pediatric safety: vol 2/56 (2/6/95)
f) Backgrounder/Slides for advisory committee: vol 1 and 2 (3/20/95)
g) GI safety update: vol 1 (3/21/95)
h) CANDA was utilized extensively in the safety review, especially regarding the optically scanned CRFs of the patients who died or discontinued treatment due to an adverse event.
i) Biopsy results: audited 20% of CRFs from each site of the patients who were biopsied, this included requested CRFs vol 1-25 (3/10/95) and vol 1-10 (3/14/95) in addition to the CRFs available in the CANDA.

3.2 Treatment Indication:

Protocols and amendments: Study 1868: vols 1.629-1.639
Open-label extension (ICM 1880): vols 1.640-1.643.

NDA amendments (requested information):

a) Procedures for review of biopsy slides: vol 1 (12/23/94); clarification (2/13/95).
b) Additional CRFs: vols 1-18 (1/25/95); vols 1-2 (1/25/95)
c) Safety update (2/6/95)
d) Revised study report: TABLE 11 (2/11/95)
e) Revised analysis: vols 1-2 (3//6/95)
f) Forty-five CRFs (30%) were reviewed in entirety; follow-up forms only were reviewed for an additional 8 patients. Case report forms for all deaths were reviewed. CRFs were reviewed for 28/29 patients listed as reaching a primary endpoint (graft/death) and for 40/43 patients listed as discontinuing from study prematurely (< 183 days). Note that the above patients classifications are not mutually exclusive.

4 **Chemistry, Manufacturing and Controls:**
Primary Reviewer: D. Boring, Ph D.

The NDA submission is incomplete but approvable pending satisfactory resolution of issues regarding specifications for the drug substance and production, and label. The Puerto Rico manufacturing site inspection is still pending. The Environmental Impact Review is still pending. For further details see Chemistry and Manufacturing primary review.

5 **Pre-Clinical Animal Pharmacology and Toxicology:**
Primary Reviewer: L Black, Ph D.

Extensive animal efficacy, toxicity, and pharmacokinetic studies were undertaken with mycophenolate mofetil. The principal animal models were the rat and cynomolgus monkey. Critical findings from these studies indicate that mycophenolate mofetil was not genotoxic or carcinogenic, and is potentially teratogenic when dosed during organogenesis. Mycophenolate mofetil was detected in the milk of lactating rats, and may be of potential concern in the choice to breast-feed. For further details see Pharmacology/Toxicology primary review.

6 **Clinical Background** (Reworking this section)

Mycophenolate mofetil (MMF, CellCept ®), the morpholinoethyl ester of mycophenolic acid (MPA), is rapidly and extensively absorbed following oral administration and is hydrolyzed to form free MPA, the active moiety. MPA is a potent and specific inhibitor of *de novo* purine biosynthesis (through inhibition of inosine monophosphate dehydrogenase), and consequently blocks the proliferation of both T and B lymphocytes. Additionally, MMF inhibits antibody formation and prevents the glycosylation of certain adhesion molecules. This mechanism of action, coupled with the demonstrated efficacy of MMF in several animal models of transplantation, provides the rationale for investigating the use of MMF as an immunosuppressive agent in renal transplantation.

The efficacy of MMF as adjunctive therapy for the prevention of acute rejection in renal allograft recipients and as adjunctive therapy for the treatment of refractory acute rejection in renal allograft recipients was evaluated in four clinical trials.

6.1 Relevant Human Experience

Approximately 9,000 renal transplants are performed each year in Europe and a similar number in North America. With the currently available immunosuppressive regimens 1-year allogenic graft survival is 80-90%. Long-term graft survival is lower, with 3-year graft survival of about 60-70%[1]. There is no consensus as to the optimal immunosuppressive regimen following renal transplantation. A variety of programs give acceptable benefit and minimize the risks of immunosuppression. Therapy with cyclosporine, corticosteroids, and azathioprine in various combinations are the most common regimens. Quadruple or sequential therapy which includes monoclonal or polyclonal antibodies are also employed. No single regimen has been shown to be optimal for all patients.

The present immunosuppressive regimens can be accompanied by serious morbidity: azathioprine is associated with neutropenia, cyclosporine is associated with nephro-toxicity, and infections and malignancies are associated with all immunosuppressive programs.

Despite the variety of immunosuppressive regimens used, up to 60% of patients still experience at least one episode of acute rejection in the first six months following transplantation. This necessitates additional immunosuppression and increases the risk of associated morbidity. Graft survival diminishes over time with only 60-70% survival at 3 years no matter which combination of immunosuppressive agents is employed.

MMF is being evaluated for use following other solid-organ transplantation and was being evaluated for the treatment of rheumatoid arthritis.

ICM 1753 was a dose-ranging pharmacokinetic study in renal allograft recipients. In ICM 1753, 6 patients each (in dose groups ranging from 100 mg once per day to 1750 mg twice daily [bid]), received MMF along with cyclosporine and corticosteroids for 4 months. In the 2000, 3000 and 3500 mg/day dose groups, the incidence of acute rejection was decreased to 17% during the 4 months of the study, compared to an incidence of 60% in the lowest 3 dose-groups (100 mg, 250 mg and 500 mg once daily (od)). MMF was stopped in 2 patients because of severe adverse events: 1 due to acute erosive gastritis, and 1 due to post-operative acute tubular necrosis persisting until Day 14 of the study.

ICM 1754 is an open study of the treatment of mild acute rejection and the prevention of acute rejection episodes during corticosteroid withdrawal in cardiac allograft recipients. In ICM 1754, 6-9 patients each received MMF (in dose groups ranging from 500 mg to 3000 mg/day), along with cyclosporine and corticosteroids for treatment of mild, grade 3, acute cellular rejection for 56 days. Two patients had severe adverse events: 1 patient in the 2000 mg group had CMV colitis and 1 patient in the 500 mg group had CMV retinitis. A third patient in the 1000 mg group had nausea possibly attributed to the drug, which resolved when the dose was decreased to 500 mg/day.

ICM 1812 was an open study of the treatment of renal, cardiac or hepatic allograft recipients with refractory, acute, cellular rejection, unresponsive to corticosteroids and OKT$_3$ or ALG. In ICM 1812, patients received 2000 to 3000 mg/day of MMF. The number of solid-organ allograft recipients that are evaluable to date, who have achieved complete or partial resolution of rejection, are as follows: 12 of 16 renal, 9 of 13 hepatic and 4 of 4 cardiac.

ICM 1803 is a study of the safety, tolerance and efficacy of 1 year therapy with MMF in solid organ allograft recipients (heart, kidney and liver). Prior to enrollment patients in ICM 1803 had received MMF in one of the aforementioned studies. Eighty-four patients have been enrolled in ICM 1803, the 1 year follow-on study, at doses ranging from 250 mg to 3500 mg/day. Two cardiac allograft recipients were discontinued from the study when they developed Grade 4 rejection. One additional patient had a dose interruption due to severe neutropenia. Neutropenia did not recur upon rechallenge with MMF,

and may have been related to MMF or to a concomitant medication.

Preliminary data from the above mentioned clinical studies suggested that MMF was both safe and well tolerated in transplant recipients.

Two further studies examining the efficac of MMF in treating acute cellular rejection in renal transplant patients are ongoing in the US and Europe. ICM 1912, the US study compares conventional triple therapy (cyclosporine, corticosteroids and azathioprine) to cyclosporine, corticosteroids and MMF in addition to IV corticosteroids in patients experiencing their first acute cellular rejection episode. The European study MYC021, a placebo controlled study, compares the addition of MMF to dual therapy for the same indication.

6.2 **Important Information from related INDs and NDAs:** The data presented in this NDA was collected under the following IND numbers:

6.3 **Foreign Experience:** This drug is not licensed or approved in any other country.

6.4 **Human Pharmacology, pharmacokinetics, pharmacodynamics:**

Mycophenolate mofetil, is rapidly absorbed following oral administration and is hydrolyzed to form Mycophenolic acid, which is the active metabolite. MMF undergoes complete presystemic metabolism to MPA. MMF is not measurable systemically in plasma following oral administration.

The mean MPA AUC following 1 g bid and 1.5 g bid dose were 33.6 and 45.0 respectively. The mean apparent volume of distribution of MPA is 3.6 and 4.0 L/Kg following IV and oral administration, respectively. MPA, at clinically relevant concentrations, is 97% bound to plasma albumin. MPAG (Mycophenolic phenolic acid glucuronide) is 82% bound to plasma albumin at MPAG concentration ranges that are normally seen in stable renal transplant patients; however, at higher concentration of MPAG, such as those seen in patients with delayed graft function or with severe renal insufficiency, the bound fraction in vitro decreases to 62%. Increased plasma levels of MMF metabolites (MPA 50% increase and MPAG about 3-6 fold increase) are observed in patients with renal insufficiency. As a result of enterohepatic recirculation, secondary increases in plasma MPA concentrations are usually observed at approximately 6-12 hours post-dose. A reduction in the AUC of MPA of approximately 40% is associated with the co-administration of MMF and cholestyramine (4 g tid), suggesting that there is a significant amount of enterohepatic recirculation.

Excretion: Negligible amounts of drug are excreted as MPA (< 1% of dose) in the urine. Orally-administered radiolabled MMF resulted in complete recovery of the administered dose, with 93% of the

administered dose recovered in the urine and 6% recovered in the feces. Most (about 85%) of the administered dose is excreted in the urine as MPAG. MPA and MPAG are usually not removed by hemodialysis. However, at high MPAG plasma concentrations, small amounts of MPAG are removed. Mean apparent half-life and plasma clearance of MPA are 17.9 hours and 193 mL/min following oral administration and 16.6 hours and 11.7 mL/min following IV administration, respectively.

Studies were performed in healthy volunteers and renal transplant patients. In general, the renal transplantation patients had a somewhat lower AUC and C_{max} than did healthy volunteers. This was most notable in the first 14 days post-transplant, and this has implications for the clinical dosing of patients. This has not been studied to date.
For more detailed information on the Pharmacodynamics of MMF refer to the Biopharmaceutics review.

7 Description of Clinical Data Sources:

The sponsor supplied data for the NDA via hard paper copy, SAS data base for the efficacy data, and a CANDA. In addition to the line listings provided in the hard copy, the safety data for Studies 022, 1866, and 023 was provided in a stand-alone computer (CANDA) which included optically scanned CRFs for patients who died or terminated the study early due to adverse events.

8 Clinical Studies

In NDA 50,722 the applicant requests an indication of mycophenolate mofetil (MMF, CellCept®) for prophylaxis against acute rejection of allogenic (cadaveric) renal grafts
Three pivotal studies are provided to support the first indication (MRE 022, ICM 1866, IICR 023),

There were no clinical efficacy studies performed with
This review will focus on NDA 50,722 with an addendum regarding NDA
More details regarding can be found in the Chemistry, Manufacturing and Controls and Biopharmaceutical Reviews.

8.1 Prophylaxis of acute rejection of renal allograft (Indication #1)

8.1.1 **Overview of Study Designs:** The following section describes the common design features as well as unique design features of each study. All three studies used a basic regimen of the combination of cyclosporine and corticosteroids. Additional adjunctive therapy was determined by randomization assignment. Subjects were randomized in a 1:1:1 ratio to either a control arm or one of two doses of MMF (1.0 g bid or 1.5 g bid). The control arm for studies ICM 1866 and IICR 023 consisted of AZA (Azathioprine), while the control arm for study MRE 022 used placebo. In study ICM 1866 subjects received 1-2 mg/kg/day of AZA (dosing in accordance with each center's standard regimen), while in study IICR 023 subjects received AZA 100-150 mg/day. Each study used a double-blind, parallel-group design. The distinguishing

characteristics of each study are listed below

MRE 022: This study was conducted exclusively in Europe. It enrolled 1st-time or 2nd-time renal allograft recipients. Control arm was Placebo plus steroids and cyclosporine. (volume 1.462)

ICM 1866: This study was performed in the United States. It enrolled 1st-time renal allograft recipients only. The control arm was Azathioprine 1-2 mg/kg/day plus cyclosporine and prednisone. This was the only study to permit ATG induction (volume 1.497)

IICR 023: This study was performed in Canada, Europe and Australia. It enrolled 1st-time or 2nd-time renal allograft recipients. The control arm was Azathioprine 100-150 mg/day plus cyclosporine and prednisone. (volume 1.552).

8.1.2 **Study Amendments:**

8.1.2.1 **Study MRE 022:** This study was initiated in July of 1992 and has been amended on three occasions. February 8, 1993, July 7 1993 and December 14, 1994. The substance of the amendments are as follows:

Amendment #1 allowed for the unblinding of MRE 022 when all patients had completed the study and all data were received by Syntex; offered long-term follow-up into study MRE 018; included Pk sampling at week 12 and at times of rejection episodes and serious events; clarifies the evaluation of lab values of clinical significance in renal transplant patients; allowed informed consent either prior to or soon after transplantation; allowed an interim check on rejection rate in the placebo group only.

Amendment #2 allowed for an additional 40 patients to be randomized based on the lower than expected event rate; cancelled the interim check on rejection rates in the placebo group; updated the Banff schema (including the collection of biopsy slides for the central review); provided the standard final report section; included pharmacokinetic sample labelling details.

Amendment #3 provided for changes in the sign-off procedure for the final report; clarified the publication strategy.

8.1.2.2 **Study ICM 1866** This study was initiated in July of 1992. During the conduct of this study, 5 amendments were made on the following dates: July 8, 1992; October 2, 1992; May 17, 1993; October 27, 1993; May 2, 1994.

Amendment #1: This amendment required that a minimum of 80% compliance with dosing of study drug be required, and that an interim analysis be made after 1/3 or approximately 120 patients were followed for 3 months. The stated purpose of this interim analysis would be to determine if the rate of rejection in the azathioprine group is substantially less than the anticipated 60% rate. Syntex might then amend the protocol and increase the sample size to maintain adequate statistical power. This amendment also provided a pharmacokinetic study would be performed on up to 60 patients enrolled in this study.

Amendment #2: This amendment allowed for the use of Antithymocyte Globulin to be administered beginning on the first post-operative day for a minimum of 5 days and for up to 14 days. This would be in accordance with the standard of care at each center. Some guidelines for dose adjusting were given. This amendment also stated that the analyses of primary and secondary efficacy variables would be prepared using the data arising from all patients enrolled on or after date of the amendment requiring administration of ATG for induction. Supplemental analysis would be prepared for two outcomes using all patients regardless of date of enrollment. These two outcomes were proposed as 1.) the proportion of patients experiencing one or more acute rejections and graft, and 2.) patient survival. Analysis on safety would be performed on all patients receiving study drug.

Amendment #3: Adverse event reporting was changed to define an adverse event as an abnormal change in physical signs, symptoms, or laboratory test values occurring in a clinical trial whether or not deemed to be causally associated with the study medication. The Banff schema was updated. Statistical assumptions were further clarified. The sample size was increased to approximately 160 patients randomized to each group for a total of approximately 480 patients.

Amendment #4: Updated the protocol on teratogenic effects of mycophenolate mofetil in rats and rabbits, and provided data on the effects upon a child born during the conduct of the trial.

Amendment #5: Clarified proposed analysis such that once the last patient had reached the primary efficacy endpoint (either six months post transplant or the first occurrence of rejection), and data integrity had been assured, statistical analyses would be performed. Once the last patient enrolled reached one year post transplant, the study drug assignment would be revealed. At that time patients would remain in their original treatment groups, but would be able to receive open label medication for the remainder of the study."

8.1.2.3 Study IICR 023 This study was initiated in August of 1992 and there were 4 amendments to the protocol on April 9, 1992, June 30, 1992, March 23, 1993, June 10,

1993.

Amendment #1: This amendment clarified the randomization numbering, permitted antilymphocyte preparations to be used if there was no response to steroids, and provided the definition for non-compliance (less than 80% of the medication taken). This amendment clarified the statistical analysis (including provisions for the stratification by site and 1st/2nd graft). Interim analysis rules were specified; descriptive summaries were further specified.

Amendment #2: Added appendix G (Criteria for Presumed Rejection), and further stipulated that patients should only have cadaveric renal transplants, additional information on the study medication formulation and directions for administration were outlined. The dose of methylprednisolone to treat rejection was lowered to include a 250 mg dose as well as the 500 mg and 1 g doses. Power calculations were further clarified; pharmacoeconomic sub-studies were added, and an unsatisfactory therapeutic response was defined as 6 weeks of dialysis.

Amendment #3: The Banff Schema was simplified. A recommendation was provided for dosing of Azathioprine based on patient weight (> 76 kg would receive 150 mg/day Azathioprine). Routine pharmacokinetic sampling was added at week 12. The interim analysis plan was amended to determine if the rate of rejection in the Azathioprine group was substantially less than the anticipated 60% rate; if so, the sample size would be modified.

Amendment #4: Made provisions for Phase II (extended follow-up phase: after the first year of treatment) and defined the length of study. The protocol sample size was increased from 360 recipients to 480 recipients. Thus the new power calculations were stated as a comparison at the 0.05 level of significance of a rejection rate of "15% or better versus a rate of 30% or worse", when 160 patients per treatment group are enrolled, power is 80%.

8.1.3 **Inclusion Criteria**

	MRE 002	ICM 1866	IICR 023
First or second cadaveric renal transplant	BOTH	FIRST	BOTH
18 years of age or older	YES	YES	YES
Able to receive oral medication within 3 days of transplantation.	YES	48 hours	YES
Capable of understanding purposes and risks of study and willing to sign informed consent	YES	YES	YES

Medical Reviewer Comment: Protocol MRE 022 states that "selected" patients not at increased risk for rejection who were receiving their second graft are eligible, however, it does not define "increased risk". Protocol IICR 023 does define increased risk to be: "patients who lost their first graft to rejection within one year of transplantation *and* who have a peak panel reactive antibody > 50%".

8.1.4 **Exclusion Criteria**

	MRE 022	ICM 1866	IICR 023
Pregnant women or nursing mothers	YES	YES	YES
Men and women unwilling or unable to use adequate contraception during and for 3 months following the conclusion of treatment with the study drug.	YES	YES	YES
Recipients of third and subsequent renal grafts and/or other solid organ grafts.	YES	1st GRAFT ONLY	YES
Patients who require concurrent dosing with other investigational drugs or prohibited immunosuppressives: OKT3, ATG, ALG induction therapy, FK506, Rapamycin, Desoxyspergualin, Cyclophosphamide, Methotrexate, vincristine, Prostaglandin (E1 or E2)	YES (*rohibits*: Azathioprine)	YES (*rohibits*: Brequinar, misorostil) (*Permits* ATG induction)	YES (*rohibits* allopurinol, prophylaxis or induction with ATG, ALG or OKT3)
Patients with severe diarrhea or other gastrointestinal disorders which would interfere with their ability to absorb oral medication.	YES	YES	YES
Patients with peptic ulcer disease	YES		YES(Active)
Patients or their donors with serologic evidence of HTLV-1, HIV or HBsAg.	YES	YES	YES
Patients with malignancies or history of malignancy, except non-metastatic basal or squamous carcinoma of the skin that has been treated successfully.	YES	YES	YES
Patients with systemic infections requiring continued therapy at the time of entry into this study.	YES	-----	YES
Patients with WBC < 2500/mm^3, platelet count less than 100,000/mm^3 or hemoglobin < 5g/dl.	YES	YES (Hgb < 6)	YES (WBC<3,000)
Patients with any form of substance abuse or psychiatric disorder or condition which in the opinion of the investigator might invalidate patient communication with the investigator.	YES	-----	YES

8.1.5 Study Blinding, Stratification and Randomization Methods

8.1.5.1 **Blinding:** Syntex generated a randomization code and labeled the drug supplies accordingly. A sealed envelope was supplied for each patient number containing the medication assignment for that patient. Reasons for opening the envelope included a serious adverse event. Any investigator who opened a disclosure envelope was required to date and sign the envelope, stating the reason for opening the envelope, and noting this in the CFR (Form SM).

Assignment: "MRE 022 will be UNBLINDED once all patients have reached the primary efficacy point in the study: ie, until all patients have received 6 months of treatment or are treatment failures, and data from all of the study sites is received in-house at Syntex. ICM 1866 will supply the medication in open- label fashion after the last patient has reached one year of therapy. IICR 023 in order to assure data integrity actual study drug assignment will not be revealed to the individual patient prior to 36 months post-transplantation for all patients".

Medication: "Study medication and matching placebo will be encapsulated in blue/brown opaque, size 1 capsules containing 250 mg of Mycophenolate mofetil or pre-gelatinized starch placebo **(MRE 002)**".
"For study **ICM 1866** mycophenolate will be encapsulated in blue capsules containing 250 mg and a matching placebo will be made. These capsules will be blister packed. In addition 50 mg of azathioprine will be placed in a white capsule and a matching placebo will be made. These will be placed in bottles. Patients will receive both blister packs and bottles. They will be instructed to take 6 capsules of mycophenolate mofetil (which would be either 6 capsules of mycophenolate mofetil for the 1.5 mg group, or 4 capsules of mycophenolate mofetil plus 2 matching placebo capsules) in the AM and PM. In addition they will take enough capsules from the azathioprine/placebo bottle to match a dose of 1-2 mg/kg/d".
"**IICR 1866** formulated the mycophenolate mofetil in a gray blue capsule at 250 mg with matching placebo, the azathioprine was placed in an opaque red capsule each containing 50 mg and a matching placebo. Patients assigned to the mycophenolate mofetil groups will receive either 1000 mg MMF bid or 1500 MMF bid and azathioprine placebo. Patients in the azathioprine group will either receive 100 or 150 mg/day according to the patients weight and mycophenolate mofetil placebo. Mycophenolate mofetil will be blister packed as in study ICM 1866".

8.1.5.2 **Stratification:** Patients were stratified by center (20 centers for MRE 022, 14 for ICM 1866, and 22 for IICR 023), and according to whether they were first or second-time

graft recipients (MRC 022, IICR 023).

8.1.5.3 **Randomization:** In studies ICM 1866 and IICR 023, patients were to be randomized prior to transplantation. In MRE 022 patients were allowed to be randomized either before or after transplantation. The original protocol specified that subjects for study MRE 022 were to sign an informed consent prior to transplantation. The first protocol amendment changed this to either prior to or soon after transplantation. The original protocol specified that randomization was to take place immediately post-transplantation.

Syntex prepared the randomization codes which were balanced within each center. MRE 022 patients were to be randomized into this study within 72 hours of transplantation (48 hours in ICM 1866). Informed consent could be obtained prior to or after transplantation. All study visits were calculated from the date of transplantation. IICR 023 patients were to be randomized prior to transplantation and all were to receive there first dose as soon as oral medication was permitted (at least 12 hours post-op).

Medical Officer Comment: The randomization appears to have been successful in that no imbalances were observed for important baseline variables among the treatment groups.

8.1.7 **Assessment of compliance with study treatment**

Patients' compliance with taking assigned study medication would be assessed by requesting that the patient returns all unused medication at each visit and by documenting the number of unused capsules (MRE 022, ICM 1866, IICR 023) (pill count).

8.1.8 **Clinical and Laboratory Evaluations**

8.1.8.1 **Prior to randomization** the following evaluations were to be completed: a history and physical, including age, sex, weight, etiology of the underlying renal disease leading to transplantation, date of renal transplantation, information on HLA and ABO matching of recipients, a review of all medications taken in the 7 days prior to study entry, and review of ongoing infections. Laboratories were to include Complete Blood Count with differential and platelet count, Biochemistry panel, Trough cyclosporine levels and cyclosporine dose, and oral corticosteroid dose is to be recorded if appropriate. Biochemistry panel includes: BUN, Creatinine, SGOT, SGPT, Calcium, Phosphorous, Bilirubin, Total Protein, Albumin, glucose, alkaline phosphatase, LDH, cholesterol, triglycerides, uric acid, chloride, bicarbonate, sodium, potassium.

8.1.8.2 **Subsequent visits**
MRE 022 and IICR 023: Day 7, 14 and 28, Months 2, 3, 4, 5, 6, 9 and 12)
ICM 1866: Day 1, 7, 14, 28, Month 2, 3, 6, 9, 12 (Calculation of creatinine clearance and GFR were to be preformed at 6 and 12 months). The following data were collected at each visit:

Assessment of renal function/rejection episodes.
Assessment of adverse events and/or infections.
Laboratory assessment (as per baseline).
Trough level of cyclosporine
Update of all medication taken by the patient.
Compliance with study medications.
Health economics (heath care utilization information).
Routine pharmacokinetic sampling at week 12.

Assessment of acute rejection episodes was to occur at each visit with a biopsy performed, unless contraindicated, when acute rejection was suspected. Study ICM 1866 specified that a routine biopsy would be performed at 12 and 36 months or at termination from study.

8.1.9 **Withdrawal of Patients from Study:**
Potential reasons for withdrawal or termination from the study included: normal study completion; adverse event/infection/intercurrent illness/new laboratory abnormality; Lack of therapeutic response (graft loss or permanent, ≥ 6 weeks, dialysis); inappropriate enrollment (patients not meeting entry criteria would be withdrawn from the study); non-compliance (patient taking < 80% of study medication in a month - IICR 023; < 80% compliance or a 2 week dose interruption during first year - ICM 1866); need for medication prohibited by the protocol; patient loss to follow-up; other.

Long term follow-up: An attempt would be made to monitor the long-term outcome of all patients exposed to MMF whether or not continuing to receive study medication. The following information would be collected at yearly post-transplant visits: patient survival, graft survival, determination of any major clinical event.

8.2 **Analysis**

8.2.1 **Outcome measures:** Per protocol the criteria to be evaluated in the study included:

- Treatment failure: acute biopsy proven rejection, death, graft loss, or lost to follow-up (including early termination for adverse events).

Medical Officer comment: There were at least two slightly variant definitions of treatment failure within the protocols: 1.) biopsy proven rejection or "treatment failure" (death, graft loss and any other reason for premature termination, OR 2) "treatment failure" (biopsy proven rejection, deaths, graft loss and other reasons for premature termination). See additional discussion in Efficacy Review section.

- Biopsy proven acute renal allograft rejection: this was to be assessed locally (at the patient's site) employing the Banff criteria (a revision was made in February 1993).
- Presumed acute rejection: if a biopsy was not preformed, the diagnosis was clinical and based upon one or more of the following criteria: Temperature > 100F (orally), graft swelling, graft tenderness, > 0.3 mg/dl rise in serum creatinine, oliguria, reduced flow in

perfusion, extraction or extraction profile on renal scan and ultrasound findings consistent with rejection.

- Chronic rejection presumptive: rising serum creatinine, > 1+ protein level on urinalysis, > 750 mg/day proteinuria, rising blood pressure, cyclosporine level within the therapeutic range.
- Patient vital status
- Graft status
- Adverse Events
- Infections or Malignancies
- Assessment of acute rejection episodes: A biopsy was to be preformed was suspicion of first rejection, unless in exceptional circumstances where it was logistically impossible or clinically contraindicated. Biopsies were to be performed as soon as possible, and prior to the second dose of corticosteroids. If the rejection episode did not respond to steroids a biopsy was to be performed and OKT3/ATG/ALG therapy was to be initiated. In the presence of delayed graft function, a diagnosis of acute rejection required a confirmatory renal biopsy. If acute rejection was suspected, cyclosporine blood levels were to be done to rule out cyclosporine toxicity.

The primary efficacy endpoint for the statistical analysis was treatment failure with the key component of this endpoint being the proportion of patients with one or more biopsy-proven rejection episodes during the first 6 months of treatment. Patients were considered to be in the 'success' category if no biopsy-proven rejection episode had occurred within the 6 months of treatment, and the patient retained a functioning kidney. Death, graft loss, or lost to follow-up were treated as a 'failure'.

Medical Reviewer Note: Patients who were lost to follow up or were terminated from study therapy were only followed for vital status, graft loss, and malignancy. Because of this a true intent to treat analysis based upon biopsy proven acute rejection was not preformed. The primary analysis is therefore a comparison of "treatment failures" as defined above.

SIMPLIFIED BANFF SCHEMA UTILIZED FOR RENAL BIOPSIES:

BIOPSY FINDINGS	BANFF CLASSIFICATION
Normal, minor changes, or infiltrates without tubular invasion	Normal or "Other" (Non-specific Changes)
Mild lymphocytic invasion of tubules (tubulitis)	Borderline Changes
Widespread interstitial infiltrate with moderate invasion of tubules	Mild Acute Re ection (Grade I)
Widespread interstitial infiltrate with moderately severe invasion of tubules, and/or mild or moderate intimal arteritis	Moderate Acute Re ection (Grade II)
Seve e intimal arteritis and/or "transmural" arteritis, fibrinoid change, and medial smooth muscle cell necrosis often with patchy infarction and interstitial hemorrhage	Severe Acute Re ection (Grade III)
Hyaline arteriolar thickening (new onset, not present in implantation biopsy), and/or extensive isometric vacuolization of tubules, smooth muscle degeneration, thrombotic microangiopathy.	"Other", Cyclosporine Toxicity
Tubular cell loss and necrosis, regenerative changes	"OTHER", Acute Tubular Necrosis
Interstitial fibrosis, tubular atrophy (new onset arterial fibrous intimal thickening suggests chronic re ection)	Chronic Transplant Nephropathy

8.2.2 Assessment of Efficacy

For all three studies, the analysis specified in the protocol was to be based upon the comparison of the proportion of patients with (ne or more biopsy proven acute re ections in the first six months of treatment between the control group and each of the MMF arms. A Bonferroni ad ustment was specified to ad ust for two comparisons (each arm of MMF versus control). Death, graft loss, withdrawal due to an adverse event or loss to follow-up were to be considered failures for this analysis. For all three studies, graft loss was defined by the protocol as graft nephrectomy, retransplantation or permanent return to dialysis (>= 6 consecutive weeks). A patient undergoing dialysis at the time of termination was considered a treatment failure. A similar definition was not provided in MRE 022. A Cochran-Mantel-Haenszel test was to be used ad usting for stratification by center. Additionally, analyses were to ad ust for the number of previous grafts for studies MRE 022 and IICR 023. All

subjects randomized were to be included in the analysis. An overall Cochran-Mantel-Haenszel test was to be performed. If this was significant, pairwise comparisons were to be made. No discussion of an adjustment for multiple comparisons for the Cochran-Mantel-Haenszel procedure was made. The use of Fisher's least significant difference was discussed for the use of analysis of variance for continuous variates.

The protocol specified analysis plans called for an analysis of patient and graft survival as secondary data analyses. In these analyses, tests of significance among the treatment arms were to be performed for each study separately using a stratified log-rank procedure (time to event analysis). During the pre-NDA meeting with the applicant, FDA expressed serious reservations that the analyses planned by the applicant would not be adequate to address FDA's concern that it be possible to determine if a reduced acute rejection rate over the first six months might still be associated with a decrease in patient and graft survival at one year. In particular, FDA requested that some form of formal procedure be used evaluate the equivalence of MMF and the control arm for each trial. FDA suggested that a confidence interval procedure approach (based upon differences between each arm of MMF and control with respect to the one year patient and graft survival rate) would be more appropriate than a significance testing procedure. The applicant agreed to this approach, but was concerned that the confidence intervals so formed might be too wide to rule out fairly large differences. FDA suggested that a pooling procedure based upon a Mantel-Haenszel approach would be acceptable if there were no substantial differences among the studies with respect to the treatment effect. The recommended procedure was to use a Mantel-Haenszel style weighted combination of the stratum specific differences for each study and then weight the study estimates together and form a confidence interval (97.5% two-sided to introduce a Bonferroni correction) for the difference. The degree of equivalence was evaluated based upon this confidence interval. No precise definition of equivalence was established at the pre-NDA meeting with the applicant.

The sponsor indicated that a number of centers had very small sample sizes and low event rates. The sponsor proposed using stratum weights equal to $w_i=n_{i1}n_{i2}/(n_{i1}+n_{i2})$, where i is the stratum and n_{ij} is the sample size for the j-th treatment in the i-th stratum. FDA commented that this is equivalent to the harmonic mean and would be an acceptable weighting scheme. FDA requested that the applicant stratify by all variables used at the time of stratification and that strata for which both treatments are not present, be excluded as is done in the standard Mantel-Haenszel analysis.

In addition to the analysis described above, the applicant performed other analyses. These analyses were based upon stratification by center, but not upon first or second allograft. In these analyses, the applicant replaced an estimated treatment rate of $p_{ij}=0$ with the following estimate:

$$p'_{ij}=\frac{y_{ij}+.5}{n_{ij}+1}$$

Both the FDA and applicant's preferred analyses are presented in this review.

The applicant proposed using Zelen's exact test of homogeneity rather than the test described by Breslow and Day (p 143, Statistical Methods in Cancer Research Volume I), this procedure was suggested due to the relatively small sample size in a number of centers. The applicant has also suggested a formula fo.

testing the homogeneity of the differences over strata rather than test for homogeneity of odds-ratio proposed by FDA. This formula was accepted by the FDA and is presented below:

$$Q = \sum \frac{(d^{(s)} - d_{..})^2}{v^{(s)}}$$

where $d^{(s)}$ is the weighted difference calculated for the s-th study, $v^{(s)}$ is the variance for the average difference for the s-th study, and $d_{..}$ is the weighted (each study is weighted inversely proportionate $v^{(s)}$) average difference over all three studies. The statistic Q is based upon pairwise comparisons between the control group and each of the MMF doses and is evaluated using a chi square distribution with 2 degrees of freedom. Additionally, the sponsor presented a modified Bonferroni adjustment (Hochberg, Y., Biometrika 1988). This approach is based upon a comparison of 95% confidence intervals for both pairwise comparisons. These intervals are evaluated based upon a definition of equivalence of 10% (chosen by the sponsor). If both intervals exclude a difference of 10% these intervals are to be presented. Otherwise, Hochberg's modified intervals are to be presented. FDA requested analyses also be based upon the standard Bonferroni adjustment.

8.2.3 Secondary Objectives

The protocols listed a number of secondary endpoints to be investigated in the three pivotal studies. These endpoints were presented in the NDA, but are only discussed in this review where particularly relevant.

Number of patients in first 6 months who require OKT3, ATG, ALG following an acute rejection episode (MRE 022, ICM 1866, IICR 023 [and 12 months]).

Number of courses of iv steroids, OKT3, ATG and ALG will be summarized (MRE 022, ICM 1866, IICR 023).

Number of acute rejection episodes experienced by each patient during the study (MRE 022, IICR 023).

The 1-year patient and graft survival (MRE 022, ICM 1866, IICR 023 [and 2 and 3 years]). This has been discussed in Section 8.2.2.

Serum creatinine levels at 6 and 12 month time points (MRE 022).

Renal function as measured by creatinine and GFR (ICM 1866, IICR 023).

Cyclosporine dose will be assessed at the 6 and 12 month time points (MRE 022).

Incidence of adverse events (includes cancer and congenital abnormalities) (MRE 022, ICM 1866, IICR 023).

The incidence of infections (MRE 022, ICM 1866, IICR 023).

Occurrence of chronic renal allograft rejection at 12 and 36 months (ICM 1866).

8.2.4 Assessment of Safety

The primary endpoint of the safety analysis was adverse events including death. Safety was also assessed by clinically significant changes in physical signs or symptoms, laboratory values which resulted in a change in concomitant medications, and interruptions or withdrawal of the study medication, or at the investigator's discretion. Data including adverse events (congenital anomalies, cancer), infections and abnormal laboratory data will be included in the safety data. The following scale was utilized to grade the severity of adverse events: Mild (Grade 1), Moderate (Grade 2), Severe (Grade 3), Life Threatening (Grade 4), Fatal (Grade 5).

The initial analysis included the entire exposure time on drug (for some patients this is > 6 months of treatment). The applicant updated the integrated safety summary during the NDA review to include follow-up for at least 1 year (for many patients follow-up will exceed 1 year).

8.3 Efficacy Results

This section describes the study results for biopsy proven acute rejection (as measured by treatment failure) and one-year patient and graft survival. The applicant's analyses for these two endpoints are first presented, followed by FDA analyses to investigate issues raised by the applicant's analyses.

8.3.1 Applicant's Analysis of Biopsy-Proven Acute Rejection (Treatment Failure)

The applicant's analyses of biopsy-proven rejection (through month 6) are provided below for each individual study.

8.3.1.1 Study MRE 022

Background

A total of 491 subjects were enrolled into this trial, with 166 assigned to placebo, 165 to MMF 2g and 160 to MMF 3g. All of these subjects were included in both the efficacy and safety analyses. Subjects were enrolled between July 19, 1992 and August 23, 1993. Twenty centers participated in this study, with the largest providing 57 subjects and the smallest providing 4 subjects. The NDA does not provide information on the distribution of subjects based upon complete stratification of center by previous transplants. Over 43 (9%) of the subjects were second allograft recipients.

The data cutoff for this report was February 11, 1994. This was the date of the last ongoing patient's scheduled 6-month visit. The study report stated that the originally planned interim analysis was not conducted. It was concluded that the overall incidence of rejection had declined and that the sample size should be increased by 40 patients per treatment group to a total of 160 subjects per arm. Subjects were randomized both before and after transplantation had taken place. The date of randomization was not incorporated into the applicant's data base. The date of enrollment was assumed to be the same as the date of transplant.

The primary endpoint analyzed was the occurrence of treatment failure as defined by the presence or absence of a biopsy-proven rejection in the first six months posttransplant. A Banff biopsy score of Grade I (mild) or more severe was used to establish the presence of an event. Patients who did not have a biopsy-proven rejection, but terminated prior to six months due to graft loss, death or any other reason were treated as treatment failures.

Statistical analysis was based upon the use of the Cochran-Mantel-Haenszel procedure adjusting for stratification by investigator. An adjustment by the transplant number (stratified as either first or second) was not made. The applicant judged that the number of subjects with a second allograft was too small to warrant this analysis. An analysis of just subjects receiving their first allograft was thought to be similar to the overall analysis. Confidence intervals were prepared at the 97.5% level.

The applicant also presented descriptive analyses investigating the relationship between the treatment effect for the primary endpoint and the following variates: investigator, age group and gender. Information on race was not collected and could not be included in the analyses.

The applicant has analyzed the acute rejection events using a time to failure approach as well as a simple proportion. The first approach used the treatment failure definition as with the simple proportion. The second approach "censored" on events other than those associated with an unsatisfactory therapeutic response. In this approach, death and graft loss were treated as censoring events and were not considered an unsatisfactory therapeutic response. Since the FDA cautioned the applicant that these analyses may be inappropriate due to problems associated with informative censoring, these analyses will not be discussed further in this review.

Analyses of the secondary efficacy variables were also conducted. The following variables were investigated: presumptive rejection, central vs. local biopsy, treatment of rejection, maintenance immunosuppression, renal function, graft and patient survival, and hospitalizations. With the exception of patient and graft survival, these analyses will not be described in this review.

No patients were excluded on the basis of protocol violations. The following table lists the protocol violations over all three treatment arms (note, these categories are not mutually exclusive). The NDA provided the individual patient IDs, but did not summarize these results by treatment arm.

PROTOCOL VIOLATIONS:

Reason	Number
Study medication not started within 72 hours	7
Received prohibited medication	2
Hepatitis B	2
History of Malignancy	7
Infections	1
Platelet count < 100 x 10^9/L	13
Inadequate Contraception	2
Blind Broken	5
Study Treatment Error	3
Cyclosporine Interrupted	1

Source: Text - Patient Disposition, p 54, V. 1.817

The following table summarizes the length of treatment by study arm. Because subjects were not followed for the primary endpoint after treatment discontinuation, this table also shows the length of follow-up with respect to the biopsy proven acute rejection. Note: treatment was discontinued for clinically determined lack of therapeutic response.

LENGTH OF TREATMENT:

Treatment Duration	Placebo	MMF 1.0 gm BID	MMF 1.5 gm BID
≤ 3 months	41 (25%)	22 (15%)	36 (22%)
> 3 months	125 (75%)	143 (85%)	124 (78%)
Total	166	165	160

Source: Table 2, V. 1.817

The previous table does not show the number of subjects withdrawing prior to six months of follow-up The following table shows the number and percent of subjects classified as having a clinical eve (death, graft loss or biopsy proven acute rejection) in the first six months, other treatment failures o.

completing six months without a clinical event. The subjects classified as other treatment failures are those discontinuing prior to six months without a previous biopsy proven rejection, death or graft loss. The majority of these premature discontinuations are made up of withdrawals due to an adverse event (50% [6/12], 74% [14/19] and 81% [29/36] for placebo, MMF 1.0 and MMF 1.5, respectively as a percentage of all subjects having an "other failure"). It appears that the differential "other failure" rate is accounted for by the differential adverse event rate.

EVENT RATES THROUGH MONTH 6 (Study 022):

Status at Six Months	Placebo	MMF 1.0 gm BID	MMF 1.5 gm BID
clinical event	81 (49%)	31 (19%)	26 (16%)
other failure	12 (7%)	19 (12%)	36 (23%)
no event	73 (44%)	115 (70%)	98 (61%)
Total	166	165	160

Source: Table 11, V. 1.817

The applicant compared the three treatment groups on the following variables at baseline: age, gender, weight, primary cause of renal failure, CMV serologic status and previous renal transplantation. The applicant has indicated that the three treatments are not evenly distributed with respect to gender. The overall study make-up was 62% male, ranging from 56% male for MMF 2 g to 69% male for MMF 3g. No other "imbalances" were discovered.

Results

The applicant recorded 205 events (treatment failure) for an overall event rate of 42%. The event rates were 30%, 39% and 56% for MMF 2g, MMF 3g and placebo, respectively. The following table shows the events defining the occurrences of treatment failure. In this table, subjects are first classified as to whether or not a biopsy-proven rejection was detected in the first six months of treatment. If no such rejection was present, the subjects were classified into one of the remaining categories apparently based upon whichever event occurred first.

TREATMENT FAILURE EVENTS:

Event	Placebo n=166	MMF 1.0 gm BID n=165	MMF 1.5 gm BID n=160
biopsy-proven rejection	77 (46%)	28 (17%)	22 (14%)
graft loss/death (no prior acute)	4 (2%)	3 (2%)	4 (3%)
unsat. response			1 (1%)
AE	6 (4%)	14 (9%)	29 (18%)
non-compliance	3 (2%)	3 (2%)	5 (3%)
other	3 (2%)	2 (1%)	1(1%)
Total	93 (56%)	50 (30%)	62 (39%)

Source: Table 11, V. 1.817

The applicant conducted a Cochran-Mantel-Haenzsel analysis of treatment failure comparing the two active treatment arms against placebo. This analysis stratified for center, but did not include stratification for the number of previous transplants (0 or 1). The Bonferroni procedure was used to adjust for the multiple comparisons made (i.e. 95% significance requires an apparent p-value of 2.5% or less). Confidence intervals were prepared using a 97.5% critical value to insure 95% coverage for both intervals. The results of these tests and intervals are presented below.

TREATMENT FAILURE COMPARISONS:

	Placebo vs. MMF 2 g	Placebo vs. MMF 3g
p-value	<.001	.001
relative risk (97.5% CI)	.53 (.40, .72)	.66 (.49, 88)

Source: Table 10, V. 1.817

The applicant repeated the above analysis for the 448 first allograft subjects only and concluded that the results are consistent with the overall analysis. The applicant stated that the small number of second allograft subjects precludes the use of this stratification factor in the CMH analysis. Second allograft patients had a higher rate of rejections and treatment failures. The overall rate for first-time allograft patients was 41%, while the overall rate was 49% for second-time allograft patients.

The applicant presented treatment failure rates for each center. No formal test of homogeneity is presented. The applicant indicates that rates at a number of the centers appear to be different from the overall rate. It is stated that these centers are small, making it impossible to conclude that these results are actually inconsistent.

Analyses by age group and gender are presented in the NDA. The following table summarizes the treatment failure rates for age and gender. No difference is apparent in the treatment effect with respect to age and gender. Tests of significance were not presented. These issues will be addressed again in Section 8.3.3 where additional FDA analyses are presented.

TREATMENT FAILURE BY AGE GROUP AND GENDER:

Group	Placebo n=166	MMF 1.0 gm BID n=165	MMF 1.5 gm BID n=160
Overall	93 (56%)	50 (30%)	62 (39%)
Age			
<40	32/53 (60%)	17/48 (35%)	18/48 (38%)
40-64	53/102 (52%)	27/102 (27%)	41/105 (39%)
65 and over	8/11 (73%)	6/15 (40%)	3/7 (43%)
Gender			
Female	33/64 (52%)	20/73 (27%)	21/50 (42%)
Male	60/102 (59%)	30/92 (33%)	41/110 (37%)

The study report indicates that the three treatment groups experienced different rates of immunosuppressive medication administered for the treatment of rejection (high-dose oral or IV corticosteroids, ATG, ALG, or OKT3). Placebo has the highest rate (52%) and MMF 2g and MMF 3g have similar rates (29% and 24%, respectively). Tests of significance were not presented for this comparison.

The applicant presented the results of statistical analyses for maintenance corticosteroid dosing over the course of the study. An analysis of variance adjusting for center, treatment and center by treatment interaction was conducted at each of the following time points: day 14, day 28, month 3 , month 4, month 5 and month 6. The number of subjects included in these analyses decreased over the course of the study because complete follow-up was not available after treatment discontinuation. These analyses

consistently reported p-values of approximately .05 for the interaction between treatment and center. The applicant concludes that these interactions are unlikely to be clinically significant. The main effects for the comparison among the treatments (averaging over center) were reported as significant by the applicant for months 3, 4 and 5. Placebo subjects tended to have a higher maintenance dose than the two MMF groups, which were similar in average maintenance dose.

The applicant also examined the maintenance dose of cyclosporine over the course of the study using analysis of variance. As with corticosteroid use, the number of subjects included in these analyses decreased over time. No overall treatment effects were discovered, but the interaction p-values became fairly small for months 4, 5 and 6 (.15, .05, and .12, respectively). No explanation was provided with the applicant concluding that the results are not likely to be clinically significant.

Serum creatinine was analyzed by the applicant as a measure of efficacy (renal function). As with corticosteroid use, the number of subjects included in these analyses decreased over time. The statistical analyses presented showed significant treatment effects as well as interactions. The overall pattern was for the placebo group to be approximately 15% higher than for the MMF arms, which were similar. The applicant concluded that the interactions are not likely to be clinically significant.

8.3.1.2 Study ICM 1866

Background

The statistical analyses presented by the applicant for study 1866 are virtually identical in form to those just presented for study 022. The design issues discussed previously for study 022 (background section) will not be repeated. The following summarizes the key study findings with respect to biopsy proven acute rejection (treatment failure).

A total of 499 subjects were enrolled into this trial, with 166 assigned to AZA, 167 to MMF 2g and 166 to MMF 3g. All of these subjects were included in the primary efficacy analysis. Four patients were randomized but never received study medication. These subjects were excluded from the secondary efficacy and safety analyses. Subjects were enrolled between July 21, 1992 and September 6, 1993. The data cutoff for the NDA was March 4, 1994. Fourteen centers participated in this study, with the largest providing 72 subjects and the smallest providing 13 subjects.

No patients were excluded on the basis of protocol violations. The following table lists the protocol violations over all three treatment arms (note: these categories are not mutually exclusive). The NDA provided the individual patient IDs, but did not summarize these results by treatment arm.

PROTOCOL VIOLATIONS:

Reason	Number
Platelet count < 100 x 10^9/L	4
Hemoglobin < 6 g/dL	1
Malignancy	1
Hepatitis B	1
study drug discontinued >28 days	3
received AZA > 2 weeks	4
no cyclosporine first 28 days	4
no study drug 5 days after transplant	3
pregnancy	3
blind broken	6

Source: Text - Patient Disposition, p 55, V. 1.852

The applicant compared the three treatment groups on the following variables at baseline: age, gender, race and weight. The applicant has indicated that there are no "statistically significantly differences" among the treatments for these variables.

The following table summarizes the length of treatment. Because subjects were not followed for the primary endpoint after treatment discontinuation, this table also shows the length of follow-up with respect to the biopsy proven acute rejection. The data presented in the NDA does not allow subjects receiving treatment for exactly six months to be separated from those subjects receiving between 3 and six months of study treatment.

TREATMENT LENGTH:

Treatment Duration	AZA	MMF 1.0 gm BID	MMF 1.5 gm BID
≤ 3 months	28 (17%)	20 (12%)	25 (15%)
> 6 months	138 (83%)	147 (88%)	141 (85%)
Total	166	167	166

Source: Table 2, V. 1.852 plus 4 subjects never receiving therapy

The previous table does not show the number or percent of subjects withdrawing prior to six months of follow-up. The NDA presents a table containing premature withdrawals from the study, but this includes withdrawals after six months. The following table shows the number and percent of subjects classified as having a clinical event (death, graft loss or biopsy proven acute rejection) in the first six months, other treatment failures or completing six months without a clinical event. The subjects classified as other treatment failures can be inferred to be those discontinuing prior to six months. The most common reason for these premature discontinuations is withdrawal due to an adverse event (60%, 44% and 76% for AZA, MMF 1.0 and MMF 1.5, respectively as a percentage of all subjects having an "other failure"). It appears that the differential "other failure" rate is accounted for by the differential adverse event rate for the highest MMF dose group.

CLINICAL EVENTS:

Status at Six Months	AZA	MMF 1.0 gm BID	MMF 1.5 gm BID
clinical event	69 (42%)	36 (22%)	31 (19%)
other failure	10 (6%)	16 (10%)	21 (13%)
no event	87 (52%)	115 (69%)	114 (69%)
Total	166	167	166

Source: Table 12, V. 1.852

Results

The applicant recorded 183 events (treatment failure) for an overall event rate of 37%. The event rates were 30%, 39% and 56% for MMF 2g, MMF 3g and AZA, respectively. The following table shows the events defining the occurrences of treatment failure. In this table, subjects are first classified as to whether or not a biopsy-proven rejection was detected in the first six months of treatment. If no such rejection was present, the subject was classified into one of the remaining categories apparently base upon whichever event occurred first.

TREATMENT FAILURE EVENTS:

Event	AZA n=166	MMF 1.0 gm BID n=167	MMF 1.5 gm BID n=166
biopsy-proven rejection	63 (38%)	33 (20%)	29 (18%)
graft loss/death (no prior acute)	6 (4%)	3 (2%)	2 (1%)
unsat. response	1 (1%)	1 (1%)	
AE	6 (4%)	7 (4%)	16 (10%)
non-compliance	2 (1%)	5 (3%)	4 (2%)
other	1 (1%)	3 (2%)	1 (1%)
Total	79 (48%)	52 (31%)	52 (31%)

Source: Table 12, V. 1.852

The applicant conducted a Cochran-Mantel-Haenzsel analysis of treatment failure comparing the two active treatment arms against AZA. This analysis stratified for center. The Bonferroni procedure was used to adjust for the multiple comparisons made (i.e. 95% significance requires an apparent p-value of 2.5% or less). Confidence intervals were prepared using a 97.5% critical value to insure 95% coverage for both intervals. The results of these tests and intervals are presented below.

TREATMENT FAILURE COMPARISONS:

	AZA vs. MMF 2 g	AZA vs. MMF 3g
p-value	.002	.002
relative risk (97.5% CI)	.65 (.48, .88)	.66 (.48, 89)

Source: Table 11, V. 1.852

The applicant presented treatment failure rates for each center. No formal test of homogeneity is presented. The applicant indicates that rates at a number of the centers appear to be different from the overall rate. It is stated that these centers are small and that the events associated with these differences are nonimmunologic (eg technical complications of surgery).

Analyses by age groups, gender and race are presented in the NDA. The following table summarizes the treatment failure rates for these subgroups. No difference is apparent in the treatment effect with respect to gender and race. The applicant comments that for the highest age category there is apparently less treatment effect, but that the number of subjects is too small. No formal statistical analysis is presented. These issues will be addressed again in Section 8.3.3 where additional FDA analyses are presented.

TREATMENT FAILURE BY AGE GROUP AND GENDER:

Group	AZA n=166	MMF 1.0 gm BID n=167	MMF 1.5 gm BID n=166
Overall	79 (48%)	52 (31%)	52 (31%)
Age			
<40	29/47 (62%)	18/62 (29%)	16/50 (32%)
40-64	45/109 (41%)	28/94 (30%)	30/105 (29%)
65 and over	5/10 (50%)	6/11 (55%)	6/11 (55%)
Gender			
Female	36/71 (45%)	22/69 (32%)	20/71 (28%)
Male	43/95 (45%)	30/98 (31%)	32/95 (34%)
Race			
Black	23/40 (58%)	17/44 (39%)	8/33 (24%)
Non-black	56/126 (44%)	35/123 (29%)	44/133 (33%)

Source: Tables 14, 15 and 16, V. 1.852.

The study report indicates that the three treatment groups experienced different rates of immunosuppressive medication. AZA has the highest rate (42%) and MMF 2g and MMF 3 g have similar rates (22% and 29%, respectively). Tests of significance were not presented for this comparison.

The applicant presented the results of statistical analyses for the corticosteroid maintenance dose over the course of the study. An analysis of variance adjusting for center, treatment and center by treatment interaction was conducted at each of the following time points: day 28, 2 months, 3 months, 4 months, and 6 months. The number of subjects included in these analyses decreased over the course of the study because complete follow-up was not made after treatment discontinuation. The analysis at 28 days produced a p-value of approximately .07 for the interaction between treatment and center. The remainin analyses also did not similarly show interactions (all p-values > .4). The applicant concludes that th

interaction is likely the result of high mean steroid dose associated with the initial induction therapy. The main effect for the comparison among the treatments (averaging over center) was reported as significant by the applicant for month 2. AZA subjects tended to have a higher maintenance dose than the two MMF groups, which were similar in average maintenance dose. No other significant differences among the treatments were reported (p>.4).

The applicant also examined the maintenance dose of cyclosporine over the course of the study using analysis of variance. As with corticosteroid use, the number of subjects included in these analyses decreased over time. No treatment main effects or interactions were discovered.

Serum creatinine was analyzed by the applicant as a measure of efficacy (renal function). As with corticosteroid use, the number of subjects included in these analyses decreased over time. The statistical analyses presented showed significant treatment effects (day 28, month 2) as well as interactions (month 2, month 4). The overall pattern demonstrated the AZA group to be somewhat higher than for the MMF arms, which themselves were similar. The applicant concluded that the interactions are not likely to be clinically significant.

8.3.1.3 Study IICR 023

Background

A total of 503 subjects were enrolled into this trial, with 166 assigned to AZA, 173 to MMF 2g and 164 to MMF 3g. All of these subjects were included in the efficacy analyses. Subjects were enrolled between August 13, 1992 and August 23, 1993. The data cutoff for this study was February 25, 1994. Twenty-one centers participated in this study, with the largest providing 63 subjects and the smallest providing 2 subjects. The NDA does not provide information on the distribution of subjects based upon complete stratification of center by previous transplants. Overall, 60 (12%) of the subjects were second allograft recipients.

Statistical analysis was based upon the use of the Cochran-Mantel-Haenszel procedure adjusting for stratification by investigator. Centers with 10 or fewer patients were pooled into 2 pooled centers (centers 4087, 4099 and 4097 were combined and centers 4105 and 4029 were combined). Otherwise, the statistical analyses presented for this study are similar in form to those discussed previously for studies 022 and 1866. The following summarizes the key study findings with respect to biopsy proven acute rejection (treatment failure).

No patients were excluded on the basis of protocol violations. The following table lists the protocol violations over all three treatment arms (note: these categories are not mutually exclusive). The NDA provided the individual patient IDs, but did not summarize these results by treatment arm.

PROTOCOL VIOLATIONS:

Reason	Number
baseline platelet count <100,000/mm^3	6
baseline hepatitis B	2
prior malignancy	2
medication not started <72 hours after transplant	12
prohibited medication	14
open-label AZA	43
period of wrong study drug	12
cyclosporine interrupted	6

Source: Text - Patient Disposition, p 35, V. 1.907

The following table shows the length of treatment. Because subjects were not followed for the primary endpoint after treatment discontinuation, this table also shows the length of follow-up with respect to biopsy-proven acute rejection. Note, treatment was discontinued for clinically determined lack of therapeutic response.

TREATMENT LENGTH:

Treatment Duration	AZA	MMF 1.0 gm BID	MMF 1.5 gm BID
≤ 3 months	36 (22%)	33 (19%)	27 (16%)
> 3 months	130 (78%)	140 (81%)	137 (84%)
Total	166	173	164

Source: Table 2, V. 1.907 with the addition of six subjects never receiving drug

The previous table does not show the number or percent of subjects withdrawing prior to six months of follow-up. The table contained in the NDA fails to separate subjects receiving exactly six months of study treatment from those receiving less than six months of treatment. The following table shows the number and percent of subjects classified as having a clinical event (death, graft loss or biopsy proven acute rejection) in the first six months, other treatment failures or completing six months without clinical event. The subjects classified as other treatment failures can be inferred to be those discontinu

prior to six months. The single largest reason for these premature discontinuations is withdrawal due to an adverse event (41%, 54% and 60% for AZA, MMF 1.0 and MMF 1.5, respectively as a percentage of all subjects having an "other failure"). It appears that the differential "other failure" rate is accounted for by the differential adverse event rate.

CLINICAL EVENTS:

Status at Six Months	AZA	MMF 1.0 gm BID	MMF 1.5 gm BID
clinical event	66 (40%)	42 (24%)	32 (20%)
other failure	17 (10%)	24 (14%)	25 (15%)
no event	83 (50%)	107 (62%)	107 (65%)
Total	166	173	164

Source: Table 12, V. 1.907

The applicant reported no differences among the three treatment groups for the following variables at baseline: age, race, weight, primary cause of renal failure, CMV serologic status, histocompatibility matching, immunologic assessments, previous transplant history, postoperative graft function, donor characteristics, B-cell crossmatch, mean cold ischemic time, and history of blood transfusions. The applicant has indicated that the three treatments are not evenly distributed with respect to gender. The overall study make-up was 40% female subjects, which ranged from 33% for AZA to 46% for MMF 2g. Pretransplant panel reactive antibody (PRA) values of more than 20% were reported as significantly different among the three treatments with values of 9%, 12% and 4% for AZA, MMF 2g and MMF 3g, respectively. This value represents the amount of pre-formed antibodies thought to be associated with the development of hyper-acute rejection (GC).

Results

The applicant recorded 206 events (treatment failure) for an overall event rate of 41%. The event rates were 50%, 38% and 35% for AZA, MMF 2g, MMF 3g, respectively. The following table shows the events defining the occurrences of treatment failure. In this table, subjects are first classified as to whether or not a biopsy-proven rejection was detected in the first six months of treatment. If no such rejection was present, the subjects was classified into one of the remaining categories apparently based upon which ever occurred first.

TREATMENT FAILURE EVENTS:

Event	AZA n=166	MMF 1.0 gm BID n=173	MMF 1.5 gm BID n=164
biopsy-proven rejection	59 (36%)	34 (20%)	26 (16%)
graft loss/death (no prior acute)	7 (4%)	8 (5%)	6 (4%)
unsat. response		1 (1%)	
AE	7 (4%)	13 (8%)	15 (9%)
non-compliance	6 (4%)	4 (2%)	5 (3%)
other	4 (2%)	6 (4%)	5 (3%)
Total	83 (50%)	66 (38%)	57 (35%)

Source: Table 12, V. 1.907

The applicant conducted a Cochran-Mantel-Haenzsel analysis of treatment failure comparing the two active treatment arms against AZA. This analysis stratified for "grouped" center, but did not include the number of previous transplants (0 or 1). The Bonferroni procedure was used to adjust for the multiple comparisons made (i.e. 95% significance requires an apparent p-value of 2.5% or less). Confidence intervals were prepared using a 97.5% critical value to insure 95% coverage for both intervals. The results of these tests and intervals are presented below.

TREATMENT FAILURE COMPARISONS:

	AZA vs. MMF 2 g	AZA vs. MMF 3g
p-value	<.029	.005
relative risk (97.5% CI)	.77 (.58, 1.01)	.68 (.50, 92)

Source: Table 1, V. 1.907

The applicant comments that first and second allografts do not appear to differ with respect to episodes of biopsy-proven acute rejection.

The applicant presented treatment failure rates for each center. No formal test of homogeneity presented. The applicant indicates that a number of the centers appear to be different from the over-

rate.

Analyses by age group, race and gender are presented in the NDA. The following table summarizes the treatment failure rates for age, race and gender. The sample size is insufficient to make any meaningful comparison on the basis of race. For both age and gender, the applicant notes apparent differences in the treatment effect. For males, there is a considerably smaller difference among the treatments. For subjects 65 years old and over, the treatment difference appears larger than the overall result. Formal tests of homogeneity are not presented by the applicant. The applicant conducted CMH analyses adjusting for gender and reported results consistent with the overall results. These issues will be addressed again in Section 8.3.3 where additional FDA analyses are discussed.

TREATMENT FAILURES BY AGE GROUP AND GENDER:

Group	AZA n=166	MMF 1.0 gm BID n=173	MMF 1.5 gm BID n=164
Overall	83 (50%)	66 (38%)	57 (35%)
Age			
<40	21/41 (51%)	21/55 (38%)	16/47 (34%)
40-64	53/111 (48%)	40/107 (37%)	38/100 (38%)
65 and over	9/14 (64%)	5/11 (46%)	3/17 (18%)
Gender			
Male	47/113 (42%)	34/94 (36%)	34/98 (35%)
Female	36/55 (66%)	32/79 (41%)	23/66 (35%)
Race			
Black	1/1 (100%)	0/1 (0%)	0/1 (0%)
Non-black	82/165 (50%)	65/171 (38%)	57/163 (35%)

Source: Tables 15, 16, and 17, V. 1.907

The study report indicates that the three treatment groups experienced different rates of immunosuppressive medication used to treat acute rejection (high dose corticosteroids, ATG, ATG, OKT3). AZA has the highest rate (48%) and MMF 2g and MMF 3 g have similar rates (31% and 24%, respectively). Tests of significance were not presented for this comparison.

The applicant presented the results of statistical analyses for the corticosteroid maintenance dose over the course of the study. An analysis of variance adjusting for center, treatment and center by treatment interaction was conducted at each of the following time points: weeks 1, 2, 3, 4, 6, and 8 and months 3, 4, and 6. The number of subjects included in these analyses decreased over the course of the study because complete follow-up was not made after treatment discontinuation. The mean dose appeared consistent over the treatments. For weeks 3, 4 and 6 the interaction between treatment and center was reported as significant. The applicant concludes that these interactions are unlikely to be clinically significant.

The applicant also examined the maintenance dose of cyclosporine over the course of the study using analysis of variance. As with corticosteroid use, the number of subjects included in these analyses decreased over time. Cyclosporine levels were reported as comparable for all time period with the exception of day 7, where the dose was higher for the MMF 3 g group. Interaction p-values became fairly small for day 14, week 4 and week 16 (.07, .06, and .8, respectively). No explanation was provided by the applicant for this result.

Serum creatinine was analyzed by the applicant as a measure of efficacy (renal function). As with corticosteroid use, the number of subjects included in these analyses decreased over time. The statistical analyses presented showed significant treatment effects, but no interactions. The overall pattern of serum creatinine was for the AZA group to be higher than for the MMF 2g group which in turn was higher than the MMF 3g group.

8.3.2 Applicant's Analysis of One-year Patient and Graft Survival

All patients in the three studies were followed for patient and graft survival through September 7, 1994. As of this date, all subjects were to have completed a minimum of one year of follow-up. The applicant excluded subjects who failed to start study medication from all analyses; four patients in ICM 1866 and six patients in IICR 023. The results for these subjects are included in the data listings provided. The following table presents the results for patient and graft survival for each study using the FDA suggested approach ("usual" Bonferroni adjustment [illegible]stification by all factors used in randomization, deleting centers without both treatments being cor[illegible] and not adjusting cell counts away from 0) as well as the overall pooled results.

1-YEAR PATIENT AND GRAFT SURVIVAL (FDA Suggested Analysis):

	Treatment			Stratified Pairwise Differences (97.5% CI)	
Study	Control	MMF 2g	MMF 3g	MMF 2g - Control	MMF 3g - Control
ICM 1866	12.2 (20/164)	8.5 (14/165)	11.4 (19/166)	-3.9 (-11.2, 3.4)	-.8 (-8.6, 7.0)
IICR 023	13.6 (22/162)	11.7 (20/171)	11.0 (18/164)	-1.4 (-8.8, 6.1)	-2.4 (10.1, 5.2)
MRE 022	11.4 (19/166)	8.5 (14/165)	10.0 (16/160)	-3.2 (-10.1, 3.7)	-1.7 (-8.6, 5.2)
ICM 1866/ IICR 02?	12.9	10.1	11.2	-2.7 (-7.9, 2.5)	-1.6 (-7.1, 3.8)
Overall	12.4	9.6	10.8	-2.9 (-7.0, 1.3)	-1.7 (-5.9, 2.6)

For each study, the applicant presented the results of Zelen's test for homogeneity. Additionally, a chi-square test for homogeneity among the studies was conducted. The results of these tests are presented in the following table:

	Test for Homogeneity P-value	
Study	MMF 2g vs Control	MMF 3g vs Control
ICM 1866	.61	.76
IICR 023	1.00	.98
MRE 022	.12	.30
Overall	.85	.95

Based upon results of the tests for homogeneity, the applicant and FDA reviewers concluded that a pooled analysis was appropriate for each study as well as overall.

8.3.3 Comments

8.3.3.1 Efficacy

The applicant's analyses discussed in the previous sections have a number of methodological problems which were further investigated during the review process. The following sections describe these issues and the analyses conducted by FDA to address these concerns.

Treatment Failure - Description of the Defining Events

The applicant's analysis was based upon the use of treatment failure, which was defined as the occurrence of one of the following events: biopsy proven acute rejection, death, graft loss or premature treatment termination. Descriptively, patients were classified by the applicant on the basis of the first event which occurred. The FDA conducted descriptive analyses based upon classifying the patients using the most serious event occurring in the first six months prioritized as follows: death, graft loss, biopsy proven acute rejection, adverse event leading to premature discontinuation and "other" premature discontinuation. These analyses moved some patients from the acute rejection and premature discontinuation groups and into the death or graft loss groups. Since all patients were followed with respect to death and graft loss, it was possible to classify patients using events occurring after premature discontinuation. The results of these analyses are contained in the following three tables.

TREATMENT FAILURE EVENTS (STUDY 022)

Event	Placebo n=166	MMF 2 gm/day n=165	MMF 3 gm/day n=160
Treatment Failure	56%	30%	39%
acute rejection	40	14	11
graft loss/death	11	7	9
AE	2	7	15
other	4	3	4

TREATMENT FAILURE EVENTS (STUDY 1866)

Event	Azathioprine n=166	MMF 2 gm/day n=167	MMF 3 gm/day n=166
Treatment Failure	48%	31%	31%
acute rejection	32	17	13
graft loss/death	11	6	8
AE	2	4	7
other	2	4	3

TREATMENT FAILURE EVENTS (Study 023)

Event	Azathioprine n=166	MMF 2 gm/day n=173	MMF 3 gm/day n=164
Treatment Failure	50%	38%	35%
acute rejection	29	18	15
graft loss/death	11	8	7
AE	4	6	7
other	6	5	5

The revised analyses still have a relatively high proportion of subjects classified as either adverse events or other premature terminations. The proportion is generally lowest in the control arms and highest in the MMF 3g/day group. As mentioned previously, subjects prematurely discontinuing treatment were followed with respect to patient and graft loss but were not followed with respect to acute rejection. Due to this the lack of follow-up, with respect to acute rejection for a relatively high proportion of subjects, the acute rejection rate is likely to be an underestimate. Subjects discontinuing early were found to have a worse outcome with respect to patient and graft loss at one year (this is discussed in a later section). Since the rate of premature discontinuation was highest for the 3 g/day group, the underestimate of the acute rejection rate is likely to be largest for the 3 g/day group. Overall, the FDA analyses are in basic agreement with the applicant's analyses.

Statistical Analysis Based Upon Stratification Factors Used in Randomization

For studies 022 and 023, patients were stratified by both center and 1st or 2nd allograft. The analyses conducted by the applicant were stratified only by center. Additionally for study 023, small centers were grouped for use in the Cochran-Mantel-Haenszel analysis. Formal tests for homogeneity were not presented by the applicant. We conducted analyses which adjusted for all factors used in randomization and tested for homogeneity between each of the treatment arms and the control group. The results of these tests are contained in the following tables.

Study	Result	MMF 2g/ Control	MMF 3g/ Control
MRE-022	p-value	<0.001	0.001
	relative risk (97.5% CI)	0.636 (.514,.787)	.714 (.568,.899)
ICM-1866	p-value	0.001	0.002
	relative risk (97.5% CI)	0.757 (.622,.921)	0.762 (.624,.929)
IICR-023	p-value	0.028	0.004
	relative risk (97.5% CI)	.802 (.641,1.005)	.751 (.602,.936)

It can be seen that the results of these tests show slightly smaller effect sizes than the analyses conducted by the applicant. Still, these analyses lead to the same conclusions as the analyses prepared by the applica

The following table shows results of the tests for homogeneity over the stratification factors used in each study using Zelen's test as implemented in SAS. It can be seen that for study ICM-1866 there is potentially an interaction with center for the 2 g versus control comparison. This interaction may be the result of a treatment effect reversal for center 3735 (Ferguson). The applicant provided the explanation that this investigator had a number of anomalous patients which led to this treatment effect reversal. The FDA reviewers did not feel that this explanation completely explained the result. The reviewer's ultimate conclusion is that there may be a real difference among the centers with respect to the treatment difference, but that the overall result is sufficiently strong relative to this potential interaction.

Study	2 g/day vs control	3 g/day vs control
MRE-022	0.22	0.78
ICM-1866	0.06	0.69
IICR-023	0.94	0.95

Six Month Acute Rejection versus One-year Patient and Graft Loss

The applicant has presented a literature review and an argument suggesting that the prevention of acute

rejection may lead to a long-term improvement in patient and graft survival. The study results were used to describe the degree of relationship between the occurrence of an acute rejection in the first six months and the one year status with respect to patient and graft loss. This investigation took into account the lack of follow-up with respect to acute rejection for those patients discontinuing prior to six months. Patients reaching six months without discontinuing as well as those who died or had a graft loss within the first six months were considered as having complete follow-up with respect to biopsy proven acute rejection. Patients discontinuing early without a prior disease-related clinical event (death, graft loss or biopsy proven acute rejection) were considered to have had only partial response. The following tables contain the results of these descriptive analyses for each pivotal study. It can be seen in each table that the rate of 1 year patient and graft loss is higher overall for patients with a previously recorded acute rejection. This is supportive of the applicant's link between acute rejection and patient and graft survival, though the relationship is weaker than the one presented by the applicant. It can also be seen that patients with only partial follow-up have the highest rate of 1 year patient and graft survival, but that because of the lack of follow-up it is impossible to determine if these patients had acute rejections after discontinuation but prior to six months post-transplant.

Study 022

Acute Rejection	Follow-up	N	1 year patient/graft loss		
			AZA	2 g	3 g
no	full	297	5%	3%	4%
	partial	67	25%	26%	19%
	overall	364	8%	6%	8%
yes		127	16%	21%	23%

Study 1866 -

Acute Rejection	Follow-up	N	1 year patient/graft loss		
			AZA	2 g	3 g
no	full	327	9%	3%	3%
	partial	47	20%	25%	33%
	overall	374	10%	6%	8%
yes		125	17%	21%	28%

Study 023

Acute Rejection	Follow-up	N	1 year patient/graft loss		
			AZA	2 g	3 g
no	full	318	9%	7%	6%
	partial	66	12%.	25%	32%
	overall	384	9%	10%	11%
yes		119	20%	18%	12%

Analyses of Age, Race and Gender

The applicant did not include formal statistical analyses based upon age, race or gender. FDA analyses were conducted to determine if meaningful treatment differentials could be ruled out based upon the pivotal studies. Essentially, equivalence analyses were conducted comparing the treatment differences over the demographic groups of interest.

The following table contains the event rate by age group. For each study, the sample size was insufficie to rule out relatively large differences. A pooled analysis was not conducted due to the lack of consistency over the studies. This lack of consistency suggests that there may not be an age effect for the age dichotomy chosen.

Study	age	Control	MMF 1.0 gm BID	MMF 1.5 gm BID
022	≤50	.59	.32	.38
	>50	.52	.29	.39
1866	≤50	.50	.29	.32
	>50	.43	.34	.31
023	≤50	.51	.39	.38
	>50	.49	.37	.30

The following table contains the event rates by gender. There is apparently a higher event rate for azathioprine in females (interaction p=.09 for study 023). There is no apparent numerical difference f the two MMF arms by gender, but the sample size is insufficient to rule out possibly meaningfu.

differences.

Study (Control)	gender	Control	MMF 1.0 gm BID	MMF 1.5 gm BID
022 (placebo)	male	.59	.33	.37
	female	.52	.27	.42
1866 (AZA)	male	.45	.31	.34
	female	.51	.32	.28
023 (AZA)	male	.42	.36	.35
	female	.65	.41	.35

Of the three studies, only study 1866 allowed for an analysis by race (black versus all others). Study 022 did not provide information on race and study 023 enrolled only 3 blacks. The following table contains the results for study 1866. This study suggested that there may be a disproportionate event rate for blacks receiving AZA, but that the sample size was insufficient to rule out meaningful differences among the treatments.

Study (Control)	race	Azathioprine	MMF 1.0 gm BID	MMF 1.5 gm BID
1866 (AZA)	Black	.58	.39	.24
	Other	.44	.28	.33

8.3.4 Overall Summary of Efficacy

The analyses presented by the applicant and supplemented by the analyses requested or conducted by the FDA indicate that MMF reduces the rate of occurrence of biopsy proven acute rejection in the first six months post-transplant. Additionally, these analyses suggest that the reduction in acute rejection is not associated with an increased rate of patient and graft loss at one year. The analyses were not able to demonstrate a relative advantage for 3g/day MMF over 2 g/day MMF. On the contrary, study 022 suggests that there may be a negative effect (toxicity) associated with the 3g/day dose without a corresponding reduction in acute rejection.

The analysis of acute rejection was complicated by both the presence of patient and graft loss as well as a

relatively high proportion of patients lost to follow-up. The presence of patient and graft loss was taken into account by the use of a combined endpoint consisting of biopsy proven acute rejection, death or graft loss. A flaw in the study designs is the lack of follow-up with respect to biopsy proven acute rejection for those prematurely discontinuing (subjects discontinuing treatment prior to biopsy proven acute rejection, death or graft loss) without an event. For the purpose of conducting the intent-to-treat analysis, an endpoint of treatment failure was analyzed. It was by using this endpoint that MMF was found to be beneficial. For this endpoint, patients were classified as events for any of the following reasons: biopsy proven acute rejection, death, graft loss or premature discontinuation of therapy. As death and graft loss were comparable over the study arms, the treatment failure endpoint was essentially comparing treatments on the basis of a combination of acute rejection and premature termination. With MMF there were fewer observed acute rejections, but more premature discontinuations and so a shorter period of follow-up with respect to biopsy proven acute rejection. This suggests that the simple acute rejection rates would lead to biased comparisons between the MMF arms and control. The use of the treatment failure endpoint was an attempt to cope with this bias, but treating all premature discontinuations as events has almost certainly overestimated the underlying event rate. This has likely led to a conservative comparison between MMF and control due to the higher premature discontinuation rates for MMF. The degree of conservatism is difficult to evaluate, and is complicated by the higher rate of patient and graft loss for subjects discontinuing early. This suggests that subjects discontinuing early may have had a correspondingly high acute rejection rate which was missed due to the lack of follow-up for acute rejection.

The analysis of patient and graft loss at one year has been evaluated with 100% follow-up at one year. As such the analysis of this endpoint was relatively easy to evaluate. The primary difficulty in the analysis this endpoint has been the relatively low number of events within each of the studies. This necessitated the use of a combined analysis which adjusted for study and stratification within study. The combined analysis produced relatively narrow confidence intervals for the comparisons of MMF to control. As indicated above, these intervals indicate that MMF has not led to a worsening relative to control for patient and graft survival at one year.

9 SAFETY REVIEW

9.1 Assessment of Safety:

The total patient exposure to MMF includes 3404 patients. In addition to renal transplant recipients other solid organ transplant recipients and rheumatoid arthritis patients had received MMF. At the time of the filing of this NDA, 1438 renal transplant patients received MMF. The data base used in this review is primarily derived from patients (n=991) treated for the prevention of acute renal allograft rejection in the three major trials of MMF (022, 1866, 023).

Syntex provided an update to the Integrated Safety Summary during the NDA review, including patients in the three prophylaxis studies (022, 1866, 023). This update collected data to Sept 1, 1995 (one year after the last patient was enrolled). The percentage of patients treated for greater than one year is 44.6%in placebo group (study 022), 50.9% in the AZA group(studies 1866, 023), 57.5% in the MMF2 grou,

(studies 022, 1866, 023), and 52.2%in the MMF3 group (studies 022, 1866, 023). An increased proportion of patients in the MMF 3 g vs MMF 2 g group received less than the protocol-mandated average daily dose of MMF; especially those at 1 year and 1.5 years (94% and 95% received a dose of >2 g to 3 grams of MMF), possibly suggesting a somewhat greater intolerance of the 3 g dose than the 2 g dose.

Medical Officer Note: Note that when a patient permanently discontinued drug they were not followed for adverse events. They were only followed for graft status, vital status or malignancy. The cut point for the initial safety report was 6 months after the last patient was enrolled. The initial analysis includes the entire exposure time on drug (for some patients this is > 6 months of treatment). Because event rates were only slightly increased, the applicant did not undertake to re-perform the analyses in the special populations, thus that data reviewed here for these populations will be based solely on the original 6 month report.

Medical Officer Comment: We agree with the sponsor that the updated safety profile was essentially similar to the original safety profile, however some of the rates have increased slightly.

Medical Officer Comment: From our overall review of the integrated safety summary, we agree with the applicant that the safety profile of the other types of patients (rheumatoid arthritis, other solid organ transplant recipients) exposed to MMF appears to be similar to that seen in the renal transplant population reported in the three major trials presented here.

9.2 Safety Analysis

The primary endpoint of the safety analysis was adverse events including death. Safety was also assessed by clinically-significant changes in physical signs or symptoms, laboratory values which resulted in a change in concomitant medications, and interruption or withdrawal of study medication. Adverse events including congenital anomalies and cancers, infections and abnormal laboratory test results were included in the safety database.

The following scale was utilized to grade the severity of adverse events:
Mild (Grade 1): Awareness of sign or symptom, but easily tolerated; of minor irritant type; no loss of time from normal activities; symptoms did not require medication or a medical evaluation; signs and symptoms were transient.
Moderate (Grade 2): Discomfort enough to cause interference with usual activities; symptoms persisted for prolonged periods of time (days); the study drug was interrupted or stopped briefly.
Severe (Grade 3): Inability to do work or usual activities; signs and symptoms were systemic in nature an required medical evaluation; they persisted for long periods of time; the drug was stopped, and treatment for the action may have been required.
Life Threatening (Grade 4): An adverse event for which there was risk of loss of life.
Fatal (Grade 5).

A post-hoc decision was made to use the National Institute of Allergy and Infectious Disease (NIAID) toxicity scale (where applicable) for severity grading of adverse events. While Recommendations for

grading of acute and subacute toxic effects were given for most protocols using a that superseded the above severity grading system if the type of event was given on the NIAID toxicity scale. However this was a post-hoc decision, applied to the data prior to the analysis.

Medical Officer Comment: The NIAID scale is most applicable to laboratory abnormalities. Insufficient data was collected to adequately quantitate many clinical events (eg diarrhea) as required in the NIAID scale; for these, the sponsor's original classification scheme is applied.

Medical Officer Comment: Event rates for Adverse Events are calculated as the number (%) of patients experiencing one or more event. For selected events, the 1 year rates were analyzed by the Kaplan-Meier Estimate. The three prophylaxis studies have been summarized in this review, combining results across comparable arms. The "three pooled" study results thus include Placebo (n=166), AZA (n=326), MMF2 (n=501) and MMF3 (n=490). Such pooling allows for more patients to be compared in the MMF arms. However, the overall adverse event rates in the MRE 022 (European Study) were lower than those in the AZA controlled studies. This tends to lower the overall MMF event rate in the "three"-study pooled analysis. Relative to the "two"-study pooled analysis, these differences will be noted for the reader's attention.

9.3 SAFETY DATA RESULTS:

9.3.1 CAUSES OF DEATH

The analysis reported here combines all three prophylaxis studies in order to increase the size of the data base.

CAUSES OF DEATH WHILE ON STUDY DRUG				
	PLACEBO (n= 166)	AZA (n=326)	MMF 2 (n=501)	MMF 3 (n=490)
TOTAL DEATHS	5 (3.0%)	10 (3.1%)	12 (2.4%)	14 (2.9%)
CARDIOVASCULAR EVENT	0	5 (1.5%)	3 (0.6%)	2 (<0.1%)
CANCER	0	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)
INFECTION/SEPSIS	3 (1.8%)	1 (<0.1%)	2 (<0.1%)	5 (1.0%)
PULMONARY EMBOLISM	0	2 (0.6%)	2 (<0.1%)	1 (<0.1%)
SUICIDE	0	0	0	0
CEREBROVASCULAR EVENT	0	0	0	1 (<0.1%)
ALLOGRAFT REJECTION	0	0	0	0
OTHER	2 (1.2%)	1 (<0.1%)	4 (0.8%)	4 (0.8%)

(Source: Vol 9/56; Table 27)

CAUSES OF DEATH OCCURRING ANY TIME POST TRANSPLANT				
	PLACEBO (n= 166)	AZA (n=326)	MMF 2 (n=501)	MMF 3 (n=490)
TOTAL DEATHS	10 (6.0%)	17 (5.2%)	22 (4.4%)	28 (5.7%)
CARDIOVASCULAR EVENT	3 (1.8%)	6 (1.8%)	6 (1.2%)	5 (1.0%)
CANCER	0	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)
INFECTION/SEPSIS	5 (3.0%)	3 (0.9%)	6 (1.2%)	10 (2.0%)
PULMONARY EMBOLISM	0	3 (0.9%)	3 (0.6%)	2 (<0.1%)
SUICIDE	0	0	0	0
CEREBROVASCULAR EVENT	0	0	1 (<0.1%)	2 (<0.1%)
ALLOGRAFT REJECTION	0	0	0	8 (1.6%)
OTHER	2 (1.2%)	4 (1.2%)	5 (1.0%)	

(Source: Vol 9/56; Table 28)

Medical Officer Comment: In analyses of data, both on-study medication and post-termination, the death rates as well as the causes of death, either on study or post termination, are similar among the various treatment groups (see above tables).

9.3.2 **GRAFT LOSS:**

REASONS FOR GRAFT LOSS OCCURRING ON STUDY DRUG				
	PLACEBO (n= 166)	AZA (n=326)	MMF 2 (n=501)	MMF 3 (n=490)
TOTAL PATIENTS WITH GRAFT LOSS	14 (8.4%)	19 (5.8%)	16 (3.2%)	18 (3.7%)
TYPE OF GRAFT LOSS:				
Transplant Nephrectomy	8 (4.8%)	16 (4.9%)	14 (2.8%)	14 (2.9%)
Six Consecutive Weeks of Dialysis Dependency	5 (3.0%)	3 (0.9%)	2 (<0.1%)	4 (0.8%)
Other	1 (0.6%)	0	0	0
PRIMARY REASON FOR GRAFT LOSS				
Graft Rejection	7 (4.2%)	11 (3.4%)	6 (1.2%)	4 (0.8%)
Recurrence of Underlying Disease	0	0	0	1 (<0.1%)
Technical Complications	1 (0.6%)	1 (<0.1%)	2 (<0.1%)	2 (<0.1%)
Other	6 (3.6%)	7 (2.1%)	8 (1.6%)	10 (2.0%)

(Source: Vol 9/56; Table 26)

Medical Officer Comment: The rates for graft loss were lower in the MMF arms as reported in the "on-study" analysis above. Reasons for graft loss appear to be similar; however, higher graft loss due to rejection was seen in the control arms. Because there were many more withdrawals due to adverse events in the MMF arm, the true rate of graft loss due to rejection can not accurately be assessed. As noted in the efficacy review, patients who withdrew tended to do worse in terms of patient and graft loss on the MMF arms (the rates are similar in the table below: graft loss any time after transplant).

The category "Other" includes a variety of reasons, such as stopping immunosuppression because of noncompliance, development of infection or other medically significant event, or thrombotic events in the graft that do not strictly fall under technical complications.

REASONS FOR GRAFT LOSS OCCURRING ANY TIME POST-TRANSPLANT				
	PLACEBO (n= 166)	AZA (n=326)	MMF 2 (n=501)	MMF 3 (n=490)
TOTAL PATIENTS WITH GRAFT LOSS	18 (10.8)	39 (12.0%)	38 (7.6%)	42 (8.6%)
TYPE OF GRAFT LOSS				
Transplant Nephrectomy	9 (5.4%)	26 (8.0%)	20 (4.0%)	22 (4.5%)
Six Consecutive Weeks of Dialysis Dependency	8 (4.8%)	13 (4.0%)	18 (3.6%)	20 (4.1%)
Other	1 (0.6%)	0	0	0
PRIMARY REASON FOR GRAFT LOSS				
Graft Rejection	10 (6.0%)	28 (8.6%)	20 (4.0%)	17 (3.5%)
Recurrence of Underlying Disease	0	0	0	1 (<0.1%)
Technical Complications	1 (0.6%)	2 (0.6%)	4 (0.8%)	2 (<0.1%)
	6 (3.6%)	9 (2.8%)	13 (2.6%)	21 (4.3%)
Missing	1 (0.6)	0	1 (<0.1%)	1 (<0.1%).

(Source: Vol 9/56; Table 25)

9.4 OVERVIEW OF SPECIFIC EVENTS:

9.4.1 Overall Adverse Event Rates:

Comparing the safety update to the original Integrated Safety Summary, the overall proportions of Adverse Events has increased slightly but the rank ordering of body system by frequency remained the same. Overall, the most commonly reported adverse events overall in the active treatment groups (AZA, MMF 2 g, and MMF 3 g) were related to body as a whole, digestive system , urogenital system metabolic and nutritional disorders, cardiovascular system, and hemic and lymphatic system. Adverse events in these systems were reported by more than 50% of the patients in at least one of the active treatment groups. For the placebo group, the most commonly reported adverse events were in the body as a whole, digestive system, urogenital system, cardiovascular system, and respiratory system . Adverse events in these systems were reported by 30% or more of patients in the placebo group (see below).

	ALL ADVERSE EVENTS		SEVERE ADVERSE EVENTS	
	Active Treatment Groups (AZA, MMF2, MMF3)	Placebo	Active Treatment Groups (AZA, MMF2, MMF3)	Placebo
Body As whole	74-80%	59%	23-29%	12%
Digestive System	66-70%	44%	12-15%	4%
Urogenital System	64-66%	55%	17-18%	4%
Metabolic/Nutrition	55-69%	30%	9-21%	3%
Cardiovascular	48-60%	42%	11-20%	7%
Heme/Lymphatic	47-6-%	17%	15-23%	2%

(Source: Vol 8/56; Tables 8&9)

In the active treatment groups (AZA, MMF 2 g, and MMF 3 g), events classified by the investigators as severe were reported most often for the body as a whole, hemic and lymphatic system, urogenital system, cardiovascular system, metabolic and nutritional disorders, and the digestive system (see below). For the placebo group, the most commonly reported severe adverse events were as follows (ranked in descending order): body as a whole, digestive system, urogenital system, cardiovascular system, respiratory system, and heme-lymph. Thus, events related to the hemic and lymphatic, and urogenital systems were represented relatively more commonly among severe events compared with overall events, and severe digestive system events were represented relatively less frequently compared with overall events.

The adverse events in the remaining body systems were reported with a frequency of less than 50%. Adverse events classified by the investigators as possibly or probably related to study drug ("drug-related"), or lacking causality, were reported by 81-86% of patients in the 4 dosage groups. By body system, drug-related adverse events for events reported in more than 20% of patients in any treatment group, were (in descending order of frequency): digestive system, body as a whole and the urogenital, skin and appendages, hemic and lymphatic, and respiratory systems. Based on their relative frequency of reporting, drug-related adverse events were more likely to have been classified under the digestive and urogenital systems than overall events (see below).

	ADVERSE EVENTS PROBABLY OR POSSIBLY RELATED TO STUDY DRUG	
Event	Active Treatment Groups (AZA, MMF 2, MMF 3)	Placebo Group
Digestive System	45-49%	34%
Body as Whole	34-38%	36%
Urogenital System	19-30%	42%
Skin/Appendages	28-30%	16%
Hemic/Lymphatic	25-33%	7%
Respiratory System	9-19%	34%
Metabolic/Nutrition	15-17%	7%
Cardiovascular	5-8%	4%

(Source: Vol 8/56; Table 10)

Severe adverse events were more likely to involve the hemic and lymphatic system . The following severe events were reported in more than 10% of patients in any treatment group (in descending order of frequency): hemic and lymphatic, urogenital, cardiovascular metabolic and nutritional, digestive, and respiratory systems.

Medical Officer Comment: Overall adverse events associated most frequently associated with MMF are those related to the Gastrointestinal and Heme/Lymphatic Systems. The following section will review selected events by body system for any severity, severe events, events possibly or probably related to study drug, and events causing a study drug dosage adjustment or discontinuation. Special focus will be directed toward GI and heme/lymphatic system events.

9.4.2 BODY SYSTEM AS WHOLE:

Among overall events classified under body as a whole, pain, abdominal pain, sepsis, infection, and fever were most frequently reported in all treatment groups (see below). Except for pain (which was more common in the AZA group compared with the MMF 2 g group, the MMF 3 g group, and the placebo group) and sepsis (which was slightly more common in the MMF 2 g and 3 g groups), the other events were evenly distributed in the active treatment groups and lowest for placebo. About 50% of the events classified as sepsis were viremia.

BODY SYSTEM AS WHOLE: Any Adverse Event				
	PLACEBO (n=166)	AZA (n=326)	MMF2 (n=501)	MMF3 (n=490)
Abdominal pain	11.4%	23.0%	20.6%	22.4%
Infection	13.3%	19.9%	16.4%	19.2%
Sepsis	13.9%	15.6%	19.0%	19.0%
Asthenia	1.2%	19.9%	9.8%	10.8%

(Source: Vol 8/56; Table 8)

For body system as a whole, sepsis, infection, abdominal pain, and fever were also the most common adverse events rated severe, along with cyst (most often lymphocele, a common postoperative complication). Abdominal pain and sepsis are further reviewed below.

ABDOMINAL PAIN				
	PLACEBO (n=166)	AZA (n=326)	MMF2 (n=501)	MMF3 (n=490)
Severe	1.2%	3.4%	3.2%	2.2%
Possibly/Probably Related to drug	7.2%	9.2%	11.2%	10.0%
Decrease or Interrupt dosage	0	1.8%	2.2%	3.7%
Discontinue due to AE	2.4%	0.3%	1.4%	1.4%

(Source; Vol 8/56; Tables 9, 10, Vol 9/56; Tables 18,19)

Medical Officer Comment: Patients were more likely to have severe abdominal pain in the active treatment groups. Drug dosage adjustment attributed to abdominal pain was more common in the active treatment arms (especially MMF3 arm); however, drug discontinuation due to study drug was more

frequent in the placebo arm.

SEPSIS				
	PLACEBO (n=166)	AZA (n=326)	MMF2 (n=501)	MMF3 (n=490)
Severe	2.4%	4.6%	6.6%	7.1%
Possibly/Probably Related to drug	13.3%	11.7%	15.6%	14.3%
Decrease or Interrupt dosage	0.6%	5.5%	5.0%	4.5%
Discontinue due to AE	0	1.8%	0.6%	1.6%

(Source; Vol 8/56; Tables 9, 10, Vol 9/56; Tables 18,19)

Medical Officer Comment: Sepsis was more frequently reported in the MMF arms for each of the adverse event categories: severe, drug-related, dose adjustment and discontinuation.

Drug related infection is more frequently a drug-related association in the placebo group (12.7%) than the MMF or AZA treatment arms (6-9%).

Among events rated severe, first occurrences of sepsis, infection, fever, and cyst were reported more frequently during the time period 31–180 days than in the initial 30 days on treatment in all four treatment groups. Abdominal pain, in the two MMF treatment groups, was more frequently reported during the interval 31–180 days post-transplant than in the initial 30 days on treatment.

9.4.3 **DIGESTIVE SYSTEM:**

Overall, diarrhea, nausea, constipation, dyspepsia, oral moniliasis, vomiting, and nausea and vomiting were the most commonly reported adverse events in the digestive system (see below). Patients in the

MMF 2 g group and particularly the MMF 3 g group were more likely to experience diarrhea and vomiting than patients in the control groups.

The most common adverse events reported in the digestive system are listed below.

DIGESTIVE SYSTEM				
	PLACEBO (n=166)	AZA (n=326)	MMF2 (n=501)	MMF3 (N=490)
Diarrhea	13.9%	20.9%	26.1%	30.4%
Nausea	3.0%	24.5%	15.2%	18.4%
Constipation	3.0%	22.4%	18.0%	14.3%
Vomiting	1.8%	9.2%	9.2%	10.6%

(Source: Vol 8/56; Table 8)

Medical Officer Note: Diarrhea was the most frequently reported event in the following categories: severe event, drug related event, and event requiring discontinuation of study drug.

DIARRHEA EVENTS				
	PLACEBO (n=166)	AZA (n=326)	MMF2 (n=501)	MMF3 (N=490)
Severe	0	0.6%	2.6%	2.9%
Possibly/Probably Related to drug	9.6%	12.6%	15.0%	20.0%
Decrease or Interrupt dosage	2.4%	1.2%	4.4%	4.5%
Discontinue due to AE	0.6%	0	0.4%	2.2%

(Source; Vol 8/56; Tables 9, 10, Vol 9/56; Tables 18,19)

Severe diarrhea was also more frequently reported in the two MMF groups compared with AZA (see above). No placebo patients reported severe diarrhea. Severe vomiting, nausea, colitis, and hepatitis (placebo=0, AZA=0.6%; MMF2=0.4%; MMF3=1.2%) were all more common in the two MMF groups

compared with the control groups. Diarrhea was also the most commonly reported drug-related digestive system event and was more frequent in the two MMF groups than in the control groups (see above).

Medical Officer Note: The increased frequency of diarrhea in the MMF3 group compared to the others was accentuated in the two-pool summary of drug-related adverse events (AZA, 20.9% MMF 2 g, 31.0%, MMF 3 g, 36.1%; see Table 19; vol 8/56).

Severe nausea was more likely to occur in the MMF arms, was more likely to be related to study drug and was most likely to require a dosage change in the MMF arm. Discontinuation of study drug due to nausea was most frequent in the Placebo arm.

NAUSEA EVENTS				
	PLACEBO (n=166)	AZA (n=326)	MMF2 (n=501)	MMF3 (n=490)
Severe	0.6%	0	0.4%	1.0%
Possibly/Probably Related to drug	2.4%	10.7%	7.2%	9.6%
Decrease or Interrupt dosage	0.6%	0.6%	1.6%	1.2%
Discontinue due to AE	1.8%	0	0.2%	1.2%

(Source; Vol 8/56; Tables 9, 10, Vol 9/56; Tables 18,19)

Medical Officer Comment: There was an increased incidence of digestive system infection and gastroenteritis among patients receiving MMF 3 g (3.7%), and gastritis among both MMF groups, compared with control (see Table 9, vol 8/56). Patients with the verbatim term *Chr. Gastritis* are summarized under the preferred term *gastritis* in the COSTART 3 thesaurus.

For the two MMF treatment groups, the first occurrence of severe diarrhea, infection, and gastrointestinal hemorrhage was most likely to be reported in the period from 31 to 180 days -post-transplant than in the initial 30 days on treatment.

Medical Officer Note: Gastrointestinal hemorrhage was reported by about 10% of the patients, and because of it's significance as a severe event we review it here (see below). Overall the Placebo group had one event that was not judged to be severe, thus having NO gastrointestinal hemorrhage events. For the MMF groups there were overall more gastrointestinal bleeding events (MMF2= 29, 5.8%; MMF3=32, 6.5%); these numbers were reduced when the investigators designated severe events: MMF2=21, 4.2%; MMF3=24, 5%.

Thus in general the MMF arms had higher proportions of gastrointestinal bleeding than the AZA and Placebo arms. Both the overall rate and the rate of severe events were similar among the MMF groups.

GASTROINTESTINAL HEMORRHAGIC EVENTS: Percent (Number)				
	PLACEBO (n=166)	AZA (n=326)	MMF2 (n=501)	MMF3
Gastrointestinal hemorrhage	0	0.6 (2)	1.4 (7)	2.5 (12)
Melena	0.6 (1)	1.5 (5)	1.4 (7)	1.4 (7)
Rectal Hemorrhage	0	0.9 (3)	1.2 (6)	0.4 (2)
Hematemesis	0	0	0.6 (3)	0.6 (3)
Hemorrhagic gastritis	0	0	0	0.4 (2)
Duodenal ulcer hemorrhage	0	0	0.4 (2)	0.2 (1)
Peptic ulcer hemorrhage	0	0.3 (1)	0	0
Stomach ulcer hemorrhage	0	0.3 (1)	0	0
Hemorrhage of colon	0	0	0.2 (1)	0
Bloody Diarrhea	0	0	0	0.2 (1)
Large intestinal perforation	0	0.3 (1)	0.4 (2)	1.0 (5)
GI perforation	0	0	0.2 (1)	0
Erosive Duodenitis	0.6 (1)	0	0	0
TOTAL	1	13	29	32

(Source: Vol 8/56; Table 8)

Upon further reflection, the applicant chose to include ulcers in the overall grouping with GI hemorrhage. Eventhough these may not have been bleeding (see below).

Medical Officer Comment: The overall pattern of events (more events in the MMF arms) is still apparent when one adds ulcers into the tabulation below, however, the degree of difference between the two patterns is somewhat diminished (see 3 bottom rows below).

GASTROINTESTINAL EVENTS: Percent (Number) (patients are exclusive)				
	PLACEBO (n=166)	AZA (n=326)	MMF2 (n=501)	MMF3
Melena/ Rectal Hemorrhage	0.6 (1)	2.5 (8)	2.6 (13)	1.8 (9)
GI bleed/ Perforations	0	1.2 (4)	3.2 (16)	4.9 (24)
Ulcers	3.0 (5)	1.5 (5)	2.0 (12)	2.5 (12)
TOTAL (All)	3.6 (6)	5.2 (17)	8.2 (41)	9.2 (45)
TOTAL: Melena Rectal Hemorrhage/ Bleeding/Perforations	0.6 (1)	3.7 (12)	5.8 (29)	6.7 (33)
TOTAL : GI bleeding/ Perforations/Ulcers	0	2.8 (9)	5.6 (28)	7.4 (36)

Combined from above tables with ulcer events added.

9.4.4 UROGENITAL SYSTEM

Urinary Tract Infection was the most common adverse event reported in the urogenital system (placebo, 37%; AZA, 34%; MFG, 40%; MMF3 g, 39%). Among less common events, kidney tubular necrosis was reported more frequently in the MMF3 g group (7.1%) than in the MMF 2 g (4.25), AZA (5.8%), or placebo (1.2%) groups. The increased proportion of patients with kidney tubular necrosis in the MMF 3 group was seen even more prominently in the "2 pool" analysis (AZA, 5.8%; MMF 2 g, 6.3%; MMF 3g, 10%).

Severe urinary tract infection was also the most common severe adverse event in this body system and was slightly more frequent in the 2 MMF groups than the 2 control groups. Urinary tract infection (UTI) was also the most common drug-related adverse event in this body system. UTI attributed to treatment

was most common in the placebo group (37%), compared with the MMF3 (22%) , MMF2 (24%) and AZA (11%) groups. Results from the safety update are nearly identical to those presented in the original ISS (Integrated Safety Summary).

Medical Officer Comment: Over all Urinary Tract Infection was the most frequent Urogenital System adverse event but it was similar in frequency across all arms.

9.4.5 METABOLIC AND NUTRITIONAL SYSTEM

Peripheral edema was the most common event reported and was most frequent in the AZA group(28.2%). Among severe events in this body system, hyperglycemia and hyperkalemia were more common in the AZA group (3.4% and 3.7% respectively). Severe hypokalemia was more common in the MMF 3 group (1.4%) ; however, these differences were very small.

Medical Officer Comment: No apparent, significant differences were seen between groups in this body system.

9.4.6 CARDIOVASCULAR SYSTEM

Hypertension was the most common adverse event reported in this body system and was slightly less common in the MMF 3 group (25%) compared with MMF 2 (28%), AZA (32%), and placebo (19%) groups. This slightly lower incidence of hypertension in the MMF 3 group was also observed in the "2 pool". There were no other clinically significant differences among the treatment groups for events in this body system.

Severe cardiovascular system events were more frequent in the AZA (19.9%) group than in the MMF2 and MMF3 (11.2% and 13.1% respectively), and placebo (7.2%)groups. There were no individual preferred terms that accounted for this difference.

Medical Officer Comment: No apparent, significant differences were seen between groups in this body system.

9.4.7 HEME AND LYMPHATIC SYSTEMS

Overall leukopenia and anemia were the most commonly reported events. Leukopenia was more frequently observed in the MMF 3 arm.

Medical Officer Comment: Leukopenia required a clinical judgement by the investigator of the measured WBC. There was not strict cutoff specified per protocol. Absolute Neutrophil Count is reviewed in the Laboratory Section below. Rates for this event generally parallel the trend seen for leukopenia: both were more frequent in the MMF 3 arm.

HEMIC AND LYMPHATIC SYSTEM (Any Event)				
	PLACEBO (n=166)	AZA (n=326)	MMF2 (n=501)	MMF3
Leukopenia	4.2%	25%	19.4%	29%
Anemia	2.4%	24%	19%	20%
Thrombocytopenia	4.8%	13.2%	8.6%	6.9%

(Source; Vol 8/56; Table 8)

Medical Officer Comment: In the "2 study pool" analysis the differences in the incidence of leukopenia were more prominent (35% in the MMF 3 group, 23% in the MMF2 group, and 25% for the AZA group).

LEUKOPENIA EVENTS				
	PLACEBO (n=166)	AZA (n=326)	MMF2 (n=501)	MMF3
Severe	1.2	3.7%	2.4%	5.3%
Possibly/Probably Related to drug	3.0%	22.1%	16.0%	24.9%
Decrease or Interrupt dosage	1.8%	19.0%	15.2%	21.8%
Discontinue due to AE	0.6%	1.8%	1.6%	2.7%

(Source; Vol 8/56; Tables 9, 10, Vol 9/56; Tables 18,19)

Medical Officer Comment: The MMF 3 arm had the highest frequency of Leukopenic events that were severe, probably or possibly related to study drug, required dosage adjustment, and/or required study drug discontinuation. Most leukopenic episodes resolved; however, a small proportion of the events were not followed to their resolution because the patient went off study drug and AE follow-up was not collected.

ANEMIA EVENTS				
	PLACEBO (n=166)	AZA (n=326)	MMF2 (n=501)	MMF3
Severe	0	16.0%	10.4%	12.4%
Possibly/Probably Related to drug	0.6%	3.4%	4.4%	4.1%
Decrease or Interrupt dosage	0.6%	0.6%	1.0%	0.8%
Discontinue due to AE	0	0.3%	0.6%	0.6%

(Source; Vol 8/56; Tables 9, 10, Vol 9/56; Tables 18,19)

Medical Officer Comment: Severe anemia was most common adverse event in this system and was most often reported in the AZA group. In the "2 pool" analysis, however, severe anemia was slightly more common in the MMF 3 group (18%) than in the AZA (16%) or the MMF 2 (15%) group. Severe leukopenia was more common in the MMF 3 group compared with the MMF2, AZA or placebo groups. In the MMF 3 group there was a slight increase in the cumulative incidence of first occurrence of severe anemia and severe leukopenia over the time intervals ending at 1 year and 18 months on treatment respectively. This was not noted in the MMF2 arm.

Thrombocytopenia was more common for AZA.

9.4.8 SKIN AND APPENDAGES

Herpes simplex was the most common adverse event in this body system and is considered in the OI section. Acne was slightly more common in the MMF treatment groups (MMF2 and MMF3 each 9.0%) compared with control patients (placebo, 6.0; AZA, 6.4%).

9.4.9 Adverse events resulting in reduced dose or interruption of study medication.
Events in the hemic and lymphatic system, digestive system, and body as a whole were the most common events resulting in study drug discontinuation or interruption.

Medical Officer Comment: Leukopenia was most common in the MMF3 and AZA groups. A higher proportion of patients in the AZA group experienced thrombocytopenia resulting in reduced dose or interruption of study drug.

A higher proportion of patients in the MMF 3 and MMF2 groups experienced Gastrointestinal adverse events resulting in reduced dose or interruption of study drug. Diarrhea, nausea, vomiting and gastrointestinal hemorrhage accounted for most of this increased incidence, but many other events were

also more common in the MMF groups, including those associated with ulceration or infection of the gastrointestinal tract (see above tables).

Abdominal pain was increased in the MMF 3 group.

9.4.10 **Adverse events resulting in discontinuation of study medication.**

Medical Officer Comment: A higher proportion of patients in the MMF 3 group experienced adverse events resulting in study drug discontinuation (see above tables). Events in the Gastrointestinal, body as a whole and heme/lymphatic categories accounted for most of the increase in the MMF3 group. For the other body systems, there was no substantial difference across treatment groups for events resulting in study drug discontinuation.

Diarrhea was most likely to be the cause of discontinuation in the MMF3 group than the other groups. However, a somewhat higher percentage of patients in the MMF3 group also terminated the study due to leukopenia.

9.5 OPPORTUNISTIC INFECTIONS

The updated safety summary indicates 43 additional opportunistic events occurring since the initial NDA safety filing. The most significant increases were in the candida and herpes zoster categories. Seven additional patients each were ranked as having candida episodes in the AZA and MMF2 arms, while 6 additional patients were noted to have herpes zoster in the MMF3 groups. Overall there has been a slight increase in the numbers of patients with herpes zoster infections since the original ISS in all four treatment groups (Placebo, 1.8% [original ISS] to 2.4%[update]; AZA, 5.2% [original ISS] to 5.8% [update]; MMF 2 g, 5.8% [original ISS] to 6.2% [update]; MMF3, 5.7% [original ISS] to 7.3% [update]).

A higher proportion of patients in the active treatment groups (AZA, 46%; MMF2 44%; MMF3, 45%) experienced one or more opportunistic infections compared with patients receiving placebo (28%).

9.5.1 CMV

Medical Officer Comment: A higher proportion of patients in the active treatment groups (AZA, 46%; MMF2 44%; MMF3, 45%) experienced one or more opportunistic infections compared with patients receiving placebo (28%). CMV viremia syndrome was the most common diagnostic category of CMV disease; the incidence was similar in all four treatment groups (13-14%).

Tissue-invasive CMV disease was more common in the active treatment group (AZA, 6.1%; MMF2, 6.8%; MMF3, 10.2%) than in the placebo group (2.4%). The incidence of CMV tissue-invasive disease was higher in MMF-treated patients. This difference was also prominent in the "2 pool" (AZA, 6.1%; MMF 2, 8.3%; MMF3, 12%). The most frequent systems involved with CMV were the gastrointestinal tract and respiratory tract.

The cumulative proportion of patients with CMV disease at Month 6 was slightly higher among patients in the active treatment groups (AZA, 20%; MMF2, 20%; MMF 3, 22%) compared with placebo (17%). A higher cumulative incidence of CMV tissue-invasive disease observed among patients receiving MMF 3 began to appear at 3 months and continued to increase through 18 months (Kaplan-Meier Rates, see table below).

First Episode of Tissue Invasive Disease				
	PLACEBO	AZA	MMF2	MMF3
3 months	1.4	5.9	6.0	8.7
6 months	3.1	6.3	6.9	11.2
12 months	3.1	7.1	7.7	11.5
18 months	3.1	7.1	7.7	12.3

The proportion of patients with CMV infection, virtually all of which was CMV urinary tract shedding an thus not clinically important, was similar in the three active treatment groups (4.6-6.1%) and was higher in these groups compared with the placebo group (0.6%).

9.5.2 Herpes Simplex

Medical Officer Comment: Although herpes simplex was the most frequent OI there was no substantial difference in the incidence of herpes simplex virus infection (16-19%) among the treatment groups. Incidence of herpes in patients receiving placebo was lower (6.9%).

9.5.3 Candida

Both initial and updated safety summaries reported that five out of six fungemia/disseminated and 5 out of 6 tissue-invasive events occurred in the MMF arms; no such events occurred in the placebo. The updated safety summary reports one additional "serious" candida infection during the follow-up period.

9.5.4 Herpes Zoster

The proportion of patients with herpes zoster infections, nearly all of which represented cutaneous disease, was similar in the three active treatment group (5.8%-7.3%) and somewhat lower in the placebo group (2.4%). For visceral disease, 4 of 5 patients were receiving MMF3, while the fifth patients was receiving AZA.

9.5.5 Pneumocystis Carinii

Among the nine patients with Pneumocystis infection (all pulmonary disease) 8 were receiving either

AZA or placebo. One patient was in the MMF 2 group. One patient in the AA group was initially classified as having Pneumocystis infection but was reclassified as having Candida infection based upon updated information.

9.5.6 **Aspergillus/Mucor**
Among the 5 patients with invasive Aspergillus/Mucor infections, 3 (0.6%) were in the MMF 3 group and 1 each were in the AZA (0.3%) and MMF2 groups (0.2%)

9.6 LABORATORY ABNORMALITIES

Medical Officer Comment: Laboratory data related to the hemic and lymphatic system are discussed below; malignancies of the hemic and lymphatic system are discussed in a section 9.8 of this summary. Selected laboratory data for hematologic, kidney, and hepatic function are reviewed below.

9.6.1 **Minimum Absolute Neutrophil Count (ANC).** Nearly all patients in all four treatment groups had a normal ANC ($\geq 2 \times 10^3/\mu L$ [$\geq 2 \times 10^9/L$]) during the first 30 days post-transplant (see Vol 9/56; table 29). In the AZA group, 2 patients (0.6%) had minimum ANC values below this level, compared with 2 (1.2%), 2 (0.4%), and 3 (0.6%) patients in the placebo, MMF 2 g, and MMF 3 g groups, respectively. A breakdown by time on study is provided below:

During the period 31–180 days on treatment (see below), a higher proportion of patients in the active treatment groups had decreased minimum ANC values. The highest rates were in the MMF groups, especially MMF3.

During the period 181–365 days on treatment (see below), a lower proportion of patients had minimum ANC values less than $2 \times 10^3/\mu L$ ($2 \times 10^9/L$), compared with the earlier time interval. However, a higher proportion of patients in the MMF 3 g group had minimum ANC values less than $2 \times 10^3/\mu L$ ($2 \times 10^9/L$), compared with the other 3 groups.

ABSOLUTE NEUTROPHIL COUNT < 2.0 x10^9/L				
Time since Transplant	Placebo	AZA	MMF2	MMF3
≤ 30 days	2/140 (1.2%)	2/293(0.7%)	2/437 (0.5%)	3/430 (0.7%)
31-180 days	1/133 (0.8%)	16/262 (6.1%)	39/426 (9.2%)	50/448 (12.4%)
181-365 days	0/102 (0%)	9/227 (4.0%)	23/241(9.5%)	20/314(8.0%)
over 365 days	0/62 (0%)	2/100(2.0%)	5/192 (2.6%)	10/186 (5.4%)

(Source: Vol 9/56;Table 29)

There were few patients with minimum ANC values less than $2 \times 10^3/\mu L$ ($2 \times 10^9/L$), most of these are in the MMF arms. Note that less than 40% of the original patient population have ANC data beyond

day 365.

ABSOLUTE NEUTROPHIL COUNT 0.5 - <7.5 x10^9/L				
Time since Transplant	Placebo	AZA	MMF2	MMF3
≤ 30 days	0/140 (0%)	1/293(0.3%)	0/437 (0%)	0/430 (0%)
31-180 days	0/133 (0%)	2/262 (0.8%)	1/426 (0.2%)	6/448 (1.5%)
181-365 days	0/102 (0%)	0/227 (0%)	3/241(0.9%)	0/314(0%)
over 365 days	0/62 (0%)	0/100(0%)	0/192 (0%)	0/186 (0%)

(Source:Vol 9/56;Table 29)

As noted in tables for severe ANC between 0.5 and 7.5 x10^9/L or less than 0.5x10^9/L most of the events occurred in the time period of 31-180 days post transplantation, and were more frequent in the MMF 3 arm.

The frequency of severe neutropenia was low:

ABSOLUTE NEUTROPHIL COUNT < 0.5 x10^9/L				
Time since Transplant~	Placebo	AZA	MMF2	MMF3
≤ 30 days	0/140 (0%)	0/293(0%)	0/437 (0%)	1/430 (0.2%)
31- 180 days	0/133 (0%)	2/262 (0.8%)	2/426 (0.5%)	8/448 (1.5%)
181-365 days	0/102 (0%)	0/227 (0%)	0/241(0%)	1/314(0.3%)
over 365 days	0/62 (0%)	0/100(0%)	0/192 (0%)	1/186 (0.5%)

(Source:Vol 9/56;Table 29)

Medical Officer Comment: Severe absolute neutrophil count events occurred in small numbers, but most significantly in the MMF arms and were most likely to occur between 31-180 days. This trend parallels the leukopenia events discussed above.

9.6.2 **Minimum Platelet Count:**

Only 1 patient each, in the placebo group, AZA group and MMF3 had a minimum platelet count of less than $25x10^3$/uL (between days 31-180). Ninety-eight percent-100% of patients in all four treatment groups had minimum platelet counts greater than $100x10^3$/uL ($100x10^9$/uL) during the intervals 181-365, 366-545, and > 545 days on treatment.

Medical Officer Comment: From a review of the data, overall the AZA group was more likely to have thrombocytopenia listed as an adverse event compared to the placebo and MMF groups.

9.6.3 **Minimum Hemoglobin:**

The greatest proportion of anemia was seen during the early post-transplantation period (<30 days) and it was similar for all 4 study groups. Patients with hemoglobin levels of >11 g/dL (110 g/L) were seen in 10% of patients on Placebo, 9% on AZA, and 8% for both MMF groups. The anemia improved remarkably in the subsequent time periods.

A higher proportion of patients in the active treatment groups (AZA, 14%; MMF2, 15%; MMF3, 17%) had hemoglobin concentrations less than 11 g/dL (110 g/L) during the interval 181-365 days on treatment compared to placebo (6.0%). The pattern was similar in the interval 366-545 days on treatment.

9.6.4 **Maximum Serum Creatinine:**

During the initial 3 days post-transplant placebo patients were more likely to have serum creatinine levels $\geq$ 2.5 mg/dl ($\geq$ 221 umol/L) compared to the active treatment groups (61% vs 47-51%, respectively). Improvements in these values were seen in later time periods as noted below.

During the interval 181-365 days on treatment a higher proportion of patients in the MMF2 and MMF3 groups (17%, 19% respectively) had creatinine values less than 1.2 mg/dL (106 umol/L), compared with AZA 9.4%) and placebo (18%). Conversely, a lower proportion of patients in the MMF 3 group (9.3%) had creatinine values $\geq$ 2.5 mg/dl ($\geq$ 221 umol/L) compared with MMF 2 (13%), AZA (13%) or placebo (15%).

Medical Officer Comment: These results parallel the graft loss results.

9.6.5 **Maximum Serum Bilirubin:**

Elevated serum bilirubin greater than 1.2 mg/dL (20 umol/L) was seen rarely. those patients (2) were seen in the AZA group, in both the intervals 181-365 and 366-545 days on treatment. Mild elevations of serum bilirubin between 1.2-6.0 mg/dL (20 umol/L) were seen in all groups, being more likely to occur in the AZA group. The overall range of rates for mild elevations was between 6-20%.

Medical Officer Comment: No apparent toxicity was demonstrated by the MMF groups as measured by serum bilirubin was demonstrated.

9.6.6 **Maximum Alkaline Phosphatase**:

During the initial 30 days on treatment, more than 1/2 of the patients in each of the four treatment groups had a maximum alkaline phosphatase value above normal (≥ 90 U/L).

During the interval 31-180 days on treatment a higher proportion of patients in all four treatment groups (placebo, 58.3%; AZA, 48%; MMF2, 58%; MMF3, 58%) had a mildly elevated maximum alkaline phosphatase value of 90-<400U/L. A similar proportion of patients in all groups (2-3%) had maximum alkaline phosphatase values of 400-1000U/L during this period. One patients each in AZA and MMF 3 reported a value of ≥ 1000 U/L. The subsequent time periods had similar findings.

Medical Officer Comment: The proportion of patients with abnormal values, and the proportion in the more extreme maximum values, were similar across the four treatment groups. Thus, no apparent toxicity was demonstrated by the MMF groups as measured by serum alkaline phosphatase was demonstrated.

9.6.7 **Maximum SGOT:**

During the initial 30 days on treatment, most patients (90-93%) had maximum SGOT in the normal range. Mildly elevated maximum SGOT values of 60-<200 U/L occurred in 7.4% of Placebo, 7.9 % of AZA, 9.3% of MMF2 and 7.2 % of MMF3 patients.

During the intervals slightly higher proportion of patients receiving MMF3 had elevated maximum SGOT, compared with the other treatment groups. For maximum SGOT values or 60-< 200 U/L, 7.0% of MMF3 patients , compared with 5% of MMF 2 patients , 3.0 % of AZA patients and 2.3 % of placebo patients had values in this range in the 31-180 day interval. In the 181-365 day interval 4.0% of MMF3 compared with 2% of MMF 2 patients , 3.3 % of AZA patients and 1.3 % of placebo patients had maximum SGOT values in this range.

Medical Officer Comment: similar low rates of SGOT elevation were seen across all arms, thus no apparent toxicity was demonstrated regarding SGOT.

9.6.8 **Maximum SGPT:**

During the initial 30 days on treatment 59-62% of patients in each treatment group had maximum SGOT values less than 50 U/L, while 32-36% had maximum SGOT values of 50 - < 200 U/L.

During the interval 31-180 days on treatment, compared to the initial 30 days on treatment, a higher proportion of patients in each group (80-88%) had maximum SGPT values in the normal range. During the intervals 181-365 days and greater than 365 days, a similar proportion of patients in each treatment group (92-97%) had maximum SGPT values in the normal range (50 U/L).

Medical Officer Comment: similar rates of SGPT elevation were seen across all arms, thus no apparent toxicity was demonstrated regarding SGPT. Overall, there was no evidence of hepatotoxicity as measured by Alkaline phosphatase, SGOT and SGPT for MMF compared to the other control groups.

9.7 SPECIAL POPULATIONS:

Medical Officer Comment: The following analysis are based upon the Initial Integrated Safety Summary They were not updated in the 1 year safety update because there was little change in overall events.

9.7.1 Adverse Events in Patients with Delayed Graft Function

Delayed graft function (DGF), defined in these studies as a requirement for dialysis in the first week post-transplant, is generally considered a consequence of preservation injury to the kidney prior to transplantation and ischemic injury at the time of transplantation. Delayed graft function may occur in up to 10% to 40% of renal allograft recipients. Pharmacokinetic studies have shown that among patients with DEF, plasma MPA concentrations are similar but MPAG concentrations may be markedly higher during the period of impaired renal function than among patients with good post-transplant function (see the Integrated Summary of Human Pharmacokinetics and Bioavailability).

In the 3 study pooled summary, 298 of 1483 patients (20%) had DGF. The proportion of patients in each treatment group with DGF was 25% in placebo (41 of 166 patients), 14% in AZA (47 of 326), 23% in MMF 2 g (113 of 501), and 20% in MMF 3 g (97 of 490). Only minimal differences in the profile of adverse events were reported in patients with DGF compared with the population without delayed function for each of the treatment groups (see below). However, a higher proportion of patients with DGF reported anemia and thrombocytopenia

Hematologic Events in Patients with Delayed Graft Function * (No DGF)				
	PLACEBO (DGF n=41) (Non n=125)	AZA (DGF n=47) (Non n=279)	MMF2 (DGF n=113) (Non n=388)	MMF3 (DGF n=97) (Non n= 393)
Leukopenia	9.8% (2.4%)	25.5% (24%)	19.5% (17%)	27.8% (26%)
Anemia	2.4% (1.6%)	23.4% (25%)	25.7% (15%)	28.9% (16%)
Thrombocytopenia	14.6% (1.6%)	17% (11.8%)	12.4% (7%)	16.5% (3.8%)

(Source: Vol ; Tables 21, 22)

Similarly, a higher proportion of DGF patients reported hyperkalemia compared with non-DGF patients. There was no disproportionate increase in hyperkalemia in the two MMF groups compared with the control groups. As expected, a substantially higher proportion of patients in the DGF group had kidney

tubular necrosis compared with the non-DGF group, but again, similar differences in DGF versus non-DGF patients were observed in each of the treatment groups. Thus, although patients with DGF have an increased incidence of certain adverse events, differences were proportional across each of the treatment groups.

Medical Officer Comment: In general, there was no evidence for a worse safety profile among DGF patients treated with MMF, compared to DGF patients treated with control therapies, however there may have been some excess hematologic abnormalities.

9.7.2 Summary of Adverse Events Classified by Gender

Medical Officer Comment: Overall, more females than males reported urinary tract infections in all four treatment groups. Among the three active treatment groups in the three-study pool, anemia, diarrhea, nausea, and herpes simplex infection were reported more frequently in female patients. In the two MMF treatment groups, leukopenia was reported more frequently by female patients (particularly in the MMF 3 g group), while in the AZA group, more males reported leukopenia (see below).

The analysis for anemia may not have been corrected for the hemoglobin levels that are normal for a women.

Although a small number, women tended to have more acidosis than men in the two MMF treatment arms. This may be do to dehydration since women were more likely than men to have diarrhea and nausea. Also there was a slight trend for increase in alkaline phosphatase and SGOT increases in women compared to men. This occurred more in the AZA arm and the levels were almost comparable in the MMF 3 arm.

Gender Comparisons of Any Adverse Event (% of Patients with one or more event)								
	PLACEBO		AZA		MMF2		MMF3	
	F= 64	M= 102	F= 123	M= 203	F= 220	M= 281	F= 187	M= 303
Urinary Tract Infection	48.4%	27.5%	39.8%	21.2%	50.5%	28.5%	43.3%	32%
Anemia	3.1%	1%	31.7%	17.2%	21.8%	13.9%	22.5%	15.8%
Leukopenia	3.1%	4.9%	19.5%	27.1%	19.1%	16.7%	30.5%	23.8%
Diarrhea	9.4%	14.7%	23.6%	16.7%	25.5%	20.6%	32.1%	23.8%
Nausea	1.6%	2.9%	28.5%	17.2%	16.4%	11%	20.3%	12.9%
Herpes Simplex	4.7%	5.9%	23.6%	14.8%	18.6%	12.1%	19.8%	12.5%

Alk Phos Inc	xx	xx	6.5%	3.4%	6.8%	3.9%	4.8%	4.3%
Acidosis	xx	xx	4.9%	6.4%	5.0%	1.1%	3.2%	2.3%
SGOT Inc	xx	xx	4.1%	1.5%	3.2%	3.2%	4.3%	1.7%

(Source: Vol ; Tables 23 A-D adapted)

9.7.3 Summary of Adverse Events Classified by Race

The proportions of black patients in the three treatment groups were AZA, 41/326, 13%; MMF 2 g, 45/336, 13%; and MMF 3 g, 34/330, 10%. Because of the relatively low numbers of black patients in each treatment group, only tentative conclusions can be made regarding racial predisposition to adverse events (see Vol ;Tables 24 A–D).

Sepsis was more frequently reported in black versus non-black patients in all three treatment groups. In patients receiving MMF, kidney tubular necrosis, anemia, hypertension, and rash were reported more frequently among black patients. In the AZA group, these events were either evenly distributed or reported more frequently among non-black patients. In the MMF 2 g group, nausea (27% vs. 17%), vomiting (16% vs.10%), and drug level increased (16% vs. 7%) were more frequent among black patients. In the MMF 3 g group, fever (29% vs. 21%), constipation (27% vs. 17%), and nausea and vomiting (18% vs. 7.8%) were reported more frequently among black patients.

Medical Officer Comment: Thus, only nausea and vomiting appear increased in MMF-treated black patients, compared to MMF-treated non-black patients.

9.7.4 Summary of Adverse Events Classified by Age

Medical Officer Comment: By protocol requirement, all patients were 18 years of age or older, and consequently no pediatric patients were enrolled in these studies. This age distribution is atypical of the general transplant population, where 5% to 10% of renal transplant patients are less than 18 years of age.

Overall, among the three active treatment groups, leukopenia was more common, and reported with approximately the same incidence, among patients 65 years old or older, in comparison with patients less than 65 years old, as was creatinine increased (see below). Cardiac and respiratory system adverse events were generally more common in the older age group.

In the MMF 2 g treatment group, events that were more frequent among patients aged 65 years or more, in comparison with patients aged 18 to 64 years, included infection constipation, gastrointestinal hemorrhage, hypercholesterolemia, creatinine increased, leukopenia, anemia, thrombocytopenia, myocardial infarction, heart arrest, dyspnea and lung disorder. Diarrhea and nausea were somewhat less in the age group $\geq$ 65 years.

In the MMF 3 g treatment group, events that were more frequent among patients aged 65 years or more, in comparison with patients aged between 18 to 64 years, were chest pain nausea diarrhea, anorexia, gastrointestinal hemorrhage, liver damage, oliguria, peripheral edema, hyperglycemia, creatinine increased leukopenia, hypotension dyspnea and conjunctivitis (see below). There appears to be a dose relationship with gastrointestinal hemorrhage in the population of ≥ 65 years. Thrombocytopenia and anemia are similar in frequency between the two age groups.

Selected Adverse Events Classified by Age in MMF 3 g Group

Event	≥ 65 years (%) (n=35)	18–64 years (%) (n=455)
chest pain	17	7.9
nausea	23	15
diarrhea	29	27
anorexia	11	2.6
gastrointestinal hemorrhage	11	1.8
liver damage	5.7	0.4
oliguria	8.6	1.1
peripheral edema	23	17
hyperglycemia	14	7.7
creatinine increased	11	5.7
leukopenia	37	26
anemia	23	26
thrombocytopenia	6	6
hypotension	11	4.2
dyspnea	20	10
conjunctivitis	11	1.5

(Source: Vol ;Table 25)

Medical Officer Comment: Except for leukopenia, creatinine increased, and dyspnea, and gastrointestinal hemorrhage there was little consistency in the MMF-treated patients for events more common in elderly patients.

9.8 MALIGNANCY

9.8.1 Summary of Malignancies In Patients Treated with Mycophenolate Mofetil

Solid Organ Transplant Patients The population assessed with regard to occurrence of malignancy comprises 2389 patients treated with MMF plus 688 control group patients (total, 3077). Malignancies were reported to occur in a total of 131 (4.3%) of patients at risk: lymphoproliferative disorder/lymphoma occurred in 26 (0.85%), other malignancies in 37 (1.2%) and skin cancer in 68 (2.2%).

9.8.2 Phase III Trials for Prevention of Acute Rejection (MRE 022, ICR 023, and ICM 1866)
One thousand four hundred ninety-three patients have been enrolled in three Phase III trials (ICM 1866, IICR 023, and MRE 022) of MMF versus either placebo or azathioprine for prevention of renal allograft rejection. Ten patients enrolled in these studies did not receive study medication, and are excluded from the safety analysis.

Sixty-Seven patients (4.5%) have developed 71 malignancies as of the data cut-off date. Ten (0.7%) have developed post-transplant lymphoproliferative disorders (PTLD), 20 (1.3%) were reported to have "other" malignancies, and 28 (1.9%) patients have developed 41 nonmelanoma skin cancers.

Malignancies in Prophylaxis Trials in Renal Transplant Patients				
	Placebo (n=166)	AZA (n=326)	MMF 2 (n=501)	MMF3 (n=490)
Lymphoma/LPD	0	1 (0.3)	4 (0.8)	5 (1.0%)
Nonmelenoma skin malignancies	0	10 (3%)	23 (4.6%)	8 (1.6%)
Other malignancies	3 (1.8%)	6 (1.8%)	4 (0.8%)	8 (1.6%)

(Based on updated 1 year safety report)

Medical Officer Comment: The rate of Lymphoma/LPD is low and similar to the literature. Overall other malignancies, and nonmelenoma skin malignancies were similar among the treatment arms.

9.9 Outcomes of Pregnancy:

Only one woman became pregnant while taking MMF 3g/day. The pregnancy was voluntarily terminated. To date there have been no infants born to female patients receiving MMF. There have been 8 pregnancies fathered by males taking MMF. The outcomes were normal in 7/8. One ended in a spontaneous miscarriage. During clinical trials one child was born with severe congenital anomalies, including cardiac abnormalities, after the father received mycophenolate mofetil at and before the time of conception; the child subsequently died in the perinatal period. The exact role of mycophenolate mofetil in this event is not known.

9.10 Pediatric Safety Review:

The only data regarding the safety of pediatric patients treated with mofetil comes from study MYC2190, a pharmacokinetic study. The following is a brief outline of the study design and a review of the safety data for these subjects.

TITLE OF STUDY: An Open-Label, dose-Ranging Pharmacokinetic, Safety and Tolerance Study of Oral Mycophenolate Mofetil in the Prevention of Rejection in Pediatric Renal and Hepatic Allograft Recipients.

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

DIAGNOSIS AND CRITERIA FOR INCLUSION:
Inclusion criteria required that patients be between 3 months and 18 years of age and weigh at least 5.4 kg; be recipients of a single-organ first, second or third (kidney only) cadaveric or living-related kidney or liver allograft; and be ABO-compatible with the allograft.

DEMOGRAPHICS:
14 renal allograft recipients have been enrolled in this ongoing study. One patient is less than 3 years of age; 3 are between 6-12 years, 10 are between 12-18 years of age. All of the patients were dosed at MMF 15 mg/kg except for 5 of the patients in the 12-18 year group who received the MMF 23 mg/kg dose. Two of the patients (2- and 8-year-old males) assigned to the 15 mg/kg bid dose group also received an initial single IV dose of MMF.
As of this report dated January 30, 1995 no premature terminations were documented and treatment with MMF was ongoing in all patients. The 14 patients have been enrolled in the study for 7-180 days, with the cumulative number of days on treatment ranging from 6-166 days. Eight patients were male and 6 were female.

DEATHS AND MALIGNANCIES: no patient who enrolled in this study has died or developed a malignancy as of the data cutoff date.

SAFETY: The sponsor states that to date, MMF has been well tolerated. Severe adverse events have been reported for 4 patients, all of whom were 12 to 18 years of age. Two of these were receiving MMF 15 mg/kg bid and 2 were receiving MMF 23 mg/kg bid. All of the adverse events classified as severe or life threatening were considered by the investigators to be probably not related to MMF. No patient enrolled in this study has died, developed a malignancy, or prematurely discontinued treatment with MMF as of the data cutoff date.

A summary of the overall adverse events reveals that 100% of the patients entered into this study experienced at least one adverse event. The following is a listing by body system.

Number of Patients with one or more Adverse Event

Body System:	Number (%)
Body as a Whole	14 (100%)
Metabolic and Nutritional	11 (78.6%)
Cardiovascular System	10 (71.4%)
Digestive System	10 (71.4%)
Respiratory System	9 (63.4%)
Skin and Appendages	9 (63.4%)
Urogenital	8 (57.1%)
Hemic and Lymphatic System	6 (42.9%)
Special Senses	4 (28.6%)
Nervous System	3 (21.4%)
Musculoskeletal	1 (7.1%)

The most frequent events for "Body as a Whole" were pain (78.6%), fever (50.0%) and abdominal pain (21.4%). Metabolic were creatinine increase (21.4%) and hypophosphatemia (21.4%). The Cardiovascular System event most frequently reported was hypertension (64.3%). The following were frequent events in the Digestive System: constipation (35.7%), diarrhea (35.7%), nausea (35.7%) and vomiting (14.3%). Urogenital events were urinary tract infection (21.4%). Leukopenia occurred in 7.1% of patients with anemia occurring 21.4% and thrombocytopenia was rare occurring in only one patient (7.1%).

Three of the 14 patients (21.4%) in this study have experienced adverse events that necessitated either a reduction in the dose of MMF or an interruption of dosing. At the time of the development of the adverse event that necessitated the change in dosing, 1 patient (in the group aged 12-18 years) was receiving MMF 15 mg/kg. The other 2 patient were receiving MMF 23 mg/kg bid; 1 was in the group aged 6 to <12 years, and 1 was in the group aged 12 to 18 years. The adverse events that necessitated a reduction in the dose of MMF or an interruption of dosing were as follows: (1) nausea, vomiting, and abdomina pain secondary to herniated bowel (MMF interrupted); (2) CMV gastric ulcer (MMF dose reduced); (3) leukopenia (MMF interrupted); and (4) varicella (MMF interrupted). Because of the limited number of petients who have been studied to date, it is not possible at this time to draw any conclusions about the relative safety and tolerability of MMF 15 mg/kg bid dose to that of the MMF 23 mg/kg bid dose.

Opportunistic infections occurred in 4 (28.6%) of the patients: 1 mucocutaneous candida, 1 CMV viral shedding in the urine, 1 CMV gastritis and 1 CMV of the kidney, 1 varicella zoster.

Medical Officer Comment: The laboratory abnormalities were similar of a similar nature when compared to the prophylaxis studies described above. Overall the profile for adverse events and opportunist infections appear similar to the prophylaxis studies. Studies including larger number of pediatric patients will be necessary to confirm the pattern seen here.

11 pages
purged

11.0 Safety Analysis

Safety analyses were performed as intent-to-treat. However, two patients randomized to the IV steroid arm never received study medication and were excluded from both the applicant's and FDA's safety analyses. Safety analyses thus include 148 patients (77 CellCept; 71 IV steroid).

Prior to Spring, 1993, adverse events which were mild or moderate in severity and not attributed to the study drug were not collected. This suggests the potential for under-reporting of non-severe adverse events.

Consistent with the study population, the overall incidence of adverse events was high in study 1868: 74.6% (53/71 patients) in the IV steroid cohort and 93.5% (72/77 patients) in the CellCept cohort experienced at least one adverse event. Although adverse events were higher in the CellCept arm for virtually all body systems examined, the differential between study arms was greatest for digestive and hematologic systems (see below), paralleling results observed in the prophylaxis trials. The majority of gastrointestinal adverse events manifested as diarrhea, nausea, or vomiting; however, a small number of GI bleeding events were recorded in both study arms (higher in the CellCept cohort).

PATIENTS EXPERIENCING GASTROINTESTINAL OR HEMATOLOGIC ADVERSE EVENTS		
	IV STEROID (N=71)	MMF 3 (N=77)
DIGESTIVE SYSTEM	**24 (33.8%)**	**54 (70.1%)**
Diarrhea	3 (4.2%)	36 (46.8%)
Nausea	4 (5.6%)	18 (23.4%)
Nausea and Vomiting	3 (4.2%)	10 (13.0%)
Vomiting	2 (2.8%)	4 (5.2%)
GI Hemorrhage	0	2 (2.6%)
Hematemesis	0	1 (1.3%)
Melena	2 (2.8%)	0
Intestinal Obstruction	0	2 (2.6%)
Pancreatitis	0	2 (2.6%)
Stomach Ulcer	2 (2.8%)	0
HEMATOLOGIC SYSTEM	**18 (25.4%)**	**39 (50.6%)**
Leukopenia	12 (16.(%)	30 (39.0%)
Anemia	8 (11.3%)	18 (23.4%)
Thrombocytopenia	4 (5.6%)	3 (3.9%)
Pancytopenia	0	1 (1.3%)

Twelve CellCept patients (15.6%) and three IV Steroid patients (4.2%) experienced both anemia and leukopenia during the six month study period.

The following table examines adverse events characteristically associated with steroid administration. While such events were numerically increased in the IV steroid arm, differences between treatment groups were small (likely reflecting concomitant use of oral steroids in both study arms as well as the limited reporting of non-serious adverse events as noted above).

ADVERSE EVENTS CHARACTERISTIC OF STEROID ADMINISTRATION

MALE	33/44 (77.3%)	42/43 (97.7%)
FEMALE	19/27 (70.4%)	30/34 (88.2%)
TOTAL	53/71 (74.6%)	72/77 (93.5%)

Opportunistic infections occurred with approximately equal frequency between the two study arms; however, Herpes Simplex and tissue invasive CMV were more frequent in the CellCept cohort (see below).

PATIENTS EXPERIENCING OPPORTUNISTIC INFECTIONS		
	IV STEROIDS (n=71)	CELLCEPT (n=77)
ANY OPPORTUNISTIC INFECTION	**25 (35.2%)**	**27 (35.1%)**
CMV viremia	2511 (15.5%)	11 (14.3%)
CMV tissue invasive disease	1 (1.4%)	7 (9.1%)
Herpes Simplex	3 (4.2%)	9 (11.7%)

Given the relatively short duration of follow-up in this study, neoplasms were rare. In the CellCept arm, two patients developed neoplasms on or post-study: a lymphoproliferative disorder (at day 65) and a CNS lymphoma (at day 198). One additional CellCept patient entered the study with a lymphoproliferative renal disorder. In the IV steroid arm, a single patient developed a neoplasm on or post-study (cerebral lymphoma at day 198).

Two deaths were recorded on each of the study arms during the six month study period: causes of death in the CellCept arm were listed as infection/sepsis and a cerebrovascular event respectively; causes of death in the IV steroid arm were cardiopulmonary arrest and end stage renal disease respectively. While no additional deatns were reported in the CellCept cohort on subsequent, but variable post-treatment follow-up, 7 additional deaths were reported on follow-up for the IV steroid cohort.

12 LABEL: See final label for further information.

13 CONCLUSIONS:

13.1 PROPHYLAXIS OF ACUTE RENAL ALLOGRAFT REJECTION:

13.1.1 Biopsy proven acute rejection was investigated in three pivotal studies ( ). The primary efficacy analysis in each of these studies demonstrated that CellCept reduces the rate of biopsy proven rejection as measured by treatment failure (biopsy proven rejection, death, graft loss or premature withdrawal). Tests of significance were based upon comparisons of the treatment failure rate at six months with adjustments made for multiple comparisons.

13.1.2 Though both doses of CellCept were found to be efficacious, there was no advantage of the CellCept 3 gram/day dose compared to the 2 gram/day dose for treatment failure. The biopsy proven acute rejection rates were comparable.

13.1.3 The traditional approach to the evaluation of anti-rejection drugs has been based upon one year patient and graft survival. It was of interest insure that the morbidity reduction brought about by a decrease in acute rejection is not being made at the expense of graft and patient loss. Combined analyses of the three pivotal trials demonstrated that CellCept was not worse than placebo or azathioprine with respect to one year patient and graft survival.

13.1.4 CellCept 3 gram/day dose had a somewhat more frequent adverse events compared to the 2 gram/ day dose, especially for leukopenia and diarrhea. This was true for severe events, and events requiring discontinuation. The profile of CellCept was similar to that of Azathioprine, however, thrombocytopenia was not seen to the extent it was related to Azathioprine.

13.1.5 CellCept groups had similar rates of malignancies to the control groups in at least 1 year of follow up.

14 RECOMMENDATIONS:

14.1 Prohpylaxis of Acute Renal Allograft Rejection:

The three controlled studies (Study 022, 1866, 023) submitted in support of CellCept for the prevention of acute renal allograft rejection meets regulatory requirements for approval of this indication. Pursuant to 21 CFR 314.105 (a) the studies performed were adequate and well-controlled investigations and establishing that the 2 g/day dose of CellCept is effective for the treatment of refractory acute renal allograft rejection. The proposed dose of 3 g/day CellCept although shown to be effective was not more effective than the 2 g/day dose and had some what more toxicity than the 2 g/day dose of CellCept.

Approval should be granted for the CellCept 2 g/day dose, however, approval should <u>not</u> be granted for the 3 g/day dose for this indication. Reference to the 3 gram/day dose may be made in the label regarding the clinical studies, however, should not be included in the recommendations for use.

15 PHASE FOUR STUDY RECOMMENDATIONS AND REQUIREMENTS:

1) RECOMMENDATIONS
   a) Additional studies in pediatric populations.
   b) Treatment strategy type studies ie starting with 3 grams/day and decreasing the dose to 2 grams/day.

2) ~~REQUIREMENTS~~ Criteria

a) The sponsor must provide additional efficacy/safety data in the "black" population. Recommended

16. ADDENDUM NDA

16.1 CONCLUSIONS:

16.2 RECOMMENDATIONS:

It is recommended that formulation not be approved at this time, pursuant to 21 CFR 314.125 (b)(9). However, when additional data is provided (see biopharmaceutical reveiw section) further consideration will be given to tnis formulation.

Concurrence:

Director/ HFD-530: Feigal. D.
Supervisory Medical Officer: Goldberger. M.
Medical Officer: Korvick. J.
Medical Officer: Lapey. D.
Biometrics Supervisor: Kammerman.L.
Biometrics: Flyer.P.

SAFETY UPDATE REVIEW

The safety update review is incorporated into the joint medical/statistical review.

STATISTICAL REVIEW

The statistical review is incorporated into the joint medical/statistical review.

Biopharmaceutics/Pharmacokinetic Review of an NDA

Mycophenolate Mofetil (CellCept®)
NDA
Submission Dates: 11/9/94, ...
...., ... !.....

Syntex, California
Reviewers: Chandrahas Sahajwalla, Ph.D.
Kofi A. Kumi, Ph.D.
Review Date: 4/10/95

SYNOPSIS

Mycophenolate mofetil (CellCept®, MMF), the morpholino-ethyl ester of mycophenolic acid (MPA), is being evaluated as an immunosuppressant for the use following renal transplantation for the prevention and treatment of graft rejection. Mycophenolate mofetil is hydrolyzed to MPA, which is a potent and specific inhibitor of de novo purine synthesis and which blocks the proliferation of both T and B lymphocytes.

The pharmacokinetics of MMF has been studied in healthy volunteers following single doses and following multiple doses in renal transplant patients. Although, pharmacokinetics has been studied in liver transplant, cardiac transplant and rheumatoid arthritis patients, these were not reviewed, because the present submission seeks approval for use in treatment and prevention of rejection in renal transplant patients. Clinical trials used a 250 mg capsule formulation, and

Absorption
The mean absolute bioavailability of oral MMF relative to IV MMF (based on MPA AUC) was 94%.

Immediately post transplant (<42 days), mean AUC and Cmax is about 50% lower in renal transplant patients than that observed in the healthy volunteers or in stable renal transplant patients.

Three studies evaluating dose proportionality have been submitted. (1) In healthy volunteers (i.v administration 1.5 mg/kg to 22.5 mg/kg). (2) In Japanese patients doses ranging from 1 G to 4 G daily dose. (3) Oral doses of 100 mg to 3.5 G per day. These studies indicate that, the mean values of MPA C_{max} and AUC appeared to increase approximately proportionally. MPA and MPAG half-life values did not change with the change in MMF dose administered. The proportionality for MPAG was lacking. It should however be noted that studies were parallel design as opposed to a cross-over design, and in very few volunteers; hence, dose proportionality data should be considered preliminary.

Distribution

The mean (SD) apparent volume of distribution of MPA is approximately 3.6 (±1.5) and 4.0 (±1.2) L/Kg following IV and oral administration, respectively. MPA, at clinically relevant concentrations, is 97% bound to plasma albumin. MPAG is 82% bound to plasma albumin at MPAG concentration ranges which are normally seen in stable renal transplant patients. Mean blood to plasma ratio of radioactivity concentrations were approximately 0.6 indicating that MPA and MPAG do not extensively distribute into the cellular fractions of blood.

Metabolism

The sponsor carried out two studies in healthy volunteers (oral single dose) to investigate metabolism of MMF, one to study the fate of MPA [^{14}C–MPA] moiety and other for N-(2-hydroxyethyl)-morpholine (HEM) [^{14}C-Morpholine].

MPA was metabolized principally by glucuronyl transferase to form pharmacologically inactive, glucuronide of MPA (MPAG). Ninety three percent of the dose was recovered in urine and 5.5% in the feces. MPAG accounted for 96.3% of the radioactivity recovered.

Following oral administration of HEM-[^{14}C]-Morpholine, the following was recovered in the urine; N-(2-carboxymethyl)-morpholine, N-(2-hydroxyethyl)-morpholine, and the N-oxide of N-(2-hydroxyethyl)-morpholine.

MPA undergoes enterohepatic recycling. This finding is based on observation of a second peak at 6-12 hours post administration and 40% reduction in the MPA AUC when MMF is coadministered with cholestyramine.

Excretion

A negligible amount of drug is excreted as MPA (<1% of dose) in the urine. Orally administered radiolabeled mycophenolate mofetil resulted in complete recovery of the administered dose (93% in the urine and 6% in feces). Most (about 87%) of the administered dose is excreted in the urine as MPAG. MPA and MPAG were usually not removed by hemodialysis. However, at high MPAG plasma concentrations (>100 μg/mL), small amounts of MPAG are removed.

Mean (SD) apparent half-life and plasma clearance of MPA are 17.9 (±6.5) hours and 193 (±48) mL/min following oral administration and 16.6 (±5.8) hours and 177 (±31) mL/min following I.V. administration, respectively.

Pharmacokinetics in healthy volunteers and renal transplant patients
Healthy Volunteers
Following oral administration of 1 g capsule, the mean MPA C_{max} was 24.5 μg/mL in 129 volunteers with Tmax of 0.80 h following the oral dose. Mean apparent $t_{1/2}$ and AUC from 117 healthy subjects given 1 g MMF were 16.0 h and 63.9 μg*h/mL.

The 90% CI for log transformed Cmax was between 61.1% to 79.4%, which is below the acceptable range.

6.

Renal Transplant Patients
The pharmacokinetics of patients immediately following transplant (<42 days) are different compared to healthy volunteers or compared to stable transplant patients (> 3 months). Immediately post-transplant, mean AUC_{total} is about 50% lower and Cmax about 65% lower. The low AUC immediately post-transplant may be considered partly due to an altered metabolic status and partly due to lower bioavailability. Following table compares the PK:

MEAN (SD)	Healthy 1.5 G Dose Studies 028, 069, 2294	Day 1 Post-Transplant 1.5 G Dose (1866)	Steady State-Post-Transplant 1.5 G Dose (1866)	Stable Renal Transplant 1.5 G Dose (CP 026)
MPA AUC	51.5 (16.1)	20.8 (12.6)	35.9 (16.5)	52.1 (17.7)
MPA CMAX	32.8 (8.15)	6.09 (5.47)	11.7 (5.92)	29.7 (14.2)
MPAG AUC	234 (86.7)	229 (142)	890 (341)	421 (139)
MPAG CMAX	44.3 (13.1)	29.0 (18.9)	99.6 (45.4)	59.8 (19.7)

In a pivotal clinical trial conducted in the USA, pharmacokinetic data were available from a subgroup of patients. In early post transplant patients, mean (SD) AUC was 26.3 (±9.6) and 35.9 (±16.5) and Cmax was 9.6 (±6.3) and 11.7 (±5.9) for the 2 g (N=19) and 3 g (N=20) daily dose groups, respectively. Data available from the two European trials only had Cmin concentrations at 12 weeks of treatment.

Special Population
Renal Insufficiency
Studies were conducted in patients with chronic stable renal failure and in the transplant patients with delayed graft function (DGF, dialysis support sometimes

necessary).

Volunteers with severe chronic renal impairment (GFR <25 mL/min/1.73 m^2) had about 75% higher MPA AUC, relative to that observed in healthy volunteers (GFR >80 mL/min/1.73 m^2). Similarly, that group had five fold increase in MPAG AUC compared to healthy volunteers group.

In patients with delayed graft function, mean MPA AUC_{0-12} was higher (about 50%) than seen in post-transplant patients without delayed graft function. Mean plasma MPAG AUC_{0-12} was 6-8 fold higher than in post-transplant patients without delayed graft function.

MPA and MPAG were usually not removed by hemodialysis. However, at high MPAG plasma concentrations (>100 μg/mL), small amounts of MPAG are removed.

Hepatic Insufficiency
In volunteers with alcoholic cirrhosis, hepatic MPA glucuronidation processes were relatively unaffected by hepatic parenchymal disease. However, hepatic disease with predominantly biliary damage, such as primary biliary cirrhosis, may show a different effect.

Pediatric
An interim report (N = 14) on a dose ranging pharmacokinetic study in pediatric patients, has recently been submitted. Very limited data following administration of 15 and 23 mg/kg bid dose has been presented in the review.

Food
Food (high fat) had no effect on MPA AUC when administered at doses of 1.5 g BID to renal transplant patients. However, MPA Cmax was decreased by 40% in the presence of food.

Drug Interactions
Following single dose concomitant administration of MMF and acyclovir (ACV), MPA concentrations were not different than MMF administered alone. However, MPAG and ACV plasma AUCs were increased. Since both MPAG and ACV undergo tubular secretion, there is a potential for further increases in concentrations of both drugs because of competition for tubular secretion.

The Cmax and AUC (0-24) of MPA were decreased by 33% and 17%, respectively when MMF was administered with antacids containing magnesium and aluminum hydroxides (eg. Maalox TC). MMF is not recommended to be taken simultaneously with antacids containing magnesium and aluminum hydroxides.

Cholestyramine decreased MPA AUC by approximately 40%; therefore, MMF is not recommended to be given with cholestyramine or other agents that may interfere with enterohepatic recirculation.

Cyclosporine concentrations were not significantly altered by coadministration with MMF.

Ganciclovir concentrations were not affected by coadministration with MMF; however, since both drugs undergo renal tubular secretion, there is a possibility of increases in both drug concentrations.

Following single dose administration of MMF with Ortho-Novum 7/7/7, no pharmacokinetic interaction was observed . However, the possibility exists for changes in the pharmacokinetics of the oral contraceptive under long term dosing conditions with MMF.

Trimethoprim/sulfamethoxazole (Bactrim) had no effect on the bioavailability; however, the possibility exists other drugs that alter the gastrointestinal flora may have an affect on the bioavailability of MMF.

Population analysis

The population analysis using multivariate analysis was performed to study associations between demographic (*e.g.*, age, reciprocal weight) or laboratory data (*e.g.*, creatinine clearance, white blood cell count) with pharmacokinetic parameters (C_{max}, AUC_{last}).

The analysis confirmed a relationship between renal function (correlation with BUN and creatinine clearance) and MPA and MPAG AUC_{0-12}; MPA and MPAG AUC was inversely proportional to creatinine clearance. There does not appear to be gender differences in renal transplant patients with respect to the pharmacokinetics of MMF. In healthy volunteers, multivariate analysis indicates that age and weight (particularly age) are important factors for MPA AUC. MPAG AUC was poorly correlated with any variable. In patients weight relationship did not appear to be important, possibly it was obscured by other factors such as pathophysiologic status and use of concomitant medication. It should be noted that pediatric data available from the interim report (N = 14) was not part of this population analysis.

Summaries of MPA pharmacokinetic parameters (descriptive statistics) by race revealed that black males (N = 4 each in healthy and patient population) had 50% lower AUC and Cmax compared to black females or compared to caucasians. Based on clinical data in limited number of blacks, it appears that giving a 3 G daily dose reduced the rejection rate to 24% compared to 39% in 2 G daily dose group. Whereas, for caucasians rejection rates in 2 and 3 G dose were 30 and 32%, respectively. However, possibly, due to the limited sample size, these differences

in blacks were not statistically significant.

Concentration Effect Relationship

Logistic regression was used to obtain a relationship between MPA AUC and probability of rejection. Logistic regression parameters obtained from Japanese patients trial (NSK 24/100) were applied to data from study 1866 (pivotal clinical trial), to predict rejections. There are several limitations (enumerated in the review) of the application of Japanese data to patients in the USA. Based on frequency distribution (by AUC) of rejections, it also appears that patients in the lower AUC were at a greater risk of rejection. Hence existence of a relationship between AUC and outcome should be further explored.

In the clinical trial (study MYCc 1866) rejection rates of 19.8% and 17.5% for the 2 G and 3 G dose, respectively. This was further substantiated, based on the number of rejections in each dose level of the subpopulation for which PK data are available in study MYCc 1866; a higher dose is not indicative of a lower rejection rate (4/15 and 4/16 rejections for 2 and 3 G dose, respectively).

Relationships between adverse events and MPA or MPAG concentrations were evaluated by plotting plasma concentrations taken at the time of a serious adverse events during these trials. Analysis revealed weak association between elevated MPAG concentrations and certain adverse events (leukopenia, nausea and vomiting, diarrhea and events classified as others). However, MPA concentrations were not elevated.

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RECOMMENDATION

The sponsor's NDA 20513 is acceptable for meeting the Biopharmaceutics requirements. I support approval of 2 G dose of MMF for the prevention of rejection of renal allograft transplant.

DRAFT

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APPENDICES

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BACKGROUND

Mycophenolate mofetil (CellCept®), the morpholino-ethyl ester of mycophenolic acid (MPA), is being evaluated as an immunosuppressant for the use following solid organ transplantation for the prevention and treatment of graft rejection. Mycophenolate mofetil is hydrolyzed to MPA, the active immunosuppressive agent. MPA is a potent and specific inhibitor of de novo purine synthesis, which blocks the proliferation of both T and B lymphocytes. MPA is further metabolized to form a glucuronide conjugate (MPAG). MPAG is considered pharmacologically inactive, but appears to be hydrolyzed to form free MPA. In this NDA, CellCept is indicated for the prophylaxis of organ rejection and for the treatment in patients receiving allogeneic renal transplant. Hence the studies conducted in rheumatoid arthritis patients and in Cardiac and Liver transplant patients were not reviewed.

This NDA submission is concerned with oral formulations of MMF. The MMF clinical trials were performed using the 250-mg capsule formulation.

METABOLISM (ADME)

RADIOLABEL DISPOSITION

Mycophenolate mofetil (MMF) is a 2-morphoethyl ester of mycophenolic acid that undergoes conversion to the active MPA (Figure 1). The sponsor carried out two studies in healthy volunteers (oral single dose) to investigate metabolism of MMF, one to study the fate of MPA [^{14}C – MPA] moiety and other for N-(2-hydroxyethyl)-morpholine (HEM) [^{14}C-Morpholine] (Figure 2).

Study No.: ICM/MYC1884/USA:

This was an open-label, single-dose study. Volunteers (4 males) received a single 1000-mg oral dose of [^{14}C-MPA]–MMF solution containing approximately 74 μCi of radiolabel. Blood, urine, and fecal samples were collected for analysis.

Blood samples were drawn up to 96 hours after the dose; urine and feces were collected up to 168 hours. Two major metabolites of MMF, MPA and MPAG, were determined in plasma and urine by two separate assays: a radiometric assay and a high-performance liquid chromatography (HPLC-UV) assay.

Results are as follows:

Radioactivity was rapidly absorbed. MMF was not detected in any plasma samples, MPA and MPAG were the major metabolites in plasma.

Summary of Mean Pharmacokinetic Parameters (± SD)

Computed Parameter	Radiometric Assay			HPLC-UV Assay	
	^{14}C	MPA	MPAG	MPA	MPAG
T_{max} (hr)	0.75 (± 0.29)[a]	0.50 (± 0.00)	1.25 (± 0.29)	0.50 (± 0.00)	1.25 (± 0.29)
C_{max}[b]	60.1 (± 3.7)	32.9 (± 2.8)	34.9 (± 2.1)	32.3 (± 2.9)	31.0 (± 2.9)
$T_{\frac{1}{2}}$ (hr)	17.6 (± 5.0)	NC[c]	NC	16.0 (± 3.1)	17.1 (± 5.1)
AUC (0–24 hr)[b]	332 (± 20)	56.3 (± 2.6)	252 (± 6)	54.9 (± 2.6)	224 (± 14)
%AUC (0–24 hr)[b]	100	17.0 (± 0.5)	76.1 (± 2.7)	NC	NC
AUC (0–96 hr)[b]	450 (± 42)	NC	NC	69.1 (± 4.6)	303 (± 31)

[a]Data represent mean (± SD) of 4 subjects.
[b]Units for C_{max} and AUC values are μgEq MPA/mL and μgEq MPA·hr/mL, respectively.
[c]NC = not calculated

Mean blood-to-plasma radioactivity concentration ratios remained relatively constant (0.557–0.618) indicating that MPA and MPAG did not extensively distribute into the cellular fractions of the blood.

Ninety three percent of the dose was recovered in urine and 5.5% in the feces. MPAG was the major metabolite in urine, accounting for 96.3% of the radioactivity recovered during the first 72 hours after dosing. Small amounts of MPA (0.6% of the dose) and an acyl glucuronide conjugate of MPA (0.3% of the dose) were also detected as minor metabolites in urine.

To determine the metabolism and excretion of a single oral dose of [^{14}C-morpholine]–mycophenolate mofetil (MMF) in healthy volunteers (Study No.: MYCS2392)
The design was similar to the previous study; the only difference was that radiolabel was in the morpholine part (Figure 2).

In plasma, Cmax of radioactivity (27.4 μg equivalents of MMF per milliliter), occurred at 0.88 hour (T_{max}). The mean $T_{1/2}$ was 4.34 hours. HPLC analysis of samples of plasma collected between 0.25 and 6 hours indicated the presence of four metabolites in plasma. One of the four metabolites, designated M1, represented an average of 2.7% of the total radioactivity (based upon $AUC_{0-5\ hr}$) in plasma. The remaining three metabolites in plasma were identified as N-(2-carboxymethyl)-morpholine (CMM), N-(2-hydroxyethyl)-morpholine (HEM), and an N-oxide of HEM (HEMNO). CMM, HEM, and HEMNO accounted for an average of 76%, 2.9%, and 10% of the total radioactivity in plasma, respectively. About 94% of radioactivity was recovered in urine 92.1% of the dose was excreted during the first 24 hours after dosing. Urine contained one major and four minor radioactive metabolites. The major metabolite was identified as CMM and

accounted for a total of 80.8% of the total dose. The remaining metabolites and their percentage of the total dose were: HEM, 2.92%; HEMNO, 4.66%; Metabolite M1, 0.127%; and a second unidentified metabolite, designated Metabolite M4, 0.388%. (The structural identity of these minor metabolites, M1 and M4, was not determined).

Analysis of urine samples by HPLC indicated that 0.436% and 57.1% of the total administered dose were recovered as MPA and MPAG, respectively.

In summary, the hydroxyethyl-morpholine moiety of MMF was rapidly and extensively metabolized to form CMM and, to a lesser extent, HEMNO.

Comparison of Human and Animal Metabolism (also see table 1, Appendix 1)

	Rat	Dog	Monkey	Human
HEM	34%	22%	22%	3%
CMM	36%	42%	53%	76%
HEMNO	15%	15%	21%	10%
AUC RATIO MPAG/ MPA	0.22	1.03	1.34	4.48
Cmax RATIO MPAG/ MPA	0.23	1.16	0.58	1.06

SUMMARY OF BIOAVAILABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS

BIOAVAILABILITY AND BIOEQUIVALENCE

Absolute Bioavailability

An Evaluation of the Pharmacokinetics and Bioavailability of Mycophenolate Mofetil Following a 1.5 g Intravenous and Oral Dose in Healthy Volunteers (CPP/MYC2294)

The primary objective was to evaluate the absolute bioavailability of 1.5 g of MMF capsule. The secondary purpose was to quantitate the urinary metabolites of MMF (MPA and MPAG) following these IV and oral doses of MMF.

An open-label, randomized, two-period, single-dose crossover study in 12 healthy subjects (6 men and 6 women mean age of 31.4 years, mean weight of 71.1 kg). On Day 1 of the first study period, blood sample tubes broke in the centrifuge during processing; consequently, the dosing regimen for the first study period was

repeated as a third study period. For oral and IV dose, blood and urine samples were collected up to 48 hours. Each subject received three doses separated by a 7--10 day washout period.

Results: MMF was measurable in plasma 20 minutes after initiation of the infusion and not detected in plasma samples following oral administration. Results are summarized in the following Table:

Parameter	MPA		MPAG (MPA Equivalents)	
Mean (S.D.)	IV	Oral	IV	Oral
Tmax (hr)				
C_{max} (µg/mL)				
$t_{\frac{1}{2}}$ (hr)				
AUC_{inf} (µg·hr/mL)				
Total AUC (µg·hr/mL)				
RS Excreted (%)				
F (%)				

The mean bioavailability of oral MMF relative to IV MMF (based on MPA total AUC) was indicating almost complete absorption of MMF. The major metabolite in the urine was MPAG and accounted for of the IV and oral MMF doses, respectively. Data showed a trend towards women having larger AUC and C_{max} values than men. However, the differences in average body weights in men and women may account for these observed differences.

In conclusion, MMF had an absolute bioavailability of about and most of the drug was recovered in urine as MPAG.

PIVOTAL BIOEQUIVALENCE

Bioequivalence of a Single Dose of Mycophenolate Mofetil Given in Either 250 Mg x 4 Capsules

To evaluate the bioequivalence of oral formulation (four 250-mg capsules and of mycophenolate mofetil (MMF), a single-center, randomized, open-label, two-period (one week wash out), single-dose, crossover study was conducted. Blood samples were drawn up to 48 hours after dosing. Fifty-one healthy male subjects with a mean age of 24.6 years (range, 18–49) were enrolled and 47 received both the capsule and tablet formulations and completed the study.

Results: Mean (SD) pharmacokinetic parameters are listed in the Following Table:

	MPA		MPAG (MPA Equivalents)	
Computed Parameter	Capsule	Tablet	Capsule	Tablet
T_{max} (hr)				
C_{max} (µg/mL)				
$t_{\frac{1}{2}}$ (hr)				
AUC_{inf} (µg·hr/mL)				
Total AUC (µg·hr/mL)				

The mean MPA C_{max} value for the lower than that for the capsule, and the mean MPA total AUC value fo lower than that for the capsule. The 90%-confidence-interval analysis showed (Table 2) that capsules and were bioequivalent with respect to MPA AUC_{last} and total AUC. However, the C_{max} confidence interval was not within the [80%, 120%] interval for untransformed parameters or the [80%, 125%] for ln-transformed parameters, and the capsules were not bioequivalent with respect to MPA C_{max}. were bioequivalent with respect to MPAG AUC_{last} and total AUC but not bioequivalent with respect to MPAG C_{max}.

formulations were not bioequivalent to clinical capsules, the sponsor has presented a justification for Cmax not being important. Discussion of this justification is addressed later in the review.

The Relative Bioavailability of Mycophenolate Mofetil Capsules (Study#: ICM 1888)

In this single dose study, the relative bioavailability of mycophenolate mofetil capsules (4 X 250 mg) was evaluated with mycophenolate mofetil as reference. Twelve healthy male volunteers participated in this study. The mean MPA pharmacokinetic parameters and the computed parameter confidence interval are contained in tables below.

Mean Pharmacokinetic Parameters for MPA after Administration of Capsules and Solution.

Pharmacokinetic Parameters	MPA Caps: Mean ± SD (%CV)	MPA Solution: Mean ± SD (%CV)	P-Value from ANOVA
AUC (0-∞) (μg*h/mL)			
AUC (0-48) (μg*h/mL)			
Cmax (μg/mL)			
Tmax (h)			

Computed Parameter Confidence Interval Summary:
Comparison of MMF (4 X 250 mg) capsules (A) vs MMF

Log Transformed Data
90% Confidence Intervals

Computed Parameters	Ratio (A/B)	Lower Limit	Upper Limit
AUC (0-48)			
AUC (0-infinity)			
Cmax			

Conclusion: Following the administration of MMF capsule and solution, the relative

bioavailability of MMF capsule with respect to the . The Cmax for MPA capsule was significantly lower than that for The extent of absorption (as determined by AUC) was equivalent for the two formulations tested. However, the C_{max} for the two formulations were not equivalent.

GENERAL PHARMACOKINETICS AND DOSAGE FORM PROPORTIONALITY
Single and Multiple Dose Pharmacokinetics and Dose Proportionality

A Pharmacokinetic and Safety Study of Intravenous Mycophenolate Mofetil Administered in Ascending Doses Separated by Washout Periods in Normal Volunteer Subjects (Study No.: ICM/MYCx1900/USA)

A randomized, double-blind, five-period, ascending single-dose study. Six healthy male subjects (mean age of 32.0 years and a mean weight of 87.2 kg) enrolled and completed the study. There were no premature terminations. Each subject received a dose of placebo (P) and four ascending doses of MMF (A, B, C, and D)

in one of five dosing sequences (1 week wash out): PABCD, APBCD, ABPCD, ABCPD, or ABCDP.

Results: MMF, MPA, and MPAG were all detected in plasma at 5 minutes, the first sampling point following start of infusion. By one-half hour after the end of the infusion, MMF was no longer quantifiable in the plasma. The following table summarizes mean pharmacokinetic parameters:

Mean (± SD) Pharmacokinetic Parameters (N = 6) for MMF, MPA, MPAG

	MMF Dose Level (mg/kg)
MMF Parameters*	
T_{max} (hr)	
C_{max} (μg/mL)	
AUC_{last} (μg·hr/mL)	
MPA Parameters	
T_{max} (hr)	
C_{max} (μg/mL)	
$t_{½}$ (hr)	
AUC_{last} (μg·hr/mL)	
Total AUC (μg·hr/mL)	
MPAG Parameters (MPA Equivalents)	
T_{max} (hr)	
C_{max} (μg/mL)	
$t_{½}$ (hr)	
AUC_{last} (μg·hr/mL)	
Total AUC (μg·hr/mL)	

* Half-life and total AUC could not be calculated because of inadequate plasma concentrations (BQL at first postinfusion time)
* Mean not reported since last measurable MPA concentration was at 10 hours.

Approximate dose proportionality was observed for mean AUC_{last} (MPA, and MPAG), total AUC (MPA, MPAG), and C_{max} (MMF, MPA, MPAG). 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).

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

Although mean values of MPA AUC_{tot} (34.1, 70.8, and 121 μg•h/mL) and C_{max} (15.8, 35.3, and 60.2 μg/mL) seemed to increase in a proportional fashion, formal dose proportionality was not demonstrated statistically (C_{max}, $p < 0.001$; AUC_{tot}, $p = 0.002$) (Table 3 and 4).

In conclusion, MPA was formed rapidly after the start of IV administration of MMF. The mean values of C_{max} and total AUC of MPA and MPAG appeared to increase approximately proportionally. MPA and MPAG half-life values did not change with the MMF dose administered.

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 (Study No. : IID/MYC2176i/USA)

In an open label study, patients (primary recipients of a single cadaveric renal transplant) received 2.0 g IV MMF per day (1.0 g twice daily [bid]) for 7 days, followed by oral MMF 3.0 g per day (1.5 g bid) thereafter. This is an interim report on the first 10 patients (5 males, 5 females; age range, 27–70 years) enrolled into the study.

Plasma concentrations of MMF, MPA and MPAG were obtained on Days 1 and 7 (IV) and 8 (P.O) (full pharmacokinetic profiles) and on Days 2, 3, 5, 9, 10, 14, and 21 (trough samples).

Results: Nine of the 10 patients completed at least 7 days of therapy with IV MMF; 3 patients terminated the study prematurely because of adverse events that occurred while they were receiving IV MMF (including 1 patient who developed markedly elevated liver function tests).

Computed mean pharmacokinetic parameters for MPA and MPAG are summarized in the following table:

Parameter Mean (S.D.)	MPA 1 G bid i.v. Day 1, N=8	MPA 1 G bid i.v. Day 7, N=8	MPA 1.5 G bid p.o. Day 8, N=7	P-values
AUC_{0-12} (µg·hr/mL)				
C_{max} (µg/mL)				
Cave				
Fluctuation %				

Parameter Mean (S.D.)	MPAG 1 G bid i.v. Day 1, N=8	MPAG 1 G bid i.v. Day 7, N=8	MPAG 1.5 G bid p.o. Day 8, N=7	P-values
AUC_{0-12} (µg·hr/mL)				
C_{max} (µg/mL)				
Cave				
Fluctuation %				

i.v. infused over 40 min

Cmax for MPA were similar on Days 1 and 7 whereas, AUC was about 35% higher, suggesting a moderate amount of accumulation on multiple dosing. MPA AUC and C_{ave} were similar (1 G bid i.v. vs. 1.5 G bid oral) on Days 7 and 8. Plasma concentrations and computed parameters for MPAG were quite different on Days 1 and 7, indicating significant accumulation upon multiple dosing (AUC was 4.3 times higher on Day 7). It appears that giving 1.5 g MMF oral dose did not increase Cave concentrations compared to 1.0 g i.v. dose.

In conclusion, MPA appeared to reach steady state levels 3 days after initiation of IV dosing (based on trough concentrations). The MPA $AUC_{0-12\ hr}$ at steady state (i.v.) was 35% higher than that following the initial dose.

It should be noted that steady state MPA Cmin concentrations following oral dose were about 50% higher than those obtained after i.v. dose. Similarly, steady state MPAG Cmin concentrations following oral dose were about 20% higher than those noted after i.v. dose.

In order to compute biavailability in patients, it would have been advantageous to collect a full profile following steady-state of oral 1.5 G bid regimen.

Pilot Study of Mycophenolate Mofetil in Patients Following Renal Transplantation Study Nos.: NSK/MYCc 24/JPN (NSK 24) and NSK/MYCc100/JPN (NSK 100)

The primary objective of these studies was to evaluate the safety and efficacy of mycophenolate mofetil (MMF) in patients following renal transplantation, at doses of 1.0, 2.0, and 3.0 g/day in NSK 24 and 4.0 g/day in NSK 100 (N=10).

The two protocols (NSK 24 and NSK 100) were identical with the exception of dosage levels. Therefore, results from these 2 studies were presented together in a single report. Both studies were open-label, multicenter studies. In NSK 24, renal transplant recipients were sequentially enrolled into dosage groups(I, II, and III n= 12, 10 and 10, respectively) receiving 0.5, 1.0 and 1.5 g MMF bid.

Thirty-two patients provided full plasma profiles on Week 1, 19 patients on Week 2, and 30 patients on Week 3, across all 4 dose groups.

Results: Acute rejection was diagnosed in 9 of the 12 patients in Group I, 4 of 9 in Group II, 2 of 10 in Group III, and in 0 of 7 in Group IV.

Decreased tolerability was observed in the 4.0 g per day group in the post transplant period, and resulted in discontinuation of dosing in 1 patient (who had a high SGPT) and a decrease in dose for longer than two weeks in 2 other patients in this group. A dose-related decrease in the incidence of clinically diagnosed acute rejection of LRD or cadaveric renal transplants was observed, with the 4.0-g group not reporting any rejection episodes. Pharmacokinetic parameters are summarized in Tables (5 and 6). MPAG to MPA AUC ratios ranged from 25.6 to 44.7 on Week 1. Plot of dose adjusted MPA AUC and Cmax are provided in Figures 3 and 4.

Proportionality was tested using dose-adjusted parameters (to 1 G dose) in a nested analysis of variance (ANOVA) model which included terms for dose and subject within dose the following p -values were obtained.

Pharmacokinetic Parameter	p-values MPA	MPAG
AUC 0-12		
Cmax		
Cmin		
ln(AUC 0-12)		
ln(Cmax)		
ln(Cmin)		

Although, dose proportionality is shown by no significant differences, the mean dose corrected AUC for MPA obtained with 4 g dose is about 20% lower than that of 2 G dose. MPAG AUC does not appear to be dose proportional, 1.5 g and 2 g dose (week 3) are similar. It should be noted that due to small sample size and parallel design, dose proportionality data indicates lack of evidence against dose proportionality.

An open label, multiple dose, safety and dose-finding study of mycophenolate mofetil in patients following renal transplantation (CL 6817)

Fifty two (32 males 18 females) patiants (receiving a single cadaveric renal allograft) were enrolled at two centers into eight sequential dosage groups. Treatment groups were QD administration of 100 mg, 250 mg, 500 mg, 1 g and 1.5 g or BID administration of 1g, 1.5 g and 1.75 g (total per day dosing of 2, 3 and 3.5 grams). Each treatment group had 6 to 7 subjects enrolled and 44 patients completed the study. Plasma samples were collected on Days 1, 7, 14 and 20 of dosing; full PK profiles were obtained on Days 1 and 20.

Pharmacokinetic parameters for MPA and MPAG obtained are summarized in the following Table:

	100 mg QD	250 mg QD	500 mg QD	1 g QD	1.5 g QD	1 g bid	1.5 g bid	1.75 g bid
Day 20 Cmax								
Day 20 Tmax								
Day 20 AUC*								
Day 20 Cavg								
Day 20 Cmin								
**Dose corrected AUC								
Day 20 Cmax								
Day 20 Tmax								
Day 20 AUC*								
Day 20 Cavg								
Day 20 Cmin								

* AUC 0-24 for QD dosing and 0-12 for BID dosing.

**AUC normalized to 1.0 g QD dosing (i.e 1 g bid is considered 2 g and AUC is multiplied by 2)

Statistical comparisons of dose normalized AUC showed p values of greater than 0.05 indicating no significant differences, plot of AUC versus dose for Day 20 also suggest dose linear kinetics of mycophenolate mofetil. However, due to small sample size, high variability and parallel design results of dose proportionality should be considered preliminary. It should also be noted that Day 1 data were highly variable with mean Tmax being at 10 hours for MPA and 16.4 hours for MPGA.

It was also noted that patients arterial and venous plasma samples obtained from patients undergoing dialysis suggest minimal dialysis clearance of MPA.

An Interstudy Evaluation of the Steady-State Pharmacokinetics of Mycophenolate Mofetil in Stable Renal Transplant Recipients: Study RS-61443-000, Amendments to Study Nos. ICM 1803, ICM/MYC1880/USA, ICM/MYC1912/USA, and IID/MYCI2176/USA.

Objectives: To determine (1) the steady-state pharmacokinetics of orally administered mycophenolate mofetil (MMF) in renal transplant recipients; (2) effect of a standardized breakfast on the steady-state pharmacokinetics of orally administered MMF; (3) diurnal variations in the steady-state pharmacokinetics of orally administered MMF; and (4) intra- and interpatient variability of MMF steady-state pharmacokinetics.

Multicenter, multiple-dose, open-label, randomized, two-period crossover study. During one period (Regimen A), the morning dose of MMF was administered 30 minutes before a high-fat breakfast on Study Day 1 and 30 minutes after breakfast on Study Day 2. During the other study period (Regimen B), the morning dose of MMF was administered 30 minutes after breakfast on Study Day 1 and 30 minutes before breakfast on Study Day 2. In both periods the PM dose of MMF was administered 12 hours after the AM dose and 2 hours after start of dinner. Following dosing on Study Day 2, blood samples for MPA and MPAG measurements were drawn only at 30, 45, 60, 75, and 90 minutes after dosing (for determination of Cmax and Tmax).

Fifteen stable renal transplant recipients (7 males and 8 females), having a mean age of 45.6 years (range, 30–73) and a mean weight of 75.5 kg (range, 45.7–129.3), participated and 13 completed both study periods. The two study periods were separated by 7–28 days.

Results: Data obtained from the full 12-hour profile are summarized below.

Mean (SD) Pharmacokinetic Parameters (N = 13):

Parameters	Fasted (AM)	Fed (AM)	Fed (PM) (B)	Fed (PM) (A)
MPA				
C_{max} (µg/mL)	23.2 (11.9)	13.9 (5.47)[a]	12.3 (6.40)[a]	12.8 (7.01)
T_{max} (hr)	0.937 (0.236)	1.88 (1.28)[a]	2.25 (2.06)[a]	2.22 (1.37)
$AUC_{0-12\ hr}$ (µg·hr/mL)	61.3 (28.7)	56.8 (20.9)	55.0 (26.5)	53.5 (24.9)
MPAG (MPA Eq.)				
C_{max} (µg/mL)	111 (26.5)	117 (33.4)	99.8 (22.8)[b]	97.5 (20.7)
T_{max} (hr)	2.97 (1.20)	3.19 (1.53)	4.19 (2.63)	4.46 (2.71)
$AUC_{0-12\ hr}$ (µg·hr/mL)	1041 (288)	1014 (262)	890 (242)[b]	873 (209)

[a] statistically significantly different from fasted (AM) dose.
[b] statistically significantly different from fed (AM) dose.

The mean C_{max} of MPA was significantly lower (about 40%) after administration of MMF following breakfast as compared with the fasting condition. Under fed conditions, Tmax of MPA was also delayed and was significantly different compared with fasting. The $AUC_{0-12\ hr}$ was similar and not significantly different. The MPAG pharmacokinetics were not affected by food. No significant diurnal effect on the pharmacokinetics of MPA was observed. However, statistically significant reduction in MPAG C_{max} and AUC was observed with PM dosing as compared with AM dosing. The intrapatient variability (ANOVA) for MPA AUC and C_{max} was 17% and 47% compared with interpatient variability of 43% and 41%, respectively . Intra- and interpatient variability for MPAG pharmacokinetics was significantly less (13% and 22% for C_{max} and 11% and 24% for AUC, respectively). However, intra-subject variability is confounded by effect of food. Intra-subject variability was computed by this reviewer, MPA Cmax had about 15% variability under fasting condition and about 30% variability when MMF is administered under fed condition.

In conclusion, no significant diurnal effect on the pharmacokinetics of MPA was observed. MPAG C_{max} and AUC were lower after the PM dose. Significantly higher intra- and interpatient variability was observed for MPA pharmacokinetics compared with MPAG pharmacokinetics following administration of MMF.

SPECIAL POPULATIONS

Pharmacokinetics Safety/Tolerance in Renally-Impaired Patients

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 (Study No.: CPP/MYCc2118/USA)

Study Design: A single-center, open-label, single-dose, parallel design study in healthy volunteers and patients with varying degrees of renal impairment (five Groups I–V, see table on the next page), including patients undergoing dialysis. For patients undergoing dialysis, samples were collected during the dialysis period to estimate dialysis clearance. Patients in Group V received a second oral dose of MMF after a 2- to 3- week washout interval. Patients in Group IV received a second 1-g IV dose of MMF after a 2- to 3- week washout interval.

Six patients/subjects were assigned to each of the five study groups, except that Group IV had 7 patients. Only 4 of the 7 patients in Group IV received the IV dose of MMF. The mean weight of the subjects/patients was 82.6 kg (range 50–159 kg).

Results: Mean MPA and MPAG parameters are presented in the following table. MPA C_{max} was statistically significantly different among the different renal function groups. MPA C_{max} in Group IVB was significantly lower than in Groups I and II. A trend toward an increase in MPA AUC_{last} was observed with increasing renal impairment; with 75% higher mean MPA AUC for group with GFR <25 mL/min/1.73 m^2 versus volunteers with GFR > 80 mL/min/1.73 m^2.

A significant amount of MPAG accumulation was observed in the severe renal impairment groups (Groups IV and V) as compared with the healthy volunteers group. All the MPAG pharmacokinetic parameters except T_{max} and C_{max} were statistically significantly different. The R-squared values from the linear regression of GFR and AUClast for MPA and MPAG were about 0.11 and 0.63, respectively.

Dialysis did not affect MPA and MPAG pharmacokinetics, and the timing of dialysis relative to dose administration had no effect on the pharmacokinetics of MPA and MPAG. Administration of MMF with and without cyclosporine in Groups IVA and IVB did not alter the pharmacokinetics of MPA or MPAG. Administration of IV and oral MMF to Groups IVA and IVB resulted in similar plasma profiles except for MPA C_{max}. Other pharmacokinetic parameters were not statistically different suggesting that MMF bioavailability was not affected in these patients.

In conclusion, MPA C_{max} was significantly different and considerable accumulation of MPAG was observed with increased renal impairment. Mean MPA AUC for patients with GFR <25 mL/min/1.73 m^2 was 75% higher compared to volunteers with GFR > 80 mL/min/1.73 m^2. MPA and MPAG pharmacokinetics were not altered by dialysis.

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)	
$CLr_{0\text{-}96}$ (L/h)	0.0457(0.334)	0.0393(0.049)	0.601(0.814)	0.12(0.224)	0.0163(0.032)	0.037(0.082)	
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)	
$CLr_{0\text{-}96}$	1.85(0.204)	1.25(0.092)	0.609(0.271)	0.257(0.199)	.0375(0.047)	0.0222(0.05)	
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)

Group I = GFR > 80 mL/min/1.73 m^2
Group II = GFR 50–80 mL/min/1.73 m^2
Group III = GFR 25–49 mL/min/1.73 m^2
Group IV = GFR < 25 mL/min/1.73 m^2
Group VA = GFR < 25 mL/min/1.73 m^2, dialysis prior to dose
Group VB = GFR < 25 mL/min/1.73 m^2, dialysis started 3 hours after dose

* $p < 0.05$

THE PHARMACOKINETICS OF ORAL MYCOPHENOLATE MOFETIL (RS61443) AFTER SINGLE AND MULTIPLE DOSING (3.0g/DAY) IN RENAL TRANSPLANT PATIENTS WITH PRIMARY NON-FUNCTION (Study No.: CPP/MYCc024/EUR)

Study Design: This was an open-label, non-comparative study in patients (N = 8) with primary renal allograft non-function who were enrolled 24-96 hours post-transplant and on the day after their first dialysis session. Patients were on mycophenolate mofetil, 3g/day (6*250 mg capsules bid) for 28 days.

Pharmacokinetic profiles of MPA and MPAG were determined for study days 1, 7, 14, 21 and 28.

Results:

Parameter/Units	MPA					
	Day 1	Day 7	Day 14	Day 21	Day 28	ANOVA p =
Mean AUC_{0-12}/mcg*h/mL (SD)	28.0 (10.2)	37.8 (15.6)	54.2 (30.2)	31.3 (0.65)	52.7 (16.7)	0.050
Mean C_{max}/mcg/mL (SD)	7.71 (2.84)	6.15 (2.66)	8.2 (3.45)	7.86 41)	13.1 (2.66)	<0.001
Mean C_{min}/mcg/mL (SD)	NC	2.58 (1.24)	4.25 (3.52)	8)	2.85 (1.13)	0.389
Mean C_{ave}/mcg/mL (SD)	NC	3.14 (1.30)	4.52 (2.51)	2.61 (.054)	4.39 (1.39)	0.387

Parameter/Units	MPAG					
	Day 1	Day 7	Day 14	Day 21	Day 28	ANOVA p =
Mean AUC_{0-12}/mcg*h/mL (SD)	446 (143)	3414 (1401)	2245 (1000)	2844 (66.3)	1643 (506)	<0.001
Mean C_{max}/mcg/mL (SD)	54.2 (17.1)	361 (125)	276 (124)	279 (5.79)	181 (55.7)	<0.001
Mean C_{min}/mcg/mL (SD)	NC	293 (110)	200 (116)	254 (35.8)	123 (33.4)	0.008
Mean C_{ave}/mcg/mL (SD)	NC	284 (117)	187 (83.3)	237 (5.44)	137 (42.1)	0.028

NC = not calculated

The results (Table above) indicate that plasma concentrations of MPAG accumulated in patients with primary non-function of their renal grafts but the accumulation of MPA was smaller. The accumulation of plasma MPAG seemed to reach a maximum between 7 and 21 days following the onset of treatment. In most patients the plasma MPAG concentrations had begun to diminish by Day 28, probably due to regaining of renal function.

Results also indicated that hemodialysis removed MPAG from the blood of patients with MPAG plasma concentrations greater than 100 mcg/mL.

Pharmacokinetics in Hepatically-Impaired Patients
Two studies (CPP 026 and CPP 030) were conducted with 1-g single doses of MMF given orally or IV, respectively, to patients with alcoholic cirrhosis of the liver. The oral study used groups of cirrhotic patients with varying degrees of hepatic impairment and included a group of healthy volunteers. The IV study used patients with severe hepatic impairment.

INVESTIGATION OF MYCOPHENOLATE MOFETIL PHARMACOKINETICS FOLLOWING A SINGLE ORAL DOSE OF 1 GRAM TO VOLUNTEERS WITH VARYING DEGREES OF HEPATIC IMPAIRMENT (Study No.: CPP/MYCc026)
Open label, parallel group, single dose study in 24 subjects (aged 40-59 years) in hepatic impairment patients as assessed by the aminopyrine breath test (APBT). Six each were assigned to the following 4 groups: no impairment, mild impairment (APBT 0.4-0.6% DOSE), moderate impairment (APBT 0.2-0.39% DOSE), severe impairment (APBT <0.2% DOSE).

Results: Results are presented in the following Table:

Parameter	MPA				
	A	B	C	D	p value from ANOVA
AUC_{last} (mcg*h/ml)	29.0	21.8	36.6	31.0	0.053
C_{max} (mcg/ml)	24.3	15.1	30.8	21.3	0.015
T_{max} (h)	0.625	1.08	0.708	0.750	0.445
RS Excreted (%)	0.645	0.253	1.01	1.66	0.143
CL/0-96 (L/h)	0.156	0.073	0.199	0.435	0.079
Parameter	**MPAG**				
	A	B	C	D	p value from ANOVA
AUC_{last} (mcg*h/ml)	231	202	387	207	0.001
C_{max} (mcg/ml)	31.4	24.8	43	26.8	0.013
T_{max} (h)	1.33	2.38	1.75	1.67	0.151
RS Excreted (%)	46.7	45.1	70.9	76.7	<0.001
CL/0-96 (L/h)	1.48	1.67	1.49	3.01	0.013

Groups: A = No impairment, B = Mild impairment, C = Moderate impairment, D = Severe impairment.

No consistent trend on the AUC of MPA compared to healthy volunteers was noted (Table above), although the moderately impaired group showed significantly higher AUC than those observed in mildly impaired group. The C_{max} of MPA was significantly different between severely impaired vs moderately impaired ($p = 0.041$), moderately impaired vs mildly impaired ($p = 0.002$) and mildly impaired vs healthy subjects ($p = 0.048$).

Hepatic impairment significantly affected the C_{max} ($p=0.013$), AUC ($p<0.001$) and renal clearance of MPAG ($p=0.013$). ABPT is a measure of oxidative phase I metabolism and MPA is primarily cleared by glucuronide. Thus a hepatic measure other than APBT may be more useful, however, in absence of any validated measure for glucuronyl transferase activity ABPT has been used.

INVESTIGATION OF MYCOPHENOLATE MOFETIL PHARMACOKINETICS FOLLOWING AN INTRAVENOUS INFUSION OF A 1 GRAM DOSE TO VOLUNTEERS WITH SEVERE HEPATIC IMPAIRMENT (Study No.: CPP/MYC030/GER)

Hepatically impaired volunteers ($N=6$) with aminopyrine breath test results less than 0.2% of dose, aged between 18-65 years enrolled and completed this open label, single dose study. All subjects had a diagnosis of hepatic impairment resulting from alcoholic cirrhosis and had previously participated in study CPP/MYC026. Single intravenous dose of 1 gram given as a 40 minute infusion (6 mg/mL in 5% dextrose solution).

Results: Results are summarized in the following Table:

Parameter	MMF	MPA	MPAG
AUC_{last} (mcg*h/mL±SD)	1.64±0.642	44.1±15.5	185±45.6
Clearance (L/min±SD)	NC	NC	0.0655±0.0215
C_{max} (mcg/mL±SD)	3.25±1.24	39.0±10.6	28.1±6.89
Half-life (h±SD)	NC	NC	5.49±3.73
% RS Excreted (%±SD)	NC	1.35±1.35	64.7±61.1
CL_{0-96} (L/h±SD)	NC	0.254±0.303	2.45±1.69

NC = not calculated

In general, hepatic glucuronidation processes appear to be unaffected by hepatic parenchymal disease (alcoholic cirrhosis). However, hepatic disease with predominantly biliary damage, such as primary biliary cirrhosis, may show a different effect.

Comparing the oral data and i.v. data:

Parameter	MPA (i.v)	MPA (oral)	MPAG (i.v.)	MPAG (oral)
AUC_{last} (mcg*h/mL±SD)	44.1±15.5	31.0	185±45.6	207
C_{max} (mcg/mL±SD)	39.0±10.6	21.3	28.1±6.89	26.8
Half-life (h±SD)	NC	NC	5.49±3.73	NC
% RS Excreted (%±SD)	1.35±1.35	1.66	64.7±61.1	76.7
CL/0-96 (L/h±SD)	0.254±0.303	0.435	2.45±1.69	3.01

Diminished hepatic extraction of MPA may be responsible for the relatively high MPA AUC following IV administration in the severely hepatically impaired group. However, following oral administration to these patients, an increase in the MPA AUC may be counteracted by a corresponding reduction in the amount of extracted drug to undergo enterohepatic circulation.

MMF Pharmacokinetics and Plasma Levels in Patients

Investigation of the time required, post surgery, to achieve stable bioavailability following single oral doses of mycophenolate mofetil in renal transplant patients (Study No.: CPP/MYCc027/GB)

Study Design: Open label sequential design. Subjects (N=11 M=7, F=4) received a single 1.5g oral dose on Day 2 and Day 5 following renal transplantation and again on a third day between 2 and 6 weeks post-transplant when the patient was in a stable medical state (Day n). Objectives were to identify the post-operative day on which the pharmacokinetic (PK) profile, following single oral doses of mycophenolate mofetil (MMF) becomes stable in renal transplant patients receiving cyclosporin A monotherapy or cyclosporin plus corticosteroids.

Six subjects terminated from the study prematurely. It is planned that a minimum of 10 evaluable subjects with PK assessments on Day 2 and Day n will eventually complete the study.

Results: The PK parameters from the interim report are summarized below:

Mean Parameters	MPA			ANOVA	MPAG			ANOVA
	Day 2	Day 5	Day n	p value	Day 2	Day 5	Day n	p value
C_{max} (mcg/mL)	9.26 ±8.90	13.9 ±10.0	19.0 ±2.34	0.458	42.5 ±10.7	54.9 ±14.4	73.6 ±16.5	0.020
AUC (mcg*h/mL)	36.6 ±15.8	70.2 ±101	47.7 ±13.7	0.591	1303 ±1055	2265 ±2105	1030 ±74.0	0.186
AUC_{last} (mcg*h/mL)	26.0 ±11.7	26.1 ±9.37	40.6 ±16.3	0.473	886 ±320	1208 ±621	928 ±19.6	0.199
$t_{\frac{1}{2}}$ (h)	40.8 ±37.4	120 ±253	17.7 ±6.59	0.548	28.0 ±25.1	33.7 ±31.9	10.3 ±2.47	0.408
T_{max} (h)	1.56 ±1.19	1.18 ±1.09	0.833 ±0.289	0.410	7.48 ±10.2	3.99 ±3.95	3.66 ±0.573	0.623

Values are shown ± SD

The MPA plasma concentrations were highly variable between subjects in the period immediately after renal transplantation.

For MPA, mean Cmax and AUC_{last} tended to increase and $T_{1/2}$ tended to decrease. For MPAG $T_{1/2}$ decreased and Cmax tended to increase whereas, AUC_{last} was similar on three occasions PK was studied. Incomplete absorption does not seem to be the reason for lower MPA Cmax and AUC in the initial period after transplantation (since MPAG AUC_{last} for Days 2,5 and n were similar).

One subject had a severe urine leak which resulted in further surgery and death. This event was not attributed to study drug.

PHARMACOKINETICS IN PATIENTS (SUB-STUDIES OF CLINICAL TRIALS)
In four pivotal clinical trials blood samples were collected to study pharmacokinetics of the drug. Samples for full profiles were collected in study MyCc1866 whereas, in the other three studies only trough level samples were collected.

Randomized, Double-Blind Comparative Study of Two Doses of Mycophenolate Mofetil or Azathioprine Each in Combination with Cyclosporine and Corticosteroids for the Prevention of Rejection in Recipients of Their First Cadaveric Renal Allograft
Study No.: ICM MYCc1866/USA: July 1992–4 March 1994 (interim cutoff date)

Study Design: This was a multicenter, double-blind, randomized, comparative, parallel-group study conducted at 14 centers. All patients were to receive standard immunosuppressive treatment including cyclosporine and corticosteroids, as well as antilymphocyte induction therapy. Patients were randomized to receive MMF

1.0 g bid (MMF 2 g), MMF 1.5 g bid (MMF 3 g) or AZA 1–2 mg/kg per day, starting within 48 hours posttransplant.

Four hundred ninety-nine patients (288 males and 211 females) 18–76 years of age were enrolled in the study (166 AZA, 167 MMF 2 g, and 166 MMF 3 g). One hundred fifteen patients withdrew from the study prematurely (37 AZA, 35 MMF 2 g, and 43 MMF 3 g).

At selected study centers, routine blood samples were collected at specified times (Day 1, 5 and last day before discharge from the hospital) for determination of mycophenolic acid (MPA) and mycophenolic acid glucuronide (MPAG) concentrations, and pharmacokinetic parameters. Additionally, blood samples were to be collected in the event of a serious adverse event or a rejection episode.

Results:
The pharmacokinetic parameters obtained are summarized in the following table:

Parameter Mean (S.D.)	MPA (1 G bid)			MPA (1.5 Gbid)		
	Day 1 (N=32)	Day 5 (N=21)	Day Last (N=19)	Day 1 (N=29)	Day 5 (N=20)	Day Last (N= 20)
Tmax (hr)	4.24 (4.08)	1.33 (0.783)	1.26 (0.724)	3.22 (3.78)	1.36 (0.956)	1.86 (2.46)
C_{max} (µg/mL)	4.72 (4.90)	7.02 (3.43)	9.61 (6.33)	6.09 (5.47)	11.9 (8.62)	11.7 (6.92)
AUC_{last} (µg·hr/mL)	13.3 (8.11)	25.0 (12.6)	26.3 (9.55)	20.8 (12.6)	39.7 (21.2)	35.9 (16.5)
Total AUC (µg·hr/mL)	13.3 (8.11)	25.0 (12.6)	26.3 (9.55)	20.8 (12.6)	39.7 (21.2)	35.9 (16.5)
Parameter Mean (S.D.)	**MPAG (1 G bid)**			**MPAG (1.5 Gbid)**		
	Day 1 (N=31)	Day 5 (N=21)	Day Last (N=19)	Day 1 (N=29)	Day 5 (N=20)	Day Last (N= 20)
Tmax (hr)	7.63 (3.89)	2.55 (1.09)	3.59 (2.64)	7.1 (4.33)	2.44 (1.21)	2.50 (1.23)
C_{max} (µg/mL)	23.1 (10.5)	63.0 (25.4)	97.1 (67.3)	29.0 (18.9)	95.1 (42.7)	99.6 (45.4)
AUC_{last} (µg·hr/mL)	160 (93.9)	624 (274)	912 (688)	229 (142)	914 (445)	890 (341)
Total AUC (µg·hr/mL)	160 (93.9)	624 (274)	912 (688)	229 (142)	914 (445)	890 (341)

The C_{max} and AUC of MPA appeared to be dose proportional and achieved steady state by Day 5 of dosing, while MPAG C_{max} and AUC were similar for the 1.0 g bid and 1.5 g bid dose groups on multiple dosing (last day before discharge).
In conclusion, as noted in other studies MPA AUC and Cmax are about one half compared to those observed in healthy volunteers. Additionally, it is noted that mean AUC for MPAG was similar for 1 and 1.5 G doses. It should also be noted that for a same given dose, MPA AUC were about one half of that observed in Japanese population (study NSK 24/100).

A Randomized, Double-Blind, Multicentre, Placebo-Controlled Study of the Addition of Mycophenolate Mofetil (RS-61443) to Cyclosporine and Oral Corticosteroids for the Prevention of Acute Renal Allograft Rejection Episodes (Study No.: MRE/MYCc022/EUR)

Study Design: This was a double-blind, randomized, multicentre, placebo-controlled study with three treatment arms. A total of 491 patients (304 male, 187 female; age range, 18–73; 166 placebo, 165 MMF 2 g, and 160 MMF 3 g) were enrolled. More than half of the patients in each treatment group had been treated in the study for over 6 months. Pharmacokinetic trough samples were obtained from 126 patients.

It should however be noted, that according to the sponsor, PK data was not collected under strict supervision and is not considered reliable in this study.

Routine trough blood samples were collected at Week 12. Samples were also to be collected in the event of a serious adverse event or rejection episode. Dr. Pichlmayr's center collected samples at 1,2,4 and 12 hours at his discretion. These data were not included in this interim report however, the sponsor plans to include that data in the final report.

Results: The mean trough concentrations of MPA and MPAG at Week 12, were 2.853 μg/mL and 59.59 μg/mL, respectively for the 2 g group and 5.474 μg/mL and 82.97 μg/mL, respectively for the MMF 3 g group. Data are indicative of increase in Cmin concentrations with increase in dose. However, it should be noted that according to the sponsor, PK data was not collected under strict supervision and is not reliable.

The serum creatinine and calculated creatinine clearance reported for the three groups of patients are: Placebo 1.6 mg/dL and 56.1 mL/min; MMF 2 g group 1.43 mg/dL and 59.9 mL/min; and MMF 3 g group 1.48 mg/dL and 62.8 mL/min.

A Randomized, Double-Blind, Multicenter Comparative Study of the Addition of Mycophenolate Mofetil (RS-61443) vs. Azathioprine to Cyclosporine and Oral Steroids for Management of Renal Allograft Recipients Immediately Posttransplant for Prevention of Rejection (Phase I) and Long-Term Management after Year One of Transplantation (Phase II) (Study No.: IICR/MYC023/INT)

A multicenter, double-blind, randomized, comparative, parallel-group study, stratified by center and first and second renal allograft. Five hundred three patients (303 males and 200 females, 161 patients AZA, 171 MMF 2 g, and 164 MMF 3 g). One hundred thirty-eight patients had terminated prematurely by the time the interim report was submitted.

Routine blood samples were collected at Week 12. Blood samples for the analysis of MPA and MPAG concentrations were also collected in the event of an adverse event resulting in withdrawal, or in the event of a serious adverse event or a rejection episode.

Results: Pharmacokinetic blood trough sampling was introduced in March 1993 (amendment 3 to protocol) and 32 samples were obtained from 30 patients in 2 G group and 21 samples from 19 patients in 3 g MMF group.

At week 12, the mean MPA and MPAG concentrations in patients taking MMF 2 g were 3.00 ± 4.44 μg/mL and 53.6 ± 25.7 μg/mL, respectively. In patients taking MMF 3 g, these concentrations were 5.40 ± 6.25 μg/mL and 76.7 ± 32.8 μg/mL, respectively. Due to wide interpatient variability observed for trough MPA and MPAG concentrations at given MMF doses, meaningful conclusions could not be drawn from pharmacokinetic data. However, these results seem to be comparable to those observed in study #022.

The mean serum creatinine and calculated creatinine clearance (at week 12) reported for the three groups of patients are: AZA 1.67 mg/dL (n = 138) and 57.6 mL/min; MMF 2 g group 1.6 mg/dL (n = 146) and 59.0 mL/min; and MMF 3 g group 1.49 mg/dL (n = 142) and 61.7 mL/min.

Pediatric Renal Transplant Patients

An open-Label, Dose-Ranging Pharmacokinetic, Safety, and Tolerance Study of Oral Mycophenolate Mofetil in the Prevention of Rejection in Pediatric Renal and Hepatic Allograft Recipients (Study No.: (IID/MYCc2l90/USA))

Ongoing, nonrandomized, ascending-dose, multicenter, 3-year, open-label study. Patients were assigned to one of three age groups (3 months to < 6 years; 6 years to < 12 years; and 12-18 years) and received one of three dose levels of oral MMF (15 mg/kg bid, 23 mg/kg bid, or 30 mg/kg bid).

Objectives were to assess in pediatric renal and hepatic allograft recipients the pharmacokinetics of oral mycophenolate mofetil (MMF) during the first year of treatment and the safety throughout treatment for up to 3 years for each of the three dose levels in each of three age groups.

Fourteen renal allograft recipients (8 male, 6 female; aged 2-18 years) with a cumulative time on treatment ranging from 6 to 166 days had enrolled by cutoff date.

MMF for oral dosing was provided in 250-mg capsules. MMF for IV administration was supplied in a sterile vial containing 542 mg of lyophilized MMF hydrochloride (equivalent to 500 mg of MMF).

Results: IV Pharmacokinetics. Limited pharmacokinetic data (Table 7) for MMF at doses of 15 and 23 mg/kg bid in a pediatric population have been presented. No patient has died, developed a malignancy, or discontinued treatment with MMF as of the cutoff date.

The sponsor plans to dose escalate MMF up to 30 mg/kg bid (not to exceed 1.75 G bid). 30 mg/kg in children is equivalent to about 2 G bid in adults. Based on data in adults, 1.0 G bid is adequate and safer compared to 1.5 G bid. Therefore,

it is recommended that in pediatric patients dose should not be exceeded beyond 15 mg/kg tid, unless a rationale for higher doses is provided by the sponsor.

DRUG INTERACTIONS

Acyclovir (Study # CPP/MYCc2166/USA):

Following single dose concomitant administration of mycophenolate mofetil (1.0 g) and acyclovir (Zovirax®, 800 mg) to twelve healthy volunteers, mean ± SD MPA AUC and Cmax were 62.0 ± 24.7 μg*h/mL and 21.9 ± 8.74 μg/mL, respectively compared to 57.0 ± 15.7 μg*h/mL and 21.1 ± 9.39 μg/mL, respectively when mycophenolate mofetil was administered alone. The mean ± SD AUC and Cmax of MPAG were 314 ± 60.1 μg*h/mL and 28.9 ± 8.12 μg/mL, respectively compared to 289 ± 72.0 μg*h/mL and 27.30 ± 7.99 μg/mL, respectively when mycophenolate mofetil was administered alone. The mean ± SD AUC and Cmax of

acyclovir after co-administration were 6577 ± 2245 ng*h/mL and 1126 ± 458 ng/mL, respectively compared to values of 5203 ± 1797 ng*h/mL and 957 ± 330 ng/mL, respectively after administration of acyclovir alone.
MPAG and Acyclovir plasma AUCs were increased 10.5% and 33.5%, respectively. Because MPAG and acyclovir plasma concentrations are increased in the presence of renal impairment, the potential exists for the two drugs to compete for tubular secretion resulting in further increases in concentrations of acyclovir and MPAG.

Antacids containing magnesium and aluminum hydroxides (Study #: ICM 1725):
Ten rheumatoid arthritis patients who were administered Maalox TC (10 mL QID) received a single dose of mycophenolate mofetil (2.0 g). The mean ± SD MPA AUC(0-24) and Cmax after concomitant administration were 66.5 ± 24.6 μg*h/mL and 14.8 ± 6.74 μg/mL, respectively compared to 79.9 ± 23.0 μg*h/mL and 23.8 ± 11.6 μg/mL, respectively after administration of mycophenolate mofetil alone. The Cmax and AUC(0-24) were 33% and 17% lower, respectively when mycopholate mofetil was administered with Maalox TC compared to when mycophenolate mofetil was administered under fasting conditions. MMF is not recommended to be taken simultaneously with antacids containing magnesium and aluminum hydroxides.

Cholestyramine (Study #: CPP/MYCc059/GB):
Following single dose administration of 1.5 g mycophenolate mofetil to 12 healthy volunteers pretreated with 4 g TID of cholestyramine (Questran® A) for 4 days, the mean ± SD MPA AUC and Cmax after concomitant administration were 44.10 ± 6.48 μg*h/mL and 28.3 ± 12.0 μg/mL, respectively compared to 72.5 ± 18.8 μg*h/mL and 30.1 ± 5.90 μg/mL, respectively after administration of mycophenolate mofetil alone. The mean ± SD MPAG AUC and Cmax after concomitant administration were 337 ± 125 μg*h/mL and 46.0 ± 12.8 μg/mL, respectively compared to 513 ± 210 μg*h/mL and 44.5 ± 19.5 μg/mL, respectively after administration of mycophenolate mofetil alone.
MPA AUC decreased approximately 40%; this decrease is consistent with interruption of enterohepatic recirculation which may be due to binding of recirculating MPAG from the intestine by cholestyramine. MMF is not recommended to be given with cholestyramine or other agents that may interfere with enterohepatic recirculation.

Cyclosporine A (Study #: MYCS2308)
Single and multiple doses of MMF (1.5 g BID) were administered to 10 stable (at least 3 months post transplant) renal transplant patients who were stabilized on cyclosporine A (Sandimmune®) (at doses of 275 to 415 mg/day in divided doses). The mean ± SD cyclosporine A AUC(0-12) and Cmax after single dose of MMF were 3512 ± 987 ng*h/mL and 699 ± 224 ng/mL, respectively compared to values of 3245 ± 1088 ng*h/mL and 700 ± 246 ng/mL, respectively one week before administration of mycophenolate mofetil. The mean ± SD AUC(0-12) and Cmax of cyclosporine A after 14 days of multiple doses of mycophenolate mofetil were 3290 ± 822 ng*h/mL and 753 ± 161 ng/mL, respectively compared to 3245 ± 1088 ng*h/mL and 700 ± 246 ng/mL, respectively one week before administration of mycophenolate mofetil. The effect of cyclosporine A on MMF

concentrations could not be evaluated in this study. However, the concentrations of mycophenolic acid in this study were similar to that observed for healthy volunteers.

Ganciclovir (Study #: IID/MYCc2180/USA):
Following single dose administration of mycophenolate mofetil (1.5 g) and IV ganciclovir (Cytovene®, 5 mg/kg) to 12 stable renal transplant patients, the mean ± SD AUC and Cmax of ganciclovir (n = 10) after co-administration were 54.3 ± 19.0 μg*h/mL and 11.5 ± 1.75 μg/mL, respectively compared to values of 51.0 ± 17.0 μg*h/mL and 10.6 ± 1.97 μg/mL, respectively after administration of IV ganciclovir alone. The mean ± SD AUC and Cmax of MPA (n = 12) after co-administration were 80.9 ± 21.6 μg*h/mL and 27.8 ± 13.9 μg/mL, respectively compared to 80.3 ± 16.4 μg*h/mL and 30.9 ± 11.2 μg/mL, respectively after administration of MMF alone. In renally impaired patients, MPAG and MPA plasma concentrations are increased so are ganciclovir concentrations; therefore, the potential exists for the two drugs to compete for tubular secretion and thus increases in the concentrations of both drugs may occur.

Oral contraceptives (Study #: MYCS2308):
Following single dose administration of mycophenolate mofetil (1.0 g) and two tablets of Ortho-Novum® 7/7/7 (1 mg norethindrone [NET] and 35 μg estradiol ethinyl [EE]) to healthy women, no pharmacokinetic interaction was observed between mycophenolate mofetil (1.0 g) and two tablets of Ortho-Novum® 7/7/7. The mean ± SD AUC and Cmax of norethindrone (n = 14) after co-administration were 90564 ± 44420 pg*h/mL and 14985 ± 5459 pg/mL, respectively compared to values of 83887 ± 47078 pg*h/mL and 13094 ± 2861 pg/mL, respectively after administration of Ortho-Novum® 7/7/7 alone. The mean ± SD AUC and Cmax of ethinyl estradiol (n = 15) after co-administration were 4455 ± 1460 pg*h/mL and 494 ± 193 pg/mL, respectively compared to values of 4357 ± 1189 pg*h/mL and 449 ± 116 pg/mL, respectively after administration of Ortho-Novum® 7/7/7 alone. The mean ± SD AUC and Cmax of MPA (n = 14) after co-administration were 65.9 ± 20.4 μg*h/mL and 23.9 ± 8.0 μg/mL, respectively compared to values of 69.9 ± 15.3 μg*h/mL and 26.2 ± 13.0 μg/mL, respectively after administration of MMF alone.

The study design did not allow the evaluation of the effect of long term MMF use on the pharmacokinetics of oral contraceptives. Therefore, even though this single dose study demonstrated no gross pharmacokinetic interaction, the possibility of changes in the pharmacokinetics of the oral contraceptive under long term dosing conditions with MMF which might adversely affect the efficacy of the oral contraceptive cannot be ruled out.

Trimethoprim/sulfamethoxazole (Study #: CPP/MYCc028/GB):
Following single dose administration of mycophenolate mofetil (1.5 g) to twelve healthy male volunteers on day 8 of a 10 day course of Bactrim® DS (trimethoprim 160 mg/sulfamethoxazole 800 mg) administered BID, no effect on the bioavailability of MPA was observed. The mean ± SD MPA AUC and Cmax after concomitant administration were 75.2 ± 19.8 μg*h/mL and 34.0 ± 6.55 μg/mL, respectively compared to values of 79.2 ± 27.9 μg*h/mL and 34.2 ± 10.7 μg/mL, respectively after administration of MMF alone.

Trimethoprim/Sulfamethoxazole may not be a good representative of drugs that may alter the gastrointestinal flora. Therefore, although no significant effect was observed on MMF bioavailability when co-administered with Bactrim, other drugs that alter the gastrointestinal flora may alter the biovailability of MMF by disrupting the enterohepatic recirculation of MPAG. Interference of MPAG hydrolysis may lead to less MPA available for absorption.

POPULATION ANALYSIS

Summaries of pharmacokinetic parameters of MPA and MPAG (AUC and Cmax) were prepared by race and gender. Descriptive statistics obtained are presented in Table 8 for healthy volunteers and in Table 9 for renal transplant patients. For these analyses, the pharmacokinetic variables AUC_{last} and C_{max} for doses other than 1 g were adjusted to a 1-g MMF dose. Also, patients with delayed graft function were excluded.

Age. There were only 4 patients aged over 65 years, which are insufficient to allow sub-group analysis. Data for these patients are provided in Appendix 2 (retained in the Division of Biopharmaceutics).

Gender: In healthy volunteers, for both MPA and MPAG (Table 8), females had slightly higher values of AUC_{last} and C_{max} than males. Significant differences ($p < 0.05$, t-test comparison) between males and females were found for observed MPA AUC_{last}, MPAG AUC_{last} and MPAG C_{max} but none of the body-weight adjusted parameters (body weight adjusted to 70 kg) were significant.

In patients, mean (SD) MPA AUC_{0-12} for males was 32.0 (14.5) and for females was 36.5 (10.6) μg•h/mL while mean (SD) MPA C_{max} was 9.96 (6.19) in the males and 10.6 (5.64) μg/mL in the females. There does not appear to be difference between male and female renal transplant patients with respect to the pharmacokinetics of MMF.

Body Weight: Steady state observed parameters were not significantly different between males and females for either MPA or MPAG AUC_{0-12} and C_{max}. However, weight adjusted MPAG AUC_{0-12} and C_{max} (1.5 G bid dose only) were different ($p < 0.05$). Weight-adjusted MPA AUC_{0-12} and C_{max} showed no statistically significant differences indicating that the body weight and gender effects in renal transplant patients may be very small. In contrast, in healthy subjects body weight did seem to account for gender-related differences in MPA AUC.

Thus a correlation existed between weight and MPA pharmacokinetic parameters for healthy volunteers but not in renal transplant patients. A weight relationship in patients may be obscured by other factors such as pathophysiologic status and use of concomitant medication.

Race: The majority (155/186, 83%) of the healthy volunteers were Caucasian. Pharmacokinetic parameters were tabulated by race. These data were not subjected to a formal statistical analysis (Tables 8 and 9).

In renal transplant patients, there were 69 Caucasians, 9 blacks, 41 Asians, 0 Hispanics, and 1 other) allowed the Asian and Caucasian subgroups to be compared. The Asian subgroup had high AUC_{0-12} and C_{max} values relative to the Caucasian group. However, the Asians weighed substantially less, the mean (SD) weight of the Asians was 54.6 (12.7) kg, while that of the Caucasians was 72.8 (16.0) kg, so that any racial difference was confounded by weight.

However, although there were very few blacks in healthy volunteers or patients, black males appear to have a 50% reduction in AUC and Cmax compared to black females or caucasians (Tables 8 and 9). It should also be noted that based on clinical data in a limited number of blacks, it appears that giving a 3 G daily dose reduced the rejection rate to 24% compared to 39% in 2 G daily dose group. However, probably due to the very few subjects, Chi-squared test (performed by Dr. Flyer, Biometrics) comparing 3 G and 2 G rejections for caucasians and blacks, was not significantly different.

Multivariate Analysis of AUC (Age, Weight, Albumin, and Other Variables, in healthy subjects):
The relationship between age, other variables, and the pharmacokinetics of MMF was also explored by a multi-variate analysis.

Figures 5 and 6 are scatterplot matrix presentations for the relationships discussed.

For MPA, both age and 70/Body Weight were highly significantly correlated with MPA AUC (r^2 = 0.485, n = 165) although a greater part of the observed variation was still not explained by these factors.

Albumin and creatinine clearance were added to a multiple regression model (see Tables 12 and 13. For MPA AUC, age accounted for the major part of the variance, with creatinine clearance accounting for the majority of the remaining explainable variance (r^2 = 0.46, n = 111).

Step-wise regression analysis indicated that the addition of the liver enzyme SGPT and total calcium to the original variables, age, creatinine clearance and albumin yielded an r^2 of 0.53 (n = 98). A major proportion of the variance is accounted for by age. The same analysis of the MPAG data included 7 terms but provided an r^2 of only 0.29 (n = 98) (see Tables 14 and 15) .

In conclusion, for healthy subjects, multivariate analysis indicates that age and weight (particularly age) are important factors for MPA AUC. MPAG AUC was poorly correlated with any variable.

Multivariate Analysis of AUC (Age, Weight, Albumin, and Other Variables, in renal transplant patients):
Figures 7 and 8 are scatterplot matrix presentations for the relationships discussed.

Age and Body Weight were both correlated with MPA AUC_{0-12}, although a substantial part of the observed variation was not explained by these factors (r^2=0.11, n = 223).

Albumin and 70/Body Weight (for MPA) were significantly correlated with AUC_{0-12}, but the r^2 value of 0.19 (n = 107).

Using a Step-wise regression mixed approach an r^2 of 0.54 (n = 81) was achieved; however, this model was not a simple model. (Tables 18 and 19).

A model with 5 terms (albumin, BUN, alkaline phosphatase, creatinine clearance, and triglycerides) provided a more plausible description of the data (r^2 = 0.47, n = 81, see Table 20 and 21. Dropping any one of these terms (including triglycerides) caused the model not to fit.

In conclusion the data provided a confirmation of the relationship between renal function, (positive correlation with BUN and creatinine clearance) for both MPA and MPAG AUC_{0-12}. Black males (N=4) had 50% lower AUC and Cmax compared to black females or compared to caucasians and should be further explored. Dose adjustment on the basis of body weight is not supported in adults.

Concentration Effect Relationship
Logistic regression modelling was done using data from study NSK 24/100 (dose range of 1 g/day to 4 g/day), a fit between plasma MPA AUC_{0-12} and the probability of rejection was obtained. The parameters obtained from logistic regression modelling (NSK 24/100) fit were applied to data obtained in study 1866 (pivotal clinical trial). Predicted rejections (summation of probabilities for all patients in 1 G and 1.5 G dose) were obtained and compared to observed rejections. The analysis presented in the NDA showed that the observed number of rejections was similar to what was predicted based on NSK 24/100 data. This is discussed in detail in Appendix 2 (report by Raymond Miller, Ph. D.).

No similar relationships have been obtained for safety events. However, plots of plasma concentrations taken at the time of serious adverse events during these trials revealed a weak association between elevated MPAG concentrations and certain adverse events (leukopenia and CMV infections); this is further discussed in Appendix 3.

Logistic regression modelling of 1866 data (performed by this reviewer) did not result in a good correlation between AUC and rejections. It should also be noted that in the final PK report of MYCc 1866, 18 patients were excluded from the analysis because AUC values were in question due to reliability of recording time for sample collection. For logistic regression purposes the sponsor included these 18 additional subjects. Reliability of such AUC data is unknown; hence our analysis only included the data that were submitted in the NDA.

Because the USA study used 2 and 3 G doses, this reviewer performed logistic regression on Japanese data for 2 and 3 G doses only, and was able to get similar results as obtained from the full data set. Further, logistic regression was applied to the 1866 data, a reasonable fit was not obtained. This could possibly be due to smaller AUC range in the US study as compared to the Japanese study (Box plot Figure 9 and 10).

There are other possible limitations of applying logistic regression from the Japanese patients to the USA patients: cultural and health care differences, eleven of the 14 patients (Japanese data 1 to 4 G dose) had rejections prior to sampling for AUC, 5/6 patients (Japanese 2 & 3 G) had rejections in first 12 Days. In the USA study, there were no rejections in the first 12 Days. Observation period was 3 months for Japanese study and 6 months for the USA Study. Fewer patients discontinued at the higher dose in the Japanese study.

Analysis did not consider other factors such as, albumin, creatinine clearance, age etc. Japanese patients have almost twice the AUC compared to USA patients as noted in the following table:

Differences in Mean (± Std Dev) Pharmacokinetics and Response:

STUDY	AUC Steady State mcg*hr/mL	**Rejections in patients with Full PK profiles
NSK 24/100 2 G Dose	43.7 (20.0)	4/11 (36%)
MYCc 1866 2 G Dose	28.0 (9.0)	4/15 (27%)
NSK 24/100 3 G Dose	61.8 (29.9)	2/11 (18%)
MyCc 1866 3 G Dose	36.1 (11.8)	4/16 (25%)

** Excludes patients with delayed graft function

Since the application of logistic regression was questionable, another approach was taken to evaluate the data. The following table gives a frequency distribution of rejection in a particular AUC range. Based on this frequency distribution, it appears that patients in the lower AUC were at a greater risk of rejection.

AUC mcg*hr/mL	Japan 1 to 4 G Dose	Japan 2 & 3 G Dose	US 2 & 3 G Dose
10-20	6/8 (75%)	1/1 (100%)	3/6 (50%)
20-30	4/6 (67%)	3/4 (75%)	2/9 (22%)
30-40	1/7 (14%)	0/5 (0%)	1/9 (11%)
40-50	1/6 (17%)	1/5 (20%)	1/4 (25%)
50-60	1/6 (17%)	1/5 (20%)	1/3 (33%)
>60	0/7 (0%)	0/2 (0%)	0/0

However, these data are in a limited number of patients and the results should be cautiously interpreted. It should also be noted that the AUCs for 2 and 3 gram doses are interspersed with no difference in the number of rejectors. However, it is unknown how an individual would respond if the dose is increased from 2 G to 3 G a day.

Based on the number of rejections in each dose level in study MYCc 1866, a higher dose is not indicative of a lower rejection rate since the number of rejections in each dose level was approximately the same i.e. 4/15 and 4/16. This is further substantiated in the clinical trial rejection rates of 19.8% and 17.5% for the 2 G and 3 G dose, respectively.

In conclusion, although the application of logistic regression was questionable, the data are suggestive of relationship between low AUC and rejections in both the populations. Existence of relationship between AUC and outcome should be further explored to find a threshold of AUC beyond which probability of rejection may not be different, even if dose is increased.

The AUC and Cmax immediately post transplant are about 50% lower compared to stable transplant patients. It is also known that the major portion of rejections occur in the initial post-transplant period. If the relationship between AUC and outcome is substantiated, a additional recommendation will be to explore usefulness of using a dosing regimen in which a higher dose is given in the immediate post transplant period and the a lower maintenance dose is given thereafter.

5 pages

purged

Chandrahas G. Sahajwalla, Ph.D.
Pharmacokinetics Evaluation Branch I, Division of Biopharmaceutics

Kofi A. Kumi, Ph.D.
Pharmacokinetics Evaluation Branch I, Division of Biopharmaceutics

Concurrence:
John Lazor, Pharm. D.
Acting Supervisor,
Pharmacokinetics Evaluation Branch I
Division of Biopharmaceutics
cc:
/NDA
/HFD 530/Div File
/HFD 530/CSO/MTarosky
/HFD 530/MO/JKorvick
/HFD 530/Biopharm/Sahajwalla (X2)
/HFD 530/Biopharm/Kumi
/HFD 530/Supervisor Biopharm/Lazor
/HFD 426/Branch Chief, Pharmacokinetics Evaluation Branch I/Fleischer

33 pages
purged

MICROBIOLOGY REVIEW

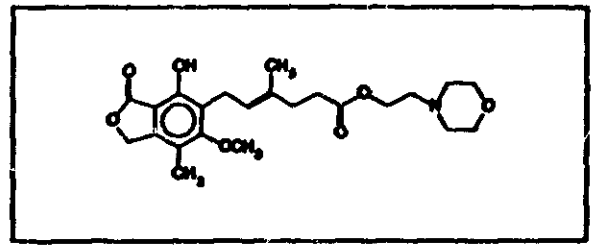
A microbiology review of the application was not requested. A microbiology review was requested of the antibiotic status of the application.

DRAFT

PHARMACOLOGIST'S REVIEW

NDA:
DATES ARRIVED, RECEIVED, and ASSIGNED: 11/10/94, 11/14/94, 11/15/94
DATE COMPLETED: 4/13/95
SPONSOR: Syntex (U.S.A.), Inc
415-354-7453
DRUG: Mycophenolate Mofetil,
M.W. 433.5, pKa 5.6
ROUTE ADMINISTERED: orally, capsules
RELATED INDs:

RELATED NDA:
(Mycophenolic Acid)



INDICATION: Immunosuppressant prophylaxis for renal graft rejection

DEFINITIONS: RS-61443 = MM = Mycophenolate Mofetil
IMP-DH = inosine monophosphate dehydrogenase
GMP = guanosine monophosphate
MPA = Mycophenolate, Mycophenolic Acid, RS-5797
MPAG = mycophenolate glucuronide

INTRODUCTION

Mycophenolate (MPA) is a product of *Penicillium stoloniferum* possessing antibiotic, immunosuppressive, anti-proliferative, and oncolytic activities. MM, a morpholino-ester pro-drug of MPA, inhibits de novo purine synthesis by reversibly blocking inosine monophosphate dehydrogenase (IMP-DH). IMP-DH is an enzyme which converts inosine monophosphate to xanthinosine monophosphate, a precursor of guanosine monophosphate. Phosphoribosyltransferase activity ("salvage pathway") may circumvent blockade by MPA, and rescue cells from GMP deprivation (Cancer Res. 32:1803, 1972). Lymphocytes, possibly due to a shortage of this latter enzyme, depend more on de novo purine synthesis than the salvage pathway. This dependency confers a degree of selectivity to the anti-proliferative effects of mm, disabling lymphocytes from responding to signals from cytokines such as IL-2.

CONCLUSIONS:

The NDA, is approvable from a pharmacology and toxicology perspective.
The relevant nonclinical comments (absence of tumorigenic or genotoxic properties; evidence of teratogenic/fetotoxic potential as well as excretion of drug in milk) for the label are appended (see Appendix 1) to this review, and are extracted from the primary reviews of the pharmacology studies conducted mainly under IND The reviews are attached for ease of reference, and are listed in time stamp order.

Lauren E. Black, Ph.D.
Reviewing Pharmacologist

Concurrences:
HFD-530/ADep/DFreeman
HFD-530/SPharm/JFarrelly
Disk:
HFD-530/JFarrelly

cc:
HFD-530/IND
HFD-530/Division File
HFD-340
HFD-530/LBlack
HFD-530/DKallgren
HFD-530/JKorvick
HFD-530/Chem
HFD-530/Micro
HFD-345/GJames

Appendix 1.

Based on review of submitted pharmacology and toxicology data, the suggested deletions (struckout) and additions (redlined) to the label follow.

other Interactions: The measured value for renal clearance of MPAG indicates removal occurs by renal tubular secretion as well as glomerular filtration. Consistent with this, co-administration of probenecid, a known inhibitor of tubular secretion, with mycophenolate mofetil in monkeys raises plasma AUC of MPAG by 3-fold. Thus, other drugs known to undergo renal tubular secretion may compete with MPAG and thereby raise plasma concentrations of MPAG or the other drug undergoing tubular secretion.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week oral carcinogenicity study in mice, mycophenolate mofetil in daily doses up to 180 mg/kg ~~(783 mg/m^2 based on body surface area (BSA))~~ was not tumorigenic. ~~For a 70 kg person (1.73 m^2 BSA) the highest dose represents 6.3 times the recommended clinical dose (2 g/day) on a mg/kg basis and 0.68 times the dose on a BSA basis.~~ when corrected for differences in body surface area (BSA).

~~on a BSA basis.~~ In a 104 week oral carcinogenicity study in rats, ~~mycophenolate~~ mofetil in daily doses up to 15 mg/kg (~~92 mg/m^2~~) was not tumorigenic. The highest dose ~~represents 0.53 (1.1 0.08~~ times the recommended clinical dose ~~of 2 g/day on a mg/kg basis and 0.08 times the dose on a BSA basis.~~ when corrected for BSA. While these animal doses were lower than those given to patients, they were maximal in those species and were considered adequate to evaluate the potential for human risk.

Mycophenolate mofetil ~~was not mutagenic in a battery of~~ in vitro ~~genotoxicity assays and~~ without metabolic activation ~~did not induce point mutations (the bacterial mutation~~ Ames assay) ~~or primary DNA damage (in the~~ yeast mitotic gene conversion assay) ~~in the presence or absence of metabolic activation. Mycophenolate mofetil was not mutagenic in vivo at oral doses up to 3000 mg/kg (the~~ mouse micronucleus aberration assay) ~~or in vitro with or without metabolic activation at concentrations up to 5 ug/mL (in the~~ Chinese hamster ovary cell [CHO] chromosomal aberration assay). ~~Chromosome aberrations were present without metabolic activation in an initial CHO cell assay, but only at concentrations (249 to 300 ug/mL) that caused excessive cytotoxicity.~~

Mycophenolate mofetil had no effects on fertility of male rats at oral doses up to 20 mg/kg/day (~~123 mg/m^2~~). This dose represents ~~0.70~~ 0.1 times the recommended clinical dose ~~of 2 g/day on a mg/kg basis and 0.11 times the dose on a BSA basis~~ when corrected for BSA. In a female fertility and reproduction study conducted in rats dosed orally at up to 4.5 mg/kg/day (~~28 mg/m^2~~), ~~the 4.5 mg/ _/day dose caused~~ malformations (principally of the head and eyes) occurred in the first generation (F1) offspring in the absence of maternal toxicity. This dose ~~represents 0.16~~ was 0.02 times the recommended clinical dose ~~of 2 g/day on a mg/kg basis and 0.02 times the dose on a BSA basis~~ when corrected for BSA. No effects on fertility or reproductive parameters were evident in the dams ~~present in the treated females (P1 females)~~, or in the subsequent ~~ly mated first~~ generation ~~offspring (P2 females or P2 males).~~

Pregnancy: Category C

In teratology studies in rats and rabbits, fetal resorptions and malformations occurred in rats at 6 mg/kg/day ~~(37 mg/m)~~ and in rabbits at 90 mg/kg/day ~~(1063 mg/m)~~ in the absence of maternal toxicity. ~~For a 70 kg person (1.73 m^2 body surface area), these dose levels represent 0.21-3.16 times the recommended clinical dose of 2 g/day on a mg/kg basis and~~ These levels are equivalent to 0.03-0.92 times the recommended clinical dose on a BSA basis. ~~The no effect levels for teratogenic changes in rats and rabbits were 2 and 30 mg/kg/day, respectively.~~

There are no adequate and well-controlled studies in pregnant women. CellCept should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (SEE WARNINGS)

Effective contraceptive measures are required with the use of CellCept. (See INFORMATION FOR PATIENTS)

Nursing Mothers

Studies in rats have shown mycophenolate mofetil to be excreted in milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from mycophenolate mofetil, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Earlier, line 285, Under "WARNINGS":

CellCept should not be used in pregnant women, particularly during the first trimester. Adverse effects on fetal development (including malformations) occurred when pregnant rats or rabbits were dosed during organogenesis. These responses occurred at doses lower than those associated with maternal toxicity and at doses below the recommended clinical dose. (SEE PREGNANCY)

DRAFT

DIVISION OF ANTIVIRAL DRUG PRODUCTS

Review of Chemistry, Manufacturing and Controls Section

NDA #:
CHEMISTRY REVIEW #: **DATE REVIEWED:** 12/1/94

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	11/10/94	11/10/94	11/10/94

NAME/ADDRESS OF APPLICANT: Syntex (USA), Inc.
3401 Hillview Ave.
Palo Alto, CA 94304

DRUG PRODUCT NAME
Proprietary: CellCept™
Nonproprietary: Mycophenolate Mofetil
Code Name/#: RS-61433

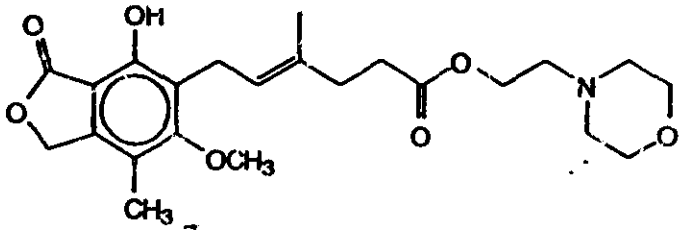
PHARMACOLOGICAL CATEGORY: Immunosuppressant

INDICATION:

DOSAGE FORM/STRENGTH: Capsule/250 mg

ROUTE OF ADMINISTRATION: Oral

CHEMICAL NAME/STRUCTURAL FORMULA:



2-morpholinoethyl(E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate
$C_{23}H_{31}NO_7HCl$
M.W.= 433.51

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS:
Chemists Review #1, IND
Deficiency Letter dated 3/6/90
Chemists Review of DMF

CONSULT REVIEWS:
Tradename reviewed by CDER Labeling and Nomenclature Commitee

REMARKS/COMMENTS

1. With regard to mycophenolate mofetil drug substance:
a. The drug substance is synthesized . The sponsor should submit any control procedures for determination of impurity carry-over

b. The current specification for melting range is too tolerant. Based on the batch analyses provided for the the proposed commercial synthesis (Direct esterification/Antibioticos supplier), a ran; no more than 2.5° C range is more representative.
c. The current ICH draft Guideline on Impurities in New Drug Substances divides organic impurities (related substances) into "specified" and "unspecified" impurities with respect to specification limits. All specified impurities in the drug substance should be qualified; however, they may be identified or unidentified. All specified impurities should be listed with specifications and limits. Any unspecified impurity is to be limited to NMT 0.1%. A limit on total organic impurities should be established. The impurities section of the DS specifications should b ended to reflect these recommendations. In addition, a specification with 2-hydroxyethylmorpholine should be incorporated
d. Individual limits sho e established fo The specification for should be removed from the specification since the proposed commercial synthesis does not utilize

e. The limit of quantitation for Regulatory metho (Determination of Purity and Related Substance Content of Mycophenolate Mofetil b and Research metho (Determination of Purity and Related Substance Content of should be provided.
f. The batch analyses for the DS using Regulatory Method list two impurities i.e. the ; from the impurities listed for Research Method The sponsor should provide a suitable explanation to this discrepancy.
g. The most current stability information available to support the 24 month re-analysis time for mycophenolate mofetil should be provided

2. With regard to mycophenolate mofetil capsules, 250 mg:

a. The drug product specifications and methods should be revised as following i) should be performed at product release as well as during stability studies. A specification with limit for should be added to the regulatory specifications ii) It is generally recommended that a spectroscopic method augmented with a chromatographic method be employed for product identification. Since is being used as one regulatory method, would be preferred as the other method.

b. Currently, full batch analyses and stability information is available only on registration batches prepared at the site with production equipment similar to the proposed commercial equipment. However, validation runs have been prepared on the commercial equipment. The certificates of analysis and stability data on all available validation batches prepared with the commercial production equipment should be provided.

c. The change in supplier o can be made, without a pre-approved protocol, in an annual report as long as the equivalency between the sources is established according to the USP monographs. On the other hand, the protocol for changes in other packaging materials can not be approved as proposed without the submission of suitability and compatibility test methods, specifications and data to demonstrate the adequacy of the protocol. In the absence of such data, the packaging change protocol and the list of alternate resin suppliers and fabricators for closure, innerseal and blister materials must be withdrawn from the NDA. This does not preclude, however, any future supplemental application when data become available.

d. The current post-approval stability commitment refers to DMF for the stability protocol, which is too general. Syntex should provide a detailed post-approval stability protocol specific for mycophenolate mofetil capsules. Syntex was advised by DAVDP (facsimile of 4/7/95) that the extension of expiration dating period of the product, packaged in PVC blisters, based on primary stability lots requires a supplemental approval and cannot be made through an annual report.

e. Syntex should provide updated stability data for all commercial packaging at the 30°C storage condition to support their proposed expiration dating of 36 months.

f. Syntex should provide information on any proposed physician samples packaging.

With regard to labeling:

a The dosage form descriptor should be included in the established name, according to the recommendations of the CDER Labeling and Nomenclature Committee, as shown on the DAVDP facsimile dated April 5, 1995.

b. The Description section of the package insert should be revised to more accurately describe mycophenolate mofetil as shown on the DAVDP facsimile dated April 5, 1995.

c. The drug product storage recommendation in both the package insert and the container label should be changed to read "Store at controlled room temperature 15-30°C (59-86°F)".

d. The dispensing recommendation in the proposed package insert, i.e., "Dispense in light-resistant containers, such as the manufacturer's original containers," appears to be an over precaution unsupported by the light stability data presented in the NDA. The sponsor should consider removing it from the labeling.

SUMMARY:

At least one batch from the facility has been used in clinical trials and has accelerated and long-term stability information available. The drug substance is an off-white powder

There have been no polymorphic forms detected. The DS is relatively stable with respect to heat, humidtiy and high intensity illumination. Syntex is proposing a two-year re-assay period when stored at the normal conditions.

Mycophenolate mofetil, 250 mg capsules will be manufactured by Syntex Puerto Rico, Inc., in Humacao, Puerto Rico. The anticipated commercial-scale batch size is expected to range fron comprises the bulk of the capsule formulation and are compendial items with adequate test methods and specifications. The formulation consists of MMF pregelatinized starch as a binder/disintegrant, croscarmallose sodium) as a disintegrant, povidone K-90 as a binder and magnesium stearate as a lubricant. In process controls for the the drug product include moisture content by capsule fill weight.

Specifications for the 250 mg capsules include appearance, assay, identity, uniformity of dosage units, dissolution, mycophenolic acid content and microbial quality. The proposed specifications are acceptable except for the wording in the identity section and addition of a loss on drying specification. The dissolution specification is adequate based on lot release batch analysis and subsequent stability studies.

The current registration batches have been prepared at Syntex, Puerto Rico on production scale equipment. No information is available concerning validation batches prepared on the actual comercial equipment.

Mycophenolate mofetil capsules 250 mg will be packaged into HDPE bottles (100 count/150 cc and 500 count/500 cc) as the proposed trade presentation and blister packs of 10 capsules per card for hospital use. Based on the current stability data, Syntex is extrapolating dating for all container/closure configurations. The current post-approval stability commitment refers to DMF for the stability protocol. This DMF reference is for a general protocol and isn't specific for mycophenolate capsules A stability protocol specific for mycophenolate mofetil must be submitted. The current protocol for container-closure changes is unacceptable as well as the list of alternate

suppliers and fabricators, and must be withdrawn.

An abbreviated Environmental Assessment report was submitted based on the criteria for rare diseases under 21CFR25.31a(b)3. The review has not been completed at this time.

The Method Validation is being conducted by the Seattle District Laboratory. The results of the validation have not been completed at this time.

The CGMP status of Synte:
are acceptable

CONCLUSIONS & RECOMMENDATIONS

The chemistry section of the NDA is incomplete at this time. However, it will be approvable when the issues outlined in the facsimiles of 4/5/95 and 4/7/95 are resolved with Syntex and the corresponding documents amended. The outstanding items to be addressed are 1) labeling 2) drug substance and drug product methods and specifications and 3) expiration dating. Furthermore, satisfactory pre-approval inspection and environmental assessment are pending as of 4/7/95.

D L Boring 4/7/95
D.L.Boring, R.Ph., Ph.D.
Review Chemist

Concurrence:
HFD-530/DFeigal
HFD-530/CChen CEC 4/7/95

cc:

Orig. NDA	HFD-530/DBoring	HFD-530/CSO
HFD-530/Div. File	HFD-530/MO	
HFD-530/DFeigal	HFD-530/Pharm	
HFD-530/CChen	HFD-530/Micro	File: NDA

DIVISION COPY

DIVISION COPY

SENSITIVE

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA

MYCOPHENOLATE MOFETIL 250 mg CAPSULES

REVIEW DIVISION: HFD-530

CENTER FOR DRUG EVALUATION AND RESEARCH

HFD-102

DATE COMPLETED: March 17,1995

ENVIRONMENTAL ASSESSMENT

NOTE: All page numbers refer to those found at the bottom right-hand corner.

1. Date:

EA dated: July 1994

Consult to HFD-102: November 28, 1994

Assigned: February 23, 1995

CSO: Dan Boring

2. Name of Applicant/Petitioner:

Syntex Laboratories, Inc.

Adequate.

3. Address:

3401 Hillview Ave.
Palo Alto, California 94304

Adequate.

4. Description of the proposed action:

a. Requested Approval:

Syntex Laboratories has submitted an abbreviated EA in support of an NDA for production and packaging of mycophenolate mofetil 250 mg capsules. The starting material for the drug substance, mycophenolic acid, will be manufactured for Syntex.

DEFICIENT.

The NDA number should be included in the approval request.

The description of the requested approval should include the applicant's name, drug product application number (if available), drug product name, dosage form, strength, a brief description of the drug product packaging, whether an EA or abbreviated EA is provided and, if applicable, the basis for the abbreviated Ea, SYNTEX has filed an NDA pursuant to Section 505(b) of the Food, Drug, and Cosmetic Act for TRADENAME® (generic name) dosage form packaged in ?. An EA has been submitted in accordance with 21 CFR § 25.31a(b)(3)").

b. **Need for Action:**

Mycophenolate mofetil is an immunosuppressive drug indicated for the prevention of acute rejection in renal allograft patients. Projected number of renal allograft patients who could potentially use mycophenolate mofetil by the year 2000 in the USA is . Assuming that this product achieves 100% market share, this is significantly less than patients. Therefore, the prevention of acute rejection in renal allograft patients is considered as a treatment for a rare disease.

By copy of meeting minutes between FDA and Syntex, April 20, 1994, FDA permits the firm to submit an abbreviated EA as a are disease, e.g 'o patients for this indication.

c. **Production Locations:**

i. **Proprietary Intermediate(s):**

None identified.

ii. **Drug Substance:**

Drug substance will be manufactured at Syntex Ireland Limited, Clarecastle, County Clare, Ireland, and Syntex Chemicals, Inc., 2075 North 55th Street, Boulder, Colorado, 80301. The manufacture of the starting material, mycophenolic acid, will occur at . The environment surrounding each facility is briefly described.

Adequate.

iii. **Finished Dosage Form:**

The manufacture of the drug product capsules will occur at Syntex Puerto Rico, Inc., Bo. Mariana Road 909, Km. 1.1, Humacao, Puerto Rico 00791. Packaging of the drug product capsules will occur at Syntex Puerto Rico, Inc. (see previous),

The environment surrounding each facility is briefly described.

Adequate.

d. Expected Locations of Use (Drug Product):

The drug product will be used by individuals throughout the United States and thus the use will not be concentrated in any specific geographical location.

DEFICIENT.

The description should specify whether the will be used in hospitals, clinics, and/or homes.

e. Disposal Locations:

Use of the drug product would result in the discharge of mycophenolate mofetil and its metabolites to POTWs, and consequently to the aquatic environment. The proposed action is expected to increase the amount of mycophenolate mofetil and its metabolites entering the environment through product use.

Returned drug product goods in the U.S. will be sent to a Syntex distribution facility in Grove City, Ohio, where they will be packaged and shipped for incineration as nonhazardous material at an approved incinerator. Currently,

) provides transportation to two incineration facilities approved by Syntex to dispose of pharmaceutical waste:

).

DEFICIENT.

The complete address should be provided for the Syntex distribution facility in Grove City, Ohio; information regarding any required permits for this facility should be provided.

5. **Identification of chemical substances that are the subject of the proposed action:**

Drug Substance:	Mycophenolate mofetil
Chemical Name:	2-(4-morpholinyl) ethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate
CAS #:	128794-94-5
Molecular Weight:	433.50
Molecular Formula:	$C_{23}H_{31}NO_7$
Structural Formula:	See page 7 of the EA
Physical Descrip.:	White to off-white crystalline powder melting at approximately 96-C
Additives:	A list of excipients is provided in Section 5(d), page 8; the ingredients of the gelatin capsule and gelatin capsule ink are provided in Confidential Appendix B, page 90.
Impurities:	None identified.

DEFICIENT.

Any significant impurities should be identified or their absence noted in the assessment.

Hazardous waste chemicals should be listed, if used.

6. **Introduction of substances into the environment: For the site(s) of production:**

a. **Potential Emitted Substances:**

The EA includes general references to organics that may be emitted during manufacturing and the regulatory or permitted levels under which these emissions must remain.

DEFICIENT.

A quantitative estimate of the emissions expected from the manufacturing of the drug substance and drug product, and from the packaging of the drug product, has not been made. A quantitative estimate should be provided, based on the number of batches predicted to be produced per year (five-year marketing plan), the raw materials to be used, the process description, the production times, etc.

Calculations should estimate the quantity of each chemical and intermediate product used or generated in the various steps of the process. The wastes generated in various steps of the process should be identified by wastestream and disposition route.

All raw materials and excipients used in production of the drug substance, proprietary drug substance intermediates, or drug product, or used in the primary packaging operations, should be provided. The list(s) should include the CAS registration number for each and the manner in which they are expected to be emitted (*e.g.*, organic solvent waste stream). Synthesis flow charts and production flow diagrams (with emission points identified) should be provided. The drug product composition (as included in the drug product labeling) should be included in the non-confidential section (see section III.E. regarding treatment of confidential and non-confidential information). Reference in the EA document to a confidential appendix which provides all other information is adequate.

b. Controls (Air, Liquid Effluent, Solid):

Permit limitations were generally not provided.

DEFICIENT.

The EA should contain a brief description of the controls associated with the air, liquid, and solid emissions identified in EA format item 6.a. Control efficiencies or treatment prior to emission should be included, if applicable. Disposition of manufacturing aids or emission controls which may contain drug substance should be discussed.

The EA should contain a brief description of the controls associated with the air, liquid, and solid emissions identified in EA format item 6.a. Control efficiencies (*e.g.*, emission of airborne particulate material is controlled by HEPA filtration with a 99.9% operating efficiency) or treatment prior to emission (*e.g.*, neutralization of aqueous waste streams) should be included, if applicable.

Disposition of manufacturing aids or emission controls which may contain drug substance (*e.g.*, filters, resins) should be discussed.

c. **Compliance with Federal, State and Local Emission Requirements:**

For all facilities, general statements were provided that permit limits would be met.

DEFICIENT.

Emissions, discharges, and wastestreams should be identified, concentrations of components should be estimated, and a comparison of these anticipated concentrations to permitted concentrations should demonstrate that approval of the NDA will not result in violation of emission requirements.

d. **Effect of Approval on Compliance with Current Emissions Requirements:**

Syntex states that actions resulting from the approval of the NDA will not result in violations of current emission requirements. However, because the anticipated emissions resulting from approval of the NDA have not been provided, this assertion cannot be validated.

DEFICIENT.

e. **Estimated Expected Emitted Concentration/Quantities:**

No estimates were provided. The maximum expected environmental concentration (MEEC) was not calculated for the production and use of the drug product.

DEFICIENT.

The MEEC should be calculated for the production and use of the drug product. Estimates should be made based on total fifth year production estimates and should be reported as the concentration of active ingredient. The specific calculations and fifth year production estimate may be included in a confidential appendix. Based on the identification of and literature about the other emitted substances, FDA can determine whether it needs more information about the potential environmental impacts of other emissions. Such additional information generally will not be needed.

The maximum expected environmental concentration (MEEC) is the predicted environmental concentration from patient use. The MEEC does not account for any depletion mechanisms.

MEEC (ppm) = (AxBxCxDxE$\times$1) = 4.83 x A x B

*1993 U.S. population is 258 x10^6, Source: U.S. Bureau of the Census, *Current Population Reports*, P25-1045 and P25-1112.

ii. Maximum Expected Environmental Concentration (MEEC) - Production and/or Disposal

Concentrations of drug substances and proprietary drug substance intermediates in wastestreams of manufacturing facilities or from disposal of pharmaceutical wastes are frequently orders of magnitude greater than the MEEC for use. These emissions are not normally covered by permits. The maximum expected concentration of drug substance and/or proprietary drug substance intermediates exiting into the environment from the last treatment facility/emission control should be estimated. The calculations used depend on the emission/treatment process and should not account for any depletion mechanisms.

NDA 50722
CELL CEPT

iii. Expected Environmental Concentration (EEC) - Use, Production or Disposal

The expected environmental concentration is the maximum expected environmental concentration from use, production, or disposal minus any applicable losses due to environmental depletion mechanisms or metabolism. **This should be calculated if the compound is toxic based on the maximum expected environmental concentration(s) (see EA format item 8 for definition of toxic)**

The expected environmental concentrations of the chemical compounds, other than the parent compound, which may exist or enter the environment (*e.g.*, metabolites) may be included if deemed useful to the discussion.

12. List of preparers, & their qualifications (expertise, experience, professional disciplines) and consultants:

Lori Bocchino, B.S.
Environmental Engineering Specialist
Environmental Health and Safety
Syntex U.S.A.

Kathryn Chellman, M.S.
Environmental Engineering Administrator
Environmental Health and Safety
Syntex U.S.A.

Marjorie S. Samples, Ph.D.
Staff Researcher I
Institute of Analytical Research
Syntex Discovery Research

Curriculum vitae of all preparers were provided.

Adequate.

13. Certification:

Provided.

Adequate.

14. **References:**

None provided. Federal, State, and local regulations applicable t
, are cited in non-confidential Attachment A; those applicable to each Syntex facility are be cited in the non-confidential Attachment C.
Adequate.

15. **Appendices:**

The non-confidential section included as attachments ar
a letter of compliance for citations for laws and regulations applicable to Syntex facilities, compliance statements for Syntex facilities, for mycophenolate mofetil and mycophenolic acid, occupational health exposure information, and curriculum vitae of document preparers. The confidential section included as attachments a confidential synthetic schematic for mycophenolate mofetil, confidential ingredients of the gelatin capsule ar confidentia confidential estimate of the market vo nycophenolate mofetil; and a confidential report summary of the

Adequate.

General Issues: All pages are identified at the bottom as "Syntex Confidential." Although this may be appropriate for the confidential sections of the EA, the sections that must be available through FOIA are not confidential. The non-confidential sections of the EA should have this footer removed.

ATTACHMENT 1

SITE: Syntex Ireland
FUNCTION: Drug Substance Manufacturing
BASIS FOR EMISSIONS EST.: Not given

Description		Exp. Date/ Renewal Date	Applicable Emission Requirements	Effect of Action on Current Emission Requirements
Air emission permits		as needed	Class II and III identified	DEFICIENT. Cannot be determined
Municipal sewer system, aqueous waste streams		upon agency or facility request	limitations provided	DEFICIENT. Cannot be determined
Onsite non-hazardous solid waste landfill		N/A	N/A	DEFICIENT. Cannot be determined
Hazardous waste incinerator		upon request none none none	not provided not provided not provided not provided	DEFICIENT. Cannot be determined DEFICIENT. Cannot be determined DEFICIENT. Cannot be determined DEFICIENT. Cannot be determined

FUNCTION: Drug Substance Manufacturing
BASIS FOR EMISSIONS EST.: Not given

Description		Exp. Date/ Renewal Date	Applicable Emission Requirements	Effect of Action on Current Emission Requirements
Air emission permits		as needed	Class II and III identified	DEFICIENT. Cannot be determined
Municipal sewer system, aqueous waste streams		upon agency or facility request	limitations provided	DEFICIENT. Cannot be determined
Onsite non-hazardous solid waste landfill		N/A	N/A	DEFICIENT. Cannot be determined
Hazardous waste incinerator		upon request none none none	not provided not provided not provided not provided	DEFICIENT. Cannot be determined DEFICIENT. Cannot be determined DEFICIENT. Cannot be determined DEFICIENT. Cannot be determined

ATTACHMENT 1

SITE: Synex Chemicals, Boulder, CO
FUNCTION: Drug Substance Manufacturing
BASIS FOR EMISSIONS EST.: Not given

Description	Permit #	Exp. Date/ Renewal Date	Applicable Emission Requirements	Effect of Action on Current Emission Requirements
Air emission permits		N/A	N/A	Permit to be obtained before commencement of production.
				Permit for air emission carbon regeneration
		8/2001	not provided	Permit for air emission carbon regeneration
		10/98	not provided	Permit for air emission carbon regeneration
		pending	not provided	
Municipal sewer system, aqueous waste streams		1/22/96	provided	DEFICIENT. Cannot be determined
Unusable spent solvent disposal		4/99	not provided	Permits for solvent recycling
		4/99	not provided	Permits for solvent recycling
		agency request	not provided	Permits for solvent recycling
		agency request	not provided	Permits for solvent recycling
		agency request	not provided	Permits for solvent recycling
		12/96	not provided	Permits for solvent recycling
		6/98	not provided	Permit for incinerator
		5/98	not provided	Permit for incinerator
		6/95	not provided	Permit for incinerator
		12/94	not provided	Permit for incinerator
		agency request	not provided	Permits for CWM Emelle facility
		agency request	not provided	Permits for CWM Emelle facility
		3/95	not provided	Permits for blending (transfer and storage)
Solid waste disposal		6/98	not provided	
		none	not provided	
		none	not provided	

Note: Page 14 indicats that primary clarifier sludge is sent to an unspecified permitted hazardous waste landfill.

ATTACHMENT 1

SITE: Syntex: Puerto Rico, Inc.
FUNCTION: Drug Product Manufacturing and Packaging
BASIS FOR EMISSIONS EST.: Not given

Description	Permit #	Exp. Date/ Renewal Date	Applicable Emission Requirements	Effect of Action on Current Emission Requirements
Air emission permits		1/3/96	provided	DEFICIENT. Cannot be determined.
Municipal sewer system, aqueous waste streams		5/96 10/94	provided most stringent of both	DEFICIENT. Cannot be determined.
Hazardous chemical wastes		5/26/97 3/21/2001	not provided not provided	Syntex RCRA Permit
Onsite solid waste incinerator		1/3/96	not provided	DEFICIENT. Cannot be determined.
Non-hazardous industrial landfill Non-hazardous solid waste (municipal landfills)		8/5/98 N/A N/A	not provided not provided not provided	

ATTACHMENT 1

SITE: Anderson Packaging, Inc.
FUNCTION: Drug Product Packaging
BASIS FOR EMISSIONS EST.: Not given

Description	Permit #/ Facility ID#	Exp. Date/ Renewal Date	Applicable Emission Requirements	Effect of Action on Current Emission Requirements
Air emission permits		none		
Municipal sewer system, aqueous waste streams		none		
Hazardous waste storage (RCRA)		not provided	not provided	DEFICIENT. Cannot be determined.
Hazardous waste disposal.		not provided not provided	not provided not provided	waste transporter, license 2604, renew annual waste disposer
Non-hazardous solid waste disposal		4/30/95 annual renewal not provided not provided not provided	not provided not provided not provided not provided not provided	waste transporter waste transporter waste disposer waste disposer waste disposer

EA Review #1, NDA

Endorsements:

MITRE:RDMavis

HFD-102/PGVincent P.G. Vincent 4/10/95

Ray Jenner 4/18/95

CC: Original NDA copy to NDA/HFD-530
EA File
CGood/HFD-102

File: E00.RJB

DRAFT DEFICIENCY LETTER

1. General Issues:

   All pages are identified at the bottom as "Syntex Confidential." Although this may be appropriate for the confidential sections of the EA, the sections that must be available through FOIA are not confidential. The non-confidential sections of the EA should have this footer removed.

2. Regarding Section 4, the description of the proposed action:

   The NDA number should be included in the approval request.

   The description of the requested approval should include the applicant's name, drug product application number (if available), drug product name, dosage form, strength, a brief description of the drug product packaging, whether an EA or abbreviated EA is provided and, if applicable, the basis for the abbreviated Ea, sYNTEX has filed an NDA pursuant to Section 505(b) of the Food, Drug, and Cosmetic Act for TRADENAME® (generic name) dosage form packaged in ?. An EA has been submitted in accordance with 21 CFR § 25.31a(b)(3)").

   The expected locations of drug product use should specify whether the capsules will be used in hospitals, clinics, and/or homes.

   The complete address of the Syntex distribution facility, and any information regarding permits for this facility, should be included in the disposal location section of the assessment. Complete permit information and identification should be provided for all incineration sites and landfills.

3. Regarding Section 5, the identification of chemical substances that are subject to the proposed action:

   Any significant impurities should be identified, or their absence noted, in the assessment.

   Hazardous waste chemicals should be listed, if used.

4. Regarding Section 6, the introduction of substances into the environment:

Concerning potential emitted substances, a quantitative estimate of the emissions expected from the manufacturing of the drug substance and drug product, and from the packaging of the drug product, has not been made. A quantitative estimate should be provided, based on the number of batches predicted to be produced per year (five-year marketing plan), the raw materials to be used, the process description, the production times, etc. Calculations should estimate the quantity of each chemical and intermediate product used or generated in the various steps of the process. The wastes generated in various steps of the process should be identified by wastestream and disposition route.

Concerning controls of emitted substances, the assessment should contain a brief description of the controls associated with the air, liquid, and solid emissions identified in format item 6.a. Control efficiencies or treatment prior to emission should be included, if applicable. Disposition of manufacturing aids or emission controls which may contain drug substance should be discussed. Complete permit information and identification should be provided for all incineration sites and landfills.

Concerning compliance with Federal, State, and local emission requirements, emissions, discharges, and wastestreams should be identified, concentrations of components should be estimated, and a comparison of these anticipated concentrations to permitted concentrations should demonstrate that approval of the NDA will not result in violation of emission requirements.

Concerning the effect of approval on compliance with current emissions requirements, Syntex states that actions resulting from the approval of the NDA will not result in violations of current emission requirements. However, the anticipated emissions resulting from approval of the NDA have not been provided, preventing this assertion from being validated.

Concerning the estimated expected emitted concentration/ quantities, the MEEC should be calculated for the production and use of drug product. Estimates should be made based on total fifth year production estimates and should be reported as the concentration of active ingredient. The specific calculations and fifth year production estimate may be included in a confidential appendix. Based on the identification of and literature about the other emitted substances, FDA can determine whether it needs more information about the potential environmental impacts of other emissions. Such additional information generally will not be needed.

All raw materials and excipients used in production of the drug substance, proprietary drug substance intermediates, or drug product, or used in the primary packaging operations, should be provided. The list(s) should include the CAS registration number for each and the manner in which they are expected to be emitted (*e.g.*, organic solvent waste stream). Synthesis flow charts and production flow diagrams (with emission points

identified) should be provided. The drug product composition (as included in the drug product labeling) should be included in the non-confidential section (see section III.E. regarding treatment of confidential and non-confidential information). Reference in the EA document to a confidential appendix which provides all other information is adequate.

The EA should contain a brief description of the controls associated with the air, liquid, and solid emissions identified in EA format item 6.a. Control efficiencies (*e.g.*, emission of airborne particulate material is controlled by HEPA filtration with a 99.9% operating efficiency) or treatment prior to emission (*e.g.*, neutralization of aqueous waste streams) should be included, if applicable. Disposition of manufacturing aids or emission controls which may contain drug substance (*e.g.*, filters, resins) should be discussed.

The maximum expected environmental concentration (MEEC) is the predicted environmental concentration from patient use. The MEEC does not account for any depletion mechanisms.

$$MEEC\ (ppm) = \frac{A \times B \times C \times D \times E}{*} = 4.83 \times A \times B$$

where

*1993 U.S. population is 258×10^6, Source: U.S. Bureau of the Census, *Current Population Reports*, P25-1045 and P25-1112.

ii. Maximum Expected Environmental Concentration (MEEC) - Production and/or Disposal

Concentrations of drug substances and proprietary drug substance intermediates in wastestreams of manufacturing facilities or from disposal of pharmaceutical wastes are frequently orders of magnitude greater than the MEEC for use. These emissions are not normally covered by permits. The maximum expected concentration of drug substance and/or proprietary drug substance intermediates exiting into the environment from the last treatment facility/emission control should be estimated. The calculations used depend on the emission/treatment process and should not account for any depletion mechanisms.

iii. Expected Environmental Concentration (EEC) - Use, Production or Disposal

The expected environmental concentration is the maximum expected environmental concentration from use, production, or disposal minus any applicable losses due to environmental depletion mechanisms or metabolism. **This should be calculated if the compound is toxic based on the maximum expected environmental concentration(s) (see EA format item 8 for definition of toxic)**

The expected environmental concentrations of the chemical compounds, other than the parent compound, which may exist or enter the environment (*e.g.*, metabolites) may be included if deemed useful to the discussion.

DIVISION OF ANTIVIRAL DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls Section

NDA #:

CHEMISTRY REVIEW #: 2 **DATE REVIEWED:** 4/28/95

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment	4/25/95	4/28/95	4/28/95

NAME/ADDRESS OF APPLICANT: Syntex (USA), Inc.
3401 Hillview Ave.
Palo Alto, CA 94304

DRUG PRODUCT NAME
Proprietary: CellCept™
Nonproprietary: Mycophenolate Mofetil
Code Name/#: RS-61433

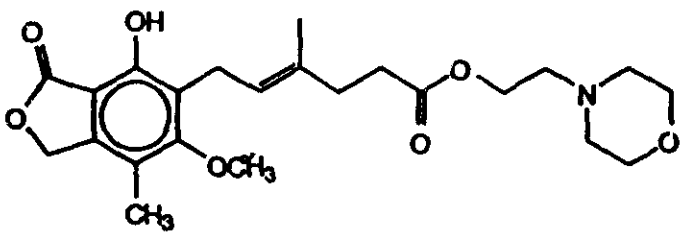
PHARMACOLOGICAL CATEGORY: Immunosuppressant

INDICATION:

DOSAGE FORM/STRENGTH: Capsule/250 mg

ROUTE OF ADMINISTRATION: Oral

CHEMICAL NAME/STRUCTURAL FORMULA:



2-morpholinoethyl(E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate
$C_{23}H_{31}NO_7HCl$
M.W.= 433.51

REMARKS/COMMENTS

The Amendment of 4/28/95 contains the applicant's responses to outstanding CMC issues related to labeling, specifications for drug substance and drug product and analytical methods. Information provided and agreements reached are summarized as follows:

1. The specifications for have been updated to add a limit of maximum for the level of Additionally, the applicant has committed to developing analytical methodology for evaluating recovered solvents for the presence of The analytical results will be submitted to the annual report.

2. The DAVDP recommendation for tightening the melting point range of the DS will not be implemented at this time. The applicant has discovered a discrepancy between melting points obtained at the Syntex, Ireland and Syntex, Palo Alto sites which cannot be attributed to instrument calibration. Syntex will continue to investigate the cause and will submit melting points from both analytical facilities for all lots produced for a period of one year in the annual report.

3. The related substances specification has been amended to reflect the language of the ICH Guideline on Impurities in New Drug Substances as agreed upon by FDA and Syntex. A draft copy of the specification was provided (Attachment 1). Additionally, Syntex has committed to exploring the development of a more sensitive analytical method for to support a specification for this impurity.

4. The specification for residual solvents has been reworded to incorporate limits for individual and total solvents. A draft copy of the specification was provided (attachment 2). Additionally, the current specification for will allow a daily intake of micrograms/day of the A consultation with the Pharm/tox reviewer indicated that this is an acceptable daily intake.

5. The limit of quantitation for Regulatory method

   was satisfactorily established at Research method was stated as having a comparable limit of quantitation. Additionally, the discrepancy regarding the listing of the

   explained by the unavailability of pure standards of the two impurities during the development of method

6. Additional stability data including six months at 40°C/75%RH, twelve months at 30°C/60%RH and re-analysis data over a two year period on eight lots of drug substance were provided. The data supports the proposed re-analysis time of 24 months.

7. The drug product specifications have been amended to incorporate as the two regulatory methods for product identification as agreed upon by FDA and Syntex (Attachment 3). Additionally, Syntex has committed to conducting for the three validation batches and for ten commercial batches and to report the results in the Annual Report.

8. The applicant has supplied release data on the three production scale validation batches manufactured at the Puerto Rico facility. The release values are all within agreed upon

proposed regulatory specifications and acceptable. The applicant has committed to submitting stability data for these lots in the Annual Report.

9. Syntex has committed to providing updated stability data in support of their proposed 36 month expiration dating in the first Annual Report. Additionally, Syntex has provided the commercial stability protocol specific for mycophenolate mofetil capsules (Attachment 4).

10. Syntex has agreed to withdraw the protocol for changes in
Additionally, Syntex has agreed to remove the list of alternate suppliers and fabricators. An updated protocol for HDPE bottle and closure components was provided (Attachment 5). Changes in HDPE components will be submitted via the Annual Report. The applicant has indicated that no physician samples will be available for this product.

11. Syntex has agreed to the following recommendations from FDA regarding labelling:
a. The product name will be expressed as:

CellCept®
(mycophenolate mofetil capsules)

b. The introductory lines of the Description Section of the package insert will read:

CellCept (mycophenolate mofetil) is the 2-morpholinoethyl ester of mycophenolic acid (MPA), an immunosuppressive agent.

c. The storage statement will be modified to read

Store at 15-30°C(59-86°F)

d. The dispensing recommendation "Dispense in light-resistant containers, such as the manufacturer's original containers" will be removed form the package insert.

12. The amendment also contained revisions to the Regulatory methods
The revisions primarily provided for editorial changes and additional instructions and details. None of the revisions impact on sample preparation or conditions. Additionally, Syntex has identified 21 data points in the drug product stability report that were in error. The data revision is minor and will have no impact on data interpretation or conclusions.

13. The CGMP status of the Syntex Colorado, Ireland, Palo Alto, and Puerto Rico sites and the The EER for NDA was released from HFD-320 on 5/02/95 (see Attachment 6).

14. Minor deficiencies were noted by HFD-004 for the abbreviated environmental assessment which were forwarded to Syntex by fax on 4/24/95. Syntex responded on 5/1/95 and the responses were forwarded to HFD-004. On 5/3/95 HFD-004 issued a Finding Of No Significant Impact (FONSI) for the NDA.

RECOMMENDATION:

The Chemistry section of the NDA is approvable, as amended.

D L Boring 5/3/95

D.L.Boring, R.Ph., Ph.D.
Review Chemist

Concurrence:
HFD-530/DFreeman 5/4/95
HFD-530/CChen 5/3/95

cc:

Orig. NDA	HFD-530/DBoring	HFD-530/CSO
HFD-530/Div. File	HFD-530/MO	
HFD-530/DFeigal	HFD-530/Pharm	
HFD-530/CChen	HFD-530/Micro	

File: NDA CMC Response

AUDIT OF PIVOTAL CLINICAL STUDIES

In a memorandum (see attachment) of January 20, 1995, Dr. David Feigal, Director, Division of Antiviral Drug Products, requested clinical site inspections of six clinical sites in support of NDA The six sites (three domestic, three foreign) were study site locations for studies

Representatives from the Division of Scientific Investigations inspected five of the six clinical sites (Birmingham, AL; Tampa, FL; Leeds, England; Nantes, France; and Columbus, OH). There were no significant findings that would impact the approvability of the application. The Form FDA 483 of each site inspection is attached.

Joyce Korvick, M.D., Medical Officer

Paul Flyer, Ph.D., Statistician

Matthew Tarosky, R.Ph., Project Manager

Tarosky

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: JAN 20 1995

FROM: Director, Division of Antiviral Drug Products, HFD-530

TO: Director, Division of Scientific Investigations, HFD-340

SUBJECT: Request for Clinical Site Inspection of NDA

Syntex Laboratores, Inc. has submitted an NDA for the use of CellCept® (mycophenolate mofetil) for prophylaxis of organ rejection in patients receiving allogeneic renal transplants. Three pivotal clinical studies (ICM 1866, IICR 023, MRE 022) have been submitted to support the proposed indication of prevention of rejection in renal allograft recipients.

We have previously provided Dr. Antoine El-Hage with information on these four clinical studies.

We have identified six sites to have a result which is different than the overall outcome. We have listed the sites and would like to have the following clinical sites inspected.

We have previously discussed with Dr. El-Hage which domestic sites must be inspected. The investigators with corresponding site locations for study ICM 1866 are as follows:

Mark Deierhoi, MD University of Alabama Department of Nephrology & Surgery UAB Station 756 Lyons Harrison Research Birmingham, AL 35294 Phone: (205) 934-2131	Ronald Ferguson, MD, PhD Ohio State University Department of Surgery Division of Transplantation College of Medicine 259 Means Hall 1654 Upham Drive Columbus, OH 43210 Phone: (614) 293-8545	Sam Weinstein, MD Tampa General Hospital 3000 E. Fletcher Ave, Suite 380 Tampa, FL 33613 Phone: (813) 971-3260

Study MRE 022 would require overseas travel. The following investigators and sites pertain to study MRE 022:

Dr. F.W. Eigler Universitatsklinikum Essen Med. Klinik, Abt Fur Nieren und Hochdruckkrankheiten Hufelandstrasse 55 D-45122 Essen Germany Phone: +49 201 723 3393	Mr. SA Sadek Clinical Sciences Building Academic Unit of Surgery, Level 8 St. James University Hospital LEEDS LS9 7TF, England Phone: +44 532 433144	Prof JP Soulillou Nephrologie-Immunology Clinique Centre Hospitalier Regional et Universitaire de Nantes Hotel Dieu, BP 1005 F-44035 NANTES (Cedex 01), France Phone: +33 4008 4715

We have discussed with Dr. El-Hage which of the foreign sites must be inspected; the two sites which have the highest priority are England (Mr. Sadek) and France (Professor Soulillou). Because of the limited amount of time, the German site does not have to be reviewed unless deficiencies are identified with the other two sites.

We request that an inspection be performed and that arrangements proceed in a timely fashion according to your inspection procedures. Since we intend to make a regulatory decision on this application by May 8, 1995, it is important to have the results of the inspection as soon as possible.

Sincerely,

David W. Feigal, Jr., M.D., M.P.H.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

concurrence:
HFD-530/DepDir/Freeman DSF 1/19/95
HFD-530/GL/Goldberger/DB for mb 1/19/95
HFD-530/MO/Korvick 1/19/95
HFD-530/SCSO/DeCicco
HFD-530/CSO/Tarosky/MDT 1-19-95

distribution:
HFD-530/NDA
HFD-530/Division File
HFD-530/MO/Korvick
HFD-530/SCSO/DeCicco
HFD-530/CSO/Tarosky

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER FDA 297 Plus Park Blvd Nashville, TN 37217 615/781-5385
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Mark H. Daierhoi, M.D.	PERIOD OF INSPECTION 2/7-22/95 / C. F. NUMBER
TITLE OF INDIVIDUAL Principal Investigator	TYPE ESTABLISHMENT INSPECTED clinical investigator
FIRM NAME UAB Dept Surgery/Div Transplantation	NAME OF FIRM, BRANCH OR UNIT INSPECTED same
STREET ADDRESS 701 S. 19th St, BH 756 Lyons-Harrison	STREET ADDRESS OF PREMISES INSPECTED
CITY AND STATE (Zip Code) Birmingham, AL 35294-0007	CITY AND STATE (Zip Code) "

DURING AN INSPECTION OF YOUR FIRM(S) (WE) OBSERVED:

PROTOCOL ICM 1866

24 of 72 subject case report forms/medical records were reviewed. The following deviations were observed:

1. At least 6 of the 72 entered subjects participated in a second study, IND

2. Per protocol, women of child-bearing potential who are not practicing an acceptable method of birth control (BCP's, patch, barrier with spermicidal jelly, or IUD) are to be excluded; yet neither medical records nor CRF's documented the use of acceptable birth control/sexual activity for female subjects of child-bearing potential. For example,

Furthermore, per protocol, women of child-bearing potential must have a negative serum pregnancy test at the time of study entry; however, entered the study 1/6/93; yet the pregnancy test was not conducted until 1/22/93.

3. Per protocol, patients with a platelet count less than 100,000/mm^3 are to be excluded; yet

4. Per protocol, patients with malignancies are to be excluded; yet

reported melanoma 12/22/92—a copy of the report was noted to be sent to sub-investigator Diethelm).

5. The following adverse events/possible side effects were not reported in the case reports:
-#10216, per clinic note dtd 7/6/93, she was experiencing probable tinea infestation. Nizoral cream was treatment to be tried; yet the condition/treatment was not reported in case report.
-#10265 experienced fairly severe hyperparathyroidism, according to correspondence dated 12/13/93 regarding clinic visit 12/13/93 (also noted in clinic notes for 11/12/93 visit); yet was not reported in case report.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Patricia S.	EMPLOYEE(S) NAME AND TITLE (Print or type) Patricia S. Smith, Investigator	DATE ISSUED 2/22/95

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER FDA 757 Plus Park Blvd Nashville, TN 37217 615/781-5385	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Mark H. Deierhoi, M.D.	PERIOD OF INSPECTION 2/7-22/95	C. F. NUMBER
TITLE OF INDIVIDUAL Principal Investigator	TYPE ESTABLISHMENT INSPECTED clinical investigator	
FIRM NAME UAB Dept Surgery/Div Transplantation	NAME OF FIRM, BRANCH OR UNIT INSPECTED same	
STREET ADDRESS 701 S. 19th St, BM 756 Lyons-Harrison	STREET ADDRESS OF PREMISES INSPECTED "	
CITY AND STATE (Zip Code) Birmingham, AL 35294-0007	CITY AND STATE (Zip Code) "	

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

6. The last paragraph of the informed consent (IRB approval date 6/10/92) used throughout the study contains blanks for whom to contact regarding subjects' rights and which doctor discussed the consent. For many subjects, these blanks were never filled in (e. In addition, as of 10/2/92 the protocol was amended to delete ALG and add ATG. This occurred prior to entry of the first subject (11/13/92). The consent was not amended, however, as it states the patient usually receives ALG at this institution.

7. The Addendum to Consent Form dated 11/93 (IRB approved 12/3/93) was not always signed in a timely manner, and for several subjects, no signed addendum was available, as the subject did not return it after receiving it in the mail. For example, no signed addendum was available for who entered the study 7/15/93 and was seen in the clinic 1/10/94. She was terminated from the study 5/11/94.

-No signed addendum fo who entered the study 7/1/93 and was followed in the study through Jan. 1995.

signed the addendum 9/22/94 (she entered 6/5/93); yet she was seen in the clinic for multiple visits Jan. 1994—.

PROTOCOL ICM 1868

Eleven of 17 case reports/medical records were reviewed and the following deviations were observed:

1. No serum pregnancy test was conducted (per protocol) on a married female (who entered the study 7/28/93.

2. No documentation of sexual activity/adequate birth control for female subject who entered the study 2/7/92.

3. Protocol inclusion criteria lists serum creatinine at the time of biopsy must be less than or equal to 5 mg/dl; yet 4 of 17 subjects were entered with values greater than

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Patricia	EMPLOYEE(S) NAME AND TITLE (Print or Type) Patricia S. Smith, Investigator	DATE ISSUED 2/22/95

FDA

Clinical Investigations Branch
Division of Scientific Investigations

7520 Standish Place (HFD-344)
Rockville, MD 20855

Phone: (301) 594-1032
FAX: (301) 594-1204

DATE: 3-21-95

TO: TAROSKY / KORVICK

FAX #: 443-9292

FROM: ANTOINE

2 PAGES + COVER

RE: inspection results / Dr. Weinstein

COMMENTS: FYI. Enclosed copy of FDA-483 items plus Dr. Weinstein "Responses". "Overall Study acceptable" will be in your division on 3/23/95 will stop & see you if you have any questions or comments.

HFD-344

TGH

TAMPA GENERAL HEALTHCARE

Affiliated with the USF College of Medicine

March 10, 1995

Shari J. Hromyak
Federal Investigator
Food and Drug Administration
3350 West Busch Boulevard
Tampa, Florida [redacted]

Dear Ms. Hromyak:

Please find below the responses to the observations left with me following the recent inspection of the Syntex ICM Study 1866. Please attach a copy of this letter to your inspection report and include it with any FOI Services request. The numbers below correspond to the item numbers on FDA form 483. I have enclosed a copy of the 483 form.

1. *Failure to report serious adverse events of this center's study subjects to the reviewing IRB's (USF and Tampa General) as stipulated in the IRB guidelines. CI policy was to report only adverse events that were serious, drug related and unanticipated problems. No IRB approval of modifications to reporting requirements was obtained.*

Response:
In my estimation, I was in compliance with the IRB required policy on reporting of adverse events as described in the IRB handbooks. Tampa General's IRB states that "each investigator is responsible for reporting any new or significant adverse effects, injuries to subjects or any unanticipated problems which involve risks to the subjects, to the IRB within ten working days." It is my belief that we complied with that obligation by reporting all safety reports and any unanticipated and/or serious drug related events. The current IRB's (University of South Florida) is more ambiguious. The Information Workbook simply states "Research investigators are responsible for reporting promptly to the appropriate IRB Chairperson, the DSR, and their Department Chair(s) any adverse effects, or injuries to human subjects, any propsed changes in the research, or any unanticipated problems which involve risk to the human research subjects or others." I have requested further clarification of the reporting policy of the USF IRB and I am awaiting a response. I will pursue this issue to resolution and will continue in the future, as in the past, to ensure that the IRB is informed of all pertinent study and patient related issues

2. *Failure to establish and maintain documentation of sponsor notification of serious adverse events as identified in the sponsor protocol.*

Response:
Information concerning the timing of sponsor notification is recorded on the serious adverse

2

event (SAE) form. The SAE form was considered the primary documentation of event notification. Additionally, as required by the protocol, Syntex was contacted by phone for all grade 3 adverse events thought to be drug related which required drug adjustments. Although numerous calls were documented on the site phone call log there were occasions when phone calls were not formally logged. In the future, we will work to assure complete documentation of our sponsor notification.

3. *Current consent forms fail to include all previous updates. For example, the last three consent forms (revised 5/17/93, 6/23/93, and 8/20/93) incorrectly identify anti-lymphocyte (ALG) as part of subject therapy. ALG was formally deleted with Syntex Protocol Amendment II dated 10/2/92 and consent dated 10/22/92.*

Response:
It was an oversight that revisions were made to a previous version o f the consent form, thus inadvertently omitting some minor previously approved consent changes. In the future, consents will be carefully reviewed to ensure the consent contains all previously approved changes.

4. *Study files fail to identify all revisions made to consent forms.*

Response:
The Institutional Review Board was provided with a copy of the consent which identified, clearly, the revisions made using highlighted colour. I feel that keeping a copy of the revised document was adequate for our files. I will, however, grant you that a second highlighted copy for our files would have made it easier for review.

Ms Hromyak, the inspection was very thorough and educational. The discussion at the conclusion of the inspection was very beneficial to me for complying with FDA regulations for current and future trials. I appreciate your acknowledgement that, overall, the study was well documented and conducted.

If you have any further questions do not hesitate to contact me at :

3000 East Fletcher Avenue
Suite 380
Tampa, Florida 33613
(813) 971-3260

Sincerely,

Samuel S. Weinstein, MD

3/31/95

Hello

To:

Tarosky | Korvic / Flyer

Fax # (301) - 443 - 9292

Enclosed FDA-483 France

Note Drug accountability Records

will talk on 4/10/95

Take care

Tony

Rm# 324

NANTES

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER
FDA
297 Plus Park Blvd
Nashville, Tennessee 37217
(615) 781-5385

NAME OF INDIVIDUAL TO WHOM REPORT ISSUED
TO: Prof Jean-Paul Soulillou

PERIOD OF INSPECTION
3/27-31/95

C. F. NUMBER

TITLE OF INDIVIDUAL
Principal Investigator

TYPE ESTABLISHMENT INSPECTED
Clinical investigator

FIRM NAME
Centre Hospitalier Regional et Univ. de Nantes

NAME OF FIRM, BRANCH OR UNIT INSPECTED

STREET ADDRESS
Hôtel Dieu, BP 1005

STREET ADDRESS OF FIRM INSPECTED

CITY AND STATE (Zip Code)
Nantes Cedex 01 France

CITY AND STATE (Zip Code)

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

I. Protocol Deviations
A. Dosing Regimen:
Subject # Transplant date Treatment arm

B. Drug Accountability:
Per protocol, subjects' compliance with taking the study medication was to be assessed during each study visit by documenting the subjects' returned number of unopened blisters; however, this was not done. Rather, drug (study med) was dispensed by the investigator to the subjects after discharge from the hospital in 5 and 6 month supplies. Subject records showing amounts dispensed/returned were generated retrospectively and do not reflect amounts returned at each visit. All dispensed blister cards are not accounted for. Subject dosing compliance cannot be verified from the available records.

C. Failure to meet inclusion/exclusion criteria:

SEE REVERSE OF THIS PAGE

EMPLOYEE(S) SIGNATURE
Patricia S Smith
ANTOINE E Hage

EMPLOYEE(S) NAME AND TITLE (Print or Type)
Patricia S. Smith Investigator
Antoine E Hage

DATE ISSUED
3/31/95

FORM FDA 483 (5/85) PREVIOUS EDITION MAY BE USED. INSPECTIONAL OBSERVATIONS PAGE 1 OF 2 PAGES

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER
FDA
297 Plus Park Blvd
Nashville Tennessee 37217
(615) 781-5385

NAME OF INDIVIDUAL TO WHOM REPORT ISSUED	PERIOD OF INSPECTION	C. F. NUMBER
TO: Prof. Jean-Paul Soulillou	3/27-31/95	
TITLE OF INDIVIDUAL	TYPE ESTABLISHMENT INSPECTED	
Principal Investigator	Clinical Investigator	
FIRM NAME	NAME OF FIRM, BRANCH OR UNIT INSPECTED	
Centre Hospitalier Regional et Univ de Nantes		
STREET ADDRESS	STREET ADDRESS INSPECTED	
Hotel Dieu BP 1005		
CITY AND STATE (Zip Code)	CITY AND STATE (Zip Code)	
F-44035 Nantes Cedex 01, France		

DURING AN INSPECTION OF YOUR FIRM I (WE) OBSERVED:

liver

II. Reporting Discrepancies

A. the primary reason for premature discontinuation as adverse event (leukopenia); however was later changed 2/9/94 (and initialled by sponsor) to reason -- "non-compliance with drug or protocol", specifically, medication interrupted for more than 3 days. The reason should be listed as "AE" as the subject experienced leukopenia which resulted in the study medication interruption.

B. # there is no documentation that the subject received the study medication 1/19-24/93 and 1/26-27/93. (This subject was transplanted 1/9/93 and was in treatment arm 1.0g BID.)

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Patricia S. Smith Antoinette Eldridge	Patricia S. Smith, Investigator Antoinette Eldridge	3/31/95

FORM FDA 483 (12/91) PREVIOUS EDITION MAY BE USED. INSPECTIONAL OBSERVATIONS PAGE 2 OF 2 PAGES

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER
FDA
297 Plus Park Blvd
Nashville, Tennessee 37217
(615)781-5385

NAME OF INDIVIDUAL TO WHOM REPORT ISSUED
TO: Mr. J. Peter Lodge, Consultant Surgeon

PERIOD OF INSPECTION
4/3-7/95

C. F. NUMBER

TITLE OF INDIVIDUAL
Co-investigator

TYPE ESTABLISHMENT INSPECTED
Clinical investigator

FIRM NAME
St. James University Hospital

NAME OF FIRM, BRANCH OR UNIT INSPECTED
SAME

STREET ADDRESS
Clinical Sciences Bldg, Surgery Unit Level 8

STREET ADDRESS OF PREMISES INSPECTED
SAME

CITY AND STATE (Zip Code)
Leeds LS9 7TF, Great Britain

CITY AND STATE (Zip Code)
SAME

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

During review of Syntex Protocol MYC022, the following protocol deviations:

1- Use of Prohibited Medication

(placebo arm) transplanted 11/18/92 received Azathioprine beginning 5/17/93 concurrently with study drug through 5/24/93 at which time the subject was prematurely discontinued from the study due to this protocol deviation.

2- Dose Interruptions / Reductions

a) (1.5g BID arm) transplanted 11/12/92 had a dose interruption for more than 14 days during the second 6 months of the study — was off study drug from 12/15-29/93; re-started 12/30/93 (last dose on study); then classified as completed study and entered in follow-up study

b). (1.0g BID) transplanted 1/5/93 received 6 capsules per day (rather than 12) on 1/9/93 due to gastroscopy

3- Treatment for Suspected Rejection

a)- (placebo) transplanted 12/8/92 was treated for rejection for more than one day prior to biopsy -- received methylprednisolone 12/15-17/92; the biopsy was not performed until 12/17/92

SEE REVERSE OF THIS PAGE

EMPLOYEE(S) SIGNATURE
Patricia S Smith
Antoine Elhage

EMPLOYEE(S) NAME AND TITLE (Print or Type)
Patricia S. Smith, Investigator
ANTOINE N. ELHAGE

DATE ISSUED
4/7/95

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER FDA 297 Plus Park Blvd Nashville, Tennessee 37217 (615) 781-5385
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Mr. J. Peter Lodge, Consultant Surgeon	PERIOD OF INSPECTION 4/3-7/95 — C. F. NUMBER
TITLE OF INDIVIDUAL Co-investigator	TYPE ESTABLISHMENT INSPECTED Clinical investigator
FIRM NAME St. James University Hospital	NAME OF FIRM, BRANCH OR UNIT INSPECTED
STREET ADDRESS Clinical Sciences Bldg, Surgery Unit, Level 8	STREET ADDRESS OF PREMISES INSPECTED SAME
CITY AND STATE (Zip Code) Leeds LS9 7TF, Great Britain	CITY AND STATE (Zip Code)

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

3- cont'd

b)- (1.5g BID arm) transplanted 12/12/92 was treated with methylprednisolone 12/19-21/92 (more than one day) prior to biopsy 12/21/92

c)- (1.5g BID) transplanted 3/15/93 was treated with methylprednisolone 4/10-12/93; yet no biopsy was done

d)- (1.0g BID) transplanted 3/1/93 was treated with methylprednisolone for more than one day (3/6-8/93) prior to biopsy 3/8/93

e)- (1.0g BID) transplanted 12/13/92 was treated with OKT$_3$ 12/15-20/92 prior to completion of initial treatment of methylprednisolone 12/14-16/92 and evaluation of response to methylprednisolone

4 Inclusion/Exclusion Criteria

a)- (1.5g BID) transplanted 1/13/93 had a history of malignancy -- excision of malignant melanoma right leg 1978

b)- (1.0g BID) transplanted 1/3/93 had a history of malignancy -- sarcoma left leg 1980

c)- (1.5g BID) history (and current, prostate cancer

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Patricia S Smith Antoine E Hage	EMPLOYEE(S) NAME AND TITLE (Print or Type) Patricia S. Smith, Investigator ANTOINE N. EL-HAGE	DATE ISSUED 4/7/95

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER FDA 297 Plus Park Blvd Nashville, Tennessee 37217 U.S.A. (615) 781-5385	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Mr. J. Peter Lodge, Consultant Surgeon	PERIOD OF INSPECTION 4/3-7/95	C. F. NUMBER
TITLE OF INDIVIDUAL Co-investigator	TYPE ESTABLISHMENT INSPECTED clinical investigator	
FIRM NAME St. James University Hospital	NAME OF FIRM, BRANCH OR UNIT INSPECTED Same	
STREET ADDRESS Clinical Sciences Bldg, Surgery Unit, Level 8	STREET ADDRESS OF PREMISES INSPECTED	
CITY AND STATE (Zip Code) Leeds LS9 7TF, Great Britain	CITY AND STATE (Zip Code)	

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

4- cont'd

d). (1.0g BID) transplanted 7/9/93 had a platelet count at entry less than 100,000/mm^3 -- 64,000 on 7/12/93 (pre-drug).

5- Drug Accountability

Per protocol, in order to assess patients' compliance with taking study medication, the subjects are to return all dispensed cards at each visit so that both empty cards as well as full blisters can be counted and documented. Twenty-one of the 28 enrolled subjects failed to return cards. Therefore, full compliance with dosing regimen for those 21 subjects cannot be verified by the available records. For example, # was missing 55 of 55 dispensed cards, was missing 74 of 75 dispensed cards. And, was missing 58 of 60 dispensed cards.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Patricia S. Smith Antoine El-Hage	EMPLOYEE(S) NAME AND TITLE (Print or Type) Patricia S. Smith, Investigator ANTOINE N. EL-HAGE	DATE ISSUED 4/7/95

FORM FDA 483 (5/85) PREVIOUS EDITION MAY BE USED. INSPECTIONAL OBSERVATIONS PAGE 3 OF 3 PAGES

FDA

Clinical Investigations Branch
Division of Scientific Investigations

7520 Standish Place (HFD-344)
Rockville, MD 20855

Phone: (301) 594-1032
FAX: (301) 594-1204

DATE: 4-12-95

TO: Mathew / Joyce

FAX #: 443-9292

FROM: A. El-Hage

4 PAGES + COVER

COMMENTS: DSI Summary findings of Dr. Ferguson inspection. The findings are "minor". However, let Joyce made a determination. If you have any? Let me know - take care

Tony

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER
FOOD & DRUG ADMINISTRATION
1141 CENTRAL PARKWAY
CINCINNATI, OHIO 45202

NAME OF INDIVIDUAL TO WHOM REPORT ISSUED
TO: Ronald M. Ferguson M.D.

PERIOD OF INSPECTION
3/22,24-26,29-31
4/1-4/9/95

C. F. NUMBER

TITLE OF INDIVIDUAL
Clinical Investigator

TYPE ESTABLISHMENT INSPECTED
Sponsor-Clinical Investigator

FIRM NAME
OSU Hospital / Dept. of Surgery

NAME OF FIRM, BRANCH OR UNIT INSPECTED
same

STREET ADDRESS
1654 Upham Dr.

STREET ADDRESS OF PREMISES INSPECTED
same

CITY AND STATE (Zip Code)
Columbus, OH 43210

CITY AND STATE (Zip Code)
same

DURING AN INSPECTION OF YOUR FIRM(S) I (WE) OBSERVED:

The deviations from the study protocol as well as descrepancies between patient medical records and study Case Report Forms(CRF) noted are described as follows:

Patient

1. Urinalyses required at the 7 and 14 day visits were not performed.

2. The Trough Cyclosporine Level required at the day 14 visit was not obtained.

Patient

1. The Trough Cyclosporine Level required at the 6-month visit was not obtained.

Patient

1. Urinalyses required at the day 7 and 6-month visits were not performed.

2. The Glomerular Filtration Rate(GFR) required at the 12-month visit was not obtained.

3. The Laboratory Evaluation Form LE for the 9-month visit indicates, under Blood Chemistries, Direct Bilirubin as "-". The laboratory report corresponding to this visit, however, indicates that a Direct Bilirubin value of 0.3 was obtained.

Patient

1. Radiology reports for chest x-rays performed on 6/15/93 and 6/20/93 indicate findings of pleural effusion/pleural fluid accumulations. These findings were not reported in the Adverse Event CRF as required at the 2-month visit(6/30/93).

2. The urinalysis required at the 3-month visit and differential required at the 4-month visit were not performed.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Hugh M. McClure III	Hugh M. McClure III Investigator	4/11/95

FORM FDA 483 (5/93) PREVIOUS EDITION MAY BE USED. INSPECTIONAL OBSERVATIONS PAGE 1 OF 1 PAGES

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER FOOD & DRUG ADMINISTRATION 1141 CENTRAL PARKWAY CINCINNATI, OHIO 45202
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Ronald M. Ferguson, M.D.	PERIOD OF INSPECTION 4/4, 4/5, 4/7-11, 4/13-15, 4/18-21, 4/25-28, 5/2-5, 5/9-13	C. F. NUMBER
TITLE OF INDIVIDUAL Clinical Investigator	TYPE ESTABLISHMENT INSPECTED Clinical Investigator
FIRM NAME OSU Hospital/Dept. of Surgery	NAME OF FIRM, BRANCH OR UNIT INSPECTED same
STREET ADDRESS 1654 Upham Dr.	STREET ADDRESS OF PREMISES INSPECTED same
CITY AND STATE (Zip Code) Columbus, OH 43210	CITY AND STATE (Zip Code) same

DURING AN INSPECTION OF YOUR FIRM I (WE) OBSERVED: (continued)

Patient

3. The Complaints/Problems check list for the 9-month visit(1/31/94) indicates the patient experienced mild dizziness since the previous visit. This complaint was not reported in the Adverse Event CRF for the 9-month visit.

4. The 24 hour Urine-Quantitative Protein required at the 6-month visit was not obtained.

Patient

1. Blood Chemistries required at the baseline visit including Total Protein, Albumin, Globulin, Cholesterol, and Triglycerides were not performed. Likewise, Blood Chemistries required at the day 14 visit including Total Protein, Albumin, Globulin, Cholesterol, Triglycerides, Calcium, Phosphorus, Uric Acid, Total Bilirubin, Direct Bilirubin, Indirect Bilirubin, Alkaline Phosphatase, SGOT/AST, SGPT/ALT, and LDH were not performed.

2. The Nursing and Allied Health Profession Notes dated 6/16/93 indicate the patient experinced dyspnea. This was not reported in the Adverse Event CRF covering this period(day 7 visit, 6/21/93). The Nursing and Allied Health Profession Notes dated 6/20/93 also report the patient "s/o diarrhea stool". This complaint was not reported in the Adverse Event CRF for the 7-day visit.

3. The Urinalysis and Trough Cyclosporine Level required at the day 14 visit were not performed.

Patient

1. Portions of the in-patient medical record including Nursing Notes and Drug Administration Forms covering a 4/28/93-7/28/93 hospitalization could not be located. The study visits performed during this period include months 3 and 4.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Hugh M. McClure III	EMPLOYEE(S) NAME AND TITLE (Print or Type) Hugh M. McClure III Investigator	DATE ISSUED 4/11/95

FORM FDA 463 (5/85) PREVIOUS EDITION MAY BE USED. INSPECTIONAL OBSERVATIONS PAGE 2 OF 4 PAGES

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER FOOD & DRUG ADMINISTRATION 1141 CENTRAL PARKWAY CINCINNATI, OHIO 45202
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Ronald M. Ferguson, M.D.	PERIOD OF INSPECTION 3/13,15,21-23,27-31 4/1,5,11/94
TITLE OF INDIVIDUAL Clinical Investigator	TYPE ESTABLISHMENT INSPECTED Clinical Investigator
FIRM NAME OSU Hospitals Dept. of Surgery	NAME OF FIRM, BRANCH OR UNIT INSPECTED Same
STREET ADDRESS 1654 Upham Dr.	STREET ADDRESS OF PREMISES INSPECTED Same
CITY AND STATE (Zip Code) Columbus, OH 43210	CITY AND STATE (Zip Code) Same

DURING AN INSPECTION OF YOUR FIRM(S) WE(I) OBSERVED:

Patient #10520(VB) continued

2. Timoptic and Ednopred were administered during the period 2/16-23/93. These medications were not reported in the Concomitant Medications Form (CM3) for the day 7 visit(2/22/93).

3. The Trough Cyclosporine Level required at the day 14 visit was not obtained.

Patient

1. The Initial Immunosuppressive Therapy Log completed at the 28 day visit indicates that the total daily dose of Prednisolone administered on 7/21/93 was 90 mg IV. However, according to the Drug Administration Forms for this day, the patient received a total daily dose of 180 mg IV(90 mg IV at 1030 and 90 mg IV at 1635).

2. The out-patient phone log dated 10/6/93 indicates that the patient took Clonidine until 10/2/93. The Concomitant Medications Form(CM3) for the 3 month visit(10/20/93) does not report Clonidine as having been taken since the last visit(2 month, 9/22/93).

3. In a correspondence dated 2/21/94 regarding an outpatient visit on 2/15/94, the patient reported to the physician that he was suffering from impotence. This visit occurred between the 6 month and 9 month study visits, but the patient's complaint was not reported in the Adverse Event CRF at the 9 month visit.

4. In a correspondence dated 11/8/94 regarding an outpatient visit on 11/1/94, the patient is said to be experiencing a fungal skin eruption for which he is under the care of a dermatologist. This outpatient visit occurred between the 12 month and 18 month study visits. The fungal eruption is not reported in the Adverse Event CRF for the 18 month visit.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or type)	DATE ISSUED
	Hugh M. McClure	Hugh M. McClure III Investigator	4/11/95

FORM FDA 482 (5/93) PREVIOUS EDITION MAY BE USED. INSPECTIONAL OBSERVATIONS PAGE 3 OF 4 PAGES

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER FOOD & DRUG ADMINISTRATION 1141 CENTRAL PARKWAY CINCINNATI, OHIO 45202
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Ronald M. Ferguson, M.D	PERIOD OF INSPECTION 3/13-21-22-24-31, 4/18-3,11'95 — C. F. NUMBER
TITLE OF INDIVIDUAL Clinical Investigator	TYPE ESTABLISHMENT INSPECTED Clinical Investigator
FIRM NAME OSU Hospital/Dept. of Surgery	NAME OF FIRM, BRANCH OR UNIT INSPECTED Same
STREET ADDRESS 1654 Upham Dr.	STREET ADDRESS OF PREMISES INSPECTED Same
CITY AND STATE (Zip Code) Columbus, OH 43210	CITY AND STATE (Zip Code) Same

DURING AN INSPECTION OF YOUR FIRM(S) WE(I) OBSERVED:

Patient

5. The Maintenance Immunosuppressive Medications Form MIM for the 18 month visit indicates that the Cyclosporin A dose given on the day of the visit and the preceding day was 550 mg qd. The Complaint/Problems check list for this visit, however, indicates that the Cyclosporine dose on the date of visit was 500 mg/d.

Patient

1. The patient underwent knee surgery between the 18 month and 24 month study visits. As part of the anesthesia performed for this procedure, the patient was administered Isoflurane, Nitrous Oxide, Morphine Sulfate, ATC, Lidocaine, Fentanyl, Propofol, and Succinylcholine. These agents were not reported in the Concomitant Medications Form (CM3) for the 24 month study visit.

2. Vancomycin and Amoxicillin were administered between the 3 month and 4 month visits but were not reported in the Concomitant Medications Form (CM3) for the 4 month visit.

3. The Differential and Urinalysis required at the day 7 visit were not performed. Likewise, the Urinalysis required at the day 28 visit was not performed.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Hugh M. McClure III	EMPLOYEE(S) NAME AND TITLE (Print or Type) Hugh M. McClure III Investigator	DATE ISSUED 4/11/95

FORM FDA 482 (5/85) PREVIOUS EDITION MAY BE USED. INSPECTIONAL OBSERVATIONS PAGE 4 OF 4 PAGES

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

TAKOSKY

APR 21 1995

Samuel S. Weinstein, M.D.
Tampa General Healthcare
3000 East Fletcher Avenue, Suite 380
Tampa, Florida 33613

Dear Dr. Weinstein:

Between February 21 and 28, 1995, Ms. Shari J. Hromyak, representing the Food and Drug Administration(FDA), conducted an inspection of your conduct, as Principal Investigator, of a clinical study (protocol ICM1866) of the investigational drug mycophenolate mofetil(RS-61443), performed for Syntex. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

We have evaluated the inspection report by Ms. Hromyak, the documents collected during the inspection and your written response to Ms. Hromyak dated March 10, 1995 regarding the items listed in the Form FDA-483. Your letter has become part of the FDA official record. We are aware that Ms. Hromyak discussed with you the non-reporting of adverse events to your IRB, the lack of written documentation of IRB approval for modification of reporting requirements; the lack of documentation as to when the sponsor was notified of adverse events and your failure to include certain revisions made to the consent forms. We note your general agreement with her findings and your intent to assure future documentation of events and notification of the sponsor and the IRB of all pertinent information related to the study.

We appreciate the cooperation shown Investigator Hromyak during the inspection.

Sincerely yours,

Alan B. Lisook, M.D.
Chief
Clinical Investigations Branch
Division of Scientific
Investigations - HFD-344
Office of Compliance
Center for Drug Evaluation
and Research

CFN:1058799
Field classification: A
Headquarters classification:
___1)NAI
_x_2)VAI-no response required
___3)VAI-response requested

If Headquarters classification is different classification, explain why:

Deficiencies noted:
_x_inadequate consent form - updated version
___inadequate drug accountability
___failure to adhere to protocol
___inadequate records
_x_failure to report ADRS to IRB
___other(specify)

cc:
HFA-224
HFD-344
HFD-340 r/f
HFD-340 Kelsey/Richardson
HFD-342
HFR-SE200
HFR-SE250
HFD-530 Review Division Div.Dir./Doc.Rm: NDA
Dr. Korvac/CSO Tarosky IND
HFC-132
HFC-230
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The Antiviral Drugs Advisory Committee Subcommittee on Immunosuppressant Drugs met on Thursday, March 30, and Friday, March 31, 1995. On Thursday, the topic was NDA: (250 mg capsules) for mycophenolate mofetil (CellCept®, Syntex Laboratories, Inc.) for use in the prophylaxis of organ rejection in patients receiving allogeneic renal transplants.

Approximately 100 people were present, including the sponsor and the FDA. There were no speakers at the open public hearing.

After a welcome from the Dr. Feigal, Supervisory Medical Officer Dr. Mark Goldberger introduced the topic. The sponsor and FDA presentations were interdigitated according to topic. First, several speakers from Syntex presented three studies submitted in support of the efficacy of CellCept® for the first indication, prevention of acute rejection in renal transplant recipients. All were randomized and double blinded multi-center trials. The European trial was placebo controlled, with the U.S. and tricontinental trials use azathioprine as the control. They argue that since escaping an acute rejection is associated with a better prognosis, this drug may have long term benefits as well as prophylaxis in the 6 month study period. Dr. Paul Flyer of the Division of Biometrics provided FDA statistical comments and Dr. Chandra Sahajwalla of DAVDP commented on biopharmaceutic and pharmacokinetic aspects of the submission. The next series of presentations focused on safety. Syntex presenters noted that GI-related complaints were the largest category of adverse events, but some hematologic abnormalities were noted, as well as the effects of immunosuppression. Dr. Joyce Korvick of DAVDP presented the FDA analysis. The company was asked the following questions:

I. Questions Regarding the Prevention of Acute Rejection in Renal Transplant Recipients

1. Has CellCept® been shown to be safe and effective in preventing acute rejection in patients who have undergone renal transplantation? If so, what treatment regimen, including dose (or doses) and duration, should be recommended?

   THERE WERE 11 VOTING MEMBERS. ALL VOTED YES.

2. If the committee recommends approval for this indication, does the committee also have specific recommendations for future trials with CellCept® for prevention of rejection associated with renal transplantation?

   Many members were concerned about the lack of data on the optimal duration of dose, and called for data past the one year that had been presented.

3. The studies for acute rejection compared the proportion of patients who experienced either an acute rejection or a "treatment failure" within the first six months of treatment. This was supplemented by the one year results of graft and patient survival. Does the committee have recommendations regarding endpoints and or overall study design for future trials of other products?

   Regarding future studies, members' suggestions included doing pharmacokinetic studies earlier in the development process, requiring a biopsy as confirmation of every rejection, longer follow up, and interaction studies with other drugs likely to be used by the population including antibiotics.

The afternoon session addressed [redacted]

The format was similar to the morning, with Drs. Flyer and Korvick providing FDA comments. For this indication, one multi-center open-label trial was submitted. CellCept® was compared to IV steroids (methylprednisolone). The group of patients eligible for such a study is relatively small, so the study was small. The appropriate statistical approach was discussed, as different approaches give quite different p values. The committee was asked the following questions:

END

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