CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-722/S-005

50-723/S-005

50-758/S-004

50-759/S-006

MEDICAL REVIEW

Medical Officer Review of NDA 50-722/S-005:
CellCept® (mycophenolate mofetil) for the prophylaxis of organ rejection in patients receiving allogeneic hepatic transplants.

Date Submitted:	1 October 1999
Date Received:	4 October 1999
Date Assigned:	4 October 1999
Date Completed:	26 July 2000

Applicant: Syntex (U.S.A.), Incorporated
3401 Hillview Avenue
Palo Alto, California 94303
Telephone number: 650.852.1861
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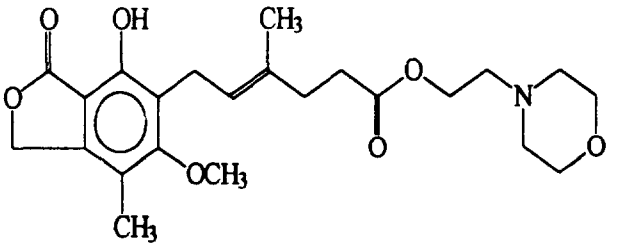
Drug:

Proprietary name:	CellCept®
Generic name:	Mycophenolate mofetil
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
Molecular formula:	$C_{23}H_{31}NO_7$
Molecular weight:	433.50 daltons
Molecular structure:	



Drug class: Antibiotic
Formulation: 250 mg capsules
Route of Administration: Oral
Related NDAs:
50-723, CellCept® tablets (500 mg)
50-758, CellCept® intravenous (500 mg)
50-759, CellCept® oral suspension (200 mg/ml)

Related INDs:

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Executive summary

Background

Mycophenolate mofetil (MMF, CellCept®) is the 2-morpholino-ethyl ester of mycophenolic acid (MPA), a fermentation product of *Penicillium stoloniferum*. MPA is the pharmacologically active compound, therefore MMF can be considered to be a "pro-drug." MPA's immunosuppressive properties are due to its ability to block nicotanimide's binding site on inosine monophosphate dehydrogenase (IMPDH), an enzyme needed for purine synthesis.

This effect is manifested clinically as an antiproliferative effect on T and B lymphocytes, inhibition of antibody formation, and the prevention of glycosylation of certain adhesion molecules on lymphocytes.

Mycophenolate mofetil has been approved for prophylaxis of organ rejection in adult renal allograft recipients (NDA 50-722; May 3, 1995), and cardiac allograft recipients (NDA 50-722/S002; February 11, 1998). There are four formulations currently approved:

- 250 mg capsules (NDA 50-722; May 3, 1995)
- 500 mg tablets (NDA 50-723; June 19, 1997)
- Solution for injection (NDA 50-758; August 12, 1998)
- Oral suspension, 200 mg/ml, (NDA 50-579; October 1, 1998)

Clinical Study

The applicant has submitted the data from one pivotal study in support of this application. The study has a multi-center, international, randomized, double-blind, double-dummy design, and it assessed the safety and efficacy of a treatment regimen of MMF, intravenous followed by oral, in conjunction with cyclosporine and corticosteroid therapy. The comparison arm was a regimen of azathioprine, cyclosporine, and corticosteroid therapy.

There were 22 clinical centers, with 565 patients (278 in the MMF treatment group, and 287 in the azathioprine treatment group) participating in the study. The majority of the patients came from the United States (15 centers), with the remaining centers located in Europe (4), Canada (2), and Australia (1).

Patients were randomized to one of the following two treatment groups :

Study Drug	Dosage Form	Mycophenolate mofetil (MMF)	Azathioprine
Group 1 MMF with Placebo azathioprine	Intravenous	1 g infusion BID	Placebo infusion
	Oral	1.5 (6 capsules) BID	Placebo capsules
Group 2 Placebo MMF with azathioprine	Intravenous	Placebo infusion BID	1-2 $mg \bullet kg^{-1} \bullet day^{-1}$ infusion
	Oral	6 placebo capsules BID	1-2 $mg \bullet kg^{-1} \bullet day^{-1}$ capsules

There were two co-primary endpoints, defined in the table below:

Endpoint	Definition
The proportion of patients in each treatment group who experienced at least one episode of biopsy-proven rejection or death/re-transplantation during the 6 months following transplantation (either on study or post-transplantation).	• Positive biopsy confirmed by site pathologist using [redacted] and • Treatment of rejection confirmed by investigators indicating that patients were given a course of therapy to treat rejection episode A patient who died or was re-transplanted within the 6 months following transplantation, without experiencing rejection was also considered to have met this rejection endpoint. A positive biopsy was considered to be in association with treatment for rejection if the positive biopsy was obtained prior to or on the same day as initiation of treatment for rejection, and in the opinion of the investigator, was felt to be associated with the treatment of rejection
The proportion of patients in each treatment group who experienced graft loss (death/re-transplantation) during the 12 months following transplantation.	Death or re-transplantation for any cause.

The results of the study were as follows (adapted from the applicant's Study Report, Vol. 17, p. 65):

Endpoint	Azathioprine	MMF	Treatment Difference (azathioprine-MMF)	p-value or CI
No. of patients enrolled	287	278		
Co-Primary rejection endpoint: Number (%) of patients experiencing biopsy-proven and treated rejection or graft loss during the initial 6 months posttransplant	137 (47.7%)	107 (38.5%)	9.2%[a]	p-Value: 0.025
Co-primary graft loss endpoint: Number (%) of patients experiencing graft loss (death or re-transplantation) during the initial 12 months posttransplant	42 (14.6%)	41 (14.7%)	Percent difference: 0.10%	95% CI = (-5.91%, 5.32%)

[a]Relative risk (MMF/azathioprine) = 0.80

These results differ slightly from what the applicant indicated in their Study Report, for they take into account three patients that had been lost to follow-up that the applicant had originally classified as treatment successes. The patients were subsequently reclassified as treatment failures. However, the difference was not felt to be significant enough to change the conclusions drawn from the study.

Efficacy

Key conclusions regarding efficacy are:

- That the applicant was able to demonstrate that MMF had a lower incidence of acute rejection at the 6-month post-transplant timepoint than azathioprine, with a background regimen containing cyclosporine and corticosteroid therapy. This result was robust even with minor deviations in the definition of rejection.

- The overall patient and graft survival at 12 months was excellent and the 95% confidence interval was sufficiently narrow to exclude an unacceptable decrease in patient and graft survival.

Safety

Key conclusions with regard to the safety of MMF in the prevention of allograft rejection in adult hepatic transplantation are:

- The nature, frequency, and severity of adverse events are similar to those observed in patients treated with azathioprine (AZA).
- The mortality rate is similar to that observed in patients treated with AZA.
- The frequency and types of malignancies are similar to those in patients treated with AZA.
- The frequency of discontinuation of treatment due to adverse events is similar to that observed in patients treated with AZA.
- The nature, frequency, and severity of adverse events during intravenous administration of MMF are similar to those observed during intravenous administration of AZA.
- Clinically meaningful influence of gender on the safety of MMF were NOT detected.
- Safety risks from oral administration of MMF were NOT observed, other than those previously reported in renal and cardiac allograft recipients.
- Safety risks from intravenous administration of MMF other than those previously reported in renal allograft recipients were NOT observed.

Special Populations

There were not enough patients over the age of 65 to be able to perform any analyses, nor were there enough non-Caucasian patients to be able to make a statement regarding ethnic group and treatment.

It was noted that gender was found to be a significant predictor of outcome at the 6-month timpoint, with males having a lower rate of rejection than females. The interaction with treatment, however, was not significant. Neither gender nor treatment interaction was found to be significant at the 12-month timepoint.

Recommendation

The medical officers' recommendation is for approval of CellCept® for prophylaxis of acute organ rejection in patients receiving allogeneic hepatic transplants, to be administered in combination with cyclosporine and corticosteroids.

The dosage recommendations will be 1.5 grams, bid, orally or intravenously, for a total daily dose of 3 grams. The intravenous infusion is to be infused over no less than 2 hours.

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Review Team

Regulatory Management Officer:	M. Bacho, B.S.
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1. Introduction and Background

Although the first hepatic transplant was performed in 1968, much of the progress in survival began with the use of cyclosporine in 1979. Prior to that, one-year survival rates of 23% to 27% had raised questions as to whether the procedure should be abandoned.

A variety of immunosuppressive regimens are used, however cyclosporine/corticosteroid based, or tacrolimus/corticosteroid based regimens are still the mainstay of many post-transplant protocols. The toxicities associated with these regimens reflect the need for alternative agents.

Mycophenolate mofetil (MMF, CellCept®) is the 2-morpholino-ethyl ester of mycophenolic acid (MPA), a fermentation product of *Penicillium stoloniferum*. MPA is the pharmacologically active compound, therefore, MMF is a pro-drug. MMF is extensively and rapidly absorbed after oral administration, and undergoes first-pass hydrolysis in the hepatic and intestinal circulation.

MPA inhibits *de novo* synthesis of guanosine nucleotides by inhibiting inosine monophosphate dehydrogenase (IMPDH), for it can mimic nicotinamide (NAD) at the enzyme's NAD-binding site. Lymphocytes are dependent on this pathway for the synthesis of these nucleotides, therefore MPA is capable limiting deoxyribonucleic acid (DNA) synthesis in lymphocytes to greater degree than in other cells that do not rely so extensively on this pathway. This is manifested as an antiproliferative effect on both, T and B lymphocytes, inhibition of antibody formation, and the prevention of glycosylation of certain adhesion molecules on lymphocytes.

The mechanism of action, supported by demonstrated efficacy in several animal models of transplantation, provided the rationale for the investigation of MMF as an immunosuppressive agent for use in treatment and prevention of rejection in organ transplantation.

1.1. Relevant Human Experience

1.1.1. Important information from related NDAs

As described above, there was supportive evidence that MMF is useful as part of the therapeutic regimen used in transplantation medicine. In May 1995, the applicant received approval for prophylaxis of organ rejection in patients receiving allogeneic renal transplants, and in February 1998, for prophylaxis of organ rejection in patients receiving allogeneic cardiac transplants.

It is noted that the sponsor was not able to provide adequate data that would allow approval of MMF for the treatment of acute refractory rejection in either of the two organ indications.

1.1.2. Foreign Experience

The applicant has provided their foreign marketing history in the form of a table which summarizes their international registration database (Vol. 2, pages 111-126). They

identify 78 countries in which they have filed for marketing privileges. The applicant indicated that in addition to the United States, the product has been approved and introduced in 30 of the 78 countries (tabulated in Appendix A of this review). The majority of regulatory bodies have granted approval for the prophylaxis of acute renal rejection, with a few granting approval for the treatment of acute refractory renal rejection.

Medical Officer Comment:

Although Slovakia was identified as a country in which the product has been introduced for prophylaxis acute renal rejection and treatment of refractory acute renal rejection, the applicant did not provide a date of introduction.

1.2. Materials reviewed

The following volumes of the New Drug Application (NDA) were reviewed: Vols. 1, 2, and 16 through 42. Electronic version of case report forms (CRFs) were reviewed utilizing Adobe Acrobat™ software. In addition, SAS transport files were reviewed with the aid of JMP™ software.

1.3. Pharmacokinetics/Pharmacodyanamics

The following studies were submitted by the applicant for review of the pharmaocokinetics of MMF in hepatic patients (table reproduced from Vol. 2, p. 82):

Protocol No.	Report No.	Study Description	Status (Cut-off Date)	Objective	Length of Study	No. of hepatic Patients on MMF
Controlled Study						
MYCS2646	P-180262	Randomized, double-blind study of the safety, efficacy, and PK of MMF (1.0 g bid IV initially, then 1.5 g bid oral) versus AZA combined with cyclosporine and corticosteroids for prevention of hepatic allograft rejection.	Ongoing (clinical cut-off 29 Mar 99)	Prevention of Rejection	3 y	277[1]
Uncontrolled Studies						
ICM1812	CL6818	Open-label safety, efficacy, and PK pilot study of MMF for treatment of refractory cellular hepatic, renal, or cardiac allograft rejection.	Completed	Treatment of Refractory Rejection	56 d	35[2]
IID2104	P-180197	Open-label, dose-finding, safety and PK study of MMF in combination with corticosteroids and cyclosporine for prevention of hepatic allograft rejection.	Completed	Prevention of Rejection	3 mo	24[2]
MYCS2378	P-180256	Randomized, open-label study of the PK and safety of MMF IV during the 1st 7 days posttransplant followed by oral MMF, in combination with cyclosporine and corticosteroids for the prevention of hepatic allograft rejection.	Completed	Prevention of Rejection	3 y	45[2]
MYCS063	P-180213	Open-label, multiple dose, two-period, crossover PK study of tacrolimus ± MMF, in stable hepatic allograft recipients.	Completed	Effect of MMF on PK of tacrolimus	2 wk	12[2]

[1] Full PK profiles for 22 patients, 2-hour mini-profiles for 110 patients.
[2] All patients participated in PK assessments.

For additional details regarding the review of these studies, please refer to Dr. Kofi Kumi's review.

1.4. Pharmacotoxicology

The applicant submitted a final study report on the their genotoxocity studies on July 7, 2000. For additional details, please refer to Dr. Steve Kunder's review.

1.5. Chemistry

Discussions with Dr. Mark Seggel, the chemistry reviewer, indicated that there were no significant chemistry issues with this NDA.

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2. Efficacy Evaluation

2.1. Protocol MYCS 2464

The clinical data supporting this application is derived from one pivotal clinical trial, Protocol MYCS-2646, entitled "A randomized, double-blind comparative study of the efficacy and safety of intravenous and oral mycophenolate and azathrioprine, each in combination with cyclosporine (Neoral®) and corticosteroids in liver transplant recipients." The study dates were January 13, 1997 to March 29, 1999, at which point the last patient enrolled reached the 12 months post-transplant timepoint. The blinded phase was discontinued, but the study will continue until the last patient reaches their 3-year post-transplant timepoint.

2.1.1. Study design

The study was a multi-center, randomized, double-blind, double-dummy design, assessing the safety and efficacy of a treatment regimen of mycophenolate mofetil (MMF, Cellcept®), intravenous followed by oral, in conjunction with cyclosporine (Neoral®) and corticosteroids in liver allograft patients. The comparison arm was a regimen of azathioprine, cyclosporine, and corticosteroids.

2.1.1.1. Objectives

The applicant indicated that there were two primary endpoint for comparisons:

1. The proportion of patients who experienced either (a) one or more episodes of biopsy-proven rejection or (b) death/re-transplantation, within the first six months post-transplantation. This was a test for the superiority of CellCept over azathioprine.
2. Graft loss (death/re-transplantation) during the first 12 months post-transplantation, to assess for equivalence of the two treatments by ruling out with a 97.5% confidence a possible difference of greater than 10% in favor of azathioprine.

In addition, there were twelve secondary objectives identified by the applicant (reproduced from the applicant's study report, p. 27):

1. The proportion of patients in each treatment group who experienced, in the first 12 months posttransplantation, (a) one or more episodes of biopsy-proven and treated rejection or (b) death/re-transplantation.
2. The proportion of patients in each treatment group (a) administered OKT3 or antithymocyte globulin (ATG) for treatment of rejection or (b) who experienced death/re-transplantation during the first 6 and 12 months posttransplantation.
3. The proportion of patients in each treatment group who experienced in the first 6 and 12 months posttransplantation (a) one or more episodes of biopsy-proven rejection or (b) death/re-transplantation.
4. The proportion of patients in each treatment group who experienced in the first 6 and 12 months posttransplantation (a) one or more episodes of biopsy-proven rejection with biochemical abnormalities suggestive of rejection or (b) death/re-transplantation.
5. The proportion of patients in each treatment group who experienced in the first 6 and 12 months posttransplantation (a) one or more episodes of biopsy-proven and treated

rejection with biochemical abnormalities suggestive of rejection or (b) death/re-transplantation.

6. The proportion of patients in each treatment group who experienced in the first 6 and 12 months posttransplantation (a) one or more episodes of treated rejection or (b) death/re-transplantation.
7. The proportion of patients in each treatment group who experienced in the first 6 and 12 months posttransplantation (a) one or more episodes of treated rejection with biochemical abnormalities suggestive of rejection or (b) death/re-transplantation.
8. The maintenance dose of steroids at 6 and 12 months posttransplantation.
9. Time from transplantation to first occurrence of the co-primary endpoint of biopsy-proven and treated rejection.
10. Time from transplantation to graft loss (death/re-transplantation) during the first 12 months posttransplantation.
11. The safety of mycophenolate mofetil versus azathioprine, both in conjunction with cyclosporine and steroids, including the incidence of opportunistic infections, lymphoproliferative disorders, and other neoplasms.
12. Medical care utilization and implied costs.

Medical Officer Comment:
Although these comparisons may be of scientific interest, it must be noted that their significance must be viewed in the context that several of these observations have interdependent endpoints. Furthermore, any statistical analyses performed on these observations will need to make adjustments for multiple comparisons.

2.1.1.2. Eligibility Criteria

In order to be eligible for the study, patients were:

a. to be least 16 years of age
b. to be receiving his/her first cadaveric orthotopic liver transplant
c. to be recipient of a single organ transplant
d. to have no known contraindication to the administration of cyclosporine, corticosteroids, azathioprine, mycophenolate mofetil, [redacted] or polysorbate 80 (Tween® 80).

If the patient was a female of childbearing potential, they were to have a documented negative serum or urine pregnancy test that was performed within one week from the study entry. In addition, they were required to utilize two reliable methods of birth control, unless they intended to abstain from heterosexual activity. The contraception methods were to be employed prior to initiation of study drug therapy, during therapy, and for six weeks after therapy was discontinued.

Patients would not be allowed to enter the study if they:

1. had previously received an organ transplant
2. had a history of malignancy (other than non-melanoma skin cancer, that had been adequately treated)
3. had active peptic ulcer disease at the time of screening
4. had an absolute neutrophil count of less than 1,000 cells/mm^3 at the time of screening

5. had an ABO incompatible transplant
6. had chronic Hepatitis B or were HbsAg positive
7. were HIV positive
8. were being treated with other investigational drugs, or prohibited immunosuppressive medications (see below)
9. were pregnant or breast-feeding
10. required dialysis within 30 days prior to transplantation

Medical Officer Comment:
It is noted that the inclusion criteria specifically identified 16 years of age as the lower limit. It is also noted that approximately 15% of all liver transplants in the United States are in patients less than 18 years of age. This potential gap in knowledge about CellCept®'s safety and efficacy in this age group (less than 16), for this indication, is to be addressed in the form of Phase IV commitments.

2.1.1.3. Study drugs and randomization methods

For a patient to be considered for randomization into the study, the inclusion/exclusion criteria needed to be satisfied within 48 hours prior to transplantation. In addition, only patients that were expected to live at least 5 days without requiring re-transplantation, and were able to initiate study drug within 24 hours after surgery were to be randomized.

Medical Officer Comment:
The fact that patients were only randomized if they were expected to live 5 days after transplantation without requiring another transplant decreased the possibility that patients would be randomized but not live long enough to receive study drug. The intent was to make the intent-to-treat population set and the per-protocol population set as similar as possible.

Patients were randomized to one of the following two treatment groups (intravenous followed by oral therapy):

Study Drug	Dosage Form	Mycophenolate mofetil (MMF)	Azathioprine
Group 1 MMF with Placebo azathioprine	Intravenous	1 g infusion BID	Placebo infusion
	Oral	1.5 (6 capsules) BID	Placebo capsules
Group 2 Placebo MMF with azathioprine	Intravenous	Placebo infusion BID	1-2 $mg \bullet kg^{-1} \bullet day^{-1}$ infusion
	Oral	6 placebo capsules BID	1-2 $mg \bullet kg^{-1} \bullet day^{-1}$ capsules

2.1.1.4. Study endpoints

The following table, reproduced from the applicant's Study Report, identifies the two primary endpoints and their definitions:

Endpoint	Definition
The proportion of patients in each treatment group who experienced at least one episode of biopsy-proven rejection or death/re-transplantation during the 6 months following transplantation (either on study or post-transplantation).	• Positive biopsy confirmed by site pathologist using [redacted] and • Treatment of rejection confirmed by investigators indicating that patients were given a course of therapy to treat rejection episode A patient who died or was re-transplanted within the 6 months following transplantation, without experiencing rejection was also considered to have met this rejection endpoint. A positive biopsy was considered to be in association with treatment for rejection if the positive biopsy was obtained prior to or on the same day as initiation of treatment for rejection, and in the opinion of the investigator, was felt to be associated with the treatment of rejection
The proportion of patients in each treatment group who experienced graft loss (death/re-transplantation) during the 12 months following transplantation.	Death or re-transplantation for any cause.

The [redacted] for the diagnosis of acute rejection was utilized. Application of these criteria required that the pathologist assess the adequacy of the biopsy specimen by noting that at least 4 triads are present, unless there were obvious diagnostic findings present. In addition, if there was more than one pathological process present on the biopsy, the pathologist was to assess which worse was most significant.

The biopsy was to be graded for the presence or absence of acute rejection based on a global assessment of the biopsy, using the following definitions:

Assessment	Definition
No rejection	No infiltrate or inflammation attributable to rejection.
Indeterminate	Portal inflammatory infiltrate that fails to meet the criteria for the diagnosis of acute rejection (as described for "mild")
Mild	Rejection infiltrate in a minority of the triads, that is generally mild and confined within the portal spaces plus at least one of the following: 1. Clear bile duct damage 2. Portal or hepatic venule subeendothelial inflammation
Moderate	As above for "mild," but expanding to most or all of the triads.
Severe	As above for "moderate," with spillover into periportal areas and moderate or severe perivenular inflammation that extends into the hepatic parenchyma and is associated with perivenular hepatocyte necrosis.

The pathologist was then to use the individual pathological findings to determine a rejection activity index for each biopsy:

Category	Criteria	Score
Portal inflammation	Mostly lymphocytic inflammation involving, but not noticeably expanding, a minority of the triads	1
	Expansion of most or all of the triads, by a mixed infiltrate containing lymphocytes with occasional blasts, neutrophils, or eosinophils	2
	Marked expansion of most or all the triads by a mixed infiltrate containing numerous blasts and eosinophils with inflammatory spillover into the periportal parenchyma	3
Bile duct inflammation damage	A minority of the ducts are cuffed and infiltrated by inflammatory cells and show only mild reactive changes such as increased nuclear:cytoplasmic ratio of the epithelial cells	1
	Most or all of the ducts infiltrated by inflammatory cells. More than an occasional duct shows degenerative changes such as nuclear pleomorphism, disordered polarity and cytoplasmic vacuolization of the epithelium	2
	As above for "2" with most or all of the ducts showing degenerative changes or focal lumenal disruption	3
Venous endothelial inflammation	Subendothelial lymphocytic infiltration involving some, but not a majority of the portal and/or hepatic venules	1
	Subendothelial infiltration involving most or all of the portal and/or hepatic venules	2
	As above for "2" with moderate or severe perivenular inflammation that extends into the perivenular parenchyma and is associated with perivenular hepatocyte necrosis	3
Total Score (sum of the components)		

Medical Officer Comment:

All specimens were sent for central review to Anthony J. Demetris, M.D., Department of Pathology, University of Pittsburgh Medical Center, for the protocol stipulated that all the specimens were to be interpreted by a pathologist at a central site. The central pathologist's reading was then to be used for all analyses. The applicant intended to assess the internal consistency between the two readings.

2.1.1.5. Termination and clinical follow-up

The guidelines for classification of a patient's withdrawal from the study were as follows:

1. The patient completed 3 years of treatment with MMF or azathioprine (normal protocol completion)
2. Patient decided to withdraw (for any reason)
3. Development of an adverse event or opportunistic infection that, in the opinion of the investigator, warranted the patient's withdrawal from study treatment
4. Unsatisfactory therapeutic response (graft loss, allograft rejection necessitating use of prohibited immunosuppressants, or re-transplantation)
5. Noncompliance with study drug (a minimum of 80% compliance with the dosing of the study drug was required) or with the protocol schedule
6. The patient required treatment with another investigational drug or other medication prohibited by the protocol

7. The sponsor or the Food and Drug Administration or other regulatory agency requested termination of treatment of an individual patient or patients under this protocol
8. Lost to follow-up: a patient who failed to appear and could not be contacted by letter or telephone
9. Death
10. Other

If a patient was withdrawn from the study for any reason other than death or "lost to follow-up" they were followed for three years from the date of enrollment. During the first year after transplantation, the following information was collected:

a. liver biopsy results
b. treatment of rejection
c. biochemical abnormalities suggestive of rejection
d. development of malignancies
e. patient and graft survival
f. incidence of hospitalization
g. use of immunosuppressive therapy

After the 1-year transplantation period information on the development of malignancies, and patient/graft survival was collected at 6 month intervals.

2.1.1.6. Sample size and Statistical plan

There were two distinct co-primary endpoints:

Hypothesis 1: MMF would be superior to azathioprine in terms of the proportion of patients with biopsy-proven and treated rejection at 6 months post-transplant. The Cochran-Mantel-Haenszel general association test, stratified by investigator, was used. The sample size, 275 per treatment group (total of 550 patients), was calculated to provide power of at least 90% to detect a treatment difference of at least 15% or larger in the 6-month rejection rates, using the binomial test and two-sided α of 0.05.

Hypothesis 2: MMF would be non-inferior to azathioprine if the proportion of MMF patients with graft loss (death or re-transplantation) at one year post-transplant was not lower than that of azathioprine by 10% or more. Equivalence was assessed based on the lower limit of the 97.5% confidence interval for the difference (azathioprine minus MMF). The same sample size (275 per treatment group) was calculated to be sufficient to demonstrate non-inferiority with 80% power, assuming the true probability of death or re-transplantation was 22.5% for both treatment groups.

For additional information, please refer to Dr. Karen Higgins review.

2.2. Study Results

The blinded phase of the study was from January 13, 1997 through March 27, 1999, at which point the last patient to be enrolled reached the 1-year post-transplant landmark.

All patients were then allowed to receive open-label drug supplies and will be followed for a total of 3 years post-transplant.

Medical Officer Comment:
It was noted that observations made at the 1-year post-transplant endpoint were going to be limited, because > 50% of the patients had discontinued study medication by that time-point. This limitation is expected to be even greater at the 3-year post-transplant time-point (see Section 3.1 of this review).

2.2.1. Enrollment and description of patients
There were 22 investigators across 23 centers throughout Australia, Europe, and America. The list of participating investigators is reproduced as Appendix B, a table that is adapted from the applicant's Study Report. The largest center contained 50 subjects (9%) and the smallest centers contained 10 patients.

One investigator, John Roberts, M.D., enrolled patients from two centers: University of California - San Francisco (UCSF) and California Pacific Medical Center (CPMC). The applicant pooled the data from the two centers, thus resulting in 22 strata.

Medical Officer Comment:

Review of the case report forms indicated that that Dr. Burdick was not the only investigator involved in the assessment of the patients; other subinvestigators, as well as the principal investigator, Dr. Klein, were involved. In addition, the number of patients enrolled at this site (10 patients) was small.

These two considerations allowed for the conclusion that Dr. Burdick's involvement in this study would be unlikely to unduly influence the outcome of this study.

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2.2.2. Patient diagnoses and complicating factors at entry

The following table, adapted from the applicant's Study Report (Vol. 17, p. 57), summarizes the demographic information of the study population:

	Azathioprine 1-2 mg/kg/day	MMF 1.5gmBID	Total
Patients Enrolled	**287**	**278**	**565**
Age (Yrs)			
Under 18	0 (0%)	1 (0%)	1 (0%)
18 - 29	10 (3%)	13 (5%)	23 (4%)
30 - 39	34 (12%)	35 (13%)	69 (12%)
40 - 49	98 (34%)	93 (33%)	191 (34%)
50 - 59	88 (31%)	87 (31%)	175 (31%)
60 - 64	31 (11%)	28 (10%)	59 (10%)
65 and over	26 (9%)	21 (8%)	47 (8%)
Missing	0 (0%)	0 (0%)	0 (0%)
Mean	49.9	49.0	49.4
Standard Deviation	10.3	11.0	10.6
Range	20.0 - 78.0	16.0 - 75.0	16.0 - 78.0
Gender			
Female	131 (46%)	119 (43%)	250 (44%)
Male	156 (54%)	159 (57%)	315 (56%)
Missing	0 (0%)	0 (0%)	0 (0%)
Ethnic group			
Asian	10 (3%)	4 (1%)	14 (2%)
Black	13 (5%)	12 (4%)	25 (4%)
Caucasian	236 (82%)	241 (87%)	477 (84%)
Hispanic	24 (8%)	17 (6%)	41 (7%)
Other	4 (1%)	4 (1%)	8 (1%)
Missing	0 (0%)	0 (0%)	0 (0%)
Weight (kgs)			
Under 50	8 (3%)	5 (2%)	13 (2%)
50 - 75	127 (44%)	117 (42%)	244 (43%)
Over 75	152 (53%)	156 (56%)	308 (55%)
Not Done	0 (0%)	0 (0%)	0 (0%)
Mean	77.9	80.7	79.3
Standard Deviation	17.7	20.0	18.9
Range	39.5 - 143.0	41.0 - 164.0	39.5 - 164.0

Medical Officer Commen:t

The age distribution for the age, ethnic group, and weight was comparable between the two treatment groups. There were more females enrolled in the azathioprine treatment group than the MMF treatment group, but this numerical difference was not felt to be significant enough to influence the study results.

Although the actual percentages were different, the relative proportion of ethnic groups to each other were similar to those of the United Network for Organ Sharing (UNOS) hepatic transplantation registry (1999 Report):

UNOS Registry 1994-1998	
Caucasian	*77.7%*
Black	*7.0%*
Hispanic	*10.0%*
Asian	*3.1%*
Other	*2.1%*

2.2.3. Patient disposition

The following table, adapted from the applicant's Study Report (Vol. 17, p. 59), summarizes the reasons for withdrawal from the study:

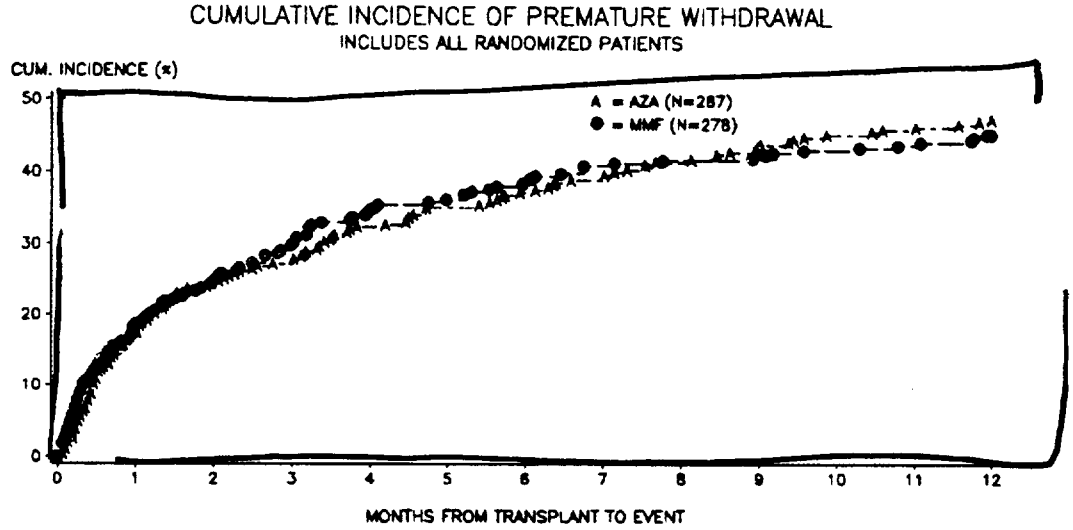
	Azathioprine	**MMF**	
	1-2 mg/kg/day	1.5 gm BID	**Total**
Total Patients Enrolled	**287**	**278**	**565**
Total (%) Patient s Ongoing	133 (46.3%)	126 (45.3%)	259 (45.8%)
Total (%) Normal Completions	0	0	0
Total (%) Premature Withdrawals from Study	154 (53.7%)	152 (54.7%)	306 (54.2%)
Primary Withdrawal Reason	NO. OF PATIENTS (%)		
Adverse Event/New Intercurrent Illness/New Lab Abnormality	95 (33.1%)	94 (33.8%)	189 (33.5%)
Unsatisfactory Therapeutic Response	12 (4.2%)	4 (1.4%)	16 (2.8%)
Inappropriate Enrollment	4 (1.4%)	4 (1.4%)	8 (1.4%)
Non-Compliance (With drug or schedule)	6 (2.1%)	7 (2.5%)	13 (2.3%)
Need for medication that was prohibited by the protocol	4 (1.4%)	5 (1.8%)	9 (1.6%)
Lost to Follow-up	0	0	0
Death	13 (4.5%)	11 (4.0%)	24 (4.2%)
Entire Study at Center Terminated			
By Sponsor	0	0	0
By Investigator	0	0	0
Other	20 (7.0%)	27 (9.7%)	47 (8.3%)
Malignancy	1 (0.3%)	2 (0.7%)	
MD Decision	2 (0.7%)	0	
Miscellaneous	1 (0.3%)	3 (1.1%)	
Patient Request	15 (5.2%)	17 (6.1%)	
Primary Graft Dysfunction	1 (0.3%)	5 (1.8%)	

Medical Officer Comment:

The applicant indicated that there were no patients lost to follow-up. Review of the case report forms, however, identified two patients on the CellCept® treatment arm that were lost to follow-up. One was lost prior to the 6-month

endpoint and one prior to the 12-month endpoint. The applicant considered them as successes in their analyses; these patients were considered failures in the FDA's analyses.

Nevertheless, one of the strengths of this study remains the quality of follow-up and virtual complete assessment of patient and graft survival at 12 months.



Medical Office Comment:

It is noted that a considerable number of patients withdrew prematurely from the study. It was not possible to determine why there was such a rate of withdrawal, but it was noted that the rate was equal between the two treatment groups with respect to the reasons, except for one category, "unsatisfactory therapeutic response." This similarity in the rate of withdrawal between the arms is represented graphically in the above Kaplan-Meier curve, reproduced from the applicant's Study Report (Vol. 17, p. 60).

It is expected that this relatively high rate of withdrawal will affect the test of superiority at the 6-month timepoint in that it would be harder to show superiority, but would favor demonstration of equivalence at the 12-month timepoint.

2.3. Applicant Analyses

2.3.1. Primary analysis

As described above, in **Section 2.1.1.1 Objectives**, the primary analysis performed by the applicant consisted of two co-primary endpoints: a six month endpoint looking at biopsy proven and treated rejection, death, or re-transplantation, and a 12 month endpoint looking at graft loss (death or re-transplantation).

Medical Officer Comment:
When assessing the efficacy of a product in transplant studies, it is important to look at the three endpoints: rejection, death, and re-transplantation,. The rationale involves the acknowledgment that a patient who experiences death or re-transplantation will no longer be able to be evaluated for rejection.

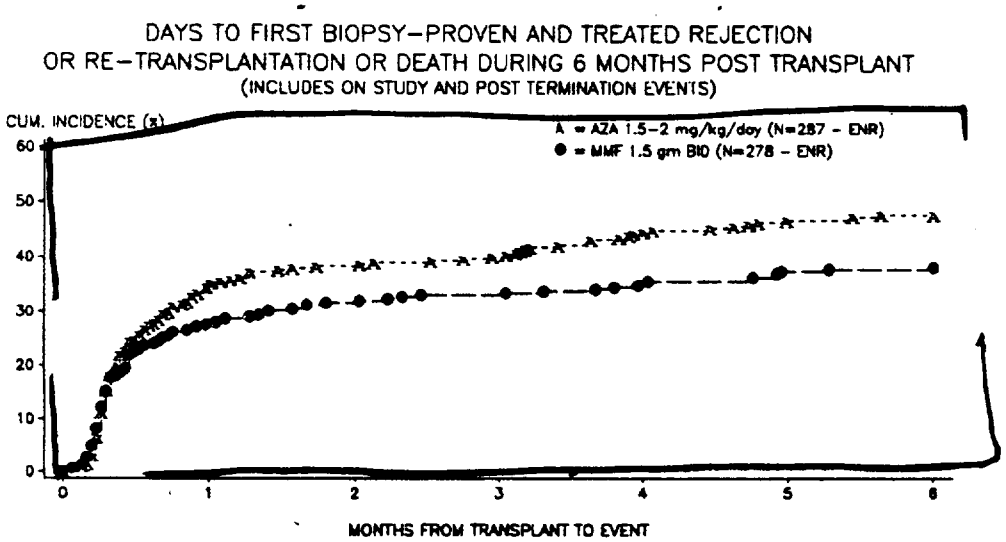
2.3.1.1. Six month endpoint

The table below summarizes the applicant's results for the six-month endpoint [adapted from the applicant's Study Report (Vol. 17, p.65)]:

Endpoint	Azathioprine	MMF	Treatment Difference (azathioprine-MMF)	p-value
No. of patients enrolled	287	278		
Number (%) of patients experiencing biopsy-proven and treated rejection or graft loss during the initial 6 months posttransplant	137 (47.7%)	106 (38.1%)	9.6%[a]	0.0196

[a]Relative risk (MMF/azathioprine) = 0.80

The following Kaplan-Meier curve is reproduced from the applicant's Study Report (vol. 17, p. 67):



LOG-RANK P-value = 0.0593

Medical Officer Comment:
The FDA analyses differed slightly in that patients that were lost to follow-up were considered failures (see below).

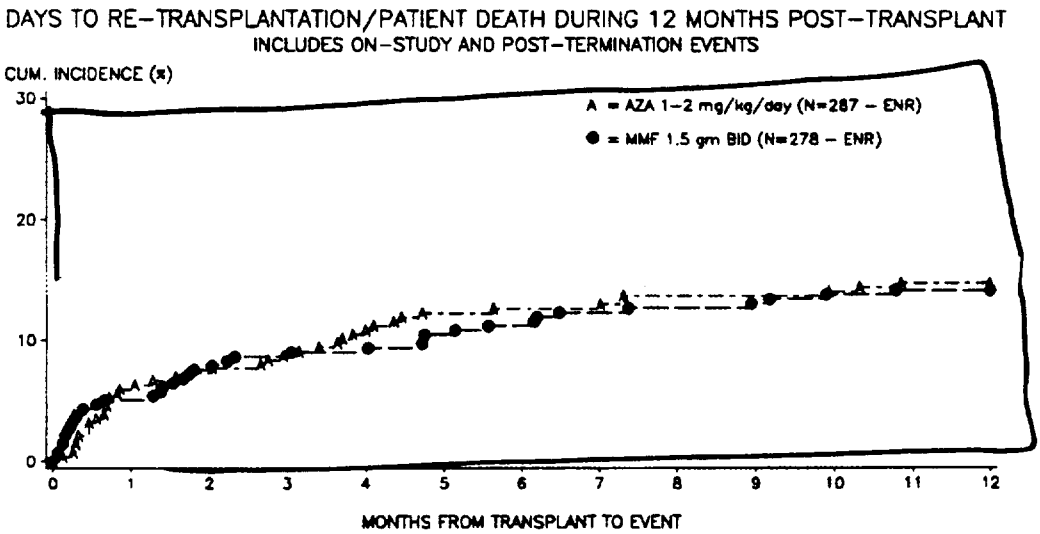
2.3.1.2. Twelve-month endpoint

The applicant's analyses identified the following results for the twelve-month endpoint:

Endpoint	Azathioprine	MMF	Treatment Difference (azathioprine-MMF)	CI
No. of patients enrolled	287	278		
Number (%) of patients experiencing graft loss (death or re-transplantation) during the initial 12 months post-transplant	42 (14.6%)	39 (14.0%)	Weighted difference[b]: 0.447%	95% CI = (-5.09%, 5.98%)

[b]Weighted point estimate of difference in proportions using stratum (investigator)

The following Kaplan-Meier curve is reproduced from the applicant's Study Report (Vol. 17, p. 76):



LOG-RANK P-value (stratified by investigator) = 0.8638

Medical Officer Comment:

The FDA analyses differed slightly in that patients that were lost to follow-up were considered failures (see below).

2.3.2. Secondary analyses

The applicant performed several secondary analyses on endpoints that were based on varying definitions of the endpoints (see **Section 2.1.1.1 Objectives**). The following two tables summarize the applicant's analyses for the secondary endpoints at the 6 months post-transplant, and 12 months post-transplant timepoints.

Six- month post-transplant summary
(Reproduced from applicant's Study Report, vol. 17, p. 69):

Endpoint	Azathioprine Treatment Group N = 287	MMF Treatment Group N = 278	Relative Risk[a]	p-Value
First biopsy proven rejection or re-transplantation or death	147 (51.2%)	117 (42.1%)	0.82	0.0286
First treated rejection or re-transplantation or death	152 (53.0%)	123 (44.2%)	0.84	0.0355
First biopsy proven and treated rejection with biochemical abnormalities or re-transplantation or death	136 (47.4%)	103 (37.1%)	0.78	0.0112
First biopsy proven rejection with biochemical abnormalities or re-transplantation or death	142 (49.5%)	112 (40.3%)	0.81	0.0248
First treated rejection with biochemical abnormalities or re-transplantation or death	151 (52.6%)	120 (43.2%)	0.82	0.0212
First treated rejection with OKT3 or ATG or re-transplantation or death	57 (19.9%)	40 (14.4%)	0.73	0.0865

[a]MMF/azathioprine

Twelve month post-transplant summary:
(Reproduced from applicant's Study Report, Vol. 17, p.71):

Endpoint	Azathioprine Treatment Group N = 287	MMF Treatment Group N = 278	Relative Risk[a]	p-Value
First biopsy proven and treated rejection or re-transplantation or death	144 (50.2%)	118 (42.4%)	0.85	0.0656
First biopsy proven rejection or re-transplantation or death	156 (54.4%)	133 (47.8%)	0.88	0.1262
First treated rejection or re-transplantation or death	160 (55.7%)	135 (48.6%)	0.87	0.0862
First biopsy proven and treated rejection with biochemical abnormalities or re-transplantation or death	143 (49.8%)	114 (41.0%)	0.82	0.0336
First biopsy proven rejection with biochemical abnormalities or re-transplantation or death	150 (52.3%)	125 (45.0%)	0.86	0.0792
First treated rejection with biochemical abnormalities or re-transplantation or death	159 (55.4%)	131 (47.1%)	0.85	0.0456
First treated rejection with OKT3 or ATG or re-transplantation or death	63 (22.0%)	49 (17.6%)	0.80	0.1943

[a]MMF rate/azathioprine rate

Medical Officer Comment:

As noted previously, these observations may be of scientific interest, but they must be interpreted with caution. These endpoints have are interdependent variables,

and the statistical significance of these findings must be interpreted in the context of multiple comparisons.

2.4. FDA analyses

The primary intent of the Division was to verify that the analyses that the applicant had performed were reproducible.

2.4.1. Primary analysis

With respect to the primary endpoints, the Division was able to verify the analyses, with the following observations:

2.4.1.1. Six-month endpoint

It is noted that the applicant's intent for the first co-primary endpoint was to demonstrate superiority to the azathioprine treatment group. There are several points that should be noted with respect to this endpoint.

Choice of comparator

Azathioprine is not approved for treatment of acute rejection in allogeneic hepatic transplant patients. Although the Division prefers that a clinical trial utilize an approved comparator when evaluating a new therapeutic agent, an applicant may propose to use a un-approved comparator under certain conditions (for example, if the clinical situation does not permit the use of a placebo).

The applicant submitted information on June 29, 2000, in the form of literature references, to support their position that azathioprine, in the dosages that were stipulated in the study protocol, is a valid comparator. Their position is that, although there are no formal controlled studies that evaluate the results of azathriporine and non-azathioprione containing regimens (with a background of cyclosporine and corticosteroids), it is a "...widely accepted immunosuppression regimen in liver transplant patients." Further, they indicate that azathioprine's benefits "...been inferred from empirical clinical experience."

The Division agrees with the applicant in principle, and acknowledges that azathioprine is part of the combination therapy used for this indication. However, the Division also emphasizes that the applicant's clinical trial must be able to show that the MMF is not merely equivalent.

Dose of Azathioprine

In the June 29, 2000 submission, the applicant indicated that the study protocol stipulated that azathioprine be dosed in the range of 1-2 mg/kg/day to "...reflect current clinical practice and to accommodate variability among the investigation sites."

However, Table 22 of the study report (Vol. 17, p. 81), which is reproduced below, indicated that the actual dose of azathioprine utilized in the study was in the lower limits of that range:

Drug	Median Initial Oral Dose	First 6 Months in Study		First 12 Months in Study	
		Median Average Daily Oral Dose	% Change from Initial Dose	Median Average Daily Oral Dose	% Change from Initial Dose
Azathioprine ($mg \bullet kg^{-1} \bullet day^{-1}$)	1.5	1.29	14%	1.26	16%
MMF (g/day)	3.0	2.50	17%	2.40	20%

This raises the question whether the results observed at the 6-month endpoint could be due to sub-optimal use of azathioprine.

Number of Studies
It is understandable that a study of this magnitude in this patient population is an undertaking, but there is some difficulty in trying to determine the true magnitude of MMF's efficacy for this endpoint with only one clinical study.

Reclassification of patients
There were two patients on the MMF treatment group that were lost to follow-up and were reclassified for the purposes of FDA analyses. These changes resulted in a p-value of 0.025; the conclusions regarding the 6-month endpoint were unchanged.

Robustness of the study's results
Although the secondary analyses were all supportive of the primary hypothesis, the magnitude of the results were not overwhelming. This may be a reflection of the number of patients that were lost due to withdrawals, reducing the overall power of the study.

In view of the above caveats with respect to this study, it is not clear that it is possible to say that MMF is *superior* to azathioprine in the treatment of acute rejection of allogeneic hepatic transplant patients. However, the data presented does allow one to determine that MMF is better than placebo for this indication.

Therefore, this reviewer's conclusion is that in combination with corticosteroids and cyclosporine, CellCept® obtained a lower rate of acute rejection at 6 months.

2.4.1.2. Twelve-month endpoint

The overall patient and graft survival at 12 months was excellent and the 95% confidence interval was sufficiently narrow to exclude an unacceptable decrease in patient and graft survival.

In addition, it is important to note that the benefits observed at the 6-month timepoint did not translate into detectable benefits at the 12-month timepoint. It is uncertain whether this is merely a reflection of the dropout rate that was observed.

2.4.2. Additional analyses

2.4.2.1. Secondary endpoints

Review of the applicant's multiple secondary endpoints showed that the results were supportive, and that a slight deviation from the primary definition of rejection would not have changed the conclusions of the study.

2.4.2.2. Baseline health characteristics

Analyses of the following baseline health characteristics: cold ischemic time, Hepatitis C status, Hepatitis B status, CMV status, and HLA mismatches showed no interaction with treatment. However, it must be noted that the study was not powered to detect significant differences in these subgroups.

2.4.2.3. Clinical benefits

An attempt was made to evaluate whether the observed improvement in the 6 month endpoint, which presumably reduced the need for additional immunosuppression to treat acute rejection, also translated into meaningful clinical benefit as would be documented by decreased hypertension, incidence of diabetes, or infections. No such benefit could be detected.

The level of immunosuppression provided by the MMF regimen, which resulted in a lower rate of acute rejection, was not associated with an increased rate of opportunistic infections.

2.4.2.4. Concomitant treatment with tacrolimus

Protocol Amendment IV (19 October 1998) allowed for the use of tacrolimus as part of the immunosuppressive regimen, in addition to the protocol-specified treatment of rejection schema. An attempt was made to determine whether patients that had tacrolimus as part of their immunosuppressive regimen experience any difference in their clinical outcome. There were 18 in the azathioprine treatment group, and 13 in the MMF treatment group, too few to be able to reach any conclusion.

3. Safety Evaluation

Since CellCept® undergoes first-pass metabolism in the liver and the metabolite is subsequently excreted in the bile, it is important to study the safety profile liver transplant patients who have the potential for transient hepatic dysfunction. Study MYCS2646, the prevention of acute rejection in liver transplant recipients, provided the randomized-comparative, database for the safety profile in this population. The previously approved indications for CellCept® include prevention of acute rejection in kidney and heart transplant recipients. These studies have established the safety profile for CellCept®.

The following executive summary of safety results was reported in the NDA for Study MYCS2646 by Roche. Subsequent discussion of additional safety data then follows in the FDA review of safety.

ROCHE SUMMARY OF SAFETY RESULTS:

"AEs (Adverse Events) led to study drug dose modification in both treatment groups. Over 12 months posttransplant, the median average daily study drug doses declined by approximately the same percentage: 16% reduction for AZA (azathioprine) and 20% reduction for MMF (CellCept®).

The most frequently reported MSAE (Medically Serious Adverse Events) was premature termination due to an AE, intercurrent illness or lab abnormality (33.1% AZA, 33.9% MMF). Leukopenia was the most frequently reported AE leading to premature withdrawal (7.3% AZA, 10.1% MMF). Other frequently reported MSAEs included severe hepatitis (20.2% AZA, 15.9% MMF) and death (13.9% AZA, 12.6% MMF). The leading cause of death was infection/sepsis (7.3% AZA, 5.4% MMF).

Malignancies were diagnosed in 12 (4.2%) AZA patients and 9 (3.2%) MMF patients. Malignancies in the AZA group included squamous cell and basal cell carcinomas, peritoneal, cervical, colon, thyroid, bile duct and renal cell carcinomas, Kaposi's sarcoma, and melanoma. Cancer was the cause of death for 2 of these 12 AZA patients. Malignancies in the MMF group included squamous cell and basal cell carcinomas, cholangiocarcinoma, prostatic carcinoma, and lymphoma/lymphoproliferative disease. Cancer was the cause of death for 1 of the 9 MMF patients.

The incidence of any OI was similar between the treatment groups (43.2% AZA, 45.5% MMF). The most common OIs were: Candida, manifested as mucocutaneous disease (17.4% AZA, 18.4% MMF), CMV viremia/syndrome (12.2% AZA, 14.1% MMF), Herpes simplex (5.9% AZA, 10.1% MMF) and CMV tissue invasion (8.0% AZA, 5.8% MMF)."

3.1 Extent of drug exposure

The duration of intravenous dosing is summarized in the following table; the majority of patients completed intravenous dosing by 14 days (97.6% of the azathioprine patients,

98.6% of the MMF patients). The median azathioprine intravenous dose during the first 14 days was 1.43 mg·kg $^{-1}$ ·day $^{-1}$; the median MMF intravenous dose was 1.83 g/day.

Median Average Daily Doses of Oral MMF and Azathioprine Over Time

Drug	Median Initial Oral Dose	First 6 Months in Study		First 12 Months in Study	
		Median Average Daily Oral Dose	% Change from Initial Dose	Median Average Daily Oral Dose	% Change from Initial Dose
Azathioprine (mg•kg^{-1}•day^{-1})	1.5	1.29	14%	1.26	16%
MMF (g/day)	3.0	2.50	17%	2.40	20%

(Reference: Table 22, vol 17, p 81)

By the end of the first two weeks, approximately 14% of all patients (15% azathioprine, 13% MMF) discontinued study drug.

The median initial dose of oral azathioprine was 1.5 mg·kg $^{-1}$·day^{-1} and the initial median oral dose of MMF was 3 g/day. Patients were allowed to reduce their dose of study drug due to adverse events; 56.8% of azathioprine patients and 65.7% of MMF patients reduced or interrupted study medication due to an AE. Over 12 months posttransplant, the median average daily azathioprine and MMF doses declined by approximately the same proportion (16% reduction for azathioprine and 20% reduction for MMF).

The median average daily dose during the first 12 months of treatment was 1.26 mg·kg $^{-1}$ day $^{-1}$ for azathioprine and 2.40 g/day for MMF. The duration of treatment was similar between the two treatment groups; 48% of azathioprine patients and 47% of MMF patients received 12 months or more of study drug (as of the data cutoff date).

Duration of Randomized Treatment

	AZA 1.5-2 mg/kg/day	MMF 1.5 gm BID	TOTAL
# OF PATIENTS ENROLLED	287	278	565
DURATION OF TREATMENT			
0 DAYS	0	1(0%)	1(0%)
1 WEEK OR LESS	20(7%)	26(9%)	46(8%)
>1 WEEK - 2 WEEKS	22(8%)	11(4%)	33(6%)
>2 WEEKS - 1 MONTH	14(5%)	21(8%)	35(6%)
>1 - 3 MONTHS	29(10%)	34(12%)	63(11%)
>3 - 6 MONTHS	27(9%)	18(6%)	45(8%)
>6 - 9 MONTHS	20(7%)	8(3%)	28(5%)
>9 MONTHS - 1 YEAR	17(6%)	28(10%)	45(8%)
>1 - 1.5 YEARS	104(36%)	95(34%)	199(35%)
>1.5 - 2 YEARS	31(11%)	33(12%)	64(11%)
>2 - 2.5 YEARS	3(1%)	3(1%)	6(1%)
>2.5 - 3 YEARS	0	0	0
>3 YEARS	0	0	0

Indication: Prophylaxis of acute rejection in allogeneic hepatic transplant patients
Study MYCS-2646: Safety

Corticosteroids were the most common (96.4% azathioprine, 99.0% MMF) immunosuppressive medication used by patients after terminating from the study. Other immunosuppressive medications included cyclosporine (77.3% azathioprine, 82.8% MMF), tacrolimus (36.4% azathioprine, 21.2% MMF), mycophenolate mofetil (18.2% azathioprine, 17.2% MMF) and azathioprine (12.7% azathioprine, 18.2% MMF). Except for tacrolimus, the incidence of use of a particular medication was similar in the two treatment groups. Tacrolimus was more frequently used in patients who had terminated from the azathioprine treatment group (36.4%, 6 month data; 37.8%, 12 month data) compared to patients from the MMF treatment group (21.2%, 6 month data; 28.0%, 12 month data). When a patient withdrew from the study, the double-blind was maintained for that patient to ensure against introducing bias in the selection of immunosuppressive medications.

Medical Officer Comment:

It is of interest to compare the numbers of patients who continue to receive study medications beyond one year among the various transplant organ studies. It should be noted that the transplant type might influence the immunosuppressive management strategy. Also, the recommended doses varied among the transplant type to be treated: kidney = 2 g/day; heart = 3 g/day; liver 3 g/day.

Percentage of patients remaining on study drug for more than 1 year

Dosage Groups	*Renal Studies*	*Cardiac Studies*	*Hepatic Studies*
Azathioprine	*50.9%*	*59.9%*	*48.0%*
CellCept® 2g/day	*57.5%*	——	——
CellCept® 3g/day	*52.2%*	*69.6%*	*47.0%*

The rates quoted above are similar; however, numerically the lowest rate of patients continuing on study medication occurred among the liver transplant patients. The reasons for discontinuation will be discussed subsequently. It should be noted that a large number of these patients elected to discontinue study medication due to the number of pills that they were required to take.

Medical Officer Comment:

Of the 54 patients exposed to tacrolimus during the study, 29 were assigned to the AZA arm and 25 were randomized to MMF. All of them had at least one adverse event. However, this is not a large enough group in which to assess the safety of this combination.

3.2. Adverse events

The type and frequency of adverse events reported during the study were generally similar between the two treatment groups for all body systems. Specific AEs reported by more than 50% of the patients in at least one of the treatment groups were pain (77.7% azathioprine, 74.0% MMF), abdominal pain (51.2% azathioprine, 62.5% MMF),

hypertension (59.6% azathioprine, 62.1% MMF), nausea (51.2% azathioprine, 54.5% MMF), headache (49.1% azathioprine, 53.8% MMF), fever (56.1% azathioprine, 52.3% MMF), insomnia (47.0% azathioprine, 52.3% MMF), diarrhea (49.8% azathioprine, 51.3% MMF) and anemia (53.0% azathioprine, 43.0% MMF). The AEs with a greater than 10% difference between the azathioprine and MMF treatment groups are abdominal pain (51.2% azathioprine, 62.5% MMF) and anemia (53.0% azathioprine, 43.0% MMF).

Summary of Patients with Adverse Events-Subset of Events With Occurrence Rate > 10%

	TREATMENT GROUP	
	AZA	MMF
	1-2 mg/kg/day	1.5 gm BID
TOTAL PATIENTS IN SUMMARY	287	277
	NO. (%) OF PATIENTS WITH ONE OR MORE ADVERSE EVENTS	
ANY BODY SYSTEM	286 (99.7%)	277(100.0%)
BODY SYSTEM		
BODY AS A WHOLE	284 (99.0%)	270 (97.5%)
DIGESTIVE SYSTEM	272 (94.8%)	266 (96.0%)
METABOLIC AND NUTRITIONAL DISORDERS	272 (94.8%)	264 (95.3%)
NERVOUS SYSTEM	251 (87.5%)	239 (86.3%)
CARDIOVASCULAR SYSTEM	239 (83.3%)	236 (85.2%)
RESPIRATORY SYSTEM	244 (85.0%)	233 (84.1%)
HEMIC AND LYMPHATIC SYSTEM	240 (83.6%)	221 (79.8%)
UROGENITAL SYSTEM	226 (78.7%)	187 (67.5%)
SKIN AND APPENDAGES	150 (52.3%)	164 (59.2%)
MUSCULOSKELETAL SYSTEM	112 (39.0%)	100 (36.1%)
SPECIAL SENSES	76 (26.5%)	85 (30.7%)
ENDOCRINE SYSTEM	29 (10.1%)	30 (10.8%)
BODY SYSTEM PREFERRED TERM		
BODY AS A WHOLE	284 (99.0%)	270 (97.5%)
PAIN	223 (77.7%)	205 (74.0%)
ABDOMINAL PAIN	147 (51.2%)	173 (62.5%)
HEADACHE	141 (49.1%)	149 (53.8%)
FEVER	161 (56.1%)	145 (52.3%)
BACK PAIN	136 (47.4%)	129 (46.6%)
REACTION UNEVALUABLE	109 (38.0%)	123 (44.4%)
ASTHENIA	97 (33.8%)	98 (35.4%)
SEPSIS	76 (26.5%)	76 (27.4%)
INFECTION	72 (25.1%)	75 (27.1%)
ASCITES	65 (22.6%)	67 (24.2%)
ABDOMEN ENLARGED	51 (17.8%)	52 (18.8%)
CHEST PAIN	38 (13.2%)	44 (15.9%)
HERNIA	25 (8.7%)	32 (11.6%)
ACCIDENTAL INJURY	43 (15.0%)	31 (11.2%)
DRUG LEVEL INCREASED	36 (12.5%)	31 (11.2%)
CHILLS	29 (10.1%)	30 (10.8%)
PERITONITIS	36 (12.5%)	28 (10.1%)
HEMORRHAGE	30 (10.5%)	27 (9.7%)
DIGESTIVE SYSTEM	272 (94.8%)	266 (96.0%)
NAUSEA	147 (51.2%)	151 (54.5%)
DIARRHEA	143 (49.8%)	142 (51.3%)
CONSTIPATION	110 (38.3%)	105 (37.9%)
VOMITING	96 (33.4%)	91 (32.9%)
ANOREXIA	49 (17.1%)	70 (25.3%)
LIVER FUNCTION TESTS ABNORMAL	55 (19.2%)	69 (24.9%)
DYSPEPSIA	60 (20.9%)	62 (22.4%)
CHOLANGITIS	39 (13.6%)	39 (14.1%)

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HEPATITIS	46 (16.0%)	36 (13.0%)
FLATULENCE	28 (9.8%)	35 (12.6%)
CHOLESTATIC JAUNDICE	31 (10.8%)	33 (11.9%)
ORAL MONILIASIS	29 (10.1%)	28 (10.1%)
INFECTION	30 (10.5%)	22 (7.9%)
JAUNDICE	39 (13.6%)	20 (7.2%)
METABOLIC AND NUTRITIONAL DISORDERS	272 (94.8%)	264 (95.3%)
PERIPHERAL EDEMA	137 (47.7%)	134 (48.4%)
HYPERGLYCEMIA	140 (48.8%)	121 (43.7%)
HYPOMAGNESEMIA	108 (37.6%)	108 (39.0%)
HYPOKALEMIA	118 (41.1%)	103 (37.2%)
HYPOCALCEMIA	86 (30.0%)	83 (30.0%)
EDEMA	81 (28.2%)	78 (28.2%)
HYPERKALEMIA	68 (23.7%)	61 (22.0%)
CREATININE INCREASED	62 (21.6%)	55 (19.9%)
GENERALIZED EDEMA	46 (16.0%)	41 (14.8%)
BILIRUBINEMIA	54 (18.8%)	40 (14.4%)
HYPOPHOSPHATEMIA	26 (9.1%)	40 (14.4%)
HYPOPROTEINEMIA	40 (13.9%)	37 (13.4%)
HEALING ABNORMAL	25 (8.7%)	29 (10.5%)
HYPOGLYCEMIA	26 (9.1%)	29 (10.5%)
BUN INCREASED	37 (12.9%)	28 (10.1%)
HYPONATREMIA	43 (15.0%)	26 (9.4%)
HYPERVOLEMIA	31 (10.8%)	25 (9.0%)
NERVOUS SYSTEM	251 (87.5%)	239 (86.3%)
INSOMNIA	135 (47.0%)	145 (52.3%)
TREMOR	102 (35.5%)	94 (33.9%)
ANXIETY	51 (17.8%)	54 (19.5%)
CONFUSION	54 (18.8%)	48 (17.3%)
DEPRESSION	48 (16.7%)	48 (17.3%)
DIZZINESS	41 (14.3%)	45 (16.2%)
PARESTHESIA	44 (15.3%)	42 (15.2%)
NERVOUSNESS	30 (10.5%)	28 (10.1%)
AGITATION	30 (10.5%)	27 (9.7%)
SOMNOLENCE	30 (10.5%)	22 (7.9%)
HYPESTHESIA	36 (12.5%)	21 (7.6%)
CARDIOVASCULAR SYSTEM	239 (83.3%)	236 (85.2%)
HYPERTENSION	171 (59.6%)	172 (62.1%)
TACHYCARDIA	45 (15.7%)	61 (22.0%)
HYPOTENSION	60 (20.9%)	51 (18.4%)
RESPIRATORY SYSTEM	244 (85.0%)	233 (84.1%)
PLEURAL EFFUSION	103 (35.9%)	95 (34.3%)
DYSPNEA	87 (30.3%)	86 (31.0%)
LUNG DISORDER	54 (18.8%)	61 (22.0%)
COUGH INCREASED	36 (12.5%)	44 (15.9%)
INFECTION	57 (19.9%)	44 (15.9%)
PHARYNGITIS	36 (12.5%)	39 (14.1%)
PNEUMONIA	33 (11.5%)	38 (13.7%)
ATELECTASIS	37 (12.9%)	36 (13.0%)
SINUSITIS	28 (9.8%)	31 (11.2%)
LUNG EDEMA	32 (11.1%)	25 (9.0%)
HEMIC AND LYMPHATIC SYSTEM	240 (83.6%)	221 (79.8%)
LEUKOPENIA	112 (39.0%)	127 (45.8%)
ANEMIA	152 (53.0%)	119 (43.0%)
THROMBOCYTOPENIA	121 (42.2%)	106 (38.3%)
LEUKOCYTOSIS	61 (21.3%)	62 (22.4%)
HYPOCHROMIC ANEMIA	31 (10.8%)	38 (13.7%)
ECCHYMOSIS	34 (11.8%)	24 (8.7%)
UROGENITAL SYSTEM	226 (78.7%)	187 (67.5%)
KIDNEY FUNCTION ABNORMAL	83 (28.9%)	71 (25.6%)
URINARY TRACT INFECTION	51 (17.8%)	50 (18.1%)
OLIGURIA	59 (20.6%)	47 (17.0%)

SKIN AND APPENDAGES	150 (52.3%)	164 (59.2%)
RASH	53 (18.5%)	49 (17.7%)
PRURITUS	30 (10.5%)	39 (14.1%)
SWEATING	29 (10.1%)	30 (10.8%)
MUSCULOSKELETAL SYSTEM	112 (39.0%)	100 (36.1%)
OSTEOPOROSIS	33 (11.5%)	23 (8.3%)
SPECIAL SENSES	76 (26.5%)	85 (30.7%)
ENDOCRINE SYSTEM	29 (10.1%)	30 (10.8%)

SOURCE: IRDM RALK -AESUM_10PCT- (20MAY99,14:07) SAS V6.12 AESUM_10PCT.TAB

(Reference: vol 17, p 97-99, Table 29)

Medical Officer Comment:

Electronic submission and selected case report forms were reviewed by the FDA. The adverse events listed above are similar in profile to the previous events listed for renal and cardiac patients. The rates of the events are similar between the two treatment groups. It is notable that numerically more patients on MMF were reported to have leukopenia, and that more patients treated with azathioprine were reported to have thrombocytopenia. This pattern was reported in previous studies of renal and cardiac transplant patients.

Pulmonary fibrosis and interstitial fibrosis were searched for in the study database and were not found. Further discussion of this issue follows in section 6.9.1.

Adverse events related to infections were common in both treatment groups (82.9% azathioprine, 83.8% MMF); sepsis was the most frequently reported infection-related AE (26.5% azathioprine, 27.4% MMF). The incidence of hepatitis C reported as an AE was 9.1% for the azathioprine treatment group and 8.3% for the MMF group. Patients who had a positive hepatitis C serologic status prior to transplant showed greater incidence of hepatitis C posttransplant (24/83, 28.9% azathioprine; 21/82, 25.6% MMF) when compared to patients who had a pre-transplant negative hepatitis C serologic status (1/196, 0.5% azathioprine; 2/189, 1.1% MMF).

Medical Officer Comment:

The types and rates of infections reported as adverse events were similar between the two treatment arms. The profiles of infections were similar to those seen in the renal and cardiac transplant studies.

3.2.1. Adverse events: discontinuations due to AEs

Overall, AEs during the first 14 days posttransplant were balanced between the two dosing groups. AEs in the first 14 days were evaluated by summarizing: (1) all AEs in this time period regardless of whether the patient was taking intravenous or oral medication; and (2) AEs during the intravenous dosing period, only. The most frequently reported AEs during the intravenous dosing period were pain (40.4% azathioprine, 46.6% MMF), hyperglycemia (33.4% azathioprine, 33.9% MMF), thrombocytopenia (26.8% azathioprine, 27.1% MMF) hypokalemia (26.8% azathioprine, 23.5% MMF),

hypertension (24.7% azathioprine, 27.4% MMF) and pleural effusion (22.6% azathioprine, 25.3% MMF).

Reduction or interruption of study drug due to AE was reported in patients from both treatment groups (56.8% azathioprine, 65.7% MMF). Leukopenia was the primary reason for study drug reduction or interruption (30.7% azathioprine, 35.7% MMF); although a slightly higher percentage of patients in the MMF group reduced or interrupted study drug due to leukopenia, the total number of patients reducing or interrupting study drug due to AEs in the hemic and lymphatic system was balanced between the two treatment groups (39.0% azathioprine, 41.9% MMF). Patients in the azathioprine treatment group showed slightly higher incidences of study drug adjustment due to thrombocytopenia (9.1% azathioprine, 5.8% MMF) and anemia (6.6% azathioprine, 3.6% MMF).

Medical Officer Comment:
Electronic submission and selected case report forms were reviewed by the FDA. The results of the review were as expected given the previous experience with renal and cardiac transplant patients.

3.2.2. Adverse events: treatment related

The number and type of adverse events considered probably or possibly related to study medication by the investigator were similar between the two treatment groups. Approximately 89% of all patients (89.2% of the patients in the azathioprine group and 88.8% of MMF patients) had an adverse event considered related to study medication. The most frequently reported AEs involved the digestive system (54.0% azathioprine, 56.3% MMF), the hemic and lymphatic system (53.7% azathioprine, 54.9% MMF) and the body as a whole (49.8% azathioprine, 49.8% MMF). The most frequent adverse events were leukopenia (35.2% azathioprine, 42.2% MMF), diarrhea (25.4% azathioprine, 28.2% MMF), nausea (19.9% azathioprine, 26.7% MMF), sepsis (20.2% azathioprine, 18.8% MMF) and anemia (19.9% azathioprine, 12.6% MMF).

Medical Officer Comment:
Electronic submission and selected case report forms were reviewed by the FDA. The results of the review were as expected given the previous experience with renal and cardiac transplant patients.

3.2.3. Serious adverse events

The most frequently reported MSAE was premature termination due to an adverse event, intercurrent illness or lab abnormality (azathioprine 95/287, 33.1%; MMF 94/277, 33.9%). This was followed by severe hepatitis (azathioprine 58/287, 20.2%; MMF 44/277, 15.9%) and death (azathioprine 40/287, 13.9%; MMF 35/277, 12.6%).

Summary of Patients with Medically Serious Adverse Events

	AZA 1-2 mg/kg/day	MMF 1.5 gm BID
TOTAL PATIENTS RECEIVING TREATMENT	287	277
MEDICALLY SERIOUS ADVERSE EVENT TYPES		
PREMATURE TERMINATION DUE TO ADVERSE EVENT INTERCURRENT ILLNESS OR LAB ABNORMALITY	95 (33.1%)	94 (33.9%)
DEATH (ON STUDY OR POST TERMINATION)	40 (13.9%)	35 (12.6%)
MALIGNANCY (ON STUDY OR POST TERMINATION) [1]	7 (2.4%)	3 (1.1%)
SEVERE NEUTROPENIA (ON STUDY)	2 (0.7%)	10 (3.6%)
SEVERE THROMBOCYTOPENIA (ON STUDY)	36 (12.5%)	19 (6.9%)
SEVERE HEPATITIS (ON STUDY)	58 (20.2%)	44 (15.9%)
GI PERFORATION (ON STUDY)	3 (1.0%)	4 (1.4%)
GI BLEEDING (ON STUDY) [2]	12 (4.2%)	15 (5.4%)

NOTE1: MMF = MYCOPHENOLATE MOFETIL, AZA = AZATHIOPRINE.
[1]EXCLUDES SQUAMOUS CELL SKIN CARCINOMA AND BASAL CELL SKIN CARCINOMA.
[2]GASTROINTESTINAL BLEEDING REQUIRING HOSPITALIZATION.
SOURCE: RALK TINDEX_MSAE (04JUN99 17:34) TINDEX_MSAE.TAB

(Reference: Vol 17, p 83, table 24)

Medical Officer Comment:

FDA review of patient summaries and electronic submission data is in agreement with the above table. The percentage of cases with hepatitis was higher in liver transplant compared to cardiac or renal. The majority of these cases were do to viral infections, notably hepatitis C and to a lesser extent CMV. It is of interest to note the different hematologic toxicity profile: AZA is twice as likely to produce severe thrombocytopenia and MMF is more likely to cause neutropenia.

3.2.4. Death

There were a total of 75 deaths at anytime posttransplant which included on-study and post-termination deaths (40, 13.9%, from the azathioprine group and 35, 12.6%, from the MMF group); infection/sepsis was the leading cause of death (7.3% azathioprine, 5.4% MMF). The category of "other" was the second most frequent cause of death (3.1% azathioprine, 4.3% MMF) and included multiple organ failure, graft failure, liver failure secondary to recurrent hepatitis C, renal failure, respiratory failure, graft versus host disease, cerebral edema, aplastic anemia, and probable pneumonia.

During 12 months posttransplant, there were a total of 66 on-study and post-termination deaths (37, 12.9%, from the azathioprine group, 29, 10.5%, from the MMF group). As above, the primary cause of death was attributed to infection/sepsis (7.3% azathioprine, 5.0% MMF). There were a total of 31 on-study deaths (18, 6.3%, azathioprine, 13, 4.7%, MMF) which occurred during 12 months posttransplant and within 15 days of study termination). Of these 31 on-study deaths, 24 deaths led to premature withdrawal from the study (Section 3.1.4); seven patients who terminated from the study for other reasons

and died within 15 days of study termination were considered on-study deaths. From the azathioprine treatment group there were 18 (6.3%) on-study deaths which included seven deaths due to infection/sepsis, six attributed to "other" (allograft failure, aplastic anemia, hemochromatosis, hemorrhage from ruptured splenic artery aneurysm, multisystem organ failure secondary to liver graft dysfunction, and primary poor function), two cardiovascular events, one cancer (peritoneal and recurrent bile duct carcinomas), one pulmonary embolism, and one allograft rejection. There were 13 (4.7%) on-study deaths in the MMF treatment group: five cardiovascular events, five infection/sepsis, and three "other" (brain death, cerebral edema, graft failure).

Medical Officer Comment:
Review of CRF and case summaries is in agreement with the above. The rates and causes of death are similar between the two treatment arms. It does not appear that MMF directly caused death in these complicated patients. Analysis of the time between discontinuation of drug and death suggested that death occurred more remotely from the time of discontinuation of drug for MMF.

3.2.5. Malignancies

One or more malignancies were diagnosed in 12 (4.2%) patients from the azathioprine treatment group and 9 (3.2%) patients from the MMF group. In the azathioprine group, 6 patients had one or more nonmelanoma skin malignancies which included squamous cell and basal cell carcinomas; 7 patients had one or more "other" malignancies which included peritoneal, cervical, colon, thyroid, bile duct and renal cell carcinomas, Kaposi's sarcoma, and melanoma. One patient, 55002, had multiple malignancies that were included in both malignancy categories noted above; hence, there were 12 unique patients with malignancies in the azathioprine group. Cancer was the cause of death for 2 (55002 and 57421) of these 12 patients. In the MMF group, 6 patients had one or more nonmelanoma skin malignancies which included squamous cell and basal cell carcinomas; 1 patient had lymphoma/lymphoproliferative disease and 2 patients had "other" malignancies (cholangiocarcinoma and prostatic carcinoma). Cancer was the cause of death for 1 (55010) of the 9 patients diagnosed with malignancies in the MMF group.

Summary of Patients With Malignancies (On Study and Post-Termination)

	TREATMENT GROUP[1]	
	AZA	MMF
	1-2 mg/kg/day	1.5 gm BID
TOTAL PATIENTS IN SUMMARY	287	277
	NO. (%) OF PATIENTS WITH ONE OR MORE MALIGNANCIES	
ANY MALIGNANCY TYPE	12 (4.2%)	9 (3.2%)
MALIGNANCY TYPE		
NONMELANOMA SKIN MALIGNANCY	6 (2.1%)	6 (2.2%)
OTHER MALIGNANCY	7 (2.4%)	2 (0.7%)
LYMPHOMA/LPD	0	1 (0.4%)

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MALIGNANCY TYPE PREFERRED TERM		
NONMELANOMA SKIN MALIGNANCY	6 (2.1%)	6 (2.2%)
SKIN CARCINOMA	6 (2.1%)	4 (1.4%)
CARCINOMA	1 (0.3%)	3 (1.1%)
CARCINOMA OF MOUTH	0	1 (0.4%)
NEOPLASM	0	1 (0.4%)
OTHER MALIGNANCY	7 (2.4%)	2 (0.7%)
GASTROINTESTINAL CARCINOMA	2 (0.7%)	1 (0.4%)
CARCINOMA	2 (0.7%)	0
CERVIX CARCINOMA IN SITU	1 (0.3%)	0
NEOPLASM	1 (0.3%)	0
PROSTATIC CARCINOMA	0	1 (0.4%)
SARCOMA	1 (0.3%)	0
SKIN CARCINOMA	1 (0.3%)	0
SKIN MELANOMA	1 (0.3%)	0
THYROID CARCINOMA	1 (0.3%)	0
LYMPHOMA/LPD	0	1 (0.4%)
LYMPHOMA LIKE REACTION	0	1 (0.4%)

NOTE: LPD = LYMPHOPROLIFERATIVE DISEASE.
* MALIGNANCY TYPE BY PREFERRED TERM.
SOURCE: IRDM RALK -TMALIG_PREF- (04JUN99,10:32) SAS V6.12
TMALIG_PREF.TAB

(reference: vol. 17, p. 86, table 26)

Medical Officer Comment:

The FDA reviewed electronic submissions and case summaries. The results of the review were as expected given the previous experience with renal and cardiac transplant patients. The overall rate of malignancy was very low in each group (3.2% for MMF, 4.2% for AZA). The rate of post-transplant lympho-proliferative disease will be followed in patients remaining in the study through 3 years.

3.2.6. Severe and life-threatening adverse events

One or more severe adverse events were reported with similar frequency in both treatment groups (77.0% azathioprine, 77.3% MMF). Thrombocytopenia was the most frequently reported event (18.5% azathioprine, 12.3% MMF).

During intravenous treatment, one or more severe AEs were reported by 40.1% of the azathioprine patients and 42.6% of the MMF patients. Thrombocytopenia (12.2% azathioprine, 9.4% MMF) was the most frequently reported event.

Infection-related severe AEs were reported by 26.8% of patients in the azathioprine treatment group and 28.2% of the MMF patients. Sepsis was the most frequently reported event (12.9% azathioprine, 7.9% MMF).

Summary of Patients With Severe Adverse Events – Adverse Events With Incidence Rate ≥ 3% for at Least One of the Treatment Groups

	TREATMENT GROUP	
	AZA	MMF
	1-2 mg/kg/day	1.5 gm BID
TOTAL PATIENTS IN SUMMARY	287	277
	NO. (%) OF PATIENTS WITH ONE OR MORE ADVERSE	
ANY BODY SYSTEM	221 (77.0%)	214 (77.3%)
BODY SYSTEM		
BODY AS A WHOLE	147 (51.2%)	135 (48.7%)
DIGESTIVE SYSTEM	92 (32.1%)	93 (33.6%)
HEMIC AND LYMPHATIC SYSTEM	94 (32.8%)	78 (28.2%)
CARDIOVASCULAR SYSTEM	63 (22.0%)	67 (24.2%)
METABOLIC AND NUTRITIONAL DISORDERS	72 (25.1%)	65 (23.5%)
RESPIRATORY SYSTEM	59 (20.6%)	56 (20.2%)
NERVOUS SYSTEM	54 (18.8%)	39 (14.1%)
UROGENITAL SYSTEM	48 (16.7%)	38 (13.7%)
MUSCULOSKELETAL SYSTEM	9 (3.1%)	7 (2.5%)
SKIN AND APPENDAGES	15 (5.2%)	7 (2.5%)
BODY SYSTEM **PREFERRED TERM**		
BODY AS A WHOLE	147 (51.2%)	135 (48.7%)
REACTION UNEVALUABLE	34 (11.8%)	42 (15.2%)
ABDOMINAL PAIN	23 (8.0%)	29 (10.5%)
PAIN	22 (7.7%)	28 (10.1%)
FEVER	22 (7.7%)	26 (9.4%)
SEPSIS	37 (12.9%)	22 (7.9%)
BACK PAIN	11 (3.8%)	18 (6.5%)
ASCITES	11 (3.8%)	17 (6.1%)
HEADACHE	13 (4.5%)	14 (5.1%)
INFECTION	18 (6.3%)	11 (4.0%)
PERITONITIS	17 (5.9%)	10 (3.6%)
HEMORRHAGE	18 (6.3%)	8 (2.9%)
DIGESTIVE SYSTEM	92 (32.1%)	93 (33.6%)
LIVER FUNCTION TESTS ABNORMAL	15 (5.2%)	17 (6.1%)
NAUSEA	14 (4.9%)	15 (5.4%)
CHOLANGITIS	15 (5.2%)	13 (4.7%)
GASTROINTESTINAL HEMORRHAGE	6 (2.1%)	13 (4.7%)
CHOLESTATIC JAUNDICE	7 (2.4%)	11 (4.0%)
DIARRHEA	15 (5.2%)	10 (3.6%)
VOMITING	11 (3.8%)	10 (3.6%)
HEPATITIS	9 (3.1%)	8 (2.9%)
HEMIC AND LYMPHATIC SYSTEM	94 (32.8%)	78 (28.2%)
THROMBOCYTOPENIA	53 (18.5%)	34 (12.3%)
LEUKOPENIA	24 (8.4%)	32 (11.6%)
ANEMIA	32 (11.1%)	22 (7.9%)
CARDIOVASCULAR SYSTEM	63 (22.0%)	67 (24.2%)
HYPERTENSION	21 (7.3%)	21 (7.6%)
HYPOTENSION	20 (7.0%)	11 (4.0%)
ARTERIAL THROMBOSIS	8 (2.8%)	10 (3.6%)

METABOLIC AND NUTRITIONAL DISORDERS	72 (25.1%)	65 (23.5%)
BILIRUBINEMIA	15 (5.2%)	11 (4.0%)
EDEMA	14 (4.9%)	10 (3.6%)
HYPERKALEMIA	5 (1.7%)	9 (3.2%)
HYPOMAGNESEMIA	12 (4.2%)	8 (2.9%)
HYPERGLYCEMIA	15 (5.2%)	7 (2.5%)
HYPOCALCEMIA	13 (4.5%)	7 (2.5%)
HYPOKALEMIA	9 (3.1%)	5 (1.8%)
SGOT INCREASED	9 (3.1%)	4 (1.4%)
RESPIRATORY SYSTEM	59 (20.6%)	56 (20.2%)
PNEUMONIA	11 (3.8%)	16 (5.8%)
DYSPNEA	13 (4.5%)	14 (5.1%)
PLEURAL EFFUSION	12 (4.2%)	10 (3.6%)
APNEA	12 (4.2%)	5 (1.8%)
RESPIRATORY DISORDER	13 (4.5%)	5 (1.8%)
NERVOUS SYSTEM	54 (18.8%)	39 (14.1%)
CONVULSION	15 (5.2%)	12 (4.3%)
THINKING ABNORMAL	9 (3.1%)	5 (1.8%)
UROGENITAL SYSTEM	48 (16.7%)	38 (13.7%)
KIDNEY FUNCTION ABNORMAL	16 (5.6%)	18 (6.5%)
ACUTE KIDNEY FAILURE	13 (4.5%)	6 (2.2%)
KIDNEY FAILURE	9 (3.1%)	6 (2.2%)
MUSCULOSKELETAL SYSTEM	9 (3.1%)	7 (2.5%)
SKIN AND APPENDAGES	15 (5.2%)	7 (2.5%)

SOURCE: IRDM RALK -AESUM_SEV_3PCT- (20MAY99,16:23) SAS V6.12

(Reference: vol. 17, p. 98, table 31)

Medical Officer Comment:

The electronic submission and case summaries were reviewed by the FDA. The rates of severe adverse events were similar between both treatment groups. The profile is that which is expected given the previous experiences with renal and transplants patients. The difference in the rates of serious hepatitis reported in this table and that reported in the medically serious adverse event table above occurs due to the addition of patients with chemically documented disease as well as those reported on the adverse event case report form.

Pulmonary or interstitial fibrosis cases were not reported in the adverse events safety database. Review of patients with severe pulmonary events did not reveal underlying fibrosis, but rather, other diseases including infection, heart failure, and pulmonary embolism. Further discussion of the postmarketing safety database will follow in section 6.9.1.

3.3. Adverse Events by Age, Race and Gender

Adverse events within each treatment group were compared by age (<18, 18 – 64, and ≥ 65 years), racial subgroup (Black, Nonblack) and gender. Because there were relatively few patients outside the 18 – 64 year age group, differences between the three age groups can not be assessed. The same is true for adverse events evaluated by racial subgroup. Analyses for age and racial subgroup are provided as appendices for reference.

The number of female and male patients within each treatment group allowed for more extensive comparisons; the following observations were made. In both the azathioprine and MMF treatment groups, males and females were similar with respect to the frequency of AEs overall as well as by body. However, some numerical differences between males and females within treatment groups were observed. In both treatment groups, females had higher incidences for vomiting (41.2% azathioprine-treated females vs. 26.9% azathioprine-treated males; 38.7% MMF-treated females vs. 28.5% MMF-treated males), nausea (62.6% azathioprine-treated females vs. 41.7% azathioprine-treated males; 59.7% MMF-treated females vs. 50.6% MMF-treated males), anemia (55.7% azathioprine-treated females vs. 50.6% azathioprine-treated males; 52.1% MMF-treated females vs. 36.1% MMF-treated males), and urinary tract infection (26.0% azathioprine-treated females vs. 10.9% azathioprine-treated males; 31.1% MMF-treated females vs. 8.2% MMF-treated males).

Medical Officer Comment:

The applicant noted women had higher rates of the following reported adverse events: vomiting, nausea, anemia, and urinary tract infection. Previous pharmacokinetic studies did not detect differences in the Cmax or AUC of MPA (mycophenolic acid). The occurrence of urinary tract infection is generally more frequent in women. FDA analysis of the pattern of discontinuation of study drug due to adverse event did not reveal any significant difference between men and women for either AZA or MMF. (AZA male 18.5%, female 18.8%; MMF male 19.9%, female 18.4%). Similar patterns between males and females were seen for adverse events which required reduction in dose or dose interruption.

3.4. Opportunistic Infections

The incidence of any opportunistic infection was similar between the dosing groups (43.2% of the azathioprine patients and 45.5% of the MMF patients). The most common opportunistic pathogen was *Candida*, manifested as mucocutaneous disease (17.4% azathioprine, 18.4% MMF). This was followed by CMV viremia/syndrome (12.2% azathioprine, 14.1% MMF), Herpes simplex (5.9% azathioprine, 10.1% MMF) and CMV tissue invasion (8.0% azathioprine, 5.8% MMF). In general, the first occurrence of any opportunistic infection was most common in the early posttransplant period (0-3 months).

Patients with a high risk of CMV infection include those who were seronegative prior to transplant surgery and received a liver from a seropositive donor. In this study, a total of 96 patients (48 from each of the two treatment groups) were seronegative for CMV and received a liver from a seropositive donor. Analysis of this subgroup of 96 patients showed an incidence of any CMV opportunistic infection of 39.6% (azathioprine group) and 43.8% (MMF group); overall, CMV opportunistic infection was reported in this study in 18.5% (azathioprine) and 19.1% (MMF) of patients. If the high-risk subgroup were excluded from analysis of the entire study population, the incidence of CMV opportunistic infection would be 14.2% (azathioprine) and 14.0% (MMF).

Summary of Opportunistic Infections

	TREATMENT GROUP	
	AZA	MMF
	1-2 mg/kg/day	1.5 gm BID
TOTAL PATIENTS IN SUMMARY	287	277
	NO. (%) OF PATIENTS WITH ONE OR MORE OPPORTUNISTIC INFECTIONS	
ANY OPPORTUNISTIC INFECTION	124 (43.2%)	126 (45.5%)
PATHOGEN DIAGNOSTIC CATEGORY		
CANDIDA	70 (24.4%)	62 (22.4%)
CANDIDA MUCOCUTANEOUS	50 (17.4%)	51 (18.4%)
CANDIDA URINARY TRACT INFECTION	15 (5.2%)	9 (3.2%)
CANDIDA INVASIVE TISSUE DISEASE	6 (2.1%)	5 (1.8%)
CANDIDA FUNGEMIA/DISSEMINATED DISEASE	5 (1.7%)	4 (1.4%)
CMV VIREMIA/SYNDROME	35 (12.2%)	39 (14.1%)
CMV VIREMIA/SYNDROME	35 (12.2%)	39 (14.1%)
HERPES SIMPLEX	17 (5.9%)	28 (10.1%)
HERPES SIMPLEX	17 (5.9%)	28 (10.1%)
CMV TISSUE INVASION	23 (8.0%)	16 (5.8%)
CMV HEPATITIS	18 (6.3%)	8 (2.9%)
CMV PNEUMONIA	3 (1.0%)	4 (1.4%)
CMV COLITIS	2 (0.7%)	2 (0.7%)
CMV GASTROENTERITIS	1 (0.3%)	2 (0.7%)
CMV GASTRITIS	0	1 (0.4%)
CMV RETINITIS	1 (0.3%)	0
HERPES ZOSTER	14 (4.9%)	12 (4.3%)
HERPES ZOSTER CUTANEOUS DISEASE	14 (4.9%)	12 (4.3%)
HERPES ZOSTER VISCERAL DISEASE	1 (0.3%)	0
CMV INFECTION	2 (0.7%)	3 (1.1%)
CMV UPINE	2 (0.7%)	3 (1.1%)
ASPERGILLUS/MUCOR	2 (0.7%)	1 (0.4%)
ASPERGILLUS DISSEMINATED OR METASTATIC	2 (0.7%)	1 (0.4%)
CRYPTOCOCCUS	2 (0.7%)	1 (0.4%)
CRYPTOCOCCOSIS	2 (0.7%)	1 (0.4%)
PNEUMOCYSTIS CARINII	1 (0.3%)	0
PNEUMOCYSTIS PULMONARY DISEASE	1 (0.3%)	0

PREFERRED TERMS AND BODY SYSTEMS.

SOURCE: IRDM RALK -AESUM_OI- (09JUN99,10:20) SAS V6.12 AESUM_OI.TAB

(reference: vol 17. P. 92, table 28)

Medical Officer Comment:

Review of the opportunistic infection data supplied by the applicant is in agreement. This profile is similar to that seen in the renal and cardiac transplant recipients. Herpes simplex occurred at a low rate, however, numerically the rate was higher in the CellCept® arm. Overall, compared to the renal and cardiac patients the rates of herpes simplex were lower in the liver transplant recipients (see label). The 3 g/day dose in cardiac and renal transplant recipients lead to a 20% rate of herpes simplex in these groups.

3.5. Laboratory abnormalities

Results of selected laboratory tests (minimum absolute neutrophil count, minimum platelets, minimum hemoglobin, maximum serum creatinine, maximum total bilirubin, maximum alkaline phosphatase, maximum SGOT and maximum SGPT) are generally comparable for the two treatment groups. The number of patients exhibiting laboratory values outside the respective normal ranges is higher in the immediate posttransplant period. In the first 30 days posttransplant, 25 (8.8%) azathioprine patients and 12 (4.4%) MMF patients had a minimum platelet count of less than 25,000/mL; 26 (9.1%) azathioprine patients and 14 (5.1%) MMF patients had a maximum total bilirubin concentration of greater than 20 mg/dL; 10 (3.5%) azathioprine and 4 (1.5%) MMF patients had a maximum alkaline phosphatase level of greater than 1000 U/L. Over time, however, the incidence of abnormal laboratory values decreased for both treatment groups.

Laboratory Summaries of Selected Tests

		Number of Patients							
		≤ 30 Days		31-180 Days		181-365 Days		>365 Days	
Test	Range	Aza N = 287	MMF N = 276	Aza N = 253	MMF N = 248	Aza N = 197	MMF N = 192	Aza N = 127	MMF N = 125
Minimum		268	252	175	136	129	123	74	89
absolute		5	5	24	46	22	18	16	6
neutrophil		0	3	9	14	6	5	7	1
count		1	1	7	9	4	4	0	2
($x10^3/\mu L$)		2	1	1	7	0	1	0	0
Minimum		85	80	180	180	152	153	106	108
platelets		108	126	42	38	24	22	14	13
($x10^3/\mu L$)		67	56	8	7	6	0	2	0
		25	12	3	1	1	0	0	0
Minimum		40	53	78	73	117	116	97	100
hemoglobin		221	195	145	139	68	58	26	22
(g/dL)		26	27	16	17	2	3	1	0
		0	1	3	2	2	0	0	0
Maximum		45	40	23	16	10	8	5	2
serum		129	140	151	152	132	112	88	75
creatinine		113	95	67	63	43	55	32	45
(mg/dL)									
Maximum		26	14	8	5	2	4	0	1
total		117	112	16	17	5	3	2	5
bilirubin		138	141	137	118	72	65	41	31
(mg/dL)		5	9	82	100	110	105	80	84
Maximum		10	4	11	17	2	4	0	4
alkaline		48	46	29	22	12	16	4	7
phosphatase		203	189	137	139	117	118	72	79
(U/L)		26	36	67	57	56	44	49	32
Maximum		27	25	14	10	3	7	2	3
SGOT (U/L)		17	17	27	18	17	9	5	6
		112	102	67	71	36	43	14	18
		130	132	139	145	134	128	105	94
Maximum		50	56	18	19	4	10	2	4
SGPT (U/L)		76	88	30	28	18	9	0	3
		140	108	94	92	54	70	31	31
		18	20	104	105	111	96	87	80

(Reference: vol. 17, p102, Table 32)

Medical Officer Comment:

Given the data presented by the applicant, and the complicated medical course the liver transplant recipient undergoes, the FDA is in agreement that generally for most patients laboratory abnormalities improved over time. This is expected

as the patient recovers from surgery, liver function improves and the medical regimen is reduced. This pattern was seen in the previous studies of cardiac and renal transplant recipients.

3.6. Pregnancies

There was one pregnancy reported during this study. Patient 55501, a 38 year old female, assigned to the azathioprine treatment group, terminated the study (and study medication) on March 5, 1998. Patient 55501 subsequently became pregnant; the pregnancy was normal with a gestation period of 38 weeks. The infant was born on January 23, 1999 via vaginal delivery. The newborn was female, weighing approximately 3 kg, and appeared normal.

3.7. Comparison of safety profile with renal and cardiac studies

Since CellCept® has already been approved for use in renal and cardiac transplant recipients, it is of interest to compare the safety profile to that in liver transplant recipients. In general the pattern is quite similar. Again, it can be noted that some events are specific to adverse events associated with those expected with the specific organ being transplanted. The following is a copy of the adverse events to be listed in the proposed label.

APPEARS THIS WAY
ON ORIGINAL

Adverse events in Controlled Studies of Renal, Cardiac or Hepatic Allograft Rejection (Reported in > 10% of Patients in the CellCept® Group)							
	Renal Studies			Cardiac Study		Hepatic Study	
	CellCept®	CellCept®	Azathio-prine	CellCept®	Azathio-prine	CellCept®	Azathio-prine
	2 g/day	3 g/day	1-2 mg• kg^{-1}•day^{-1} or 100-150 mg/day	3 g/day	1.5-3 mg• kg^{-1}•day^{-1}	3 g/day	1-2 mg• kg^{-1}•day^{-1}
	(n=336) %	(n=330) %	(n=326) %	(n=289) %	(n=289) %	(n=277) %	(n=287) %
Body as a Whole							
Pain	33.0	31.2	32.2	75.8	74.7	74.0	77.7
Abdominal pain	24.7	27.6	23.0	33.9	33.2	62.5	51.2
Fever	21.4	23.3	23.3	47.4	46.4	52.3	56.1
Headache	21.1	16.1	21.2	54.3	51.9	53.8	49.1
Infection	18.2	20.9	19.9	25.6	19.4	27.1	25.1
Sepsis	17.6	19.7	15.6	18.7	18.7	27.4	26.5
Asthenia	13.7	16.1	19.9	43.3	36.3	35.4	33.8
Chest pain	13.4	13.3	14.7	26.3	26.0	15.9	13.2
Back pain	11.6	12.1	14.1	34.6	28.4	46.6	47.4
Accidental injury	-	-	-	19.0	14.9	11.2	15.0
Chills	-	-	-	11.4	11.4	10.8	10.1
Ascites	-	-	-	-	-	24.2	22.6
Abdomen enlarged	-	-	-	-	-	18.8	17.8
Hernia	-	-	-	-	-	11.6	8.7
Peritonitis	-	-	-	-	-	10.1	12.5
Hemic and Lymphatic							
Anemia	25.6	25.8	23.6	42.9	43.9	43.0	53.0
Leukopenia	23.2	34.5	24.8	30.4	39.1	45.8	39.0
Thrombocyto-penia	10.1	8.2	13.2	23.5	27.0	38.3	42.2
Hypochromic anemia	7.4	11.5	9.2	24.6	23.5	13.7	10.8
Leukocytosis	7.1	10.9	7.4	40.5	35.6	22.4	21.3
Ecchymosis	-	-	-	16.6	8.0	-	-
Urogenital							
Urinary tract infection	37.2	37.0	33.7	13.1	11.8	18.1	7.8
Hematuria	12.1	11.3	-	-	-	-	14.0

Indication: Prophylaxis of acute rejection in allogeneic hepatic transplant patients
Study MYCS-2646 - Safety

Adverse events in Controlled Studies of Renal, Cardiac or Hepatic Allograft Rejection (Reported in > 10% of Patients in the CellCept® Group) (Cont'd.)

	Renal Studies		Cardiac Study		Hepatic Study		
	CellCept®	CellCept®	Azathio-prine	CellCept®	Azathio-prine	CellCept®	Azathio-prine
	2 g/day	3 g/day	1-2 mg•kg^{-1}•day^{-1} or 100-150 mg/day	3 g/day	1.5-3 mg•kg^{-1}•day^{-1}	3 g/day	1-2 mg•kg^{-1}•day^{-1}
	(n=336) %	(n=330) %	(n=326) %	(n=289) %	(n=289) %	(n=277) %	(n=287) %
Kidney tubular necrosis	6.3	10.0	5.8	-	-	-	-
Kidney function-abnormal	-	-	-	21.8	26.3	25.6	28.9
Oliguria	-	-	-	14.2	12.8	17.0	20.6
Cardiovascular							
Hypertension	32.4	28.2	32.2	77.5	72.3	62.1	59.6
Hypotension	-	-	-	32.5	36.0	18.4	20.9
Cardiovascular disorder	-	-	-	25.6	24.2	-	-
Tachycardia	-	-	-	20.1	18.0	22.0	15.7
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	28.6	27.0	28.2	64.0	53.3	48.4	47.7
Hyper-cholesteremia	12.8	8.5	11.3	41.2	38.4	-	-
Hypo-phosphatemia	12.5	15.8	11.7	-	-	14.4	9.1
Edema	12.2	11.8	13.5	26.6	25.6	28.2	28.2
Hypokalemia	10.1	10.0	8.3	31.8	25.6	37.2	41.1
Hyperkalemia	8.9	10.3	16.9	14.5	19.7	22.0	23.7
Hyperglycemia	8.6	12.4	15.0	46.7	52.6	43.7	48.8
Creatinine increased	-	-	-	39.4	36.0	19.9	21.6
BUN increased	-	-	-	34.6	32.5	10.1	12.9
Lactic dehydro-genase increased	-	-	-	23.2	17.0	-	-

Indication: Prophylaxis of acute rejection in allogeneic hepatic transplant patients
Study MYCS-2646 - Safety

Adverse events in Controlled Studies of Renal, Cardiac or Hepatic Allograft Rejection (Reported in > 10% of Patients in the CellCept® Group) (Cont'd.)							
	Renal Studies			Cardiac Study		Hepatic Study	
	CellCept®	CellCept®	Azathio-prine	CellCept®	Azathio-prine	CellCept®	Azathio-prine
	2 g/day	3 g/day	1-2 mg• kg^{-1}•day^{-1} or 100-150 mg/day	3 g/day	1.5-3 mg• kg^{-1}•day^{-1}	3 g/day	1-2 mg• kg^{-1}•day^{-1}
	(n=336) %	(n=330) %	(n=326) %	(n=289) %	(n=289) %	(n=277) %	(n=287) %
Bilirubinemia	-	-	-	18.0	21.8	14.4	18.8
Hypervolemia	-	-	-	16.6	22.8	-	-
Generalized edema	-	-	-	18.0	20.1	14.8	16.0
Hyperuricemia	-	-	-	16.3	17.6	-	-
SGOT increased	-	-	-	17.3	15.6	-	-
Hypo-magnesemia	-	-	-	18.3	12.8	39.0	37.6
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	-	-
Hypocalcemia	-	-	-	-	-	30.0	30.0
Hypo-proteinemia	-	-	-	-	-	13.4	13.9
Hypoglycemia	-	-	-	-	-	10.5	9.1
Healing abnormal	-	-	-	-	-	10.5	8.7
Digestive							
Diarrhea	31.0	36.1	20.9	45.3	34.3	51.3	49.8
Constipation	22.9	18.5	22.4	41.2	37.7	37.9	38.3
Nausea	19.9	23.6	24.5	54.0	54.3	54.5	51.2
Dyspepsia	17.6	13.6	13.8	18.7	19.4	22.4	20.9
Vomiting	12.5	13.6	9.2	33.9	28.4	32.9	33.4
Nausea and vomiting	10.4	9.7	10.7	11.1	7.6	-	-
Oral monoliasis	10.1	12.1	11.3	11.4	11.8	10.1	10.1
Flatulence	-	-	-	13.8	15.6	12.6	9.8
Anorexia	-	-	-	-	-	25.3	17.1
Liver function tests abnormal	-	-	-	-	-	24.9	19.2
Cholangitis	-	-	-	-	-	14.1	13.6
Hepatitis	-	-	-	-	-	13.0	16.0
Cholestatic jaundice	-	-	-	-	-	11.9	10.8

Indication: Prophylaxis of acute rejection in allogeneic hepatic transplant patients
Study MYCS-2646 - Safety

Adverse events in Controlled Studies of Renal, Cardiac or Hepatic Allograft Rejection (Reported in > 10% of Patients in the CellCept® Group) (Cont'd.)							
	Renal Studies			Cardiac Study		Hepatic Study	
	CellCept®	CellCept®	Azathio-prine	CellCept®	Azathio-prine	CellCept®	Azathio-prine
	2 g/day	3 g/day	1-2 mg•kg^{-1}•day^{-1} or 100-150 mg/day	3 g/day	1.5-3 mg•kg^{-1}•day^{-1}	3 g/day	1-2 mg•kg^{-1}•day^{-1}
	(n=336) %	(n=330) %	(n=326) %	(n=289) %	(n=289) %	(n=277) %	(n=287) %
Respiratory							
Infection	22.0	23.9	19.6	37.0	35.3	15.9	19.9
Dyspnea	15.5	17.3	16.6	36.7	36.3	31.0	30.3
Cough increased	15.5	13.3	15.0	31.1	25.6	15.9	12.5
Pharyngitis	9.5	11.2	8.0	18.3	13.5	14.1	12.5
Lung disorder	-	-	-	30.1	29.1	22.0	18.8
Sinusitis	-	-	-	26.0	19.0	11.2	9.8
Rhinitis	-	-	-	19.0	15.6	-	-
Pleural effusion	-	-	-	17.0	13.8	34.3	35.9
Asthma	-	-	-	11.1	11.4	-	-
Pneumonia	-	-	-	10.7	10.4	13.7	11.5
Atelectasis	-	-	-	-	-	13.0	12.9
Skin and Append-ages							
Acne	10.1	9.7	6.4	12.1	9.3	-	-
Rash	-	-	-	22.1	18.0	17.7	18.5
Skin disorder	-	-	-	12.5	8.7	-	-
Pruritus	-	-	-	-	-	14.1	10.5
Sweating	-	-	-	-	-	10.8	10.1
Nervous System							
Tremor	11.0	11.8	12.3	24.2	23.9	33.9	35.5
Insomnia	8.9	11.8	10.4	40.8	37.7	52.3	47.0
Dizziness	5.7	11.2	11.0	28.7	27.7	16.2	14.3
Anxiety	-	-	-	28.4	23.9	19.5	17.8
Paresthesia	-	-	-	20.8	18.0	15.2	15.3
Hypertonia	-	-	-	15.6	14.5	-	-
Depression	-	-	-	15.6	12.5	17.3	16.7
Agitation	-	-	-	13.1	12.8	-	-
Somnolence	-	-	-	11.1	10.4	-	-
Confusion	-	-	-	13.5	7.6	17.3	18.8
Nervousness	-	-	-	11.4	9.0	10.1	10.5

Indication: Prophylaxis of acute rejection in allogeneic hepatic transplant patients
Study MYCS-2646 - Safety

Adverse events in Controlled Studies of Renal, Cardiac or Hepatic Allograft Rejection (Reported in > 10% of Patients in the CellCept® Group) (Cont'd.)							
	Renal Studies			Cardiac Study		Hepatic Study	
	CellCept®	CellCept®	Azathio-prine	CellCept®	Azathio-prine	CellCept®	Azathio-prine
	2 g/day	3 g/day	1-2 mg•kg^{-1}•day^{-1} or 100-150 mg/day	3 g/day	1.5-3 mg•kg^{-1}•day^{-1}	3 g/day	1-2 mg•kg^{-1}•day^{-1}
	(n=336) %	(n=330) %	(n=326) %	(n=289) %	(n=289) %	(n=277) %	(n=287) %
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	-	-

Reference Vol 2, p 47-51)

Medical Officer Comment:

In general the profile of adverse events seen in the liver transplant patients is similar to that in the kidney and heart transplant patients. Comparisons across types of organ transplanted can be made for the 3 g/day dose of CellCept®. Generally, adverse events related to the type of surgery and transplanted organ were seen in higher frequency in those specific organ transplant recipients. For example, the frequencies of pulmonary and cardiac adverse events were highest among the heart transplant patients. Likewise, adverse events related to the kidney were more frequently noted among the renal transplant patients. Abdominal pain, sepsis, ascites, enlarged abdomen, hernia and peritonitis were seen more frequently among the liver transplant recipients. Again, adverse events related to the digestive system (diarrhea, anorexia, abnormal liver function tests, cholangitis, hepatitis, cholestatic jaundice) were seen more frequently among the liver transplant recipients. Tremor and insomnia were seen more frequently in liver transplant patient, perhaps related to the metabolic changes seen in these patients. For the Hemic and Lymphatic Systems, liver transplant recipients had the highest rate of thrombocytopenia and leukopenia compared to the other types of transplant. This most probably is related to the type of transplant and the various immunosuppressive regimens given.

3.8. Post-marketing Adverse Events:

During the 5 year period since the original approval of CellCept®, interstitial pulmonary fibrosis has been reported rarely. The Office of Post-Marketing Drug Risk Assessment (OPDRA, FDA) was consulted during the review of the cardiac transplant indication review. At that time it was felt that there were not enough cases which demonstrated the potential relationship to warrant inclusion in the label at that time. The current NDA

supplement provided the opportunity for the FDA to review the current post-marketing database. Consult was again made to OPDRA, and as a result a recommendation was made to include information on interstitial pulmonary fibrosis in the post-marketing section of the proposed label.

The following is a quote from the summary of the OPDRA 2000 consult.

"OPDRA initially identified interstitial lung disease (especially pulmonary fibrosis) as a potential safety signal in 1998; this document updates those findings. As of May 24, 2000, AERS and the published literature contain a total of nine unconfounded cases of interstitial lung disease; seven of the cases were diagnosed as pulmonary fibrosis.

In six of the nine cases, the most common post-transplant pulmonary infections were ruled out. None of the patients was stated to be receiving any concomitant medications known to cause interstitial lung disease. The time to onset after starting mycophenolate was less than three months in eight of the nine reports. Four of the cases of fibrosis and one of interstitial inflammation were confirmed by open lung biopsies. There were five positive dechallenges, two in one patient who had two positive rechallenges. The three fatal cases suggest that, once developed, the disease may progress to such an extent that it might not be reversible upon discontinuation of mycophenolate mofetil.

OPDRA recommends that interstitial pulmonary events be added to the CellCept® labeling in the **Postmarketing Experience** section under **ADVERSE REACTIONS**. A possible wording is as follows:

> *"Respiratory:* Interstitial lung disorders, including fatal pulmonary fibrosis, have been reported and should be considered in the differential diagnosis of pulmonary symptoms ranging from dyspnea to respiratory failure in post-transplant patients."

Medical Officer Comment:
OPDRA consult was reviewed by the primary reviewing division and it was felt that this was a reasonable addition to the label given the above information.

4. FDA summary

4.1. Efficacy

When used with cyclosporine and corticosteroids CellCept® was effective in preventing graft rejection in allogeneic liver transplantation. Although the active control, azathioprine, is not approved for prevention of graft rejection in liver transplantation, and the optimal safe and effective dose has not been established in this indication, there was a lower rate of treatment failure, defined as acute rejection, graft loss or death, which is sufficiently convincing that CellCept® would have been superior to a placebo control.

Patient and graft survival at 12 months were comparable between treatment groups. Thus, the lower rate of acute rejection at 6 months does not appear to have been achieved at the expense of an unacceptable decrease in 12 month patient or graft survival. However, because of the high rate of premature discontinuation of study drug before 12 months (greater than 50%), analyses of equivalence should be interpreted with caution.

4.2. Safety

Key conclusion with regard to the safety of MMF in the prevention of allograft rejection in adult hepatic transplantation are:

- The nature, frequency, and severity of adverse events are similar to those observed in patients treated with AZA.
- The mortality rate is similar to that observed in patients treated with AZA.
- The frequency and types of malignancies are similar to those in patients treated with AZA.
- The frequency of discontinuation of treatment due to adverse events is similar to that observed in patients treated with AZA.
- The nature, frequency, and severity of adverse events during intravenous administration of MMF are similar to those observed during intravenous administration of AZA.
- Clinically meaningful influence of gender on the safety of MMF were NOT detected.
- Safety risks from oral administration of MMF were NOT observed, other than those previously reported in renal and cardiac allograft recipients.
- Safety risks from intravenous administration of MMF other than those previously reported in renal allograft recipients were NOT observed.

Post-marketing safety information regarding interstitial pulmonary fibrosis has been accumulating. It is recommended that this rare event be included in the post-marketing section of the label (above):

4.3. Special populations

Pregnancy: *Category C.* 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.

Medical Officer Comment:
No pregnancies occurred in patients randomized to the CellCept® arm of the pivotal liver transplant study. The applicant continues to monitor reports to its pregnancy registry. No changes in recommendations regarding the avoidance of pregnancy while on CellCept® are warranted at this time.

Phenylketonurics: CellCept® Oral Suspension contains aspartame, a source of phenylalanine (0.56 mg phenylalanine/mL suspension).

Gender, age and ethnic group
There were not enough patients over 65 years of age, nor of ethnic origin other than Caucasian to perform meaningful analysis in the pivotal study in liver transplant recipients. It is noted that other studies have shown that there is a difference in outcome based on ethnic groups; this study may have been too small to be able to detect a difference.

Gender was found to be a significant predictor of outcome at the 6-month timpoint, with males having a lower rate of rejection than females. The interaction with treatment, however, was not significant. Neither gender nor treatment interaction was found to be significant at the 12-month timepoint. Adverse events were similar between treatment groups within gender, however, there were more women in both treatment group with the following adverse events: vomiting, nausea, anemia, and urinary tract infection. Previous pharmacokinetic studies did not detect differences in the Cmax or AUC of MPA (mycophenolic acid). The occurrence of urinary tract infection is generally more frequent in women. FDA analysis of the pattern of discontinuation of study drug due to adverse event did not reveal any significant difference between men and women for either AZA or MMF (AZA male 18.5%, female 18.8%; MMF male 19.9%, female 18.4%). Similar patterns between males and females were seen for adverse events which required reduction in dose or dose interruption.

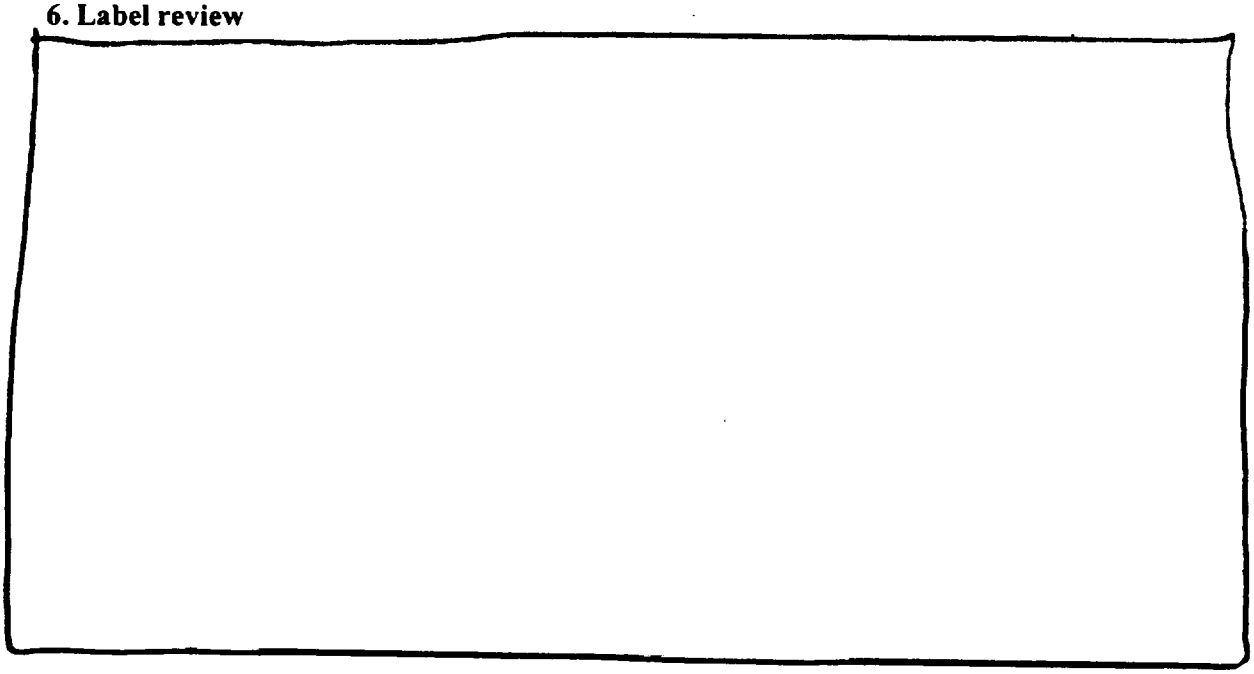
Pediatric population
There was only one patient under the age of 18 treated in this study. The Division's current plans are to waive the requirement for pediatric studies in the neonate population, and to defer the submission of the results from studies in children older than 2 months until May 31, 2003.

5. Regulatory recommendations

The medical officers' recommendation is for approval of CellCept® for the prophylaxis of organ rejection in patients receiving allogeneic hepatic transplants. The dose will be 1.5 grams, bid, orally or intravenously, for a total daily dose of 3 grams. The intravenous infusion is to be infused over no less than 2 hours.

In addition, a statement should be added to the label regarding interstitial pulmonary events (see below, **Section 6. Label review**).

6. Label review



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EFFICACY:

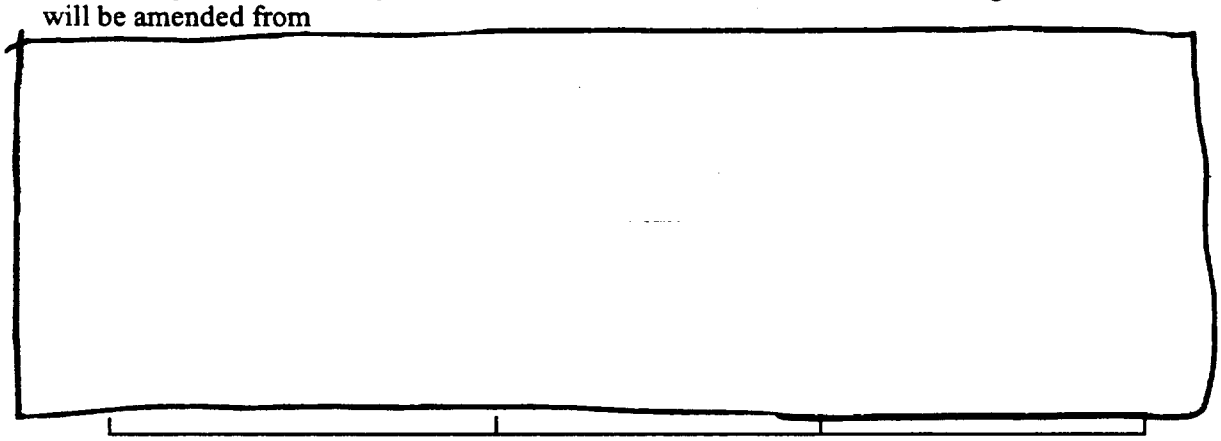
The **Indications and Usage** section will be amended to include hepatic patients and will read as follows:

"INDICATIONS AND USAGE: Renal, and Cardiac and Hepatic Transplant:
CellCept is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac or hepatic transplants

CellCept should be used concomitantly with cyclosporine and corticosteroids.

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

The description of the study results in the **Clinical Studies** section, including the table, will be amended from



to read as follows:

"Results: In combination with corticosteroids and cyclosporine, CellCept obtained a lower rate of acute rejection at 6 months and a similar rate of death or re-transplantation at 1 year compared to azathioprine."

	Rejection at 6 Months/ Death or Retransplantation at 1 year	
	AZA N = 287	*CellCept N = 278*
Biopsy proven, treated rejection at 6 months (includes death or retransplantaion)	*137 (47.7%)*	*107 (38.5 %)*
Death or retransplantation at 1 year	*42 (14.6%)*	*41 (14.7%)*

Indication: Prophylaxis of acute rejection in allogeneic hepatic transplant patients
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SAFETY:
Interstitial pulmonary events should be added to the CellCept® labeling in the **Postmarketing Experience** section under **ADVERSE REACTIONS.** A possible wording is as follows:

Respiratory: Interstitial lung disorders, including fatal pulmonary fibrosis, have been reported and should be considered in the differential diagnosis of pulmonary symptoms ranging from dyspnea to respiratory failure in post-transplant patients."

7. Phase IV Commitments
Discussions with applicant focused on the following areas as potential Phase IV commitments:

- Collection and reporting on the 3-year follow-up safety and efficacy data from the ongoing Phase 3 Study MYCS-2646, irrespective of whether the patient remained on study drug.
- Conduct of an appropriate study, or studies, on the pharmacokinetics and safety of CellCept® in African-American liver transplant recipients.
- Conduct of an appropriate study, or studies, on the pharmacokinetics and safety of CellCept ® in pediatric liver transplant recipients less than 12 years of age, especially in pediatric patients less than 3 years of age with biliary atresia.

/S/

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Lead Medical Officer
Division of Special Pathogen and
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Marc Cavaillé-Coll, M.D., Ph. D.
Medical Team Leader
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Immunologic Drug Products

/S/

Renata Albrecht, M.D.,
Acting Division Director
Division of Special Pathogen and
Immunologic Drug Products

cc:
Original NDA 20-871
HFD-590/Div. Dir/Goldberger
HFD-590/Acting Div. Dir/Albrecht
HFD-590/MedTL/Cavaillé-Coll
HFD-590/MO/Korvick
HFD-590/MO/Roca
HFD-590/Chem/Seggel
HFD-590/Pharmtox/Kunder
HFD-590/ RPM/Bacho
HFD-880/Biopharm/Kumi
HFD-725/Biometrics/Higgins

Appendix A: Countries in which CellCept® has been introduced

Country	Dosage Form	Indication	Marketing Information (Date Introduced)
Argentina			
	Capsules 250 mg	Prevention of Acute Renal Rejection	21-May-1996
	Capsules 250 mg	Treat. Refractory Acute Renal Rejection	21-May-1996
	Tablets 500 mg	Prevention of Acute Renal Rejection	23-Apr-1997
	Tablets 500 mg	Treat. Refractory Acute Renal Rejection	23-Apr-1997
Australia			
	Capsules 250 mg	Prevention of Acute Renal Rejection	23-Jan-1997
Austria			
	Capsules 250 mg	Prevention of Acute Renal Rejection	01-May-1996
	Tablets 500 mg	Prevention of Acute Renal Rejection	01-Jul-1996
Belgium			
	Capsules 250 mg	Prevention of Acute Renal Rejection	01-Aug-1998
	Tablets 500 mg	Prevention of Acute Renal Rejection	01-Aug-1998
Brazil			
	Tablets 500 mg	Prevention of Acute Renal Rejection	14 Sep-1996
	Tablets 500 mg	Treat. Refractory Acute Renal Rejection	14-Sep-1996
Colombia			
	Capsules 250 mg	Prevention of Acute Renal Rejection	01-Jun-1997
	Capsules 250 mg	Treat. Refractory Acute Renal Rejection	01-Jun-1997
	Tablets 500 mg	Prevention of Acute Renal Rejection	01-Jul-1998
	Tablets 500 mg	Treat. Refractory Acute Renal Rejection	01-Jul-1998
Denmark			
	Capsules 250 mg	Prevention of Acute Renal Rejection	01-Jul-1996
	Tablets 500 mg	Prevention of Acute Renal Rejection	07-Oct-1996
Ecuador			
	Capsules 250 mg	Prevention of Acute Renal Rejection	01-Sep-1997
	Capsules 250 mg	Treat. Refractory Acute Renal Rejection	01-Sep-1997
Eire			
	Capsules 250 mg	Prevention of Acute Renal Rejection	01-Mar-1996
Finland			
	Capsules 250 mg	Prevention of Acute Renal Rejection	15-May-1996
	Tablets 500 mg	Prevention of Acute Renal Rejection	26-Jun-1996
France			
	Capsules 250 mg	Prevention of Acute Renal Rejection	15 Nov-1996
	Tablets 500 mg	Prevention of Acute Renal Rejection	15-Nov-1996
Germany			
	Capsules 250 mg	Prevention of Acute Renal Rejection	15-Feb-1996
	Tablets 500 mg	Prevention of Acute Renal Rejection	15-Sep-1996
Greece			
	Capsules 250 mg	Prevention of Acute Renal Rejection	12-Sep.1996
	Tablets 500 mg	Prevention of Acute Renal Rejection	12-May-1998
India			
	Capsules 250 mg	Prevention of Acute Renal Rejection	01-Aug-1999
	Capsules 250 mg	Treat. Refractory Renal Rejection	01-Aug-1999
	Capsules 250 mg	Cardiac Transplantation	01-Aug-1999
	Tablets 500 mg	Prevention of Acute Renal Rejection	01-Aug-1999
	Tablets 500 mg	Treat. Refractory Acute Renal Rejection	01-Aug-1999

Indication: Prophylaxis of acute rejection in allogeneic hepatic transplant patients
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Country	Dosage Form	Indication	Marketing Information (Date Introduced)
	Tablets 500 mg	Cardiac Transplantation	01-Aug-1999
Italy			
	Capsules 250 mg	Prevention of Acute Renal Rejection	05-Sep-1996
	Tablets 500 mg	Prevention of Acute Renal Rejection	01 -Jan-1997
Luxembourg			
	Capsules 250 mg	Prevention of Acute Renal Rejection	01-Oct-1996
	Tablets 500 mg	Prevention of Acute Renal Rejection	01-Oct-1996
Netherlands			
	Capsules 250 mg	Prevention of Acute Renal Rejection	01-May-1996
	Tablets 500 mg	Prevention of Acute Renal Rejection	01-May-1996
New Zealand			
	Capsules 250 mg	Prevention of Acute Renal Rejection	12-May-1996
	Vials i.v. powder for solution/500 mg	Prevention of Acute Transplant Rejection in Allogeneic Renal Transplant	08-Jul-1 999
Philippines			
	Capsules 250 mg	Prevention of Acute Renal Rejection	01-Nov-1996
	Capsules 250 mg	Treat. Refractory Acute Renal Rejection	01-Nov.1996
Portugal			
	Capsules 250 mg	Prevention of Acute Renal Rejection	14-Feb-1996
	Tablets 500 mg	Prevention of Acute Renal Rejection	14-Feb-1996
Singapore			
	Capsules 250 mg	Prevention of Acute Renal Rejection	03-Apr-1997
	Capsules 250 mg	Treat. Refractory Acute Renal Rejection	03-Apr-1997
Slovakia			
	Capsules 250 mg	Prevention of Acute Renal Rejection	N/A
	Capsules 250 mg	Treat. Refractory Acute Renal Rejection	N/A
	Tablets 500 mg	Prevention of Acute Renal Rejection	N/A
	Tablets 500 mg	Treat. Refractory Acute Renal Rejection	N/A
Spain			
	Capsules 250 mg	Prevention of Acute Renal Rejection	16-May-1996
	Tablets 500 mg	Prevention of Acute Renal Rejection	15-Sep-1996
Sweden			
	Capsules 250 mg	Prevention of Acute Renal Rejection	14-Feb-1996
	Tablets 500 mg	Prevention of Acute Renal Rejection	01-Jul-1996
Switzerland			
	Capsules 250 mg	Prevention of Acute Renal Rejection	02-Jan-1996
	Tablets 500 mg	Prevention of Acute Renal Rejection	02-Jan-1996
Taiwan			
	Capsules 250 mg	Prevention of Acute Renal Rejection	10-Jul-1997
	Capsules 250 mg	Treat. Refractory Acute Renal Rejection	10-Jul-1997
Thailand			
	Capsules 250 mg	Prevention of Acute Renal Rejection	23-Jul-1996
	Capsules 250 mg	Treat. Refractory Acute Renal Rejection	23-Jul-1996
United Kingdom			
	Capsules 260 mg	Prevention of acute Renal Rejection	14-Feb-1996
Uruguay			
	Capsules 250 mg	Prevention of Acute Renal Rejection	30-Apr-1997
	Capsules 250 mg	Treat. Refractory Acute Renal Rejection	30-Apr-1997
Yugoslavia			
	Capsules 250 mg	Prevention of Acute Renal Rejection	01-Sep-1996
	Capsules 250 mg	Treat. Refractory Acute Renal Rejection	01-Sep-1996

Indication: Prophylaxis of acute rejection in allogeneic hepatic transplant patients
Study MYCS-2646

Country	Dosage Form	Indication	Marketing Information (Date Introduced)
	Tablets 500 mg	Prevention of Acute Renal Rejection	01-Sep-1996
	Tablets 500 mg	Treat. Refractory Acute Renal Rejection	01-Sep-1996

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Indication: Prophylaxis of acute rejection in allogeneic hepatic transplant patients
Study MYCS-2646

Appendix B: Clinical sites

Name of Principal Investigator:	Affiliation:
Henri Bismuth, MD	Hopital Paul Brousse, France
Valentin M. Cuervas-Mons, MD	Clinica Puerta de Hierro, Spain
Richard B. Freeman, MD	New England Medical Center, USA
Robert D. Gordon, MD [*]	Emory University Hospital, USA
David Grant, MD	London Health Sciences Ctr.-Univ. Campus, Canada
Munci Kalayoglu, MD	University of Wisconsin, USA
Andrew S. Klein, MD	Johns Hopkins Hospital, USA
Goran Klintmalm, MD, PhD	Baylor University, USA
Alan N. Langnas, DO	University of Nebraska Medical Center, USA
Gary A. Levy, MD, FRCP	Univ. of Toronto Multi-Organ Transp, Canada
Christopher L. Marsh, MD	University of Washington Medical Center, USA
Geoff McCaughan, MD, PhD, MBBS	Royal Prince Alfred Hospital, Australia
Sue V. McDiarmid, MD	UCLA Medical Center, USA
Paul McMaster, MD	Queen Elizabeth Hospital, United Kingdom
Robert Merion, MD	University of Michigan, USA
J. Michael Millis, MD	University of Chicago Medical Center, USA
Peter Neuhaus, MD	Virchow-Klinikum, Germany
John Rabkin, MD	Oregon Health Sciences University, USA
John Roberts, MD	University of California, San Francisco, USA
John Roberts, MD	California Pacific Medical Center, USA
Myron E. Schwartz, MD	The Mount Sinai Medical Center, USA
Lewis Teperman, MD	New York University, USA
Russell H. Wiesner, MD	Mayo Clinic, USA

[*] Thomas G. Heffron, MD replaced Robert D. Gordon, MD in 1999 at Emory University Hospital, USA.