CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-722/S-005

50-723/S-005

50-758/S-004

50-759/S-006

STATISTICAL REVIEW(S)

JUL 19 2000

STATISTICAL REVIEW AND EVALUATION

NDA#:	NDA 50-722 / S005
Name of Drug:	CellCept® 250 mg Capsules (mycophenolate mofetil)
Applicant:	Roche Global Development, Syntex (U.S.A.) Inc.
Indications:	Prophylaxis of organ rejection in patients receiving allogeneic hepatic transplants
Documents Reviewed:	Volumes 44.1, 44.2, 44.43 – 44.55 and electronic submission
Review Type:	Clinical data
Statistical Reviewer:	Karen M. Higgins, ScD, HFD-725
Medical Reviewers:	Joyce Korvick, MD, HFD-590, and Rigoberto Roca, MD, HFD-590
Project Manager:	Matthew Bacho, HFD-590

I. INTRODUCTION

Mycophenolate mofetil (CellCept, MMF) has been shown to be safe and effective in the prophylaxis of organ rejection in patients receiving renal and cardiac transplants. This supplemental NDA submitted on the behalf of Syntex (USA), Inc., by Roche, seeks to extend the current indication of CellCept capsules to the prophylaxis of organ rejection in patients receiving allogeneic hepatic transplants. In addition to the capsules (NDA 50-722), the following 3 formulations are already approved.

1. CellCept tablets (NDA 50-723) on June 19, 1997
2. CellCept Intravenous (NDA 50-758) on August 12, 1998
3. CellCept oral suspension (NDA 50-759) on October 1,1998

Cross-reference letters will be sent to the NDAs for the tablet, intravenous, and suspension formulations.

This supplement was submitted on October 4, 1999. It contains information from one controlled clinical study, along with pharmacokinetic and clinical open-label, uncontrolled studies. These additional studies provided only descriptive efficacy information. The primary clinical evidence of the efficacy of CellCept in hepatic transplant patients comes from the single phase III study, study MYCS2646. The purpose of study MYCS2646 was to compare the safety and efficacy of a treatment regimen of CellCept given with cyclosporine (Neoral) and corticosteroids, to that of a standard treatment of azathioprine, cyclosporine and corticosteroids in liver allograft recipients. Discussion of the efficacy of CellCept in liver transplant patients from this one large clinical trial will be the focus of this review. Please see the medical officers' review and the clinical

pharmacology and biopharmaceutics review for a discussion of safety and of the submitted pharmacokinetic studies.

Reviewer's comment: The control treatment, azathioprine, is not an approved treatment for this indication. The applicant states that the regimen was a widely accepted immunosuppression regimen in liver transplant patients at the time the study was designed. However, there have been no formal controlled studies to compare results with and without azathioprine in a regimen of cyclosporine and corticosteriods in liver transplant patients. Further, the dose selected for azathioprine may not be the optimal dose for this indication.

II. STUDY DESIGN

Study MYCS2646 was a multicenter, double-blind, randomized, comparative study. The purpose of this study was to compare the efficacy and safety of CellCept to that of azathioprine both administered in conjunction with cyclosporine and corticosteroids in liver transplant patients. The majority of patients in this study came from the United States. There were a total of 565 patients (73% from the US) from 22 centers. Fifteen centers were located in the US and four were located in Europe, two in Canada, and one in Australia. The largest center contained 50 subjects (9%) while the two smallest centers contained 10 subjects each.

Subjects were selected for entry into the study after transplant surgery and if they were expected to live at least 5 days without the need for re-transplantation. Other inclusion/exclusion criteria included that it was the patient's first cadaveric orthotopic liver transplant, that the patient was a recipient of a single organ transplant, and that the patient was 16 years of age or older. After subjects were found to be qualified for the study, subjects would be randomized by center to either the test drug, CellCept IV (500 mg/vial) and 250 mg capsule, or the control, azathioprine IV (100mg/vial) and 50 mg capsule. Of the 565 subjects enrolled in this study, 287 were randomized to received azathioprine and 278 to receive CellCept. Subjects randomized to CellCept received 1 g of IV MMF bid. After 8 IV doses the patient switched to 1.5 g oral MMF bid. Patients randomized to azathioprine received azathioprine once a day at a dose selected by the investigator from between 1-2mg/kg/day. Depending on the patient's ability to take oral medication, a patient could receive either IV or oral.

Reviewer's comment: Although the applicant stated that there was flexibility in the azathioprine dose, for almost half of the subjects the doses were fixed based on weight, size of capsules and limits of 1-2 mg/kg/day. Azathioprine oral dose was supplied in 50 mg capsules. Subjects' weight ranged from 39.5 kg to 164 kg with a median of 77.9. For subjects under 75 kg there was only one dose of study drug available to them due to the size of the capsules. At the request of the FDA the applicant submitted the results from a logistic regression on the azathioprine subjects modeling the 6 month rejection endpoint by the average dose of azathioprine in the first month (submission dated 7/3/00). There was no significant effect of dose (p=0.56), however, there was a slight decrease in rejection rates with increase dose of azathioprine. Note that this relationship could be simply a function of subjects' weight or ability to tolerate higher doses.

Data were recorded on patients on a schedule of assessment until the last enrolled patient reached one year post transplantation. The study remained blinded until the last subject who enrolled reached 1 year posttransplant. Subjects would continue on the medication for a total of 3 years to follow development of malignancies and patient survival. All subjects were to be followed whether or not they withdrew from study medications.

Reviewer's comment: There were 3 patients who were lost to follow-up. By the 6 month endpoint 1 subject randomized to CellCept without a death/rejection/re-transplantation withdrew early and is censored at 64. This subject was lost to follow-up by the 3 month visit. By the 12 month endpoint 2 subjects without death/rejection/re-transplantation withdrew early and are censored at 277 and 338. One of the subjects was from the CellCept arm, withdrew for non-compliance, and was lost to follow-up by the 12 month visit. The other subject was from the azathioprine arm and withdrew due to adverse event/intercurrent illness/laboratory abnormality. This subject attended the 12 month visit on day 338, but was considered lost to follow-up by the 18 month visit.

The primary objectives of this study were to compare between the two treatment groups

1. the proportion of patients who experienced, in the first 6 months posttransplantation, one or more episodes of biopsy-proven and treated rejection or death or re-transplantation, and
2. the proportion of patients who experienced, in the first 12 months posttransplantation, graft loss (death or re-transplantation).

The first objective would test for the superiority of CellCept over azathioprine and the second would test for equivalence of the two treatments by ruling out a possible difference of greater than 5% in favor of azathioprine.

Reviewer's comment: A report was sent in by Roche in April 2000 stating that errors were found in the data from one site. However, the discrepancies found do not affect the analyses of the primary endpoints. These errors include 4 biopsies not reported on CRFs, errors in grade or date of biopsy, inclusion/exclusion and informed consent. Of the 4 biopsies not reported, 3 were negative for rejection and one was positive. However, the patient with the positive rejection had a subsequent rejection at day 93 so it is included in the 6 month analysis. Roche repeated all analyses that were affected by the errors of this site. These analyses were only minimally different than those in the original report and using the locked database. For this reason, the remainder of this review will use the locked database.

II. BASELINE CHARACTERISTICS

Demographic variables age, weight, gender, and race were balanced between the two treatments. The mean age of patients on the azathioprine arm was 49.9 years and on the CellCept was 49.0 years. The mean weight was 77.9 for azathioprine subjects and 80.7 for CellCept subjects. The percentage of females was 46% on azathioprine and 43% on CellCept. The distributions of race were similar between the two treatments. The study had a total of 2% Asian, 4% Black, 84% Caucasian, 7% Hispanic and 1% other.

Baseline health characteristics are given in the Table 1. These variables are similar between the two treatments. Viral hepatitis was the most common primary cause of hepatic failure in both treatment arms. The majority of patients had identical ABO matching. The majority of recipients and donors were Hepatitis B and C negative. There was also a large percentage of recipients who were Hepatitis C positive (29%).

Table 1 Baseline Health Characteristics

	Azathioprine n = 287	CellCept n = 278
Underlying disease diagnosis Primary cause of Hepatic Failure	Alcoholic Liver Disease: 11 (4%) Alcoholic Hepatitis: 3 (1%) Alcoholic Cirrhosis: 34 (12%) Primary biliary Cirrhosis: 40 (14%) Sclerosing Cholangitis: 37 (13%) Cryptogenic Cirrhosis: 36 (13%) Fulminant Hepatic Failure: 6 (2%) Viral Hepatitis: 80 (28%) Other: 40 (14%)	Alcoholic Liver Disease: 13 (5%) Alcoholic Hepatitis: 1 (0%) Alcoholic Cirrhosis: 39 (14%) Primary biliary Cirrhosis: 24 (9%) Sclerosing Cholangitis: 28 (10%) Cryptogenic Cirrhosis: 40 (14%) Fulminant Hepatic Failure: 6 (2%) Viral Hepatitis: 76 (27%) Other: 51 (18%)
ABO matching	Identical: 275 (96%) Compatible: 10 (3%) Incompatible: 2 (1%)	Identical: 268 (96%) Compatible: 5 (2%) Incompatible: 5 (2%)
Donor Age	39.5 (17.5) years range: 6 – 77	38.6 (16.7) years range: 7 – 75
Cold Ischemic Time	9.1 (3.3) hours range: 0.8 – 18.4	8.8 (3.1) hours range: 2 – 19.9
CMV Status of Donor/Recipient	Positive/Positive: 122 (43%) Positive/Negative: 48 (17%) Negative/Positive: 62 (22%) Negative/Negative: 39 (14%) Not Done: 16 (6%)	Positive/Positive: 112 (40%) Positive/Negative: 48 (17%) Negative/Positive: 54 (19%) Negative/Negative: 47 (17%) Not Done: 17 (6%)
Hepatitis B Status of Donor/Recipient	Positive/Positive: 0 (0%) Positive/Negative: 0 (0%) Negative/Positive: 2 (1%) Negative/Negative: 277 (97%) Note Done: 8 (3%)	Positive/Positive: 1 (0%) Positive/Negative: 2 (1%) Negative/Positive: 1 (0%) Negative/Negative: 270 (97%) Note Done: 4 (1%)
Hepatitis C Status of Donor/Recipient	Positive/Positive: 4 (1%) Positive/Negative: 1 (0%) Negative/Positive: 79 (28%) Negative/Negative: 195 (68%) Not Done: 8 (3%)	Positive/Positive: 2 (1%) Positive/Negative: 1 (0%) Negative/Positive: 81 (29%) Negative/Negative: 188 (68%) Not Done: 6 (2%)

III. PRIMARY EFFICACY ANALYSES

There were two primary endpoints for this study. The first was a combination of biopsy-proven and treated rejection, re-transplantation, and death at 6 month and the second was graft and patient survival at 12 months. As stated in the protocol, the rejection endpoint will be tested for superiority of CellCept over azathioprine while the survival endpoint will be tested for equivalence between the two arms.

- 6 Month Rejection Endpoint

The statistical analysis compared the rates of rejection/death/re-transplantation of CellCept versus azathioprine using a Cochran-Mantel-Haenszel general association test, stratified by investigator. This test calculates a pooled estimate of the Odds Ratio (OR) and compares it to the value 1.0, no effect. Prior to pooling the sites to obtain an adjusted OR, a test of homogeneity is conducted. If the test is rejected, then a difference in treatment effect across sites is concluded and a pooled analysis should not be conducted. The Breslow Day test was conducted to test for homogeneity and was not rejected with a p-value of 0.1928, implying it is appropriate to conduct the Cochran-Mantel-Haenszel test.

The results of the primary analysis (Table 2) showed that CellCept had significantly lower rates of rejection/re-transplantation/death at 6 months than azathioprine with a p-value of 0.0196. The rates for each component of this endpoint are also given in Table 2. Note that the first event to

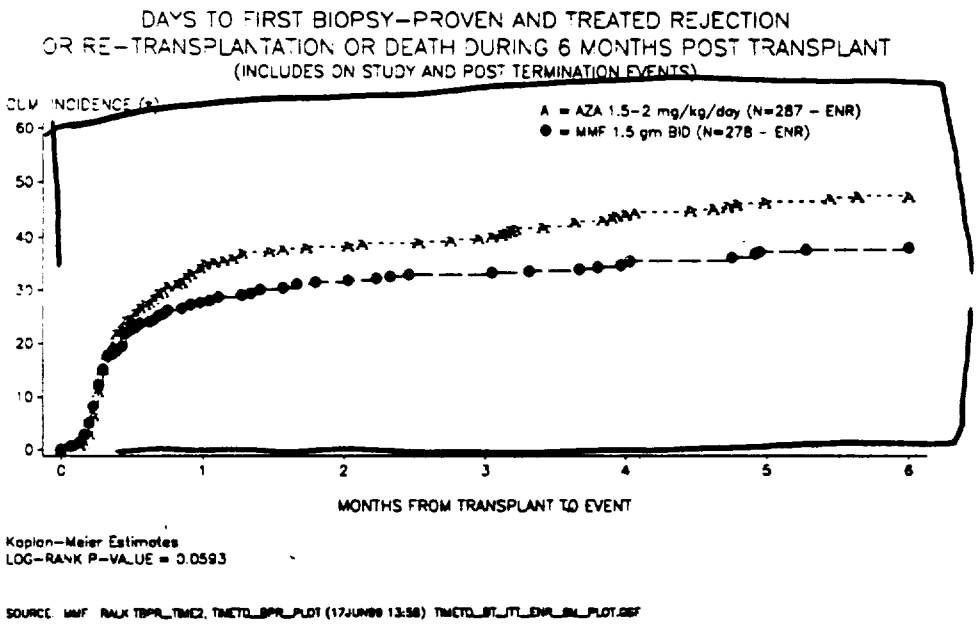
occur was counted in the percentages. A time to event analysis was also conducted. Figure 3 from the applicant's study report (reproduced below) shows the days to rejection, re-transplantation or death for the two treatments. As can be seen in this figure the curves start separating at approximately 15 days post-transplant to a difference of about 10% by 6 months.

Table 2 Results of 6 Month Rejection Endpoint

Endpoint	Azathioprine n = 287	MMF n = 278	Treatment Difference (azathioprine – MMF)	p-value
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%)	106 (38.1%)	9.6% Relative Risk (MMF/azathioprine) = 0.80	0.0196
Biopsy-proven and treated rejection	110 (38.3%)	82 (29.5%)		
Re-transplantation	5 (1.7%)	7 (2.5%)		
Death	22 (7.7%)	17 (6.1%)		

Reviewer's comment: There was no significant site by treatment interaction. However, there was a significant investigator effect (p=0.004, logistic regression). This effect has been seen in previous transplant studies.

Figure 3 Days to First Biopsy-Proven and Treated Rejection or Re-transplantation or Death During 6 Months Posttransplant (Includes On-Study and Post-Termination Events)



Reviewer's comment: As was mentioned above, one subject randomized to the CellCept arm was lost to follow-up. In the Cochran-Mantel-Haenszel analysis above this subject was considered a success at 6 months. Another common way to handle subjects who are lost to follow-up is to consider them as failures. The rate of failure for the 6 month endpoint for the CellCept arm would change to 38.4% (107/278) in this case. The p-value obtained for this analysis increases to p = 0.025.

- 12 Month Death and Re-transplantation Endpoint

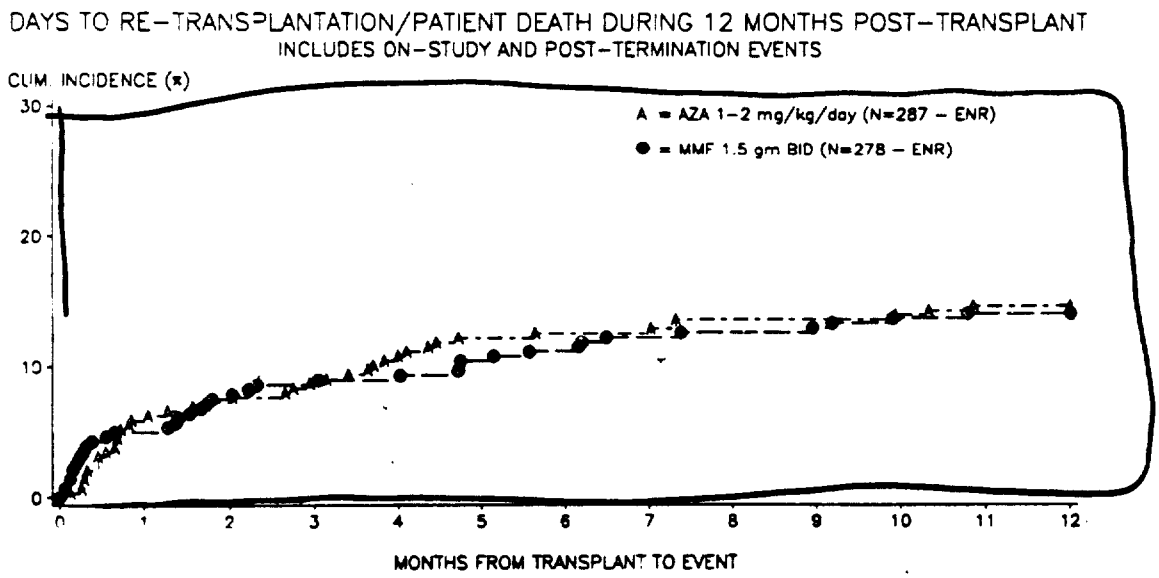
The endpoint of death or re-transplantation at 12 months was a co-primary endpoint. The study was designed to show equivalence between the two treatments on patient and graft survival. Equivalence of the two treatments would be concluded by ruling out a possible difference of greater than 5% in favor of azathioprine. A confidence interval weighted by center was calculated for the difference in rates of death/re-transplantation. The entire confidence interval (azathioprine – CellCept) would need to be above –5%.

Table 3 contains the results from the analysis of the 12 month endpoint. The observed rate of death/re-transplantation for CellCept was lower than the observed rate for azathioprine (14.0% vs. 14.6%). The weighted difference (weighing on site) was 0.447%. The confidence interval extends slightly beyond the FDA's limit of –5% to -5.09%. A time to event analysis was also conducted. Figure 6 from the applicant's study report (reproduced below) shows the days to death/re-transplantation for the two treatments. This figure shows that the two curves are quite similar.

Table 3 Results of 12 Month Death and Re-transplantation Endpoint

Endpoint	Azathioprine n = 287	MMF n = 278	Treatment Difference (azathioprine – MMF)	CI
Co-primary graft loss endpoint: Number (%) of patients experiencing graft loss (death or re-transplantation) during the initial 12 months posttransplant	42 (14.6%)	39 (14.0%)	Weighted difference: 0.447%	95% CI = (-5.09%, 5.98%)
Re-transplantation	11 (3.8%)	14 (5.0%)		
Death	31 (10.8%)	25 (9.0%)		

Figure 6 Days to Re-Transplantation/Patient Death During 12 Months Posttransplant (Includes On-Study and Post-Termination Events)



Reviewer's comment: As was mentioned above, two subjects randomized to the CellCept arm were lost to follow-up prior to the 12 month visit. In the analysis above these subject were considered as successes at 12 months. Another common way to handle subjects who are lost to follow-up is to consider them as failures. The rate of failure for the 12 month endpoint for the CellCept arm would change to 14.7% (41/278) in this case. The point estimate for CellCept is slightly lower than that for azathioprine. The confidence interval becomes (-5.91, 5.32).

Reviewer's comment: Reducing early rejection does not seem to be highly predictive of re-transplantation or death by 12 months. If the goal in treatment is merely to reduce the number of rejections then this treatment has been shown to be effective compared to an unapproved comparator. However, if rejection is considered to be a surrogate to graft or patient survival it has been shown to be a poor surrogate. CellCept has not shown to have any benefits over the unapproved comparator in patient and graft survival. Further, its benefits in reducing rejection decrease over time as shown by the differences in rejection rates at 12 months being smaller and no longer statistically significantly different (see Secondary Endpoints below).

IV. WITHDRAWALS

There was a high premature withdrawal rate in this study; 54% of subjects withdrew from the study medication early. Since this could have great effects on the study conclusions the reason for and timing of withdrawals was looked at closely for differences between the two treatment arms. Note that the superiority analysis on acute rejection may be more conservative under the assumption that patients who withdrew from the study received similar follow-up treatment regimens. While the survival analysis which looks for equivalency may be less conservative.

There were 306 premature withdrawals from this study, 154 (53.7%) from the azathioprine group and 152 (54.7%) from the CellCept group. The reasons for withdrawal were similar between the two treatments and are given in Table 4 below. The primary reason for withdrawal was adverse event/new intercurrent illness/new lab abnormality (33.1% for azathioprine and 33.8% for CellCept). The largest difference in reason for withdrawal was for unsatisfactory therapeutic response where slightly more in azathioprine group withdrew.

Table 4 Reasons for Withdrawal

	Azathioprine n = 287	**CellCept n = 278**	**Total n = 565**
Total (%) Patients Ongoing	133 (46.3%)	126 (45.3%)	259 (45.8%)
Total (%) premature withdrawals	154 (53.7%)	152 (54.7%)	306 (54.2%)
Primary Reason for Withdrawal			
AE/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	6 (2.1%)	7 (2.5%)	13 (2.3%)
Need med. prohibited by protocol	4 (1.4%)	5 (1.8%)	9 (1.6%)
Death	13 (4.5%)	11 (4.0%)	24 (4.2%)
Malignancy	1 (0.3%)	2 (0.7%)	3 (0.5%)
MD decision	2 (0.7%)	0 (0.0%)	2 (0.4%)
Miscellaneous	1 (0.3%)	3 (1.1%)	4 (0.7%)
Patient request	15 (5.2%)	17 (6.1%)	32 (5.7%)
Primary graft Dysfunction	1 (0.3%)	5 (1.8%)	6 (1.1%)

On the CellCept arm 38.5% withdrew by 6 months and 45.3% by 12 months. On the azathioprine arm 37.3% withdrew by 6 months and 47.4% by 12 months. The time to withdrawal curves are similar for the two treatments (not shown). There are more early terminations (by 7 days post-transplant) in the CellCept arm (19, 6.8%) than in the azathioprine arm (11, 3.8%). However, by day 14 the withdrawal rates are very similar (11.9% on CellCept and 10.1% on azathioprine). Of the withdrawals by day 7, there are more serious reasons for withdrawals in the CellCept arm (8 primary nonfunctioning graft or death versus 2 on azathioprine). This trend can also be seen in Figure 6. above.

The mean numbers of days on treatment (number of days "on-study") were similar between the two arms (287 days on CellCept and 297 days on azathioprine). These numbers include entire study period (past 1 year post-transplant). As would be expected, the mean number of days of treatment is associated with both the 6 and 12 month outcomes. Subjects who had a biopsy-proven and treated rejection, re-transplantation, or death by 6 months had a smaller mean number of days on treatment than those who did not have an outcome (CellCept: 219 for those with outcome vs. 345 for those without outcome, azathioprine: 216 for those with outcome vs. 352 for those without). Subjects who had re-transplantation or death by 12 months had a mean number of days on treatment that was much shorter than those without (CellCept: 43.2 for those with outcome vs. 338 for those without, azathioprine: 51 for those with outcome vs. 327 for those without).

Reviewer's comments: Differing rates of withdrawal can point to a large deficiency in the clinical trail especially if the rates of withdrawal were high. The above discussion shows that there was very little difference in the rate of withdrawal and reason for withdrawal between the two treatments.

V. ADDITIONAL ANALYSES

- Severity of Rejection

The first acute rejection episode was classified by the [redacted] criteria of mild, moderate, or severe acute rejection (see Table 5 below). CellCept has a smaller percentage in all of the categories of rejection. There were similar distributions of [redacted] scores within each treatment. Approximately 50% were mild, 40% moderate and less then 10% severe. An exploratory analysis to determine how rejection rates at 6 months affect graft and patient survival at 12 months was conducted (Table 6). In this table the 12 month endpoint is stratified by outcome at 6 months. Only a small percentage of those without rejection at 6 months go on to fail at 12 months for both arms. As for those who had a rejection at 6 months, CellCept had a lower rate of failure at 12 months for the mild rejecters and a higher rate for the moderate and severe rejecters.

Table 5 6 Month Outcome by [redacted] Score

		Azathioprine n = 287	CellCept n = 278
No Event		150 (52%)	172 (61%)
Level of Rejection	Missing	4 (1%)	0 (0%)
	Mild	57 (20%)	44 (16%)
	Moderate	40 (14%)	33 (12%)
	Severe	9 (3%)	5 (2%)
Death/Re-transplantation		27 (9%)	24 (9%)

Table 6 12 Month Outcome Stratified by 6 Month Outcome

		Graft loss and Death at 12 months	
6 month outcome		Azathioprine	CellCept
No Event		3/150 (2%)	5/172 (3%)
Level of Rejection	Missing	1/4 (25%)	0/0 (0%)
	Mild	7/57 (12%)	3/44 (7%)
	Moderate	3/40 (8%)	5/33 (15%)
	Severe	1/9 (11%)	2/5 (40%)
Death/Re-transplantation		27/27 (100%)	24/24 (100%)

- Secondary Endpoints

The applicant defined a large number of secondary rejection endpoints. These endpoints are based on slight changes in the determination of rejection. Of the 6 supporting secondary analyses for the 6 month rejection endpoint, all showed superiority except 1 which showed a similar trend in rates (p=0.087). Seven secondary analyses were conducted on rejection at 12 months post-transplantation. In all of these analyses the CellCept arm had lower rates of rejection/re-transplantation/death than the azathioprine arm, however the difference was smaller than at 6 months and only 2 of the 7 had p-values less than 0.05. This could be both a result of the treatment withdrawal, making the two groups more similar, and of a lessening of the benefits of CellCept over time. Overall, the results of these analyses were supportive and show that a slight deviation in definition of rejection would not have drastically changed the outcome of the study.

- Efficacy by Baseline Characteristics

Analyses by demographic variables (age, race, gender) using logistic regression models did not show any large differences in outcome between the two treatments. Age was found to be a significant predictor of outcome by 6 months with older subjects having lower rates of rejection/re-transplantation/death (excluding 5 subjects between 70-80). However, an interaction with treatment was not significant showing no treatment by age effect. Age was not a significant predictor of 12 month re-transplantation/death endpoint nor was the interaction with treatment. Sex was also found to be a significant predictor of outcome by 6 months with males having lower rates of rejection than females. The interaction with treatment again was not significant nor was sex or the interaction significant in the model of the 12 month outcome. Due to the small number of non-Caucasian subjects no conclusion could be drawn regarding race and treatment. Analyses by baseline health characteristics (Hepatitis C status, Cold Ischemic Time, CMV status, Hepatitis B status, HLA mismatches) showed no interaction with treatment. Note that this study was not powered to detect significant treatment differences in the different subgroups and the total number of patients in some of the subgroups are small.

Reviewer's comment: Note that the results with Age are possibly due to the manner in how subjects are selected to receive liver transplants, with younger patients having greater chance of receiving transplants regardless of their health status than older patients.

Analysis by US/Canada versus Europe/Australian sites showed no interaction with treatment. However, Europe was found to have higher rates of rejection by about 10% at 6 months for both treatment arms (p=0.0668, logistic regression).

VI. CONCLUSIONS
(Which May Be Conveyed to the Applicant)

1. The results of Study MYCS2646 demonstrate efficacy of CellCept compared to azathioprine for the 6 month endpoint of biopsy-proven and treated rejection, re-transplantation, or death. This result is robust to minor deviations in the definition of rejection.

2. The results for the 12 month survival endpoint fail to demonstrate equivalence, within a delta of 5%, of CellCept and azathioprine in rates of 12 month death or re-transplantation. However, the confidence limit was close at 5.09%. These results were less robust to alternative missing data analysis where the limit increased to 5.91%.

RECOMMENDED REGULATORY ACTION:

From a statistical perspective, the data provided by the sponsor support the approval of CellCept for the indication of prophylaxis of organ rejection in patients receiving allogeneic hepatic transplants.

/S/ 7/19/00

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cc:
Orig. NDA 50-722 / S005
HFD-590
HFD-590/Dr. Albrecht
HFD-590/Dr. Cavaille-Coll
HFD-590/Dr. Korvick
HFD-590/Dr. Roca
HFD-590/Mr. Bacho
HFD-725/Dr. Huque
HFD-725/Dr. Higgins
HFD-725/Ms. Robinette
This review contains 10 pages.