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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

50-791

Medical Review(s)

Medical Officer's Review of NDA 50-791

Myfortic® (ERL080) for Renal Transplantation

Identifying Information

Applicant Identification

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Contact Person:

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Director, Drug Regulatory Affairs

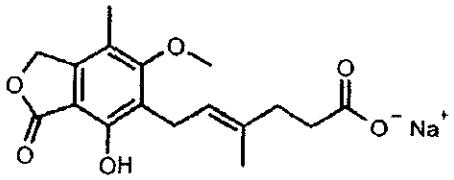
Submission / Review dates:

Date of submission: April 30, 2003
CDER stamp date: April 30, 2003
Date review begun: November 3, 2003
Date review completed: January 30, 2004

Drug Identification

Established name: Mycophenolic acid
Research name: ERL080
Trade name: MYFORTIC®
Chemical name: (E)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoic acid sodium salt

Chemical Structure:



Molecular Formula:	$C_{17}H_{19}O_6$ Na
Molecular Weight:	342.32
Pharmacologic Category:	Immunosuppressant for transplantation
Dosage Form:	Tablet
Strength:	180 mg & 360 mg
Route of Administration	Oral
Related IND/NDA:	IND 57,005

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Clinical Review for NDA 50-791

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The reviewing Medical Officer (MO) recommends an action of **Approval** for NDA 50-791; use of Myfortic® (mycophenolic acid) for the prophylaxis of organ rejection in allogeneic *de novo* and stable renal transplant recipients.

The approval of Myfortic® for the prevention of rejection in renal transplantation was supported by two adequate and well controlled studies in *de novo* and stable renal transplant recipients, conducted by Novartis and reported in NDA 50-791. The Myfortic dose used in these studies was based on the amount of mycophenolic acid that is delivered by the approved dose of Cellcept® (mycophenolate mofetil) for prevention of rejection in renal transplantation, and supported by pharmacokinetic studies conducted by Novartis, comparing the systemic exposure to mycophenolic acid when delivered by oral doses of mycophenolate sodium or mycophenolate mofetil.

Safety and efficacy information from the clinical studies conducted by Novartis were included in the proposed label for Myfortic®. Since mycophenolic acid (MPA) is the active moiety of Cellcept® and Myfortic®, additional safety information associated with systemic exposure to MPA included in the approved Cellcept® label (from March 2003), including post-marketing safety information and other class labeling was also included in the proposed Myfortic® label. NDA 50-791 is a 505 (b)(2) submission, please refer to the Team Leader's Review, Dr. Cavaillé-Coll for details.

Myfortic® is the sodium salt of mycophenolic acid, an immunosuppressant agent related to CellCept® (mycophenolate mofetil). In NDA 50-791, the Application that is the subject of this review, Novartis (the Applicant) is seeking the approval for Myfortic® 720 mg oral tablet administered twice daily, for prophylaxis of organ rejection in allogeneic renal transplant recipients.

Myfortic® (sodium salt of mycopenolic acid) delivers the active ingredient mycophenolic acid (MPA). MPA has a cytostatic effect on T- and B-lymphocytes due to MPA's inhibitory effects on inosine monophosphate dehydrogenase, which lead to inhibition of the *de novo* pathway for guanosine nucleotide synthesis. T- & B-lymphocytes are

dependent on the *de novo* pathway for proliferation. Hence, MPA's mode of action is primarily to suppress T- & B-lymphocyte responses.

The efficacy and safety data provided by the Applicant in the submission and reviewed by the reviewing MO included Study-B301, Study-B302, and Study-0107, and the 120-Day Safety Update Report. In these studies the safety data for Myfortic® 720 mg po bid was compared to mycophenolate mofetil 1 gm po bid for the prophylaxis of organ rejection in allogeneic renal transplant patients. In Study-B301 a *de novo* renal transplant population was studied, and in Study-B302 a maintenance renal transplant population was studied. Study-0107 was a small study intended to evaluate the relative gastrointestinal tolerability of ERL080 compared to mycophenolate mofetil in renal transplant recipients with gastrointestinal complaints secondary to mycophenolate mofetil. This study was prematurely terminated when it appeared it would be unable to demonstrate superior tolerability of ERL080 compared to mycophenolate mofetil.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The MO is requesting that the Applicant conduct a Segment III prenatal/postnatal developmental toxicity study in pregnant female rates with Myfortic® as a phase IV post marketing commitment. The MO is requesting the study, because the 505 (b)(2) submission does not contain a reference to this study that can be used to address the requirements for a Segment III developmental toxicity study.

The Agency waived additional requirements for studies in pediatric age group 0-10 years of age. The use of Myfortic® in pediatric age group 0-10 does not represent a meaningul therapeutic benefit over existing treatments (Myfortic® is available in fixed capsule strengths of 180 mg or 360 mg, whereas mycophenolate mofetil is marketed in suspension, capsule, and intravenous formulation), and it is not likely to be used in a substantial number of patients [In 2003, there were 276 pediatric renal transplant recipients aged 0-10 years (UNOS data, United States)]. The Applicant has provided the Agency with pharmacokinetic data for older children (>10 years) that allows appropriate extrapolation for dosing requirements in patients with a body surface area of $> 1.19\ m^2$. Myfortic® doses for patients with a body surface area of $< 1.19\ m^2$ cannot be accurately administered using currently available formulations of Myfortic® tablets.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

In NDA 50-791, the Applicant submitted the reports for two adequate and well controlled clinical studies (B301 & B302) in renal transplant patients. Study-B301 compared the efficacy of Myfortic® 720 mg po bid to CellCept® 1 gm po bid in combination with Neoral® and corticosteroids in *de novo* renal transplant recipients. Study-B302 was primarily a safety study and efficacy was a secondary endpoint comparing Myfortic® 720 mg po bid to CellCept® 1 gm po bid in combination with Neoral® and corticosteroids in maintenance renal transplant recipients. A third clinical study in renal transplant patients complaining of gastrointestinal symptoms of intolerance to CellCept®, Study-0107, was unable to demonstrate superiority of Myfortic® compared to CellCept® with respect to gastrointestinal tolerance. In addition, the submission included the 120-Day safety update report for Myfortic®.

Study-B301 was a multicenter, randomized, double-blind, parallel study designed to demonstrate the non-inferiority of Myfortic® 720 mg po bid compared to CellCept® 1 gm po bid in combination with Neoral® and corticosteroids in a *de novo* adult (18-75 years) renal transplant population (12 months analysis). The enrollment period for the study was Dec 1998 through Apr 2001. Clinical sites recruited patients from the North America and Europe. A total of 423 patients were randomized to two treatment groups (Myfortic® 213 patients vs. CellCept® 210 patients). The baseline demographic characteristics of the enrolled population showed a mean age of 47 years, 88% Caucasian / 7% Black / 4% Other race / 1% Oriental. Forty one percent of patients were over the age of 50 years. In the study, common reasons for renal insufficiency were glomerulonephritis, polycystic kidney disease, hypertension, and diabetes mellitus. The primary population of interest in the study was the Intent-to-Treat (ITT) population for the 12 month period (ITT population was defined as all randomized patients who received at least one dose of randomized study medication). At the end of the 12 months, all patients were offered to stay on study drug, or switch to Myfortic® for an extended evaluation period until Myfortic® is available at the country where the patient was enrolled.

Study-B302 was a multicenter, double-blind, randomized, parallel group study designed to evaluate the safety and efficacy of ERL080 720 mg po bid compared to MMF 1 gm po bid in an adult (18-75 year) population for maintenance renal transplant patients. The study period was from Feb 1999 to Oct 2001. Participating clinical centers were from North America and Europe. The primary objective of the study was to evaluate the rate of gastrointestinal and neutropenic adverse events (including other adverse events) for 12 months after administration of study medications. A secondary objective of the study was to evaluate the efficacy of ERL080 compared to MMF for the 12-Month period after administration of study medications.

A total of 322 patients were randomized in the study (ERL080 159 and MMF 163 patients). The baseline demographics characteristics of the study population were a mean age of 48 years, Caucasians represented 74% of patients followed by Blacks ~19% and Orientals 3%. The proportion of females in the ERL080 group 39% was higher than the proportion of females in the MMF 29% group (p=0.079 approaching significance). Glomerulonephritis followed by hypertension were the two most common causes of end stage renal disease. The primary population of interest was the ITT population (defined as all randomized patients who received at least one dose of randomized study medication. At the end of the twelve months, all patients were offered to stay on study drug, or switch to Myfortic® for an extended evaluation period until Myfortic® is available at the country where the patient was enrolled.

Study-0107 was a double-blind, randomized, parallel group study designed to demonstrate superiority of ERL080 compared to MMF for gastrointestinal tolerability in maintenance renal transplant patients with GI complaints secondary to MMF. All patients in this study were also treated with Neoral® and steroids. This study was terminated prematurely because it did not appear that it would be able to demonstrate superior tolerability of Myfortic® compared to MMF. The total number of patients randomized into this study was 149 (ERL080 74 vs. MMF 75) patients. The baseline demographic characteristics demonstrate a slightly younger population in the ERL080 (mean age 43 years) group compared to the MMF (mean age 46 years) group; gender, race, weight, and height were comparable in both groups. The MO did not review this study in detail, because it was terminated when it appeared that it would be unable to demonstrate superior tolerability with ERL080 compared to MMF.

B. Efficacy

The two efficacy studies for NDA 50-791 were Studies B301 & B302. In both clinical studies, Myfortic® (ERL080) was compared to CellCept® (MMF). The MMF regimen used is FDA approved for prevention of organ rejection in renal transplant recipients. Both ERL080 and MMF require conversion in the gastrointestinal tract to the active moiety mycophenolic acid (MPA). Therefore MMF was an acceptable comparator to the Agency for the clinical studies submitted in NDA 50-791. The results of efficacy from the two clinical studies support the use of ERL080 in the prophylaxis of organ rejection in *de novo* and maintenance renal transplant recipients.

Study-B301, was a multicenter, double-blind, randomized, parallel group, designed to evaluate the efficacy and safety of ERL080 720 mg po bid oral tablet compared to MMF 1 gm po bid oral tablet, in combination with Neoral® and steroids in the prophylaxis of organ rejection in *de novo* renal transplant patients (non-inferiority). Primary efficacy was measured by the difference in the rates for the composite endpoint (biopsy-proven acute rejection, graft loss, death, and lost to follow-up), at Month-6 and Month-12 post-transplantation for the two treatment groups in the Intent-to-Treat (ITT) population. Eligible patients were adult males and females (18-75 years) with end-stage renal

disease. The primary efficacy results were supported by results from the co-primary endpoint graft loss or death or lost to follow-up at 12 months), the per protocol population and by the secondary efficacy endpoints (the individual variables for the composite primary endpoint).

The difference in the point estimates of the efficacy (composite endpoint) of the two treatments (ERL080-MMF) at Month-6 was -0.4 [95% CI of {-8.7, 8.0%}]. The pre-specified lower/upper bound of the 95% confidence interval used to define non-inferiority was {-12.0, 12.0}. A similar difference in the point estimate was observed for the Month-12 period 0.5 [95% CI {-8.1, 9.2%}] (table).

B301 Primary Efficacy endpoints at 6 & 12 months post-transplantation (ITT population)
Source: Modified Table 9-1 Vol 140

Variables	Period	ERL 720 mg bid N=213	MMF 1 gm bid N=210	(ERL080-MMF) 95% CI {%, %}
Composite primary efficacy endpoint at	6 months	55 (25.8%)	55 (26.2%)	-0.4 {-8.7, 8.0}
	12 months	61 (28.6%)	59 (28.1%)	0.5 {-8.1, 9.2}
Biopsy-proven acute rejection	6 months	46 (21.6%)	48 (22.9%)	
	12 months	48 (22.5%)	51 (24%)	-1.8 {-9.8, 6.3}
Graft loss	6 months	7 (3.3%)	9 (4.3%)	
	12months	9 (4.2%)	9 (4.3%)	-0.5 {-4.3, 3.2}
Death	6 months	1 (0.5%)	2 (1%)	
	12 months	2 (0.9%)	5 (2.4%)	
Lost to Follow-Up**	6months	3 (1.4%)	0	
	12months	5 (2.3%)	0	
Graft loss, Death, Lost to Follow-Up***	12 months	20 (9.4%)	18 (8.6%)	

Composite primary efficacy endpoint (Treatment failure) = biopsy-proven acute rejection, graft loss or death, death, lost to follow-up
**Lost to Follow-up indicates patients who were lost to follow-up without prior biopsy-proven acute rejection, graft loss or death
*** Lost to Follow-up indicates patients who were lost to follow-up without graft loss or death (9 Myfortic patients and 4 MMF patients)
Ab-Rx = Antibody treatment
All patients in the study received Neoral® and steroids

Analysis of results in the per protocol population (PP) defined as the subset of the ITT population that did not violate the protocol in a "significant" way, and the secondary efficacy variables supported the primary efficacy endpoint for the ITT population (table).

Study-B301 Secondary efficacy endpoints (ITT population, Month-0 to 12)
Source: PTT 9.1-1 & 9.1-13

Variables	Period	ERL080 N=213	MMF N=210
Any acute rejection	6 months	52 (24.4%)	55 (26.2%)
	12 months	54 (25.4%)	58 (27.6%)
Treated acute rejection	6 months	51 (23.9%)	52 (24.8%)
	12 months	52 (24.4%)	54 (25.7%)
Antibody-Treated acute rejection	6 months	11 (5.2%)	10 (4.8%)
	12 months	11 (5.2%)	10 (4.8%)
Biopsy-proven chronic rejection	6 months	8 (3.8%)	12 (5.7%)
	12 months	12 (5.6%)	16 (7.6%)

Study-B302 was a multicenter, randomized, double-blind, parallel study designed to evaluate the safety and efficacy of ERL080 720 mg po bid compared to MMF 1 gm po bid, in combination with Neoral® ± corticosteroids for the prophylaxis of organ rejection in maintenance renal transplant recipients. Therefore these patients were already on an immunosuppressive regimen post-transplantation prior to enrollment in the study. The, run-in period, where all patients were exposed to MMF for 2-week prior to randomization, may potentially select a less sensitive population to detect differences in tolerability of ERL080 to MMF.

The primary efficacy endpoint in Study-B302 was similar to the composite primary efficacy endpoint for Study-B301, treatment failure (biopsy-proven acute rejection, graft loss, death, and lost to follow-up). A co-primary efficacy endpoint (graft loss or death or lost to follow-up) and the secondary efficacy variables supported the primary efficacy endpoint. The difference in the point estimate of the primary efficacy composite endpoint for the two treatment groups was -2.4 [95% CI {-7.4, 2.7%}], which was within the pre-specified bounds of the 95% CI used to define non-inferiority in the study. Analysis of the co-primary endpoint and the secondary variables supported the primary composite endpoint (table).

Study-B302 Primary & Secondary Efficacy Endpoints (ITT population)
Source: Modified PTT 9.1 Vol 150

		ERL080	MMF	ERL080-MMF 95% CI
***Composite Primary variable**	6 months	7 (4.4%)	11 (6.7%)	-2.4 (-7.4,2.7%)
	12 months	12 (7.5%)	20 (12.3%)	-4.2 (-11.3, 1.8%)
Secondary variables				
BPAR	6 months	2 (1.3%)	2 (1.2%)	
	12 months	2 (1.3%)	5 (3.1%)	
Acute rejection	6 months	2 (1.3%)	3 (1.8%)	
	12 months	2 (1.3%)	6 (3.7%)	
Treated acute rejection	6 months	2 (1.3%)	2 (1.2%)	
	12 months	2 (1.3%)	3 (1.8%)	
Acute rejection requiring Ab therapy	6 months	0	0	
	12 months	0	0	
BPCR	6 months	4 (2.5%)	4 (2.5%)	
	12 months	4 (2.5%)	8 (4.9%)	-1.1% (-5.6, 3.3%)
Graft loss	6 months	0	1 (0.6%)	
	12 months	0	1 (0.6%)	
***Death	6 months	0	1(0.6%)	
	12 months	2 (1.3%)	4 (2.5%)	
#Lost to follow-up	6 months	5 (3.1%)	7 (4.3%)	
	12 months	8 (5%)	10 (6.1%)	-1.1% (-6.1, 3.9%)
##Graft loss or death or lost to follow-up	12 months	10 (6.3%)	17 (10.4%)	

*Composite primary variable (Treatment failure) = Biopsy proven acute rejection (BPAR), graft loss, death, lost to follow-up
***Patient #5110013 (MMF) died post-study on Day-290. This patient withdrew consent on Day-273, and was discontinued from the study. Patient was listed in the composite variable as a "lost to follow-up"
#Lost to Follow-up indicates patients who were lost to follow-up without prior biopsy-proven acute rejection, graft loss or death
##Lost to Follow-up indicates patients who were lost to follow-up without prior graft loss or death (8 Myfortic patients and 12 MMF patients)

Study-0107 was intended to evaluate the relative gastrointestinal tolerability of ERL080 compared to MMF in renal transplant recipients with gastrointestinal complaints secondary to MMF. This study was prematurely terminated when it appeared it would be unable to demonstrate superior tolerability with ERL080 compared to MMF.

The extended B301 & B302 studies, included patients from the core Studies B301 & 302 who agreed to continue or switch to ERL080 therapy. In both studies, the rates for the efficacy variables were comparable at 24 & 30 month follow-up periods (0-12 Months core study + 12 & 18 months extension phase) in patients initially treated with 0-12 Month ERL080 vs. patients treated with 0-12 Month MMF. Note that the extended studies represented a non-random selected subset of the population originally enrolled in studies B301 & B302. Therefore, comparisons should be interpreted with caution.

C. Safety

The safety report for NDA 50-791 incorporated safety data from the three clinical studies B301, B302, 0107. The safety data in the submission contained the 12-Month efficacy and safety data from the 2 phase III studies in *de novo* and maintenance renal transplant patients, and from the 5-week Study-0107. Safety data was also provided for the open-label extended phase for Studies B301 & B302. The cut-off date for safety data in the original submission from April 30, 2003 was June 14, 2002 for the original studies, and January 17, 2003 for the extension studies.

In Study-B301, comparable numbers of patients from the two treatment groups were exposed to study drug, Neoral®, and corticosteroids. The majority of patients in the study were exposed to study drug up to Month-12 window visit (ERL080 71%, 151/213 patients vs. MMF 75%, 158/210 patients). Approximately 41% of patients from both treatment groups received antibody therapy. The most common reasons for discontinuing treatment prior to the Month-12 window was the occurrence of an adverse event [ERL080 36 (16.9%) patients vs. MMF 29 (13.8%) patients], followed by an unsatisfactory therapeutic effect [ERL080 11 (5.2%) vs. MMF 8 (3.8%)], graft loss [ERL080 5 (2.3%) patients vs. MMF 6 (2.9%)]; other less common reasons included abnormal laboratory finding, withdrawn consent, lost to follow-up or death.

As expected in a *de novo* renal transplant population such as this one, adverse events were reported by almost all patients in both treatment groups. In general, the rates for adverse events were comparable in both treatment groups. Gastrointestinal adverse events were comparable for the 0-12 Month period (ERL080 group 79.8% compared to the MMF group 77.1%); also, the rates for GI AEs were comparable at all window visits. Rates of infections were comparable in both treatment groups. Bone marrow suppression (reflected in WBC, platelet, and RBC counts), was observed to be comparable in both treatment groups. No patients in either treatment group experienced

a neutrophil count of $\leq 0.5 \times 10^9$ /L. Common AEs with a difference of >5% between treatment groups included infections, surgical/medical procedures, and investigations. For infections, the difference in rates was accounted for by an increased rate of urinary tract infections in the MMF group; however, these infections were minor, and are expected in a renal transplant study. Therefore no meaningful conclusion can be drawn from this observation.

There were 7 deaths reported in the 0-12 Month period; 2 were in the ERL080 group, and 5 were in the MMF group. In the ERL080 group, one death at Day-92 was secondary to complications of congestive heart failure, the other death at Day-343 was secondary to sepsis related. At the time of death all 7 patients had a functioning graft. None of the deaths were directly attributed to the study drug.

The most commonly reported serious AEs in the Study-B301 were related to the GI-tract or renal system. The overall rates for serious AEs in the study were comparable in both treatment groups. Severe AEs were reported by 38% of patients in the ERL080 group and 41% of patients in the MMF group. Severity rates were comparable between the two treatment groups. Sixteen percent of patients in the ERL080 group discontinued study drug due to an AE compared to Fourteen percent in the MMF group. The most common reason for discontinuing study drug from an AE was related to GI AEs (5%) in both treatment groups. Both treatment groups had a similar rate of malignancies (2%). Laboratory events for hematological variables and biochemistry were comparable between the two treatment groups. Patient mean weight, creatinine, and urea values improved after transplantation in both treatment groups.

In Study-B302, patients in both treatment groups were exposed to a comparable dose of study drug at all window visits. Approximately 90% of patients in the ERL080 group received ERL080 for 12 months. Six percent of patients in the ERL080 group prematurely discontinued study drug due to an AE (2 deaths, 2 diarrhea, 2 leukopenia, 2 infection,1 ↑ creatinine), and 4% of patients in the MMF group prematurely discontinued study drug due to an AE (1 death, 2 diarrhea,2 malignancy, 1 ↑ creatinine). The majority of dose reductions in both treatment groups occurred during the first 6 months of the study. The cause for dose reductions (44% for both treatment groups) was commonly related to AEs (15% for both treatment groups) or dosing errors. Exposure to concomitant immunosuppressive regimens (Neoral® and corticosteroids) was comparable in both treatment groups.

By the 12-Month point, the majority patients from Study-B302 had experienced an AE (ERL080 94% vs. MMF 93%). The majority of AEs occurred in the 0-3 Month period of the study. The most common AEs were diarrhea and nausea in the ERL080 group and diarrhea and nasopharyngitis in the MMF group. The rates for AEs were comparable for the two treatment groups.

In Study-B302, the GI AE rates were similar in the ERL080 group 57% compared to the MMF group 57% for the 0-12 Months; these rates were lower (as expected) than the

rates observed in the *de novo* Study-B301. Nausea and vomiting were among the most common GI AEs affecting more patients in the ERL080 group. The majority of patients experienced nausea and vomiting within the first 3 months of the study. A potential limitation of Study-B302 when assessing GI tolerance is that the run-in period of at least 2 weeks on MMF before randomization could have selected patients who tolerated the effects of mycophenolic acid, and favored elimination of those who were more sensitive to the gastrointestinal adverse events. No patients in the ERL080 group developed severe neutropenia compared to one patient in the MMF group. A similar number of patients from both treatment groups developed expected malignancies (6%).

A total of 7 deaths were reported in Study-B302; none of the deaths could be directly attributed to the study drug. There were 2 deaths in the ERL080 group. This was a 23 year-old ♀ who died on Day-350 from multiple organ failure. The remaining patient died from a cryptococcal brain abscess related to AIDS. The MMF group had 5 deaths during the 0-12 Month study period. Severe AEs were comparable for the two treatment groups. A total of 9 patients in the ERL080 group and 10 patients in the MMF group discontinued study medication prematurely. In the ERL080 group the most common reason for discontinuing study drug was a severe infection in 5/9 patients followed by leukopenia and diarrhea. And in the MMF group, the most common cause of discontinuing study drug was a GI complaint in 4 patients followed by an elevated creatinine value or neoplasm, 2 patients for each.

Overall, the safety data for Study-0107 was comparable to the safety data from Study-B302.

Studies B301Ext & B302Ext (extension phase), did not demonstrate any new safety risks associated with use of ERL080.

The 120-Day Safety Update contained safety data from the extension studies through March 31, 2003. The new analysis for the extension studies extended the cohort for Study-B301 up to 24 months for all patients in the extension phase and for 30 months for patients who reached the 30-Month point.

As of May 31, 2003 the total number of subjects exposed to ERL080 was 2396 patients across the clinical (including193 subjects in the pharmacologic) studies. A total of 766 patients were followed for ≥12 months and 220 patients were followed for ≥36 month. Overall, there were no new unexpected safety issues reported in the 120-Day Safety Update compared to the data reported in the original submission.

D. Dosing

The proposed dosing for Myfortic® is 720 mg po bid. Myfortic® is supplied as 360 mg and 180 mg tablets. No dosing adjustments are required in patients with renal or hepatic impairment. Myfortic® tablets should not be crushed, chewed, or cut prior to ingesting; and tablets should be administered on an empty stomach (1 hour before or two hours after food intake). Myfortic® is indicated for prophylaxis of organ rejection in renal transplant recipients.

E. Special Populations

Gender: The clinical studies in NDA 50-791 contained more male than female subjects; however, each of the clinical Studies B301 & B302 had more than 30% female representation. In both studies, female subjects experienced a higher rate of urinary tract infections compared to male subjects. This finding was expected based on the natural rates for urinary tract infection in females. Results from the two pivotal studies do not suggest that females are at an increased risk of adverse events from the use of Myfortic®.

Age: Clinical studies of Myfortic® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant or other drug therapy.

Ethnicity: Study-B301 included 30 (<10%) Black patients. Seventeen patients were in the ERL080 group and thirteen patients in the MMF group. The rate of drug-related AEs was higher in the MMF group compared to the ERL080 group; however, no meaningful conclusions can be drawn due to the small numbers of Black patients enrolled in the study.

Study-B302 included 28 (18%) and 34 (21%) Black patients enrolled in the ERL080 and MMF groups respectively. The rates for AEs, severe and serious infections were comparable between the two treatment groups. No meaningful conclusions can be drawn, because of the small number of Black patients in the study.

Hepatic & Renal Impairment: No dose adjustments are required in patients with hepatic or renal impairment; however, it is recommended that patients be closely monitored.

Pregnancy: There are no adequate and well controlled studies in pregnant women, Myfortic® should be used in pregnant women only if the potential benefit outweighs the potential risk to the fetus. Myfortic® is a Pregnancy Category C drug.

Pediatrics: The Applicant submitted one pediatric Study-0106 designed to evaluate the pharmacokinetics of ERL080 following a single dose in stable pediatric renal transplant patients (n=24) on Neoral®. There were no pediatric efficacy and safety studies in NDA 50-791. The safety and effectiveness of Myfortic® have been established in the age group 5-16 years in stable pediatric renal transplant patients. Use of Myfortic® in this age group is supported by evidence from adequate and well controlled studies of Myfortic® in stable adult renal transplant patients. Pediatric doses for patients with body surface area <1.19 m^2 cannot be accurately administered using currently available formulations of Myfortic® tablets. There are no pharmacokinetic data available for pediatric patients < 5 years.

Sary O. Beidas, MD
Reviewing Medical Officer/HFD-590

Concurrence Only:

/S/

Renata Albrecht, MD
Division Director
DSPIDP, HFD-590

cc: Division File

HFD-590/MO/Sbeidas
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HFD-590/Dir/RAlbrecht
HFD-590/Chem/Rsood
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HFD-590/PharmT/SHundley
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Executive Summary of MO Review for NDA 50-791 Myfortic
for preventin of graft rejection in renal transplantation.

Renata Albrecht
2/27/04 04:38:58 PM
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Medical Officer's Review of NDA 50-791

Myfortic® (mycophenolic acid) Delayed Release Tablets for Renal Transplantation

Identifying Information

Applicant Identification

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Contact Person:

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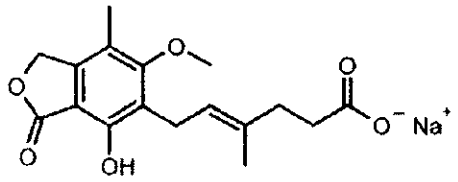
Submission / Review dates:

Date of submission: April 30, 2003
CDER stamp date: April 30, 2003
Date review begun: November 3, 2003
Date review completed: January 30, 2004

Drug Identification

Established name: Mycophenolic acid
Research name: ERL080
Trade name: MYFORTIC®
Chemical name: (E)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoic acid sodium salt

Chemical Structure:



Molecular Formula:	$C_{17}H_{19}O_6$ Na
Molecular Weight:	342.32
Pharmacologic Category:	Immunosuppressant for transplantation
Dosage Form:	Delayed Release Tablets
Strength:	180 mg & 360 mg
Route of Administration	Oral
Related IND/NDA:	IND 57,005

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Clinical Review for NDA 50-791

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The reviewing Medical Officer (MO) recommends an action of **Approval** for NDA 50-791; use of Myfortic® (mycophenolic acid) for the prophylaxis of organ rejection in allogeneic *de novo* and stable renal transplant recipients.

The approval of Myfortic® for the prevention of rejection in renal transplantation was supported by two adequate and well controlled studies in *de novo* and stable renal transplant recipients, conducted by Novartis and reported in NDA 50-791. The Myfortic dose used in these studies was based on the amount of mycophenolic acid that is delivered by the approved dose of Cellcept® (mycophenolate mofetil) for prevention of rejection in renal transplantation, and supported by pharmacokinetic studies conducted by Novartis, comparing the systemic exposure to mycophenolic acid when delivered by oral doses of mycophenolate sodium or mycophenolate mofetil.

Safety and efficacy information from the clinical studies conducted by Novartis were included in the proposed label for Myfortic®. Since mycophenolic acid (MPA) is the active moiety of Cellcept® and Myfortic®, additional safety information associated with systemic exposure to MPA included in the approved Cellcept® label (from March 2003), including post-marketing safety information and other class labeling was also included in the proposed Myfortic® label. NDA 50-791 is a 505 (b)(2) submission.

Myfortic® is the sodium salt of mycophenolic acid, an immunosuppressant agent related to CellCept® (mycophenolate mofetil). In NDA 50-791, the Application that is the subject of this review, Novartis (the Applicant) is seeking the approval for Myfortic® 720 mg orally administered twice daily, for prophylaxis of organ rejection in allogeneic renal transplant recipients.

Myfortic® (sodium salt of mycopenolic acid) delivers the active ingredient mycophenolic acid (MPA). MPA has a cytostatic effect on T- and B-lymphocytes due to MPA's inhibitory effects on inosine monophosphate dehydrogenase, which lead to inhibition of the *de novo* pathway for guanosine nucleotide synthesis. T- & B-lymphocytes are dependent on the *de novo* pathway for proliferation. Hence, MPA's mode of action is primarily to suppress T- & B-lymphocyte responses.

The efficacy and safety data provided by the Applicant in the submission and reviewed by the reviewing MO included Study-B301, Study-B302, and Study-0107, and the 120-Day Safety Update Report. In these studies the safety data for Myfortic® 720 mg po bid was compared to mycophenolate mofetil 1 gm po bid for the prophylaxis of organ rejection in allogeneic renal transplant patients. In Study-B301 a *de novo* renal transplant population was studied, and in Study-B302 a maintenance renal transplant population was studied. Study-0107 was a small study intended to evaluate the relative gastrointestinal tolerability of ERL080 compared to mycophenolate mofetil in renal transplant recipients with gastrointestinal complaints secondary to mycophenolate mofetil. This study was prematurely terminated when it appeared it would be unable to demonstrate superior tolerability of ERL080 compared to mycophenolate mofetil.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The MO is requesting that the Applicant conduct a Segment III prenatal/postnatal developmental toxicity study in pregnant female rates with Myfortic® as a phase IV post marketing commitment. The MO is requesting the study, because the 505 (b)(2) submission does not contain a reference to this study that can be used to address the requirements for a Segment III developmental toxicity study.

The Agency waived additional requirements for studies in pediatric age group 0-10 years of age. The use of Myfortic® in pediatric age group 0-10 does not represent a meaningful therapeutic benefit over existing treatments (Myfortic® is available in fixed capsule strengths of 180 mg or 360 mg, whereas mycophenolate mofetil is marketed in suspension, capsule, and intravenous formulation), and it is not likely to be used in a substantial number of patients [In 2003, there were 276 pediatric renal transplant recipients aged 0-10 years (UNOS data, United States)]. The Applicant has provided the Agency with pharmacokinetic data for older children (>10 years) that allows appropriate extrapolation for dosing requirements in patients with a body surface area of $> 1.19\ m^2$. Myfortic® doses for patients with a body surface area of $< 1.19\ m^2$ cannot be accurately administered using currently available formulations of Myfortic® tablets.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

In NDA 50-791, the Applicant submitted the reports for two adequate and well controlled clinical studies (B301 & B302) in renal transplant patients. Study-B301 compared the efficacy of Myfortic® 720 mg po bid to CellCept® 1 gm po bid in combination with Neoral® and corticosteroids in *de novo* renal transplant recipients. Study-B302 was primarily a safety study and efficacy was a secondary endpoint comparing Myfortic® 720 mg po bid to CellCept® 1 gm po bid in combination with Neoral® and corticosteroids in maintenance renal transplant recipients. A third clinical study in renal transplant patients complaining of gastrointestinal symptoms of intolerance to CellCept®, Study-0107, was unable to demonstrate superiority of Myfortic® compared to CellCept® with respect to gastrointestinal tolerance. In addition, the submission included the 120-Day safety update report for Myfortic®.

Study-B301 was a multicenter, randomized, double-blind, parallel study designed to demonstrate the non-inferiority of Myfortic® 720 mg po bid compared to CellCept® 1 gm po bid in combination with Neoral® and corticosteroids in a *de novo* adult (18-75 years) renal transplant population (12 months analysis). The enrollment period for the study was Dec 1998 through Apr 2001. Clinical sites recruited patients from the North America and Europe. A total of 423 patients were randomized to two treatment groups (Myfortic® 213 patients vs. CellCept® 210 patients). The baseline demographic characteristics of the enrolled population showed a mean age of 47 years, 88% Caucasian / 7% Black / 4% Other race / 1% Oriental. Forty one percent of patients were over the age of 50 years. In the study, common reasons for renal insufficiency were glomerulonephritis, polycystic kidney disease, hypertension, and diabetes mellitus. The primary population of interest in the study was the Intent-to-Treat (ITT) population for the 12 month period (ITT population was defined as all randomized patients who received at least one dose of randomized study medication). At the end of the 12 months, all patients were offered to stay on study drug, or switch to Myfortic® for an extended evaluation period until Myfortic® is available at the country where the patient was enrolled.

Study-B302 was a multicenter, double-blind, randomized, parallel group study designed to evaluate the safety and efficacy of ERL080 720 mg po bid compared to MMF 1 gm po bid in an adult (18-75 year) population for maintenance renal transplant patients. The study period was from Feb 1999 to Oct 2001. Participating clinical centers were from North America and Europe. The primary objective of the study was to evaluate the rate of gastrointestinal and neutropenic adverse events (including other adverse events) for 12 months after administration of study medications. A secondary objective of the study was to evaluate the efficacy of ERL080 compared to MMF for the 12-Month period after administration of study medications.

A total of 322 patients were randomized in the study (ERL080 159 and MMF 163 patients). The baseline demographics characteristics of the study population were a

mean age of 48 years, Caucasians represented 74% of patients followed by Blacks ~19% and Orientals 3%. The proportion of females in the ERL080 group 39% was higher than the proportion of females in the MMF 29% group (p=0.079 approaching significance). Glomerulonephritis followed by hypertension were the two most common causes of end stage renal disease. The primary population of interest was the ITT population (defined as all randomized patients who received at least one dose of randomized study medication. At the end of the twelve months, all patients were offered to stay on study drug, or switch to Myfortic® for an extended evaluation period until Myfortic® is available at the country where the patient was enrolled.

Study-0107 was a double-blind, randomized, parallel group study designed to demonstrate superiority of ERL080 compared to MMF for gastrointestinal tolerability in maintenance renal transplant patients with GI complaints secondary to MMF. All patients in this study were also treated with Neoral® and steroids. This study was terminated prematurely because it did not appear that it would be able to demonstrate superior tolerability of Myfortic® compared to MMF. The total number of patients randomized into this study was 149 (ERL080 74 vs. MMF 75) patients. The baseline demographic characteristics demonstrate a slightly younger population in the ERL080 (mean age 43 years) group compared to the MMF (mean age 46 years) group; gender, race, weight, and height were comparable in both groups. The MO did not review this study in detail, because it was terminated when it appeared that it would be unable to demonstrate superior tolerability with ERL080 compared to MMF.

B. Efficacy

The two efficacy studies for NDA 50-791 were Studies B301 & B302. In both clinical studies, Myfortic® (ERL080) was compared to CellCept® (MMF). The MMF regimen used is FDA approved for prevention of organ rejection in renal transplant recipients. Both ERL080 and MMF require conversion in the gastrointestinal tract to the active moiety mycophenolic acid (MPA). Therefore MMF was an acceptable comparator to the Agency for the clinical studies submitted in NDA 50-791. The results of efficacy from the two clinical studies support the use of ERL080 in the prophylaxis of organ rejection in *de novo* and maintenance renal transplant recipients.

Study-B301, was a multicenter, double-blind, randomized, parallel group, designed to evaluate the efficacy and safety of ERL080 720 mg po bid compared to MMF 1 gm po bid, in combination with Neoral® and steroids in the prophylaxis of organ rejection in *de novo* renal transplant patients (non-inferiority). Primary efficacy was measured by the difference in the rates for the composite endpoint (biopsy-proven acute rejection, graft loss, death, and lost to follow-up), at Month-6 and Month-12 post-transplantation for the two treatment groups in the Intent-to-Treat (ITT) population. Eligible patients were adult males and females (18-75 years) with end-stage renal disease. The primary efficacy results were supported by results from the co-primary endpoint graft loss or death or lost to follow-up at 12 months), the per protocol population and by the secondary efficacy endpoints (the individual variables for the composite primary endpoint).

The difference in the point estimates of the efficacy (composite endpoint) of the two treatments (ERL080-MMF) at Month-6 was -0.4 [95% CI of {-8.7, 8.0%}]. The pre-specified lower/upper bound of the 95% confidence interval used to define non-inferiority was {-12.0, 12.0}. A similar difference in the point estimate was observed for the Month-12 period 0.5 [95% CI {-8.1, 9.2%}] (table).

B301 Primary Efficacy endpoints at 6 & 12 months post-transplantation (ITT population)
Source: Modified Table 9-1 Vol 140

Variables	Period	ERL 720 mg bid N=213	MMF 1 gm bid N=210	(ERL080-MMF) 95% CI {%, %}
Composite primary efficacy endpoint at	6 months	55 (25.8%)	55 (26.2%)	-0.4 {-8.7, 8.0}
	12 months	61 (28.6%)	59 (28.1%)	0.5 {-8.1, 9.2}
Biopsy-proven acute rejection	6 months	46 (21.6%)	48 (22.9%)	
	12 months	48 (22.5%)	51 (24%)	-1.8 {-9.8, 6.3}
Graft loss	6 months	7 (3.3%)	9 (4.3%)	
	12months	9 (4.2%)	9 (4.3%)	-0.5 {-4.3, 3.2}
Death	6 months	1 (0.5%)	2 (1%)	
	12 months	2 (0.9%)	5 (2.4%)	
Lost to Follow-Up**	6months	3 (1.4%)	0	
	12months	5 (2.3%)	0	
Graft loss, Death, Lost to Follow-Up***	12 months	20 (9.4%)	18 (8.6%)	

Composite primary efficacy endpoint (Treatment failure) = biopsy-proven acute rejection, graft loss or death, death, lost to follow-up
**Lost to Follow-up indicates patients who were lost to follow-up without prior biopsy-proven acute rejection, graft loss or death
*** Lost to Follow-up indicates patients who were lost to follow-up without graft loss or death (9 Myfortic patients and 4 MMF patients)
Ab-Rx = Antibody treatment
All patients in the study received Neoral® and steroids

Analysis of results in the per protocol population (PP) defined as the subset of the ITT population that did not violate the protocol in a "significant" way, and the secondary efficacy variables supported the primary efficacy endpoint for the ITT population (table).

Study-B301 Secondary efficacy endpoints (ITT population, Month-0 to 12)
Source: PTT 9.1-1 & 9.1-13

Variables	Period	ERL080 N=213	MMF N=210
Any acute rejection	6 months	52 (24.4%)	55 (26.2%)
	12 months	54 (25.4%)	58 (27.6%)
Treated acute rejection	6 months	51 (23.9%)	52 (24.8%)
	12 months	52 (24.4%)	54 (25.7%)
Antibody-Treated acute rejection	6 months	11 (5.2%)	10 (4.8%)
	12 months	11 (5.2%)	10 (4.8%)
Biopsy-proven chronic rejection	6 months	8 (3.8%)	12 (5.7%)
	12 months	12 (5.6%)	16 (7.6%)

Study-B302 was a multicenter, randomized, double-blind, parallel study designed to evaluate the safety and efficacy of ERL080 720 mg po bid compared to MMF 1 gm po bid, in combination with Neoral® ± corticosteroids for the prophylaxis of organ rejection

in maintenance renal transplant recipients. Therefore these patients were already on an immunosuppressive regimen post-transplantation prior to enrollment in the study. The, run-in period, where all patients were exposed to MMF for 2-week prior to randomization, may potentially select a less sensitive population to detect differences in tolerability of ERL080 to MMF.

The primary efficacy endpoint in Study-B302 was similar to the composite primary efficacy endpoint for Study-B301, treatment failure (biopsy-proven acute rejection, graft loss, death, and lost to follow-up). A co-primary efficacy endpoint (graft loss or death or lost to follow-up) and the secondary efficacy variables supported the primary efficacy endpoint. The difference in the point estimate of the primary efficacy composite endpoint for the two treatment groups was -2.4 [95% CI {-7.4, 2.7%}], which was within the pre-specified bounds of the 95% CI used to define non-inferiority in the study. Analysis of the co-primary endpoint and the secondary variables supported the primary composite endpoint (table).

Study-B302 Primary & Secondary Efficacy Endpoints (ITT population)
Source: Modified PTT 9.1 Vol 150

		ERL080	MMF	ERL080-MMF 95% CI
***Composite Primary variable**	6 months 12 months	7 (4.4%) 12 (7.5%)	11 (6.7%) 20 (12.3%)	-2.4 (-7.4,2.7%) -4.2 (-11.3, 1.8%)
Secondary variables				
BPAR	6 months 12 months	2 (1.3%) 2 (1.3%)	2 (1.2%) 5 (3.1%)	
Acute rejection	6 months 12 months	2 (1.3%) 2 (1.3%)	3 (1.8%) 6 (3.7%)	
Treated acute rejection	6 months 12 months	2 (1.3%) 2 (1.3%)	2 (1.2%) 3 (1.8%)	
Acute rejection requiring Ab therapy	6 months 12 months	0 0	0 0	
BPCR	6 months 12 months	4 (2.5%) 4 (2.5%)	4 (2.5%) 8 (4.9%)	-1.1% (-5.6, 3.3%)
Graft loss	6 months 12 months	0 0	1 (0.6%) 1 (0.6%)	
***Death	6 months 12 months	0 2 (1.3%)	1(0.6%) 4 (2.5%)	
#Lost to follow-up	6 months 12 months	5 (3.1%) 8 (5%)	7 (4.3%) 10 (6.1%)	-1.1% (-6.1, 3.9%)
##Graft loss or death or lost to follow-up	12 months	10 (6.3%)	17 (10.4%)	

*Composite primary variable (Treatment failure) = Biopsy proven acute rejection (BPAR), graft loss, death, lost to follow-up
***Patient #5110013 (MMF) died post-study on Day-290. This patient withdrew consent on Day-273, and was discontinued from the study. Patient was listed in the composite variable as a "lost to follow-up"
#Lost to Follow-up indicates patients who were lost to follow-up without prior biopsy-proven acute rejection, graft loss or death
##Lost to Follow-up indicates patients who were lost to follow-up without prior graft loss or death (8 Myfortic patients and 12 MMF patients)

Study-0107 was intended to evaluate the relative gastrointestinal tolerability of ERL080 compared to MMF in renal transplant recipients with gastrointestinal complaints

secondary to MMF. This study was prematurely terminated when it appeared it would be unable to demonstrate superior tolerability with ERL080 compared to MMF.

The extended B301 & B302 studies, included patients from the core Studies B301 & 302 who agreed to continue or switch to ERL080 therapy. In both studies, the rates for the efficacy variables were comparable at 24 & 30 month follow-up periods (0-12 Months core study + 12 & 18 months extension phase) in patients initially treated with 0-12 Month ERL080 vs. patients treated with 0-12 Month MMF. Note that the extended studies represented a non-random selected subset of the population originally enrolled in studies B301 & B302. Therefore, comparisons should be interpreted with caution.

C. Safety

The safety report for NDA 50-791 incorporated safety data from the three clinical studies B301, B302, 0107. The safety data in the submission contained the 12-Month efficacy and safety data from the 2 phase III studies in *de novo* and maintenance renal transplant patients, and from the 5-week Study-0107. Safety data was also provided for the open-label extended phase for Studies B301 & B302. The cut-off date for safety data in the original submission from April 30, 2003 was June 14, 2002 for the original studies, and January 17, 2003 for the extension studies.

In Study-B301, comparable numbers of patients from the two treatment groups were exposed to study drug, Neoral®, and corticosteroids. The majority of patients in the study were exposed to study drug up to Month-12 window visit (ERL080 71%, 151/213 patients vs. MMF 75%, 158/210 patients). Approximately 41% of patients from both treatment groups received antibody therapy. The most common reasons for discontinuing treatment prior to the Month-12 window was the occurrence of an adverse event [ERL080 36 (16.9%) patients vs. MMF 29 (13.8%) patients], followed by an unsatisfactory therapeutic effect [ERL080 11 (5.2%) vs. MMF 8 (3.8%)], graft loss [ERL080 5 (2.3%) patients vs. MMF 6 (2.9%)]; other less common reasons included abnormal laboratory finding, withdrawn consent, lost to follow-up or death.

As expected in a *de novo* renal transplant population such as this one, adverse events were reported by almost all patients in both treatment groups. In general, the rates for adverse events were comparable in both treatment groups. Gastrointestinal adverse events were comparable for the 0-12 Month period (ERL080 group 79.8% compared to the MMF group 77.1%); also, the rates for GI AEs were comparable at all window visits. Rates of infections were comparable in both treatment groups. Bone marrow suppression (reflected in WBC, platelet, and RBC counts), was observed to be comparable in both treatment groups. No patients in either treatment group experienced a neutrophil count of $\leq 0.5 \times 10^9$ /L. Common AEs with a difference of >5% between treatment groups included infections, surgical/medical procedures, and investigations. For infections, the difference in rates was accounted for by an increased rate of urinary

tract infections in the MMF group; however, these infections were minor, and are expected in a renal transplant study. Therefore no meaningful conclusion can be drawn from this observation.

There were 7 deaths reported in the 0-12 Month period; 2 were in the ERL080 group, and 5 were in the MMF group. In the ERL080 group, one death at Day-92 was secondary to complications of congestive heart failure, the other death at Day-343 was secondary to sepsis related. At the time of death all 7 patients had a functioning graft. None of the deaths were directly attributed to the study drug.

The most commonly reported serious AEs in the Study-B301 were related to the GI-tract or renal system. The overall rates for serious AEs in the study were comparable in both treatment groups. Severe AEs were reported by 38% of patients in the ERL080 group and 41% of patients in the MMF group. Severity rates were comparable between the two treatment groups. Sixteen percent of patients in the ERL080 group discontinued study drug due to an AE compared to Fourteen percent in the MMF group. The most common reason for discontinuing study drug from an AE was related to GI AEs (5%) in both treatment groups. Both treatment groups had a similar rate of malignancies (2%). Laboratory events for hematological variables and biochemistry were comparable between the two treatment groups. Patient mean weight, creatinine, and urea values improved after transplantation in both treatment groups.

In Study-B302, patients in both treatment groups were exposed to a comparable dose of study drug at all window visits. Approximately 90% of patients in the ERL080 group received ERL080 for 12 months. Six percent of patients in the ERL080 group prematurely discontinued study drug due to an AE (2 deaths, 2 diarrhea, 2 leukopenia, 2 infection,1 ↑ creatinine), and 4% of patients in the MMF group prematurely discontinued study drug due to an AE (1 death, 2 diarrhea,2 malignancy, 1 ↑ creatinine). The majority of dose reductions in both treatment groups occurred during the first 6 months of the study. The cause for dose reductions (44% for both treatment groups) was commonly related to AEs (15% for both treatment groups) or dosing errors. Exposure to concomitant immunosuppressive regimens (Neoral® and corticosteroids) was comparable in both treatment groups.

By the 12-Month point, the majority patients from Study-B302 had experienced an AE (ERL080 94% vs. MMF 93%). The majority of AEs occurred in the 0-3 Month period of the study. The most common AEs were diarrhea and nausea in the ERL080 group and diarrhea and nasopharyngitis in the MMF group. The rates for AEs were comparable for the two treatment groups.

In Study-B302, the GI AE rates were similar in the ERL080 group 57% compared to the MMF group 57% for the 0-12 Months; these rates were lower (as expected) than the rates observed in the *de novo* Study-B301. Nausea and vomiting were among the most common GI AEs affecting more patients in the ERL080 group. The majority of patients experienced nausea and vomiting within the first 3 months of the study. A potential

limitation of Study-B302 when assessing GI tolerance is that the run-in period of at least 2 weeks on MMF before randomization could have selected patients who tolerated the effects of mycophenolic acid, and favored elimination of those who were more sensitive to the gastrointestinal adverse events. No patients in the ERL080 group developed severe neutropenia compared to one patient in the MMF group. A similar number of patients from both treatment groups developed expected malignancies (6%).

A total of 7 deaths were reported in Study-B302; none of the deaths could be directly attributed to the study drug. There were 2 deaths in the ERL080 group. This was a 23 year-old ♀ who died on Day-350 from multiple organ failure. The remaining patient died from a cryptococcal brain abscess related to AIDS. The MMF group had 5 deaths during the 0-12 Month study period. Severe AEs were comparable for the two treatment groups. A total of 9 patients in the ERL080 group and 10 patients in the MMF group discontinued study medication prematurely. In the ERL080 group the most common reason for discontinuing study drug was a severe infection in 5/9 patients followed by leukopenia and diarrhea. And in the MMF group, the most common cause of discontinuing study drug was a GI complaint in 4 patients followed by an elevated creatinine value or neoplasm, 2 patients for each.

Overall, the safety data for Study-0107 was comparable to the safety data from Study-B302.

Studies B301Ext & B302Ext (extension phase), did not demonstrate any new safety risks associated with use of ERL080.

The 120-Day Safety Update contained safety data from the extension studies through March 31, 2003. The new analysis for the extension studies extended the cohort for Study-B301 up to 24 months for all patients in the extension phase and for 30 months for patients who reached the 30-Month point.

As of May 31, 2003 the total number of subjects exposed to ERL080 was 2396 patients across the clinical (including193 subjects in the pharmacologic) studies. A total of 766 patients were followed for ≥12 months and 220 patients were followed for ≥36 month. Overall, there were no new unexpected safety issues reported in the 120-Day Safety Update compared to the data reported in the original submission.

D. Dosing

The proposed dosing for Myfortic® is 720 mg po bid. Myfortic® is supplied as 360 mg and 180 mg tablets. No dosing adjustments are required in patients with renal or hepatic impairment. Myfortic® tablets should not be crushed, chewed, or cut prior to ingesting; and tablets should be administered on an empty stomach (1 hour before or two hours after food intake). Myfortic® is indicated for prophylaxis of organ rejection in renal transplant recipients.

E. Special Populations

Gender: The clinical studies in NDA 50-791 contained more male than female subjects; however, each of the clinical Studies B301 & B302 had more than 30% female representation. In both studies, female subjects experienced a higher rate of urinary tract infections compared to male subjects. This finding was expected based on the natural rates for urinary tract infection in females. Results from the two pivotal studies do not suggest that females are at an increased risk of adverse events from the use of Myfortic®.

Age: Clinical studies of Myfortic® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant or other drug therapy.

Ethnicity: Study-B301 included 30 (<10%) Black patients. Seventeen patients were in the ERL080 group and thirteen patients in the MMF group. The rate of drug-related AEs was higher in the MMF group compared to the ERL080 group; however, no meaningful conclusions can be drawn due to the small numbers of Black patients enrolled in the study.

Study-B302 included 28 (18%) and 34 (21%) Black patients enrolled in the ERL080 and MMF groups respectively. The rates for AEs, severe and serious infections were comparable between the two treatment groups. No meaningful conclusions can be drawn, because of the small number of Black patients in the study.

Hepatic & Renal Impairment: No dose adjustments are required in patients with hepatic or renal impairment; however, it is recommended that patients be closely monitored.

Pregnancy: There are no adequate and well controlled studies in pregnant women, Myfortic® should be used in pregnant women only if the potential benefit outweighs the potential risk to the fetus. Myfortic® is a Pregnancy Category C drug.

Pediatrics: The Applicant submitted one pediatric Study-0106 designed to evaluate the pharmacokinetics of ERL080 following a single dose in stable pediatric renal transplant patients (n=24) on Neoral®. There were no pediatric efficacy and safety studies in NDA 50-791. The safety and effectiveness of Myfortic® have been established in the age group 5-16 years in stable pediatric renal transplant patients. Use of Myfortic® in this age group is supported by evidence from adequate and well controlled studies of Myfortic® in stable adult renal transplant patients. Pediatric doses for patients with body surface area <1.19 m^2 cannot be accurately administered using currently available formulations of Myfortic® tablets. There are no pharmacokinetic data available for pediatric patients < 5 years.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Myfortic® (ERL080) is an enteric-coated formulation of mycophenolate sodium. Similar to CellCept®, Myfortic® is metabolized in vivo to systemically deliver the active moiety mycophenolic acid (MPA). Myfortic® is an immunosuppressant agent. Novartis is seeking approval for Myfortic®, administered in combination with cyclosporine and steroids, for the prophylaxis of organ rejection in patients receiving allogeneic renal transplant.

B. State of Armamentarium for the Prevention of Rejection in Allogeneic Renal Transplantation

Renal transplantation is the treatment of choice for endstage renal disease (ESRD) in the United States. The primary causes for ESRD in descending order are glomerulonephritis, diabetes mellitus, hypertension, polycystic kidney disease, and other. For the year 2001, there were 14,024 renal transplants in the United States(UNOS data). The number of live kidney donors has continued to increase. In 2001, the number of live donors was 5,969 (43%) compared to 8,055 (57%) cadaveric kidney donors. Estimates for 1 and 3 year graft survival are 88% and 79% respectively (UNOS Data, cohorts for the 1 & 3 year graft survival rate were transplanted in 1999-2000 and 1997-1998 respectively). One and three year patient survival rates were 95% and 91% respectively (1996-2001 UNOS Data).

There are numerous agents approved for use in the prevention of rejection in allogeneic renal transplantation. For example, the calcineurin inhibitor class of immunosuppressants used in the prevention of rejection in renal transplantation includes cyclosporine, and tacrolimus. Sirolimus, a macrocyclic lactone, represents another class of immunosuppressants, is indicated for the prophylaxis of organ rejection in renal transplant recipients. The antimetabolites are another class used for the same indication described above and includes azathioprine and mycophenolate mofetil. A fourth class of agents used primarily in induction of immunosuppression (used in combination with calcineuron inhibitors, antimetabolites, and steroids for treatment of acute rejection) are antibodies such as, antithymocyte/lymphocyte immunoglobulin, muromonab-CD3. Basiliximab and daclizumab are antibody formulations also approved for the indication of prophylaxis of acute organ rejection in renal transplantation in combination with other immunosuppressive agents.

C. Important Milestones in Product Development

- At a pre-IND meeting, Novartis indicated it intended to support the approval of ERL080 for prevention of rejection in kidney transplantation based on pharmacokinetic data demonstrating that ERL080 delivered an exposure to mycophenolic acid equivalent to that provided by Cellcept® (mycophenolate mofetil). FDA recommended additional clinical studies to evaluate the gastrointestinal tolerance of ERL080. A concern was that potential differences in GI tolerance might adversely affect the ability to comply with concomitant oral medications needed to maintain an adequate level of immunosuppression, prevent or treat the adverse events associated with the regimen including but not limited to, hypertension, diabetes, and infections. Thus, Novartis was advised to conduct a safety and efficacy study in *de novo* renal transplantation patients comparing MMF to ERL080.
- Novartis developed ERL080 for use in renal transplantation under IND 57,005. A face to face, Phase III meeting/Type C with the Applicant was held at the Division on September 18, 2000. The purpose of the meeting was for Novartis representatives to update the Agency on their clinical program for ERL080 and to discuss labeling claims based on the pivotal studies (B301, B302, 0107) to support the NDA. The agreements from the meeting were: Novartis committed to an enrollment target of 700 patients from studies B301 & B302 for the 12-month studies. The Agency in a teleconference in March 24, 2000 had recommended that the safety database would include a minimum of 300 patients exposed to the therapeutic dose of ERL080 for 12 months. The Agency also noted that review of the NDA application would be incomplete if the submitted efficacy safety data lacked the co-primary endpoints analysis at 12 months to include acute rejection at 6 months, rates of death at 12 months, and graft loss at 12 months. Therefore the Applicant was advised to wait for the availability for the 12 months data on all subjects.
- A pre-NDA meeting/Type B was held on December 14 , and was followed up by a teleconference on December 20, 2001. The major issues raised by the Agency that required a follow up teleconference were data presented by Novartis on December 14 that demonstrated that the proposed drug formulation for ERL080, Myfortic® exposed patients to an average of 32% more mycophenolic acid (MPA) than the comparator mycophenolate mofetil (MMF). This information raised the potential concern that this formulation would be delivering a dose of MPA that was not comparable to that delivered by the approved dose of MMF, but similar to a dose of MMF that was not approved for this indication, 1.5 gm bid. Dr. Cavaillé-Coll outlined three possible ways Novartis could address the Division's concerns about ERL080's pharmacokinetics. The three possibilities were, Novartis could develop a new dosage form that is bioequivalent to MMF, or Novartis could conduct an additional efficacy and safety clinical study, or Novartis

could conduct a pharmacokinetic study with a randomized crossover design intended to demonstrate equivalent systemic exposure to MPA when administered as ERL080 or MMF. Higher exposures to MPA could result in potentially increased human toxicity such as gastrointestinal intolerance or neutropenia. The Agency also communicated to the Sponsor that ERL080 is considered an "old" antibiotic as outlined in Section 507 of the Federal Food, Drug, and Cosmetic Act under section 505(b) or 505(j) for drugs that contain "old" antibiotics need not include patent information and are not eligible for exclusivity under sections 505(c) or 505(j).

D. Other Relevant Information

As of February 25, 2004, Myfortic® was launched (indication: for the prevention of organ rejection in renal transplantation) in India and Switzerland, Latvia, Brazil and Indonesia. Myfortic® is authorized for use in Argentina, Aruba, Australia, Bahrain, Chile, Columbia, Costa Rica, Curacao, Dominican Republic, Ecuador, El Salvador, European Union, Guatemala, Honduras, Hong Kong, Israel, Jamaica, South Korea, Lebanon, Mexico, Nicaragua, Panama, Peru, Philippines, Singapore, Syria, Taiwan, Trinidad and Tobago, United Arab Emirates, Uruguay, and Venezuela. Myfortic® has not been withdrawn for reasons of safety in any country.

As of May 31, 2003, the cut-off date for the 120-Day Safety Update there were no serious post marketing AEs reported by the Applicant.

E. Important Issues with Pharmacologically Related Agents

Myfortic® (ERL080) is an enteric-coated formulation of the sodium salt of mycophenolic acid. The active moiety is mycophenolic acid (MPA) is delivered systemically in the gastrointestinal tract. Thus both Myfortic® and CellCept®, deliver the same active component, i.e. MPA, when administered systemically to transplant patients. Because Myfortic® is similar to CellCept®, it is expected to have a similar safety profile as CellCept®. The main safety issues related to the approved CellCept® product are toxicities related to immunosuppression inclusive of infections and malignancy, bone marrow toxicity, and gastrointestinal intolerance.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Please refer to the Biopharmaceutical Review by Dr. Jang-Ik Lee for details. In brief, Myfortic® is an enteric-coated, delayed-release formulation of mycophenolate sodium. Myfortic® delivers mycophenolic acid (MPA) the active ingredient. The MPA content in Myfortic® 720 mg and CellCept® 1000 mg is almost identical (3% difference). After administration of Myfortic® (in stable renal transplant patients on chronic cyclosporine therapy), gastrointestinal absorption of MPA is 93%, and the absolute bioavailability of MPA was 71%. Administering Myfortic® in the fasting state results in a T_{max} for MPA of 1.5-2.5 hours, compared to mycophenolate mofetil's T_{max} of 1 hour. MPA is >98% protein (primarily albumin) bound, and the inactive metabolite, mycophenolic acid glucuronide (MPAG), protein binding is >82%.

The half-life of MPA is 11.7 hours, and the half-life for the MPAG is 15.7 hours. The majority of MPA (>60%) is eliminated in the urine in the MPAG form, and <3% is eliminated as MPA. Myfortic® should be administered to patients on an empty stomach 1 hour before or two hours after food intake. The efficacy and safety of Myfortic® were not assessed under fed conditions.

MO Comment: *Because the pharmacokinetics of Myfortic® are sufficiently different from Cellcept®, substitution of one product for the other should only be done under physician's supervision.*

The pharmacokinetics of Myfortic® in adults are not affected by age, gender, or weight. No dosage adjustment is required in patients with hepatic or post-transplantation renal impairment.

B. Pharmacodynamics

Myfortic® should be administered with immunosuppressive regimens containing corticosteroids and Neoral®. The basis for selecting Myfortic® 720 mg is based on the identical content of MPA for Myfortic® 720 mg and CellCept® 1000 mg formulation. In addition, single and multiple dose relative bioavailability studies to support labeling dosage were conducted in Studies W152, B301, B302, and 2301. The first study, Study-W152 was a single dose relative bioavailability study that demonstrated that Myfortic® 720 mg and CellCept® 1000 mg achieved the same MPA AUC. Studies B302 & 2302 were multiple dose studies designed to evaluate the relative bioavailability of Myfortic®

to Cellcept® (please refer to Dr. Jang-Ik Lee's Biopharmaceutical Review for details). Study-2302 was conducted to demonstrate the relative bioavailability of Myfortic® 720 mg to CellCept® 1000 mg, after the pharmacokinetic portion for Study-B301 showed ~33% difference in bioavailability between the two treatment groups. Potentially expected hazards from the clinical exposure to mycophenolic acid include bone marrow immunosuppression, infections, and malignancies.

MO Comment: *The PK substudy of the pivotal efficacy and safety trial, Study-B301, did not demonstrate a comparable exposure to mycophenolic acid in both treatment groups. The Applicant was required to evaluate MPA exposure in a randomized cross-over study design after multiple oral dosing with ERL080 and MMF. Study-2302, was designed to evaluate the relative exposure to MPA, of multiple dose Myfortic® 720 mg and CellCept® 1000 mg. Study-2302 achieved its goal for demonstrating comparable MPA exposure at the specified dosages. The apparent difference between treatment groups in the PK sub-study of Study-B301 may have been due to the use of a parallel group design without randomized cross-over periods.*

The drug-drug interaction profile for Myfortic® has not been studied in detail. Co-administration of Myfortic® with azathioprine, cholestyramine or other agents that may interfere with enterohepatic recirculation is not recommended. In addition, concomitant administration of Myfortic® with magnesium or aluminum containing antacids may result in decreases in MPA's AUC and C_{max}, therefore, the simultaneous administration of Myfortic® with magnesium or aluminum containing antacids should be avoided.

When oral contraceptives are co administered with Myfortic®, additional birth control methods should be considered. Cyclosporine may potentially alter the gastrointestinal flora, thereby disrupting the enterohepatic recirculation of MPA and potentially leading to a decrease in MPA exposure.

IV. Description of Clinical Data and Sources

A. Overall Data

The primary source of data used by the MO to evaluate the efficacy and safety of Myfortic® for use in renal transplantation was the NDA submission, which included the study results, patient data sets

B. Tables Listing the Clinical Trials

Clinical Study Program for Myfortic® (ERL080)

Study number	Design	Duration	Study drug	Number of patients
Pivotal renal Studies				
B301	R, DB, DD, AC, MC, MD, E, S, T, PK, de novo	12 months	ERL080 MMF	213 210
B301 extended	OL, MC, MD, E, S, T, maintenance	12 month 24 month 18 month 30 month	ERL080 (exMMF) ERL080 ERL080 (exMMF) ERL080	125 122 103 99
B302	R, DB, DD, AC, MC, MD, E, S, T, PK, maintenance	12 months	ERL080 MMF	159 163
B302 extended	OL, MC, MD, E, S, T, maintenance	12 month 24 month 18 month 30 month	ERL080 (exMMF) ERL080 ERL080 (exMMF) ERL080	112 110 75 77
Gastrointestinal intolerance evaluation				
0107	R, DB, DD, AC, MC, MD, E, S, T, maintenance with GI intolerance to MMF	5 week	ERL080 MMF	74 75
0107 Extended	OL, MC, MD, E, S, T, maintenance	7 month 8+ month 18 month 19+ month	ERL080 (exMMF) ERL080 ERL080 (exMMF) ERL080	63 65 32 33

AC= active controlled, DB= double blind, DD= double dummy, E= efficacy, GI= gastrointestinal, MC= multicenter, MD= multiple dose, PK= pharmacokinetics, R= randomized, S= safety, T= tolerability
exMMF= These were patients in the MMF who were switched to ERL080.

C. Postmarketing Experience

As of February 25, 2004, Myfortic® has been launched in India and Switzerland, Latvia, Brazil and Indonesia. Myfortic® is authorized for use in Argentina, Aruba, Australia, Bahrain, Chile, Columbia, Costa Rica, Curacao, Dominican Republic, Ecuador, El Salvador, European Union, Guatemala, Honduras, Hong Kong, Israel, Jamaica, South Korea, Lebanon, Mexico, Nicaragua, Panama, Peru, Philippines, Singapore, Syria, Taiwan, Trinidad and Tobago, United Arab Emirates, Uruguay, and Venezuela. Myfortic® has not been withdrawn for reasons of safety in any country.

As of May 31, 2003, the cut-off date for the 120-Day Safety Update, there were no serious postmarketing AEs reported by the Applicant.

D. Literature Review

The Applicant provided copies of relevant published articles from the literature to support the submission (Volumes 147 & 154 in the submission).

V. Clinical Review Methods

A. How the Review was Conducted

The primary efficacy trial in NDA 50-791 was Study-B301 conducted in *de novo* renal transplant patients supported by the efficacy results from Study-B302 conducted in stable renal transplant patients. The safety data used to review the Application includes the data from Study-B301, Study-B302, and Study-0107. A total of 446 patients were exposed to ERL080 for 12 Months in the clinical studies (B301, B302, 0107) to support the registration of ERL080 assuming that it is non-inferior and as safe as MMF (448 patients).

The MO review for Study-0107 is brief, since this study was a small study (a total of 159 patients: 74 patients exposed to ERL080 vs. MMF 75 patients) intended to evaluate the relative gastrointestinal tolerability of ERL080 compared to MMF in renal transplant recipients with gastrointestinal complaints secondary to MMF. This study was prematurely terminated when it appeared it would be unable to demonstrate superior tolerability of ERL080 compared to MMF. In addition, the instrument used in the study to measure gastrointestinal tolerability was not yet validated. No claims by the Applicant were made in reference to the gastrointestinal instrument used in the study.

MO Comment: *The MO reviewed a random sample of 10% of patients from Study-B301 and Study-B302 to validate and evaluate the robustness of the data in the submission. In addition, the MO reviewed all submitted CRFs and narratives for deaths, and serious AEs.*

The MO reviewed the files containing the clinical study protocols, CRFs, and clinical study reports, and found that there were minor differences mostly noted in the tables due to an upgrade in MedDRA that occurred while the studies were conducted. These minor changes did not affect the conclusions made by the Applicant. Therefore the Applicant's analysis is accepted. Further exploratory analyses were performed by the

MO to address specific clinical questions and is addressed in different sections in the review.

B. Overview of Materials Consulted in Review

The MO consulted the following sources during the conduct of this review:

- Files containing the clinical studies (B301, B302, 0107)
- Electronic Clinical Report Forms for deaths, dropouts, 10% random sample
- Electronic tables in support of the clinical studies
- Office of Drug Safety, HFD-420 review for the proposed proprietary name Myfortic®
- Files containing copies of literature reports submitted by the Applicant

C. Overview of Methods Used to Evaluate Data Quality and Integrity

Inspection by the Division of Scientific Investigation (DSI) was not requested or required by the Agency for NDA 50-791. The NDA includes 1 single multicenter study for efficacy and 1 single multicenter study for safety. Myfortic®, the substance the Applicant is seeking approval for, is chemically related to a known drug—CellCept®— and the clinical sites where the studies were conducted have participated in other transplant clinical trials.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The clinical studies done in NDA 50-791 were performed in accordance to the standard operating procedures of the Applicant. These standards require adherence to Good Clinical Practices, and included Directive 91/507/EEC (Rules Governing Medicinal Products in Europe), Declaration of Helsinki in reference to conducting research involving Human Patients, and US 21 CFR dealing with clinical studies/Patient Consent/IRB approval.

E. Evaluation of Financial Disclosure

The Applicant reported no instances of financial conflicts for the clinical studies in NDA 50-791. Most of the principal investigators (PI) responded to the financial disclosure information. In study B301 6/36 principal investigators did not respond to the financial disclosure statement; none of the 6 enrolled any patients. Similarly, in B302 6/40 principal investigators did not respond to the financial disclosure statement, 1/6 did not enroll patients in the trial. For the remaining studies in NDA 50-791 (0101, 0102, 0104, 0105, 0106, 0109, A2302, 151, 152, 154) there was 100% accounting for financial disclosure statements with no information to disclose by the principal investigators.

MO Comment: *Five PIs in Study-B302 did not submit a financial disclosure statement. The Applicant collected financial disclosure statements retrospectively. Study-B302 is not an efficacy study, it was primarily a safety study in maintenance renal transplant patients. The lack of a financial statement for the 5 PIs (# of patients 17) is not expected to affect the results of the study (Center#/patient#: 514/1, 518/5, 524/4, 526/6, 529/1).*

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Myfortic® is effective in preventing rejection in renal transplantation. This efficacy is suggested by three clinical studies in *de novo* and stable renal transplant recipients (Studies B301, B302, and 0107). These studies were submitted by the Applicant to support the indication for use of Myfortic® in renal transplant recipients.

Study-B301: Study B301 was a multicenter, double-blind, randomized, parallel group study designed to evaluate the efficacy and safety of Myfortic® vs. CellCept® in *de novo* renal transplant recipients. The study was conducted in the United States and Europe. Myfortic® was administered to patients at a dose of 720 mg po bid compared to an equivalent dose of CellCept® 1 gm po bid; therapy was initiated within 48 hours of post-transplantation. Patients also received standard cyclosporine and prednisone doses as part of the immunosuppressive regimen for renal transplantation.

The primary objective of the study was to demonstrate non-inferiority of ERL080 compared to MMF as measured by the incidence of biopsy-proven acute rejection, graft, loss, death or loss to follow up in the first 6 months after transplantation in *de novo* renal transplant recipients. Secondary objectives for the study included comparing efficacy variables at 6 and 12 months post-transplantation, evaluating the safety of ERL080 compared to MMF, and to characterize the PK of ERL080 in a subgroup of transplant patients.

A total of 423 adult patients were randomized and treated; the ERL080 group had 213 patients and the MMF group had 210 patients. The per protocol population (PP), defined as the subset of the Intent-to-Treat (ITT) population that did not violate the protocol in a significant way, included 201 (94.4%) patients in the ERL080 group and 202 (95.7%) patients in the MMF group.

The baseline demographic characteristics of the ITT population were comparable in age, gender, race, weight and height. Patients had an average age of 47 years (range 18-72 years), 41% of patients were over the age of 50. Women comprised 36% of the population in the ERL080 group and 32% of the ITT population in the MMF group. The majority of patients were Caucasian 88%, and the remainder were Black ~7%, Oriental ~1%, and Other races ~3%.

Transplant-related baseline characteristics in the ITT population were comparable across treatment groups (donor age, gender, transplant type, cause of end stage renal disease, and HLA mismatches). Unmatched transplant-related baseline characteristics in the ITT population are listed in the table below; however, these differences are minor and were unlikely to affect the results or interpretation of study results.

Study-B301 Selected Unmatched Demographic Characteristics (ITT population)
Source: Table 7.4 Vol 140, p:36

Variable		ERL080	MMF
PRA	0%	173 (81.2%)	183 (87.1%)
	1-20%	35(16.4%)	24 (12.4%)
CMV serology	D+/R-	36 (16.9%)	26 (12.4%)
	D+/R+	90 (42.3%)	115 (54.8%)
Cold ischemia time	≥24 hours	44 (20.7%)	28 (13.3%)
Race	Black donors	(6%)	(3%)

PRA = panel reactive antibodies; D/R = Donor / Recipient

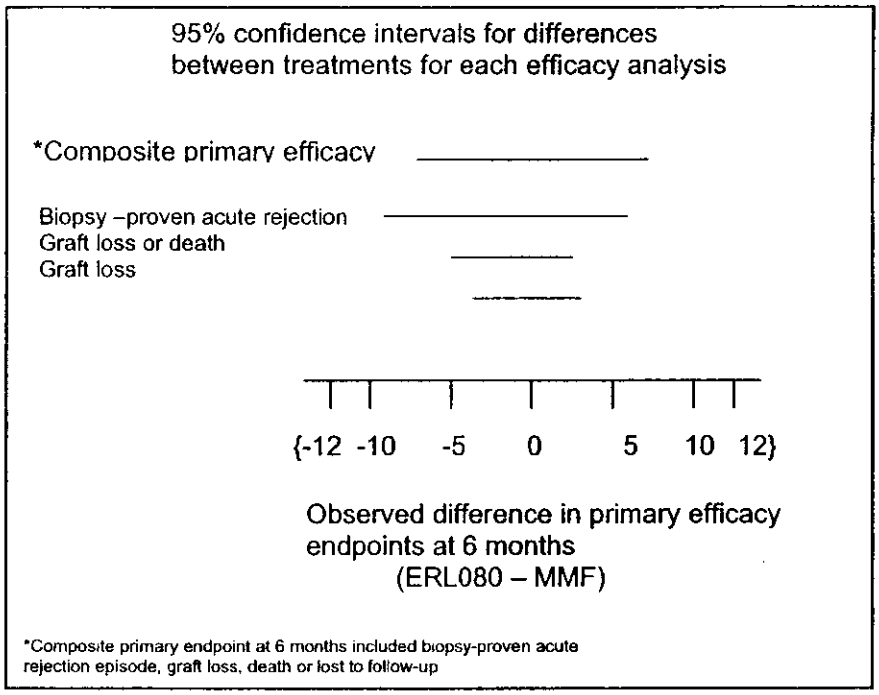
MO Comment: *Prolonged cold ischemia time and a higher rate of CMV D+/R- patients in the ERL080 group may potentially favor a better efficacy outcome in the MMF group. On the other hand, a preponderance of CMV D+/R+ may favor a better outcome for the ERL080 group. These differences were minor and in the totality of data cancel one another and therefore are unlikely to affect the results of efficacy. Therefore, randomization of patients in the study was satisfactory.*

The incidence rates of the primary efficacy points were comparable across treatment groups. The calculated 95% confidence intervals around the difference between treatment groups remained well within the prespecified delta of plus or minus 12% used to describe non-inferiority at the 6-month and 12-month time points.

B301 Primary Efficacy endpoints at 6 & 12 months post-transplantation (ITT population)
Source: Modified Table 9-1 Vol 140

Variables	Period	ERL 720 mg bid N=213	MMF 1 gm bid N=210	(ERL080-MMF) 95% CI {%, %}
Composite primary efficacy endpoint at	6 months	55 (25.8%)	55 (26.2%)	-0.4 {-8.7, 8.0}
	12 months	61 (28.6%)	59 (28.1%)	0.5 {-8.1, 9.2}
Biopsy-proven acute rejection	6 months	46 (21.6%)	48 (22.9%)	
	12 months	48 (22.5%)	51 (24%)	-1.8 {-9.8, 6.3}
Graft loss	6 months	7 (3.3%)	9 (4.3%)	
	12months	9 (4.2%)	9 (4.3%)	-0.5 {-4.3, 3.2}
Death	6 months	1 (0.5%)	2 (1%)	
	12 months	2 (0.9%)	5 (2.4%)	
Lost to Follow-Up**	6months	3 (1.4%)	0	
	12months	5 (2.3%)	0	
Graft loss, Death, Lost to Follow-Up***	12 months	20 (9.4%)	18 (8.6%)	

Composite primary efficacy endpoint (Treatment failure) = biopsy-proven acute rejection, graft loss or death, death, lost to follow-up
**Lost to Follow-up indicates patients who were lost to follow-up without prior biopsy-proven acute rejection, graft loss or death
*** Lost to Follow-up indicates patients who were lost to follow-up without graft loss or death (9 Myfortic patients and 4 MMF patients)
Ab-Rx = Antibody treatment
All patients in the study received Neoral® and steroids



Study-B302: Study-B302 was a multicenter, double-blind, randomized, parallel group study designed to evaluate the safety and efficacy of ERL080 720 mg po bid compared to MMF 1 gm po bid (in combination with Neoral® ± corticosteroids) in an adult (18-75 years) population for prophylaxis of organ rejection in stable renal transplant patients. The study period was from Feb 1999 to Oct 2001. Participating clinical centers were from North America and Europe. The primary objective of the study was to evaluate the rate of gastrointestinal and neutropenic adverse events (including other adverse events) for 12 months after administration of study medications. A secondary objective of the study was to evaluate the efficacy of ERL080 compared to MMF for the 12-Month period after administration of study medications.

A total of 322 patients were randomized in the study (ERL080 159 and MMF 163 patients). The baseline demographics characteristics of the study population were a mean age of 48 years, Caucasians represented 74% of patients followed by Blacks ~19% and Orientals 3%. The proportion of females in the ERL080 39% was higher than the proportion of females in the MMF 29% group (p=0.079). Glomerulonephritis followed by hypertension were the two most common causes of end stage renal disease. The primary population of interest was the ITT population defined as all randomized patients who received at least one dose of randomized study medication. At the end of the twelve months, all patients were offered to stay on, or switch to Myfortic® for an extended evaluation period until Myfortic® is available at the country where the patient was enrolled.

The primary efficacy endpoint in Study-B302 was similar to the composite primary efficacy endpoint for Study-B301. The difference in the point estimate of the primary efficacy composite endpoint for the two treatment groups was -2.4 95% CI {-7.4, 2.7%}, which was within the pre-specified 95% CI limit used to define non-inferiority in the study. Analysis of the co-primary endpoint and the secondary variables supports the primary composite endpoint (table below).

Study-B302 Primary & Secondary Efficacy Endpoints (ITT population)
Source: Modified PTT 9.1 Vol 150

		ERL080	MMF	ERL080-MMF 95% CI
***Composite Primary variable**	6 months 12 months	7 (4.4%) 12 (7.5%)	11 (6.7%) 20 (12.3%)	-2.4 (-7.4,2.7%) -4.2 (-11.3, 1.8%)
Secondary variables				
BPAR	6 months 12 months	2 (1.3%) 2 (1.3%)	2 (1.2%) 5 (3.1%)	
Acute rejection	6 months 12 months	2 (1.3%) 2 (1.3%)	3 (1.8%) 6 (3.7%)	
Treated acute rejection	6 months 12 months	2 (1.3%) 2 (1.3%)	2 (1.2%) 3 (1.8%)	
Acute rejection requiring Ab therapy	6 months 12 months	0 0	0 0	
BPCR	6 months 12 months	4 (2.5%) 4 (2.5%)	4 (2.5%) 8 (4.9%)	-1.1% (-5.6, 3.3%)
Graft loss	6 months 12 months	0 0	1 (0.6%) 1 (0.6%)	
***Death	6 months 12 months	0 2 (1.3%)	1(0.6%) 4 (2.5%)	
#Lost to follow-up	6 months 12 months	5 (3.1%) 8 (5%)	7 (4.3%) 10 (6.1%)	-1.1% (-6.1, 3.9%)
##Graft loss or death or lost to follow-up	12 months	10 (6.3%)	17 (10.4%)	

*Composite primary variable (Treatment failure) = Biopsy proven acute rejection (BPAR), graft loss, death, lost to follow-up
***Patient #5110013 (MMF) died post-study on Day-290. This patient withdrew consent on Day-273, and was discontinued from the study. Patient was listed in the composite variable as a "lost to follow-up"
#Lost to Follow-up indicates patients who were lost to follow-up without prior biopsy-proven acute rejection, graft loss or death
##Lost to Follow-up indicates patients who were lost to follow-up without prior graft loss or death (8 Myfortic patients and 12 MMF patients)

***MO Comment**: This study was not well designed to look at the secondary endpoint, biopsy-proven chronic rejection (BPCR).Therefore, the secondary variables relating to chronic rejection were excluded from the analysis. Ideally one would need baseline biopsies for comparison and regularly scheduled protocol biopsies to reliably ascertain the true rate of chronic rejection.*

B. General Approach to Review of the Efficacy of the Drug

The efficacy Study-B301 was the pivotal trial to demonstrate that Myfortic® is non-inferior to CellCept®. Study-B302 was primarily a safety study, the efficacy data from that study was used to support the efficacy data from the pivotal Study-B301.

C. Detailed Review of Trials by Indication

"Study-B301 Multicenter, double-blind, randomized, parallel group study on efficacy and safety of ERL080 vs. mycophenolate mofetil (CellCept®) in *de novo* renal transplant recipients (12-months analysis)."

Study dates: December 4, 1998 through April 19, 2001.

Investigators & Centers: This was a multicenter study conducted at 30 centers in North America (United States 6/30 centers, Canada 2/30 centers) and Europe (Austria 3/30, Germany 6/30, Hungary 4/30, Italy 2/30, Norway 1/30, Spain 4/30, United Kingdom 2/30).

Objectives: The primary objective of the study was to demonstrate non-inferiority of ERL080 compared to MMF treatment in the first 6 months post- *de novo* renal transplant with respect to prevention of graft rejection. The primary composite endpoint, treatment failure, was defined as the first occurrence of biopsy-proven acute rejection, graft loss, death or loss to follow-up at 6 months after transplantation. A co-primary endpoint, was defined as the cumulative incidence of graft loss, lost to follow-up or death at 12 months.

***MO Comment**: Lost to follow-up for the primary endpoint indicated patients who were lost to follow-up without prior biopsy-proven acute rejection, graft loss, or death; whereas in the co-primary endpoint it indicated patients who were lost to follow-up without prior graft loss or death.*

Secondary objectives to support the primary objective were to demonstrate non-inferiority of ERL080 compared to MMF treatment in the first 6 months post transplant period by measuring the incidence of biopsy-proven rejection, comparison of other efficacy variables at Months 6 & 12, evaluate the safety of ERL080 compared to MMF, and to characterize the PK of ERL080 in a subgroup of patients.

***MO Comment:** The Agency asked the Applicant to provide an analysis of primary and secondary efficacy and safety objectives at 6 and 12 twelve months to identify potential problems with efficacy and safety that may not have been detected at 6 months. A*

subset of patients from the study (when patients consented) were carried forward under an open-label design where patients on MMF were switched to ERL080 and observed further. The small non-random selected subset of patients enrolled in this extension phase, and the open-label study design create a potential for bias that may limit the interpretation of the data beyond 12 months post-transplantation.

Indications & Usage: The Applicant is requesting the following indication in the label- "Myfortic (mycophenolate sodium delayed-release tablet) is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants, administered in combination with cyclosporine, USP (MODIFIED) and corticosteroids."

Study Design: Study-B301 is a multicenter, double-blind, double-dummy, randomized, parallel-group, phase III clinical trial of adult patients undergoing renal transplantation of primary cadaveric, living unrelated, or human leukocyte antigen (HLA) mismatched living related donor kidneys. Subjects who met the inclusion criteria were enrolled and randomized to receive ERL080 or MMF, in combination with standard immunosuppressive therapy (Neoral® and prednisone) within a 48 hour window post-transplantation. Patients were followed for 12 months on treatment until the database was locked at Month-12. Patient evaluations occurred on Days-1,3,5,8; Weeks-2,3,4,6,8, 12; and Months-4,6,9,12. Follow-up of patients who were discontinued from the study was scheduled for 1 year post-randomization. After completion of the 12 month treatment phase, all patients from the ERL080 and the MMF groups were given the choice to continue on ERL080.

MO Comment: *One of the limitations of the study is the lack of long term data for rejection and safety beyond the 12 month interval. Nevertheless, the Applicant has incorporated an open-label extension section into the study in an attempt to capture long term data. Enrollment in the extension study was optional and subject to potential selection bias. This may limit the interpretation of long term data collected beyond 12 months post transplantation.*

MO Comment*: The generalizability of efficacy data from this study may be a potential limitation in that the distribution of donor type (cadaveric vs. living) in the study may not reflect the current trend towards increased proportion of living donors in the United States.*

Inclusion & Exclusion Criteria: This study enrolled adults (age 18-75 years) who were candidates for their first renal transplant and able to provide written informed consent. A standard immunosuppressive regimen consisting of Neoral® and steroids was administered to all patients. Females of childbearing potential were included if a serum pregnancy test was negative and were agreeable to use effective contraception.

MO Comment*: The exclusion criteria in the protocol were reviewed by the MO and reasonably exclude higher risk subjects who may not be good candidates for this study, for example, second transplants, recipients of organs from non-heart beating donors,*

ABO incompatibility, PRA of >50%, patients with a known hypersensitivity to the study drugs, recent investigational drug use, history of cancer in the last 5 years, substance abuse, presence of an infection or an uncontrolled illness.

Study Drug & Dosing schedule: ERL080 was provided in 360 mg enteric coated tablets; and in a matching placebo formulation. MMF was provided in 250 mg capsules and in a matching placebo capsules formulation.

After meeting inclusion/exclusion criteria, patients were then randomized in a 1:1 ratio during the immediate 48 hours post-transplantation to ERL080 720 mg po bid or MMF 1 gm po bid. Therefore a patient in the ERL080 group would receive 2 enteric coated ERL080 360 mg tablets and 4 placebo MMF capsules twice a day. Whereas patients in the MMF group would receive MMF 4x250 mg capsules and 2 placebo ERL080 enteric coated tablets twice a day. Neoral® was simultaneously administered with the study medications on an empty stomach (1 hour prior to or 2 hours after meals).

MO Comment: *Because grapefruit or its juice is known to alter cyclosporine bioavailability in transplant recipients which may affect rejection, toxicity rates, and hence alter efficacy and safety results, patients were not permitted to eat or drink grapefruit in this study. Also, ERL080 was administered on an empty stomach (1 hour before or 2 hours after meals). The manner in which the product was studied and the effect of food on the rate of absorption (delay in Tmax) should be considered when formulating recommendations for dosing and administration.*

MO Comment*: Patients in this study, appropriately signed informed consent during the screening phase prior to initiation of treatment with study drug or transplantation.*

Clinical sites were permitted to use induction therapy with antibodies; however antibody use was expected to be consistent for all patients at the site according to the protocol standards set by the site.

Randomization & Blinding: Patients in the study were randomized according to a randomization scheme that was reviewed by the Quality Management Biostatistics Group in Novartis. Patients were stratified by study site. The randomization list was locked after approval. The clinical research team at Novartis, and research site personnel were blinded to individual patient data.

MO Comment: *The Applicant provides a clear account of the Randomization process. Novartis personnel involved in the analysis of the study broke the blinding code after the database was locked at the 6-month assessment analysis. Breaking the blinding code by Novartis does not affect the study at the 6-month period, because the database was locked; however, the 12-month analysis may be subject to potential bias if there was communication between Novartis personnel and investigator sites.*

Population / Procedures: This study was comprised of three populations. The Intent-to-Treat (ITT) population, was also the primary efficacy analysis population and was defined as all randomized patients who received at least one dose of randomized study medication. A second population, the Per Protocol population (PP) was defined as the subset of the ITT population that did not violate the protocol in a "significant" way. Lastly, the third population is the safety population, defined as the ITT population that had at least one safety assessment.

***MO Comment**: The total number of patients randomized in the study was 424 patients. Of these 424 patients, one patient withdrew consent prior to receiving study medication. Therefore the ITT population included 423 patients.*

Patients were evaluated according to the evaluation schedule on figure-3. Day-1 was identified as the day when a patient received the first dose of study drug.

Figure 3-1. Diagram of visit and evaluation schedule

		Day				Week					Month				
Evaluations	Screening[1]	Baseline[2]	3	5	8	2	3	4	6	8	3	4	6	9	12[3]
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Informed consent, medical history, Tx info (recipient, donor), serology, pregnancy test	X														
Incl./excl. criteria	X	X													
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Compliance check								X		X	X	X	X	X	X
Laboratory test (hematology, chemistry, urinalysis, CsA blood levels)		X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK measurements[4]						X					X		X		
End of study															X
Others[5]	<——— As needed ———>														

[1] Screening evaluations to be performed within 7 days prior to randomization
[2] Baseline: Day 1, within 2 hours prior to randomization. Randomization: within 48 hours after transplantation.
[3] Or in case of premature discontinuation
[4] PK measurements in selected centers only
[5] Rejection episodes, renal biopsy, adverse events, serious adverse events, infections, hospitalization, comments, immunosuppressive therapy, and concomitant therapy

***MO Comment:** The procedure schedule provided reasonable consistency in those evaluation time points for evaluating patient safety and capturing important endpoint variables. Assessment of patients took into account collecting data pertaining to history, physical examination, vital signs, hematology, biochemistry, urine, measurement of cyclosporine whole blood trough levels, and sampling for PK assessment when required.*

Endpoints: The protocol specified primary efficacy endpoint for the study, treatment failure at 6 months, was defined as the first occurrence of biopsy-proven acute rejection, graft loss, death, or lost to follow-up at 6 months post-transplantation. And the co-

primary efficacy endpoint was defined as the cumulative incidence of graft loss, lost to follow-up, and death at 12 months.

MO Comment: *The composite primary efficacy point, treatment failure at 6 months, in the ITT population supported by the co-primary endpoints provides the most robust analysis for the efficacy portion of this study.*

Statistics: In this efficacy study, the ITT population was the primary analysis population. An estimated population sample size of 400 patients (200 in each treatment group) was based on a 95% two-sided confidence interval (CI) in the event rates for the difference of (ERL080—MMF) at 6 months post-transplantation. To conclude non-inferiority at a power of 0.85, the 95% two-sided CI for (ERL080—MMF) had to lie within the interval {-12, +12}. For this to occur, the estimated difference for the event rate (ERL080—MMF) could not be more than 3.5% and assuming a clinical success rate for treatments in the range of 85%.

MO Comment: *The study was sufficiently powered and the sample size was sufficient to test for non-inferiority of ERL080 to MMF. Patients lost to follow-up were treated as a treatment failure in the ITT population, since their outcome is uncertain. For the primary endpoint analysis, treatment failure, the variable, lost to follow-up was defined as patients who were lost to follow-up without prior biopsy-proven acute rejection, graft loss or death. Whereas for the co-primary endpoint, lost to follow-up indicated patients who were lost to follow-up without graft loss or death.*

Patient Disposition: The MedDRA preferred terms were used in this study as the basis for tabulating and summarizing the described variables for events.

Study Results:

Population: A total of 424 patients enrolled in Study-B301. The ITT population included 423 patients; 213 in the ERL080 group and 210 in the MMF group. A second population, the PP population included 201 (94.4%) patients in the ERL080 group and 202 (95.7%) patients in the MMF group.

MO Comment: *Patient # 0512 00001 was randomized but did not receive any medication because he withdrew consent. This patient was not included in the analyses of the populations analyzed. Thus the ITT population included only 423 participants.*

Baseline demographic characteristics: The baseline demographic characteristics (age, sex, race, height & weight) for the ITT population were generally comparable. The mean age of patients in the study was 47 years (range 18-72 years). Patients over the age of 50 were well represented in the study [88 (41.3%) ERL080 & 86 (41%) MMF]. Gender representation was as follows, 137♂(64.3%):76♀(35.7%) patients in the ERL080 group compared to 142♂(67.6%):68♀(32.4%) patients in the MMF group. The majority of patients were Caucasian 88%; followed by Black race 8% (ERL080 group) and 6% (MMF group); Other races 3-4%, and lastly Oriental race 1%.

MO Comment: *The number of geriatric (≥65 years) patients in the study was small [ERL080 14/213 (6.5%) and MMF 10/210 (4.7%)], this was partly because the cutoff birth date for inclusion in the study was 72 years of age.*

End stage renal disease secondary to glomerulonephritis 67 (31.5%) vs. 54 (25.7%), polycystic disease 42 (19.7%) vs. 26 (12.4%), hypertension 23 (10.8%) vs. 20 (9.5%), and diabetes mellitus (DM) 23 (10.8%) vs. 33 (15.7%) accounted for the majority of cases in the ERL080 and MMF groups respectively.

MO Comment: *The distribution of reasons for ESRD was comparable across treatment groups, or varied only slightly in a way that would not be expected to influence the outcome. In 1999, DM was listed as the cause of ESRD in ~22% of renal transplant recipients (United States data from USRDS[1]). Whereas in Study-B301, DM was listed as the cause of ESRD in ~11% of renal transplant recipients. Although speculative, this may suggest that investigators may have chosen to exclude patients with DM. A potential reason for excluding these patients may have been the known association between DM and gastroparesis secondary to autonomic neuropathy. Hence, some investigators may have been unwilling to enroll diabetic patients in a study using an enteric coated formulation, which has the potential of leading to unpredictable pharmacokinetics for Myfortic® in such a population.*

Donor transplant-related baseline characteristics in the ITT population were comparable for donor age ERL080 43.7 (16%) vs. 44.6 (14.4%) MMF, male donors in the ERL080 123 (57.5%) vs. 118 (56.2%) MMF, Caucasian donor 180 (84.5%) vs. 185 (88.1%) MMF, respectively. Donor HLA mismatches and positive serology for EBV and HbsAg were also comparable. Gender donors/recipient rates were comparable in both groups. Other donor characteristics are listed in the table below. A majority comparable number of patients in both groups had a cold ischemia time of <24 hours [163 (76.5%) patients in the ERL080 and 178 (84.8%) patients in the MMF group].

Selected Donor Baseline Characteristics Study-B301

		ERL080 1.44 gm/day N=213	MMF 2 gm/day N=210
Transplant type	Cadaveric heart beating	180 (84.5%)	173 (82.4%)
	Living related	23 (10.8%)	26 (12.4%)
	Living unrelated	9 (4.2%)	11 (5.2%)
	Cadaveric non-heart beating	1 (0.5%)	0
Panel Reactive Antibodies	0%	173 (81.2%)	183 (87.1%)
	1-20%	35 16.4%	24 11.4%
	21-50%	5 2.3%	0
	51-100%	0	1 (0.5%)
CMV serology	D+/R+	90 (42.3%)	115 (54.8%)
	D+/R -	36 (16.9%)	26 (12.4%)

[1] http://www.usrds.org United States Renal Data System.

Selected Donor Baseline Characteristics Study-B301

		ERL080 1.44 gm/day N=213	MMF 2 gm/day N=210
	D -/R+	48 (22.5%)	29 (13.8%)
	D -/ R -	26 (12.2%)	32 (15.2%)
Cold ischemia time	Mean	17 hours	15.6 hours
	≥24 hours	44 (20.7%)	28 (13.3%)

D= donor, R=recipient

MO Comment: *Notable differences in the rates for CMV serology are observed in the table. Although the difference of 4% between the two treatment groups for D+/R- may favor a better outcome in the MMF group, this difference may be offset by the 12.5% difference for D+/R+ favoring a better outcome in the ERL080 group. The overall numbers of CMV D+/R- cases are small and the small imbalance is not large enough to influence the study outcome, especially if one takes into consideration the distribution of all of the risk factors..*

MO Comment: *Overall, the randomization process was satisfactory. There were no significant imbalances in distribution of donor characteristics that could influence study outcomes. Currently, in the United States, the rate of living donors has exceeded cadaveric donors (living donors ~60% vs. cadaveric donors ~40%, UNOS). In Study-B301, the majority of donors were cadaveric ~85%. Recipients of organs from living donors are expected to have lower rates of delayed graft function, acute rejection, graft loss or death; also, requirements for immunosuppression in these patients may be less than that of recipients of organs from cadaveric donors. This may potentially affect the generalizability of the study results to the United States transplant population and should be reflected in the label.*

HLA Mismatches: Total HLA mismatches for HLA loci A, B, and DR were comparable between the two groups. The rate for 0-3 mismatches was 132 (62%) patients in the ERL080 and 126 (60%) for the MMF group; and for 4-6 mismatches the rate was 79 (37.1%) in the ERL080 group and 81 (38.6%) in the MMF group.

Prior Medical conditions: Patients in Study-B301 had a comparable rate of medical problems prior to their transplant. Among the minor differences observed were a higher rate of blood and lymphatic system disorders [20.7% ERL080 vs. and 26.2% MMF group], and cardiac disorders [29.1% ERL080 vs. 35.2% MMF] in the MMF group. Patients in both groups had similar baseline rates for history of infections, malignancies, and surgical procedures. Rate of "pain NOS" was 15 (7%) for the ERL080 group and 24 (11.4%) in the MMF group.

MO Comment: *The baseline pretransplant medical condition rates reported for surgical procedures, pain, history of infections, and malignancies is for the most part comparable in the two groups. A higher rate of history of blood and lymph disorders as well as*

cardiac disorders may potentially suggest sicker patients in the MMF group, which may provide an advantage for success in the ERL080 group.

Protocol Violations: Twelve (5.6%) patients in the ERL080 group and eight (3.8%) patients in the MMF group were excluded from the PP analyses because of protocol violations. The most common reason for exclusion due to a protocol violation was antibody induction therapy not given uniformly to patients at a center (7 patients in ERL080 group, and 4 patients in MMF group), followed by a cold ischemia time of >36 hours (3 patients in ERL080 group, and 2 patients in MMF group). There were two patients in each group who received immunosuppressive therapy before transplantation.

MO Comment: *Patients excluded from the PP analyses were not excluded from the ITT analyses. The PP population, at best was used to provide potential support to the ITT efficacy analyses. The irregularities in use of induction of antibody therapy among some centers raises some concern; however, the overall numbers are small and are not expected to influence results of the study. The Applicant did not explore or provide reasons for the irregularities observed in administering antibody therapy.*

Other common protocol violations that did not result in exclusion from the PP analyses were, study medication not proportionally reduced in case of dose reductions [14 (6.6%) ERL080 and 11 (5.2%) in the MMF group], study medication is interrupted for more than 2 days during the first 2 weeks after transplant or more than 14 days thereafter within a 2 month period [10 (4.7%) in the ERL080 and 9 (4.3%) in the MMF group]. A total of two patients on ERL080 were unblinded prematurely at the investigative sites secondary to pancreatitis (patient #0511 00010 from the USA and patient # 0031 00012 from Norway).

MO Comment: *These minor protocol violations did not influence the results or outcome of the study.*

The MO reviewed the Applicant's statements on instances of protocol deviations and concurs that these deviations were minor and did not affect the results or the interpretation of the study.

Study-B301 Protocol Violators (ITT Population - 0-12 Months)
Source: Post-Text Listing 7.2-1

Trt Group	Demographic variables	Protocol Violation	Exclude from PP Population
ERL	0002_00001[39/F/Ca/48.4]	Study medication is not proportionally reduced in case of dose reductions	No
	0002_00009[50/F/Ca/84.6]		No
	0002_00012[30/F/Ca/]		No
	0003_00004[47/M/Ca/98.0]		No
	0003_00010[49/F/Ca/54.0]		No
	0011_00003[41/M/Ca/81.0]		No

	0031_00006[60/M/Ca/76.0]		No
	0045_00008[54/F/Ca/]		No
	0053_00007[58/F/Ot/95.4]		No
	0501_00004[72/M/Ca/90.2]		No
	0511_00024[25/F/Ca/38.2]		No
	0513_00023[28/M/Bl/78.3]		No
	0514_00006[70/M/Or/72.4]		No
	0516_00005[51/M/Ca/68.3]		No
	0012_00010[38/M/Ca/90.3]	Platelets less than 75 10E9/L at baseline visit	Yes
	0012_00012[52/M/Ca/68.6]	HBsAg viral serology result is trace or positive	No
	0012_00012[52/M/Ca/68.6]	HIV viral serology result is trace or positive	No
	0016_00013[45/M/Ca/96.5]	Cadaveric non-heart beating transplant	Yes
	0022_00001[37/M/Ca/66.0]	First dose of study drug not given within 48 hours following transplant	No
	0022_00001[37/M/Ca/66.0]	Study medication is interrupted for more than 2 days during the first 2	No
	0022_00005[24/M/Ca/52.0]	weeks or more than 14 days thereafter within a 2 month period	No
	0022_00010[60/F/Ca/65.5]		No
	0023_00002[25/M/Ca/70.0]		No
	0053_00002[59/M/Ca/87.2]		No
	0064_00006[25/F/Ca/56.5]		No
	0501_00006[57/M/Ca/76.2]		No
	0515_00010[64/F/Ca/81.0]		No
	0516_00002[49/F/Ca/66.6]		No
	0023_00016[49/M/Ca/96.0]	First dose of study drug not given within 48 hours following transplant	No
	0053_00002[59/M/Ca/87.2]	Cold ischemic time > 36 hours	Yes
	0053_00005[42/F/Ca/75.2]		Yes
	0054_00006[23/M/Ca/70.4]		Yes
	0064_00002[33/M/Ca/58.0]	Antibody induction therapy not uniformly given to all patients in a centre	Yes
	0064_00006[25/F/Ca/56.5]		Yes
	0012_00001[65/F/Ca/64.0]		Yes
	0511_00004[62/M/Ca/95.5]		Yes
	0514_00003[66/F/Ca/91.9]		Yes
	0514_00016[51/M/Or/76.6]		Yes
	0515_00001[31/F/Bl/68.1]		Yes
	0511_00021[30/F/Ca/57.0]	Malignancy within last 5 years or present malignancy other than excised basal cell carcinoma of skin	No
	0512_00003[52/F/Bl/61.4]	Pretreatment with immunosuppressive therapy before transplantation	No
	0515_00001[31/F/Bl/68.1]		No
	0513_00024[46/M/Bl/120.0]	Presence of uncontrolled diabetes mellitus	No
MMF	0002_00003[59/M/Ca/85.0]	Study medication is not proportionally reduced in case of dose reductions	No
	0003_00002[47/F/Ca/80.3]		No
	0042_00005[39/M/Ca/70.5]		No
	0042_00001[31/F/Ca/59.0]		No
	0045_00010[63/F/Ca/60.0]		No
	0045_00011[54/F/Ca/52.5]		No
	0512_00002[38/M/Ca/57.4]		No
	0516_00016[46/F/Ca/92.9]		No
	0514_00019[56/M/Ca/102.4]		No
	0011_00004[59/F/Ca/60.1]	Study medication is interrupted for more than 2 days during the first 2	No
	0022_00023[56/F/Ca/70.8]	weeks or more than 14 days thereafter within a 2 month period	No
	0511_00003[43/M/Ca/75.8]		No
	0064_00007[30/M/Ca/70.5]		No
	0045_00010[63/F/Ca/60.0]		No
	0512_00008[46/F/Ca/64.8]		No
	0513_00009[35/M/Ca/70.8]		No
	0054_00002[47/M/Ca/67.2]		No
	0023_00020[41/M/Ca/84.0]		No
	0016_00012[60/F/Ca/78.0]	Antibody induction therapy not uniformly given to all patients in a centre	Yes
	0514_00015[72/M/Ot/98.4]		

0064_00004[36/F/Ca/74.3]		Yes
0514_00019[56/M/Ca/102.4]		Yes
0022_00018[57/M/Ca/67.7]	HBsAg viral serology result is trace or positive	No
0022_00023[56/F/Ca/70.8]	Platelets less than 75 10E9/L at baseline visit	No
0053_00008[43/M/Ca/84.8]	Cold ischemic time > 36 hours	Yes
	Study medication is interrupted for more than 2 days during the first 2 weeks or more than 14 days thereafter within a 2 month period	No
0054_00008[45/M/Ca/94.8]	Second or subsequent kidney transplant/multiple transplants/HLA living related donor	Yes
0054_00010[38/M/Ca/87.9]	HBsAg viral serology result is trace or positive	No
0501_00008[59/M/Ca/90.0]	Pretreatment with immunosuppressive therapy before transplantation	No
0511_00011[55/M/Ca/97.7]	WBC less than 2.5 10E9/L at baseline visit	No
0511_00012[42/F/Ca/96.2]	Cold ischemic time > 36 hours	Yes
0514_00015[72/M/Ot/98.4]		No
0513_00019[54/F/Ca/61.2]		No
0513_00003[64/F/Bl/98.2]	Panel reactive antibodies greater than 50% case of dose reductions	Yes
0514_00011[63/M/Or/74.0]	Presence of uncontrolled diabetes mellitus	No
0514_00015[72/M/Ot/98.4]	Pretreatment with immunosuppressive therapy before transplantation	No
0515_00011[44/M/Bl/130.0]	Malignancy within last 5 years or present malignancy other than excised basal cell carcinoma of skin	No

Patient Disposition: For the 0-6 Months period, 58 (27.2%) patients in the ERL080 group prematurely discontinued treatment compared to 46 (21.9%) of patients in the MMF group. Also, for the 0-6 Months period, 9 (4.2%) patients in the ERL080 group and 7 (3.3%) patients in the MMF group were discontinued from the study. Reasons and accounting for discontinuing treatment or study for both periods, 0-6 & 0-12 Months are listed in the table below.

The most common reasons for discontinuing treatment early in both groups were adverse events, unsatisfactory therapeutic effect, lost to follow-up, protocol violations, and graft loss (See table below). Other less frequent causes for early treatment discontinuation were: withdrawn consent, death, and abnormal laboratory findings.

MO Comment: *The Applicant performed two analyses for the endpoint (D/C treatment and D/C study), the latter includes all events, and the former treats discontinuations of study medication as censored. In the table below, patients in the D/C treatment group were included in the ITT analysis, these patients were not all counted as failures. Whereas patients who were assigned to the D/C study were counted as failures in the ITT analysis.*

Study-B301 Early Treatment or Study Discontinued (ITT population) 0-6 & 0-12 months*
Source: Table-7.1 Vol 140, p:32, ModifiedTable 10.2-2C

	ERL080 N=213		MMF N=210	
	0-6 Month	**0-12 Month**	**0-6 Month**	**0-12 Month**
D/C treatment	58 (27.2%)	62 (29.1%)	46 (21.9%)	52 (24.8%)
Reasons:				
Adverse events	35 (16.4%)	36 (16.9%)	29 (13.8%)	29 (13.8%)
Unsatisfactory therapeutic effect	10 (4.7%)	11 (5.2%)	5 (2.4%)	8 (3.8%)
Lost to follow-up	0	1 (0.5%)	0	0

Study-B301 Early Treatment or Study Discontinued (ITT population) 0-6 & 0-12 months*
Source: Table-7.1 Vol 140, p:32, ModifiedTable 10.2-2C

	ERL080 N=213		MMF N=210	
	0-6 Month	**0-12 Month**	**0-6 Month**	**0-12 Month**
Withdrawn consent	2 (1%)	2 (1%)	0	0
Protocol violations	5 (2.3%)	5 (2.3%)	4 (1.9%)	5 (2.4%)
Graft loss	5 (2.3%)	5 (2.3%)	6 (2.9%)	6 (2.9%)
Death	0	1 (0.5%)	2 (1%)	4 (1.9%)
Abnormal laboratory finding	1 (0.5%)	1 (0.5%)	0	0
D/C study	9 (4.2%)	13 (6.2%)	7 (3.3%)	13 (6.3%)
Reasons:				
Lost to follow-up	5 (2.3%)	7 (3.3%)	3 (1.4%)	5 (2.4%)
Withdrawn consent	3 (1.4%)	4 (1.9%)	2 (1%)	3 (1.4%)
Death	1 (0.5%)	2 (1%)	2 (1%)	5 (2.4%)

D/C = discontinued. The time window for the Month-12 visit extended from day 312-450
*There were no drug D/C after 360 days.

MO Comment: *A comparable proportion of patients in the ERL080 discontinued study medication due to an AE. Common causes of D/C study medication in both groups included GI AE (ERL080 10 vs. MMF 11 patients), renal disorder (ERL080 6 vs. MMF 7 patients), or graft loss (ERL080 5 vs. MMF 6 patients). Overall, when looking at the specific causes for D/C treatment secondary to an AE, the rates were comparable across both treatment groups. There were no significant differences in rates between the two treatment groups in study discontinuation. The relatively high rates for treatment discontinuation are expected in a de novo renal transplant study where patients have end stage renal disease and are exposed to immunosuppressive regimens for the first time.*

Pharmacokinetic Evaluation: A subgroup of patients in Study-B301 had PK studies done at 3 investigator sites (Centers 031, 016, 011). Twenty two patients were in the ERL080 group and 26 patients were in the MMF group. Of note is the uneven demographic characteristics for the PK groups. For example, males comprised 59.1% in the ERL080 group and 80.8% in the MMF group. Also, the mean age in the ERL080 group was 46 years, and 53 years in the MMF group. Finally mean body weight was 74.1 kg in the ERL080 group and 82.4 kg in the MMF group.

MO Comment: *The patients selected for the PK study were a subgroup of participants from the double-blind, randomized Study-B301; unblinding was not allowed for the PK portion of the study. The Applicant states that the differences in demographics were not statistically significant and were not expected to diminish the significance for the PK results from MPA exposure. Pharmacokinetic results from this subgroup of patients revealed that the cumulative MPA exposure by AUC at the three measured points of the PK study (Days-15, 90, & 180 post-transplant) led to ERL080 delivering ~32% higher*

MPA exposure in the ERL080 group than in the MMF group. The use of a non-random, parallel group design instead of a randomized crossover design introduces a potential for bias. Thus, the comparison of systemic MPA exposure across treatment groups should be interpreted with caution.

Mean MPA AUC (·µg h/mL) values Study-B301, PK subpopulation analysis			
	Day-15	**Day-90**	**Day-180**
ERL080	29.1	50.7	55.7
MMF	23.3	39.1	37.2

***MO Comment**: Please refer to the Biopharmaceutical Review by Dr. Jang-Ik Lee for further details. At the pre-NDA meeting, concerns were raised over difference in extent of exposure to mycophenolic acid. The exposure was significantly higher in the ERL080 group compared to the MMF group. Because one could not tell whether this represented a true difference or the effect of using a selected non-random, parallel group design, the Applicant conducted an additional randomized, crossover design PK study to evaluate the relative exposure to MPA with ERL080 compared to MMF (Study-2302).*

***MO Comment:** PK data from Study 2302 demonstrated that MPA exposure from ERL080 (720 mg po bid) was comparable to MMF (1000 mg po bid) when administered to stable renal transplant recipients.*

Efficacy Results: In Study-B301, the primary efficacy endpoint for the ITT population was treatment failure, defined as, biopsy-proven acute rejection, graft loss, patient death or lost to follow-up at 6 months post transplantation. The incidence rates for treatment failure, were 55/213 (25.8%) patients in the ERL080 group and 55/210 (26.2%) patients in the MMF group. At 6 months, the difference in the point estimate of the primary efficacy endpoint, treatment failure, (ERL080-MMF) was -0.4% [95% CI {-8.7, 8.0}], with a 95% CI that was well within the pre-specified bounds of the ±12% interval used to define non-inferiority. Similarly, at 12 months post transplantation, the results for treatment failure were comparable to the results reported for the 6 months primary efficacy endpoint (See table).

***MO Comment**: The efficacy analysis presented by the Applicant was accepted by the FDA , and is presented as submitted by the Applicant, with minor changes in the co-primary endpoint that resulted after clarification of the differences in the definition for lost to follow-up in the primary endpoint and the co-primary endpoint.*

B301 Primary Efficacy endpoints at 6 & 12 months post-transplantation (ITT population)
Source: Modified Table 9-1 Vol 140

Variables	Period	ERL 720 mg bid N=213	MMF 1 gm bid N=210	(ERL080-MMF) 95% CI {%, %}
Composite primary efficacy endpoint at	6 months	55 (25.8%)	55 (26.2%)	-0.4 {-8.7, 8.0}
	12 months	61 (28.6%)	59 (28.1%)	0.5 {-8.1, 9.2}
Biopsy-proven acute rejection	6 months	46 (21.6%)	48 (22.9%)	
	12 months	48 (22.5%)	51 (24%)	-1.8 {-9.8, 6.3}
Graft loss	6 months	7 (3.3%)	9 (4.3%)	
	12months	9 (4.2%)	9 (4.3%)	-0.5 {-4.3, 3.2}
Death	6 months	1 (0.5%)	2 (1%)	
	12 months	2 (0.9%)	5 (2.4%)	
Lost to Follow-Up**	6months	3 (1.4%)	0	
	12months	5 (2.3%)	0	
Graft loss, Death, Lost to Follow-Up***	12 months	20 (9.4%)	18 (8.6%)	

Composite primary efficacy endpoint (Treatment failure) = biopsy-proven acute rejection, graft loss or death, death, lost to follow-up
**Lost to Follow-up indicates patients who were lost to follow-up without prior biopsy-proven acute rejection, graft loss or death
*** Lost to Follow-up indicates patients who were lost to follow-up without graft loss or death (9 Myfortic patients and 4 MMF patients)
Ab-Rx = Antibody treatment
All patients in the study received Neoral® and steroids

MO Comment: *The composite efficacy results for the ITT population provides reasonable assurances that ERL080 is comparable in efficacy to MMF at Month-6 & 12 in de novo renal transplantation when administered in a combined regimen with Neoral® and steroids. In addition, the co-primary endpoint of graft loss, death, lost to follow-up at 12 months, was comparable for the two treatment groups.*

MO Comment: *For the primary endpoint, lost to follow-up indicated patients who were lost to follow-up without prior biopsy-proven acute rejection, graft loss or death. And for the co-primary endpoint, lost to follow-up indicated patients who were lost to follow-up without graft loss or death.*

Biopsy-proven Acute rejections (ITT population): A total of 48/213 (22.5%) patients in the ERL080 and 51/210 (24.3%) patients in the MMF had experienced an acute rejection episode at 12 months. The majority of those instances of rejection were single episodes (41/48 patients in the ERL080 and 41/51 in the MMF group). Of the 48 patients in the ERL080, 6 patients had 2 episodes of rejection, and 1 patients had ≥3 episodes of rejection, and in the MMF group, 10/51 patients had 2 episodes of rejection.

The total number of patients in each group that had a kidney biopsy was 90/213 (42.3%) patients in the ERL080 group, and 87/213 (41.4%) in the MMF group. Around

10% of patients in both groups had 2 biopsies performed. Table below lists kidney biopsy results for patients identified with rejection.

B301 Renal Biopsy Results (ITT population up to Month-12)

	*Banff 97 type	ERL080	MMF
Mild acute	Type Ia	24 (11.3%)	21 (10%)
	Type Ib	7 (3.3%)	9 (4.3%)
Moderate acute	Type IIa	11 (5.2%)	13 (6.2%)
	Type IIb	5 (2.3%)	2 (1%)
Severe acute	Type III	1(0.5%)	5 (2.4%)

*Racusen LC, Solez K, Colvin RB, et al. The Banff 97 working classification of renal allograft pathology. Kidney International 1999;55(2):713-723.

The incidence of abnormal findings on renal biopsy other than acute rejection was comparable between the two treatment groups. Two frequent abnormal findings were acute tubular necrosis (ERL080 9.4% vs. MMF 11.4%) and drug-induced toxicity (ERL080 6.1% vs. MMF 4.8%).

MO Comment: *The majority of biopsies were prompted by a clinical event (83/90 in the ERL080 group, and 79/87 in the MMF group), the remainder biopsies in both groups were obtained for the purpose of follow-up. Few centers did routine surveillance biopsies per local practice. In this study, there were 2 biopsies performed in the MMF group that were protocol specified. The rate of biopsies performed were comparable between the two groups, which is expected given the fact that all patients in the study were receiving similar immunosuppressive regimens. The distribution of Banff 97 severity grades were comparable among the two groups.*

Graft Loss: The rates for graft loss in the ITT population for the 0-12 Month period were comparable for all window visits. In total there were 9 patients in each group with graft loss. The most common cause for graft loss was acute rejection (ERL080 1 patient vs. MMF 3 patients), followed by renal vein thrombosis (ERL080 4 patients vs. MMF 0 patients), and infarcted kidney (ERL080 0 vs. MMF 3 patients).

MO Comment: *In the original NDA (PTT 9.2-7, Vol 141, p:432), the Applicant reported 8 patients with graft loss in the ERL080 group. An additional patient with graft loss was added to the ERL080 group. The addition was secondary to an omission, and was reported in the 120-Day Safety Update report (#513_0023 a 28-year-old Black patient was discontinued from the study due to an unsatisfactory therapeutic response. Repeat biopsies demonstrated recurrence of original disease = glomeulonephritis; there was no evidence of acute rejection).*

Lost to Follow-Up: At 12 months, there were 9 (4.2%) patients in the ERL080 group and 4 (1.9%) patients in the MMF group lost to follow-up. The first patient lost to follow-up was reported at visit Day 71-99.

MO Comment: *Patients lost to follow-up were listed as failures. The rate of lost to follow-ups for a de novo transplant study during the first 12 months, is slightly higher than expected. Lost to follow-up indicates patients who were lost to follow-up without prior biopsy-proven acute rejection, graft loss or death.*

Per Protocol Analysis (PP): The PP efficacy analyses was intended to support the results of analyses for the ITT population. In general, the PP efficacy analyses were supportive of the efficacy analyses for the ITT population. At Month-12 efficacy rates were comparable in the PP population to the ITT population for the composite [55 (27.4%) patients in the ERL080 group, and 56 (27.7%) patients in the MMF group] and for the individual component efficacy endpoints.

MO Comment: *The PP population efficacy analysis supported the efficacy analysis for the ITT population. Also, comparing event rates (for example: biopsy-proven acute rejection, graft loss, death or loss to follow-up within 6 & 12 months of transplantation) at each participating site demonstrated a consistency in rates among centers with high volume of patients (10-18 patients/center randomized and enrolled). Centers with low volume of patients (<10) showed a variability in event rates ranging from 0-100% (Vol 141, table 9.1 & 9.2) . These results are expected, therefore no unusual patterns were identified within the study centers.*

Secondary efficacy endpoints: The incidence rates for each secondary efficacy endpoint is listed in the table below, were comparable between the two treatment groups. As noted, in the table, the incidence rates for the secondary efficacy endpoints were comparable for each endpoint between the two treatment groups at the Month-6 and Month-12 evaluation periods.

Study-B301 Secondary efficacy endpoints (ITT population, Month-0 to 12)
Source: PTT 9.1-1 & 9.1-13

Variables	Period	ERL080 N=213	MMF N=210
Any acute rejection	6 months	52 (24.4%)	55 (26.2%)
	12 months	54 (25.4%)	58 (27.6%)
Treated acute rejection	6 months	51 (23.9%)	52 (24.8%)
	12 months	52 (24.4%)	54 (25.7%)
Antibody-Treated acute rejection	6 months	11 (5.2%)	10 (4.8%)
	12 months	11 (5.2%)	10 (4.8%)
Biopsy-proven chronic rejection	6 months	8 (3.8%)	12 (5.7%)
	12 months	12 (5.6%)	16 (7.6%)

MO Comment: *The secondary efficacy endpoints support the primary efficacy endpoint (composite biopsy-proven acute rejection) analyses.*

Graft loss: Incidence of graft loss was comparable between the two treatment groups. Acute rejection (ERL080 1 vs. MMF 3 patients), renal vein thrombosis (ERL080 4 vs. 0 MMF), and kidney infarction (ERL080 0 vs. MMF 3 patients) were the three most frequent causes for graft loss.

Study-B301 extension phase: The primary efficacy composite variable for the 30-Month cohort (12 months in the core study "ERL080 or MMF treated" + 18 month in the extended open-label ERL080 treatment phase) were comparable for the ERL080 treated group 21/99 (21.2%) and the exMMF group 24/103 (23.3%). There were 2 deaths in either group (2%), 2 patients in the ERL080 suffered graft loss compared to none in the exMMF group, and biopsy-proven acute rejection occurred in 19/99 (19.2%) patients in the ERL080 group compared to 23/103 (22.3%) in the exMMF group.

Study-B302:

Title: "Multicenter, double-blind, randomized, parallel group study on tolerability and safety of ERL080 vs. mycophenolate mofetil (CellCept®) in maintenance renal transplant patients (12-month analysis)."

Study dates: February 9, 1999 through October 6, 2001.

Investigators & Centers: This multicenter study was conducted at 34 centers in North America (Canada 5/34 and the United States 19/34) and Europe(Germany 3/34, Belgium 2/34, Austria 2/34, Spain 2/34, and Italy 1/34).

Objectives: The primary objective of the study was to evaluate the incidence and severity of:

- GI AEs at 3 months after administration of study medication
- neutropenia within the first 3 months after administration of study medication

A secondary objective of the study was to evaluate the efficacy of ERL080 compared to MMF in stable renal transplant patients. The primary efficacy endpoint, treatment failure, was defined as the first occurrence of biopsy-proven acute rejection, graft loss, death, or lost to follow-up at 6 months post-transplantation. A co-primary endpoint and secondary efficacy variables were also used (reader is referred to Study-B302 efficacy table). Similar to Study-B301, the definition for lost to follow-up depended on whether one was looking at the primary endpoint or the co-primary endpoint (Clinical Review p:29).

***MO Comment**: Similar to Study-B301, the Agency requested from the Applicant that the analyses for efficacy and safety be inclusive of the 12 months period from administration of study medication.*

Indications & Usage: The Applicant is seeking approval for the indication of "prophylaxis of organ rejection in patients receiving allogeneic renal transplants, administered in combination with cyclosporine, USP (MODIFIED) and corticosteroids."

Study Design: Study-B302 is a multicenter, randomized, double-blind, double-dummy, parallel, 12-month study of the safety and efficacy of ERL080 compared to MMF treatment in stable renal transplant patients on Neoral® with or without steroids. Patient population consisted of adults 18 to 75 years who were already 6 months post renal transplantation with a primary or secondary cadaveric or living donor kidney transplant. The study started out with a screening visit, and was followed by an open-label run-in period at which patients received MMF capsules (4X250 mg po bid) and Neoral® with or without steroids for 2 weeks. Patients who successfully completed the run-in period and fulfilled the inclusion and exclusion criteria were randomized (1:1) to receive ERL080 720 mg po bid or MMF 1 gm po bid for 1 year.

***MO Comment:** The study was designed to enroll stable patients (on MMF for at least 4 weeks). The run-in period could have allowed further adaptation to the potential GI effects of MMF. Thus the enrollment criteria and run-in period selected a population less sensitive to the GI effects of MPA exposure. This may not represent the ideal population to detect differences in tolerability.*

After the 12-month period, patient were given the option to continue on ERL080 therapy in the 24-month open-label extension period or until ERL080 was marketed in the country where the clinical study site was located.

Inclusion & Exclusion Criteria: (checked at enrollment in the run-in period, and reassessed at randomization)

- Adult males and females (18-75 years), 6 months post-renal transplant (primary or secondary cadaveric, living related, living unrelated donor)
- Currently on an immunosuppressive regimen of MMF 1 gm bid and Neoral® ± steroids for at least 4 weeks prior to screening
- Stable graft function (serum creatinine ≤2.3 mg/dL), no change in immunosuppressive regimen due to graft malfunction, stable physical and laboratory values for the prior 2 month to enrollment, baseline serum creatinine increased <20% compared to screening
- Protection for women of childbearing protection (pregnancy test prior to screening, and effective contraception required during the trial)
- Patients were willing to participate in the study and signed a written informed consent

MO Comment: *The inclusion criteria are appropriate for the study. The rationale behind patients having to be on at least 4 weeks of immunosuppressive therapy is probably to ensure that they would not be enrolling patients who were unstable. Adults, from both genders were allowed to participate in this study.*

The exclusion criteria included:

- Patients with ≥3 renal transplants , or previous transplantation of another organ
- Evidence of graft rejection, or therapy for acute rejection within 2 months prior to screening, creatinine value >2.3 mg/dL at screening or baseline, at baseline a serum creatinine that increased >20% compared to value at screening
- Hypersensitivity to ERL080 or MMF or other formulation component
- "Platelet count <75,000/mm^3, with an absolute neutrophil count <1,500/mm^3, and or leukocytopenia (<2,500/mm^3), and or hemoglobin <9 g/dL prior to enrollment"
- Use of investigational drugs within 2 weeks prior to screening
- History of malignancy in last 5 years (except excised non-melanoma skin cancer)
- Clinically significant infections, severe diarrhea, active peptic ulcer, uncontrolled diabetes mellitus, or positive for HIV infection
- Women of childbearing potential planning for pregnancy or lactating and unwilling to use effective contraception
- Evidence of substance abuse

MO Comment: *The exclusion criteria were reasonable and provide adequate protection from including patients who would make poor candidates for this study.*

Protocol Amendments: The first protocol amendment dated February 15, 1999 provided clarifications to the protocol to increase the robustness of the study, for example, since this was a study in stable renal transplantation, patients who were ≥6 months post transplantation could enroll, also graft loss was added to serious AEs. The second protocol amendment dated January 24, 2000 changed the definition for minimum MMF treatment duration at the entry before enrollment into the study from 3 months to 4 weeks. Amendment 1 to supplement 1 dated November 16, 2001 provided a 24-month open-label extension period to permit patients who provide consent, to continue ERL080 until marketing of the product was available at their respective country site.

Study Drug & Dosing Schedule: ERL080 was provided in 360 mg enteric coated tablets and matching placebo tablets. Similarly, MMF 250 mg capsules and the matching MMF placebo capsules were provided to participants in the study.

MO Comment: *The dosing schedule for ERL080 and MMF is similar in Study-B301 and in Study-B302 (ERL080 720 mg po bid and MMF 1 gm po bid, dosed on an empty stomach 1 hour before or 2 hours after food intake).*

When necessary (WBC count <4,000/mm^3), an investigator could reduce the dose of medication or stop administering the study drug until the event resolves. A patient was considered to have violated the protocol if the study medication was interrupted for >2 days during the first 2 weeks following randomization, or >14 days within a 2-month period. Such a protocol violation may lead to discontinuing study medication (at the investigator's discretion) but not the study.

MO Comment: *The reasons provided for discontinuing study medication were reasonable and included: AEs, abnormal laboratory value, unsatisfactory therapeutic result, protocol violation, patient did not require study medication, withdrawal of consent, lost to follow-up, administrative issues, death or graft loss. For additional details, please see the safety evaluation section of this review.*

Concomitant Therapy:

Immunosuppressive regimens: All patients were to receive Neoral® ± steroids. The target cyclosporine whole blood therapeutic levels were 100-200 ng/mL. If a patient was receiving steroids, the protocol required that the patient remain of the same dose for the first 3 months of the double-blind treatment period. Other immunosuppressive agents were not allowed.

In the event of a suspected acute rejection, patients were required to undergo a core biopsy prior to or within 24 hours of starting anti-rejection therapy. Acute rejection was treated with methylprednisolone 500-1000 mg intravenously for 3 days. In severe cases of rejection Grade III, antithymocyte globulin/OKT3 could be used for first-line treatment, and the patient's study medication could be interrupted during that period. Steroid resistance was defined as no stabilization or improvement of creatinine within 5 days of methylprednisolone therapy or when the patient had received a total of 1.5 mg of methylprednisolone.

Other therapies: Centers that used GI prophylactic therapy, were required to consistently administer such therapy to all patients at that specific site. The prophylactic GI therapy should remain unchanged for 3 months after starting the treatment. Potential nephrotoxic agents (aminoglycosides, NSAIDS), and drugs that may interfere with cyclosporine pharmacokinetics required careful monitoring of cyclosporine blood trough levels.

MO Comment: *The drug interactions section of the approved label contains the statement: "It is recommended that Myfortic® and antacids not be administered simultaneously", because antacids (for example: Maalox) lead to a decrease in exposure to Myfortic® (Please refer to Dr. Jang-Ik Lee's Biopharmaceutical Review). The Applicant's stated consistency in application of prophylactic therapy at specific clinical sites, provides assurances that both treatment groups probably received similar GI prophylactic therapy.*

MO Comment: *The use of GI prophylactic therapy in this study may decrease the detection of differences in GI tolerance; however, because this is a double-blind, randomized study, the study design may minimize the potential for introducing bias. The Applicant required drug accountability at the study sites. Study-B302 is comprised of stable transplant patients, and therefore the MO does not expect large variations in medication use in the same patient. Potential use of grapefruit juice (known to alter cyclosporine bioavailability) was not addressed in the protocol.*

Randomization & Blinding: Patients were enrolled into the study after meeting inclusion/exclusion criteria and signing of the written informed consent. The Applicant provided each patient with a randomization number generated by a computer from the first day of dosing with study medication. Patients, investigators, study center personnel, and Data management personnel at Novartis were blinded until the 12-month analysis was complete. However, Novartis clinical trial personnel were unblinded to patient codes at the 6-month analysis of data from all patients and at the 12-month analysis of data. Patients in the study were stratified by site.

MO Comment: *Breaking the blinding code by Novartis clinical personnel at the 6-month period does not affect the study results; however, the 12-month analysis may be subject to potential bias if there was communication between unblinded Novartis clinical trial personnel and investigator sites.*

Population & Procedures: The ITT population was defined as all randomized patients who received at least one assessment after administration of study medication. The safety population included all randomized patients who received at least one dose of study medication and had one or more safety assessments.

MO Comment: *As mentioned in the MO's comment above, patients who could not tolerate the MMF capsule during the run-in period, may have been excluded from the study since they were not randomized to be included in the study populations.*

The visitation schedule in Study-B302 is provided in Figure 3-2 (source: Vol 149/178, p:8-22). Patients are screened prior to enrollment in the run-in period, and baseline evaluations were completed at randomization, defined as Day-1 of administration of study medication.

Figure 3-2. Study evaluation schedule

Weeks / Months	-2		2	4	8	3	4	6	9	12 end of study
Day	Screening[1] visit (Day-14)	Baseline[2] Day 1								
Visit	1	2	3[3]	4	5	6	7[4]	8	9[5]	10
Informed consent & medical history	X									
Inclusion/ exclusion	X	X								
Vital signs	X	X	X	X	X	X	X	X	X	X
Study medication check / compliance check		X		X	X	X	X	X	X	X
Laboratory tests:										
- Hematology	X	X	X	X	X	X	X	X	X	X
- Chemistry	X[6]	X	X	X	X	X	X	X	X	X
- Urine dipsticks		X	X	X	X	X	X	X	X	X
- CsA blood levels	X	X	X	X	X	X	X	X	X	X
- Viral serology	X									
- Pregnancy test	X									
Rejection episodes & renal biopsies		As necessary								
GI AEs, AEs, SAEs & infections		As necessary								
Hospitalizations		As necessary								
Comments		As necessary								
Immunosuppressive & concomitant therapies		As necessary								
End of treatment[7]										X
End of study[8]										X

[1] Screening assessments must occur prior to enrollment into run-in period.
[2] Day of randomization and administration of the first dose of study medication.
[3] Or at time of premature treatment discontinuation.
[4] Or at time of premature discontinuation from study period.
[5] Only serum creatinine.
[6] If frequent visits presented a hardship to the patient, he/she had the option of a telephone contact with the study coordinator to determine adverse effects.

MO Comment: *The visitation schedule allowed for the collection of the basic laboratory and clinical information for safety monitoring during the conduct of the study. Intervals for monitoring cyclosporine blood trough levels are adequately dispersed in this study..*

Efficacy Assessments: The primary objective for Study-B302 was safety, and efficacy was a secondary objective. The composite primary efficacy point (incidence of biopsy-proven acute rejection, graft loss, death, or lost to follow-up) was used in the study. Secondary composite variables (including biopsy-proven chronic rejection + events in the primary composite variable) were used to support the primary efficacy endpoint. The Applicant added a third composite variable (biopsy-proven acute rejection, graft loss, or death) due to the high number of patients that were lost to follow-up.

Statistics: To determine power, the Applicant quoted published reports that suggest a ≥20% GI AE rate in patients treated with MMF. Therefore, if each treatment group is comprised of 150 subjects, the power of detecting a 50% reduction in rate for GI AEs was 68% (MMF 20%, ERL080 10%), 79% (MMF 25%, ERL080 12.5%), and 87% (MMF 30%, ERL080 15%) respectively.

Study Results: The ITT population was the primary population analyzed in Study-B302. A total of 324 patients were randomized; 2 patients in the ERL080 withdrew consent before receiving study medication and therefore were not included in the final

analysis tables. There was a total of 159 patients in the ERL080 treatment group and 163 patients in the MMF treatment group.

MO Comment: *The total number of patients in the Safety population is 322 patients after accounting for the 2 patients who were randomized but withdrew consent prior to receiving study medication.*

Demographic Characteristics: The baseline demographic characteristics for the ITT population at Month-0 to 6, were comparable between the two treatment groups as observed from PTT 7.4-1 (table below).

Study-B302 Baseline demographic characteristics (Recipients, ITT population, 0-6 Months) Source: Modified from PTT 7.4-1,2,3, Vol 149; p:134-136

Demographic variable		ERL080 N=159	MMF N=163	ERL080 – MMF p-value
Age in years	Mean	48.6	46.8	
	Range	22-75	20-70	
	>65 years	9 (5.7%)	7 (4.3%)	
	20-65	150 (94.2%)	158 (95.7%)	
Sex	♂	97 (61%)	115 (70.6%)	0.079
	♀	62 (39%)	48 (29.4%)	
Race	Caucasian	118 (74.2%)	119 (73%)	
	Black	28 (17.6%)	34 (20.9%)	
	Oriental	5 (3.1%)	4 (2.5%)	
Weight	Mean	83 kgs	82.7 kgs	
Height	Mean	169.3 cm	170.9 cm	
Prior Renal Transplants	One	144 (90.6%)	143 (87.7%)	
	Two	14 (8.8%)	19 (11.7%)	
*End Stage Renal Disease	GN	42 (26.4%)	42 (25.8%)	
	HTN	29 (18.2%)	35 (21.5%)	
	Diabetic	19 (11.9%)	19 (11.7%)	
	Polycystic	21 (13.2%)	15 (9.2%)	
	Unknown	15 (9.4%)	15 (9.2%)	
	Other	15 (9.4%)	22 (13.5%)	
Viral Serology	EBV (-)	32 (20.1%)	38 (23.3%)	
	EBV (+)	89 (55.9%)	86 (52.8%)	
	Not done	38 (23.9%)	39 (23.9%)	
	HIV negative	156 (98.1%)	157 (96.3%)	
	HbsAg (-)	150 (94.3%)	158 (96.9%)	

GN = Glomerulonephritis, HTN = Hypertension

* The most common reasons for End Stage Renal Disease. Other causes not listed in the table were comparable in rates, for example: pyelonephritis, drug induced toxicity, interstitial nephritis, obstructive disorder, renal hyperplasia.

MO Comment: *The baseline demographic characteristics for both groups were comparable. There was a small difference in gender enrollment; more women were enrolled in the ERL080 group, this difference was close to reaching statistical*

significance. However, the difference in gender distribution was not associated with a difference in mean weight or height between the two treatment groups.

MO Comment: *Rates for viral serologies were comparable in both groups; however, baseline CMV serology (D/R status) at time of transplantation is lacking in this study. CMV infection is not expected to be an issue in such a stable renal transplant population, because the risk of CMV is highest during the first 6 months post-transplantation.*

Prior Medications: All patients in Study-B302 were on immunosuppressive therapy prior to enrollment. Medication classes and use were comparable across both treatment groups. There were no observed instances of significant differences.

Medical Conditions at Screening: At screening, both treatment groups in the ITT population had comparable rates of prior or concurrent medical conditions.

MO Comment: *Medical conditions at screening were comparable for both treatment populations. When there was a difference, this did not appear to confer an advantage to the ERL080 treatment group. Also, most patients had hypertension [ERL080 151 (95%) vs. MMF 152 (93.3%)]. Other frequent medical conditions in both treatment groups included hyperlipidemia, and hypercholesterolemia in the ERL080 group 46 (28.9%), 47 (29.6%) compared to 46 (28.2%), 38 (23.3%) in the MMF group respectively.*

MO Comment: *At screening patients in the ERL080 group had a higher rate of a history of anemia, and infections compared to the MMF group. GI events at screening were comparable in both treatment groups. The difference in history of infections at screening relates to the higher rate of urinary tract infections in the ERL080 group 16 (10.1%) compared to the MMF group 11 (6.7%), and pneumonia [ERL080 13 (8.2%) vs. MMF 8(4.9%)].The rate of history of CMV and Herpes infections at screening was comparable in both groups.*

MO Comment: *The difference in cardiac disorders is accounted for by the higher rate of coronary artery disease in the ERL080 group. Endocrine disorders were observed with more frequency in the ERL080 group at screening, were mostly related to hyperparathyroidism (ERL080 13, 8.2% vs. MMF 4, 2.5%). Immune system disorders were mostly related to the higher rate of drug hypersensitivity in the ERL080 group.*

Patient Disposition: A total of 322 randomized patients (patient accounting starts with randomization and blinding, which occurred at the end of the 2-week MMF, run-in period) were accounted for in Study-B302, which comprised the ITT population (ERL080 159 vs. MMF 163). During the run-in period (prior to randomization), a total of 9 patients discontinued the study (5 patients withdrew consent, 2 were protocol violations , and 1 patient was lost to follow-up, and the last patient was an administrative withdrawal).

The majority of patients completed 180 days of treatment [ERL080 148 (93%) vs. MMF 150 (92%)]. The most common reasons for discontinuing study medication prior to 180 days were either subject withdrawing consent (ERL080 3 vs. MMF 7) or an AE (ERL080 6 vs. MMF 3). Less common reasons included protocol violations (ERL080 1 vs. MMF 1), administrative problem (ERL080 1), lost to follow-up (MMF 1), and death (MMF 1).

For the 6-Months period, 5 (3.1%) patients in the ERL080 group and 9 (5.5%) patients in the MMF group were discontinued from the study. Reasons for discontinuing the study were: ERL080 group- lost to follow-up 4 patients, withdrawal of consent 1 patient; and for the MMF group – lost to follow-up 7 patients, withdrawal of consent 1 patient, and 1 death.

For the 0-12 Month period, early treatment discontinuation and study discontinuation accounting are listed in the table below.

Study-B302 Early treatment or study discontinued (ITT population, 0-12 Months)
Source: Table-7.1 Vol 148, p:32

		ERL080	MMF
D/C Treatment	**< 360 days**	**16 (10.1%)**	**19 (11.7%)**
	360-450 days	**0**	**1 (0.6%)**
Reasons	AE	9 (5.7%)	4 (2.5%)
	Abnormal laboratory	1	1
	Protocol violation	1	2
	Consent withdrawal	3 (1.9%)	9 (5.5%)
	Lost to follow-up	1	1
	Administrative	1	0
	Death	0	2
D/C Study		**10 (6.3%)**	**14 (8.6%)**
Reasons	Lost to follow-up	5 (3.1%)	8 (4.9%)
	Consent withdrawal	3 (1.9%)	3 (1.8%)
	Death	2 (1.3%)	3 (1.8%)

***MO Comment**: The Applicant performed two analyses for the endpoint (D/C treatment and D/C study), the latter includes all events, and the former treating discontinuations of study medication as censored. In the table below, patients in the D/C treatment group were included in the ITT analysis, these patients were not all counted as failures. Whereas patients who were assigned to the D/C study were counted as failures in the ITT analysis.*
In this stable renal transplant population, the number of patients discontinuing study medication early is expected to be far less than that observed in the de novo population (In B301 early treatment discontinuation rates were ERL080 29% vs. MMF 25%), which is the case as noted in the table above. A comparable number of patients discontinued treatment early (ERL080 10% vs. MMF 12%); also a comparable number of patients were discontinued from the study (ERL080 6% vs. MMF 9%).

Protocol violations: Listed in Table 7-2 from the Applicant's submission.

Table 7-2. Most frequent protocol deviations (≥ 2 patients in either group) (ITT population)

Patient deviation	ERL (N=159) n (%)	MMF (N=163) n (%)
MMF plus Neoral administration < 4 weeks prior to screening	21 (13.2)	25 (15.3)
Clinically significant infection requiring continued therapy	11 (6.9)	13 (8.0)
Noncompliance with visit schedule after premature discontinuation of study medication	7 (4.4)	13 (8.0)
Use of immunosuppressive therapy other than Neoral	5 (3.1)	5 (3.1)
Serum creatinine > 20% increase from screening or > 2.8 mg/dL	5 (3.1)	3 (1.8)
Study medication was not proportionally reduced in cases of dose reduction	5 (3.1)	1 (0.6)
MMF < 2 g/day or > 2 g/day	4 (2.5)	4 (2.5)
MMF interrupted for > 2 days during the run-in period	2 (1.3)	3 (1.8)
Third or subsequent kidney transplants/multiple transplants/other organ transplants	2 (1.3)	1 (0.6)
Study medication interrupted > 2 days during first 2 weeks or > 14 days thereafter within a 2-month period	2 (1.3)	1 (0.6)
Serum creatinine > 2.8 mg/dL	1 (0.6)	2 (1.2)

Source: Post-text table 7.2-2.
Note: Includes all protocol deviations reported as of the cutoff date for this report, except for Patient no. 516 0021 (ERL060 group), who had not been tested for HIV at baseline, but was subsequently diagnosed with HIV, and later died due to acquired immunodeficiency syndrome.

MO Comment: *The most common protocol violation was secondary to patients receiving MMF and Neoral® for less than 4 weeks prior to screening. However, most of these patients were already on cyclosporine other than Neoral®. Protocol violations were comparable in both treatment groups, and therefore are not expected to affect the results of the study.*

Efficacy Results: The table below lists the primary and secondary efficacy results for Study-B302 for the two periods 0-6 Months, and 0-12 Months.

Study-B302 Primary & Secondary Efficacy Endpoints (ITT population)
Source: Modified PTT 9.1 Vol 150

		ERL080	MMF	ERL080-MMF 95% CI
***Composite Primary variable**	6 months 12 months	7 (4.4%) 12 (7.5%)	11 (6.7%) 20 (12.3%)	-2.4 (-7.4,2.7%) -4.2 (-11.3, 1.8%)
Secondary variables				
BPAR	6 months 12 months	2 (1.3%) 2 (1.3%)	2 (1.2%) 5 (3.1%)	
Acute rejection	6 months 12 months	2 (1.3%) 2 (1.3%)	3 (1.8%) 6 (3.7%)	
Treated acute rejection	6 months 12 months	2 (1.3%) 2 (1.3%)	2 (1.2%) 3 (1.8%)	
Acute rejection requiring Ab therapy	6 months 12 months	0 0	0 0	
BPCR	6 months 12 months	4 (2.5%) 4 (2.5%)	4 (2.5%) 8 (4.9%)	-1.1% (-5.6, 3.3%)
Graft loss	6 months 12 months	0 0	1 (0.6%) 1 (0.6%)	
***Death	6 months 12 months	0 2 (1.3%)	1(0.6%) 4 (2.5%)	
#Lost to follow-up	6 months 12 months	5 (3.1%) 8 (5%)	7 (4.3%) 10 (6.1%)	-1.1% (-6.1, 3.9%)
##Graft loss or death or lost to follow-up	12 months	10 (6.3%)	17 (10.4%)	

*Composite primary variable (Treatment failure) = Biopsy proven acute rejection (BPAR), graft loss, death, lost to follow-up
***Patient #5110013 (MMF) died post-study on Day-290. This patient withdrew consent on Day-273, and was discontinued from the study. Patient was listed in the composite variable as a "lost to follow-up"
#Lost to Follow-up indicates patients who were lost to follow-up without prior biopsy-proven acute rejection, graft loss or death
##Lost to Follow-up indicates patients who were lost to follow-up without prior graft loss or death (8 Myfortic patients and 12 MMF patients)

MO Comment: *Patient# 5110013, was listed as "lost to follow-up," and therefore was correctly counted as a failure in the analysis.*

MO Comment: *The Applicant's analysis for the primary efficacy endpoint, treatment failure, was accepted by the Agency. The 6 & 12 month results for treatment failure demonstrate that Myfortic® was non-inferior to MMF (Please refer to the Statistical Review by Dr. Kyung Yul Lee). The secondary efficacy variables supported the primary efficacy analysis.*

Study-B302 extension phase: The primary efficacy composite endpoint for the 30-Month cohort (12-Months on ERL080 or MMF followed by 18 months of ERL080) was a rate of 6/77 (7.8%) for the ERL080 group and 3/75 (4%) in the exMMF group. An equal rate of patients experienced biopsy-proven rejection (4%) and graft loss (1.3%) in both treatment groups. There were 3 deaths (4%) in the ERL080 group compared to none in the MMF group.

MO Comment: *Enrollment in the extension phase of the study was optional, therefore the potential for selection bias in this portion of the study is likely. One should be cautious in drawing conclusions beyond the core 12 month study. The rates for efficacy events were comparable in the ERL080 group and in the exMMF group. Given the limited number of patients who were continued in either group, no meaningful conclusions can be drawn.*

D. Efficacy Conclusions

In *de novo* and stable renal transplant recipients, ERL080 is effective in preventing graft rejection. The efficacy is supported by two randomized, double-blind, controlled studies that demonstrated ERL080 is non-inferior to MMF , an active control approved for this indication.

Study-B301, a multicenter, double-blind, randomized, parallel group, designed study to evaluate the safety and efficacy of ERL080 720 mg bid vs. MMF 1 gm bid, demonstrated that ERL080 is therapeutically equivalent to MMF in *de novo* renal transplant patients. The ITT population included 423 patients. The primary efficacy endpoint was the treatment failure (biopsy-proven acute rejection, graft loss, death, lost to follow-up) incidence of biopsy proven rejection at Month-6. At 6-Months, the difference in the point estimate of the primary efficacy composite endpoint, treatment failure (ERL080-MMF), for the two treatment groups was -0.4 95% CI {-8.7, 8.0}, which was within the pre-specified bounds of the 95% CI used to define non-inferiority in the study. At Month-12, the results for the analysis of the primary efficacy endpoint were comparable to the Month-6 evaluation. The co-primary efficacy endpoint Month-12 (graft loss or death or lost to follow-up was also comparable in both treatment groups, and supports the primary efficacy endpoint results.

Results of the primary efficacy endpoint in the PP population supported the results of the primary efficacy endpoint in the ITT population. Similarly, the secondary efficacy endpoints supported the primary efficacy endpoint in the ITT population.

Study-B302 was a multicenter, randomized, double-blind, parallel study designed to evaluate the safety and efficacy of ERL080 720 mg po bid compared to MMF 1 gm po bid, in combination with Neoral® ± corticosteroids for the prophylaxis of organ rejection in stable renal transplant recipients. Therefore all of these patients were already on an immunosuppressive regimen post-transplantation prior to enrollment.

The primary efficacy endpoint in Study-B302 was similar to the composite primary efficacy endpoint for Study-B301. A secondary composite efficacy endpoint was analyzed using the same variables for the composite primary efficacy endpoint plus biopsy-proven chronic rejection. The difference in the point estimate of the primary efficacy composite endpoint, treatment failure (ERL080-MMF), for the two treatment groups was -2.4 95% CI {-7.4, 2.7}, which was within the pre-specified bounds of the 95% CI used to define non-inferiority in the study. Analysis of the secondary variables supports the primary composite endpoint.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The safety of Myfortic® (mycophenolic acid) Delayed Release Tablets was found to be comparable to that of Cellcept® (mycophenolate mofetil) in renal transplantation patients. Although Myfortic® (mycophenolic acid) Delayed Release Tablets were formulated with an enteric coating intended to minimize the gastrointestinal toxicities associated with MPA, the product was not better tolerated than Cellcept®.

The safety of Myfortic® is supported by information from two 12-Month, randomized, double-blind, controlled studies comparing ERL080 to MMF in *de novo* and stable renal transplant recipients, respectively. The most common potential hazards associated with ERL080 are similar to those of MMF and include increased susceptibility to infection and the possible development of lymphoma and other neoplasms as a result of immunosuppression. Other common hazards include the gastrointestinal system (intolerance to the drug, gastrointestinal bleeding, peptic ulcers, intestinal perforation), and bone marrow suppression (neutropenia). These hazards are well reflected in the WARNINGS and PRECAUTIONS sections of the approved labeling, dated February 27, 2004.

Study-B301, was a randomized, double-blind, multicenter, parallel study designed to evaluate the safety and efficacy of Myfortic® 720 mg po bid compared to Cellcept® 1 gm po bid in combination with Neoral® and corticosteroids in *de novo* adult renal transplant population. Because of the study design (randomized, double-blind), safety assessment based on symptoms was less likely to be affected by bias. The total number of patients randomized in the study was 423 patients (ERL080 213 and MMF 210 patients).

Exposure to study drug, Neoral®, and corticosteroids was comparable across the two treatment groups. The majority of patients in the study were exposed to study drug for a minimum of 12 months [ERL080, 154/213 (72.3%) patients vs. MMF 162/210 (77.1%) patients]. In addition, approximately 41% of patients from both treatment groups received antibody therapy.

As expected in a renal transplant population, adverse events were reported by most patients in both treatment groups. Overall, the rates for adverse events were comparable in both treatment groups. The difference in rates for GI AEs in the ERL080 group 79.8% compared to the MMF group 77.1% was small, and the rates for GI AEs were comparable at all window visits. Given the broad scope of GI AEs, the slight difference in rates between the two treatment groups is clinically insignificant. There were no unexpected infections in either treatment group, and rates for infections were comparable in both treatment groups. Bone marrow suppression rates (reflected in WBC, platelet, and RBC counts) were comparable in both treatment groups. No patients

in either treatment group experienced a neutrophil count of $\leq 0.5 \times 10^9$ /L. However, 2 patients from the 120-Day Safety Update from MYPROMS-2405 study were reported with an absolute neutrophil count $\leq 0.5 \times 10^9$/L. Common AEs with a difference of >5% between treatment groups included infections, surgical/medical procedures, and investigations. For infections, the difference in rates was accounted for by an increased rate of urinary tract infections in the MMF group; however, these infections were minor, and are expected in a renal transplant study therefore no meaningful difference can be extrapolated. There were no unexpected investigations in the study, most investigations were performed for routine hematology, biochemistry, urine analysis, or related blood test.

There were 7 deaths reported in the 0-12 Month period; 2 were in the ERL080 group, and 5 were in the MMF group. In the ERL080 group, one death at Day-92 was secondary to complications of congestive heart failure, the other death at Day-343 was secondary to sepsis. At the time of death all 7 patients had a functioning graft. These deaths are expected in a *de novo* renal transplant population. None of the deaths were directly assigned to study drug. Assigning causation of death to the study drug would be difficult in this population due to the underlying disease(s), other immunosuppressive treatments, and other potentially confounding factors that may affect how one interprets causation of death.

The overall rates for serious AEs in the study were comparable in both treatment groups. The most commonly reported serious AEs in the Study-B301 were related to the GI-tract or renal system. Severe AEs were reported by 38% of patients in the ERL080 group and 41% of patients in the MMF group. Severity rates were comparable across the two treatment groups. Seventeen percent of patients in the ERL080 group discontinued study drug due to an AE compared to fourteen percent in the MMF group. The most common reason for discontinuing study drug from an AE was related to GI AEs (5%) in both treatment groups. The difference in rates for discontinuing study drug across the two treatment groups was small. In addition, this was a *de novo* population newly exposed to MPA, and was expected to result in cases of intolerance leading to discontinuation of study drug. The similar rates in both treatment groups for discontinuing study drug related to GI AEs was expected. Both treatment groups had a similar rate of malignancies (2%). Laboratory events for hematological variables and biochemistry were comparable across the two treatment groups. Although, there were a few cases of neutropenia (neutrophil count $<1.5 \times 10^9$/L), severe neutropenia (neutrophil count $<0.5 \times 10^9$) was uncommon. Patient mean weight, creatinine, and urea values improved after transplantation in both treatment groups.

Study-B302, was a double-blind, multicenter, randomized, study designed to evaluate the safety and efficacy of ERL080 720 mg po bid compared to MMF 1 gm po bid in combination with Neoral® ± steroids, in a stable renal transplant population. The total number of patients randomized in the study was 322 patients (ERL080 159 and MMF 163 patients). The 2-week, open-label, MMF run-in period prior to randomization, may

have somewhat lessened the likelihood that patients intolerant to MPA were enrolled (9 patients were identified who did not complete the run-in period).

Study drug exposure rates were comparable at all window visits in both treatment groups. Approximately 90% of patients in the ERL080 group and 88% of the patients in the MMF received study medication for 12 months. When dose reductions in study medication were required, this usually occurred during the first 6 months of the study. The cause for dose reductions (44% for both treatment groups) was commonly related to AEs (15% for both treatment groups) or dosing errors. Exposure to concomitant immunosuppressive regimens (Neoral® and corticosteroids) was similar across the treatment groups.

By end of study, the majority of patients from Study-B302 had experienced an AE (ERL080 94% vs. MMF 93%). The majority of AEs occurred in the 0-3 Month period of the study. Diarrhea and nausea were the most common AEs in the ERL080 group and diarrhea and nasopharyngitis for the MMF group. The broad range of AEs observed in the trial were within the general expectations for what one would find in a stable renal transplant population. Overall, the rates for AEs were comparable for the two treatment groups. The overall rate of infections and the severity rate for infections were comparable across the treatment groups respectively. Urinary tract infections, and pneumonias were among the more common serious infectious AEs. However, the rates for urinary tract infections were comparable across the two treatment groups. Similarly, the rates for pneumonia were comparable for the two treatment groups.

GI AEs were similar in the ERL080 group 57% compared to the MMF group 57% for the 0-12 Months. Nausea and vomiting were among the most common GI AEs affecting more patients in the ERL080 group 25% vs. MMF group 19%; however, the difference in the rates was small. In a population that had prior significant prolonged exposure to MMF, the rates of GI AEs were still high over the period of 12 months on study but were similar across treatment groups. No patients in the ERL080 group developed severe neutropenia compared to one patient in the MMF group. A similar number of patients from both treatment groups developed expected malignancies (6%). Again, these rates for bone marrow suppression and malignancy are within the expected range in a stable renal transplant population exposed to immunosuppressive agents.

There were 2 deaths in the ERL080 group. One was a 23 year-old ♀ who died on Day-350 from multiple organ failure. The remaining patient died from a cryptococcal brain abscess related to AIDS. Although, the patients in the ERL080 died from an infection (an expected side effect of immunosuppression and underlying disease), the cause of death cannot be reliably assigned to study drug due to the many confounding variables present in such a population. The MMF group had 5 deaths during the 0-12 Month study period.

The rates of severe AEs were comparable for the two treatment groups. A total of 9 patients in the ERL080 group and 4 patients in the MMF group discontinued study

medication prematurely due to an AE. In the ERL080 group the most common reason for discontinuing study drug was a severe infection in 5/9 patients followed by leukopenia and diarrhea. And in the MMF group, the most common cause of discontinuing study drug was a GI complaint. The difference in the rates for discontinuing study drug due to an AE was comparable for the two treatment groups.

Study-0107: There were no new safety issues reported from this study. The rates for AEs from Study-0107 were in general comparable to Study-B302. This finding is expected, because Study-0107 was carried out in stable renal transplant patients.

The 120-Day Safety Update contained safety data from the extension studies through March 31, 2003; and for the MYPROMS studies, and the heart study up to May 31, 2003. The new analysis for the extension studies extended the cohort for Study-B301 up to 24 months for all patients in the extension phase and for 30 months for patients who reached the 30-Month point.

As of May 31, 2003 the total number of subjects exposed to ERL080 was 2396 patients across the clinical (including193 subjects in the pharmacologic) studies. This number includes 1353 patients enrolled in ongoing phase IIIB/IV studies (MYPROMS & FREEDOM), and the heart study (75 patients). A total of 766 patients were followed up to ≥12 months and the number of patients followed up for ≥36 month was 220. Overall, there were no new unexpected safety issues reported in the 120-Day Safety Update compared to the data reported in the original submission.

B. Description of Patient Exposure

Study-B301

Extent of Exposure: The dosing schedule for Myfortic® was 720 mg po bid compared to MMF 1 gm po bid, with the intent to provide similar exposure to MPA in both treatment groups of Study-B301. In addition, all patients received Neoral® and steroids (prednisone) for immunosuppression. The average daily doses for study medication, Neoral®, and steroids were respectively comparable across the two groups over the 12 months interval. Over the 12 month period of the study, ERL080, MMF, Neoral®, and steroid doses were reduced in a comparable manner between the two groups. Therefore, the exposure to MPA, cyclosporine, and steroids was largely comparable across both treatment arms.

MO Comment: *From review of the data in the submission, patients in both groups were comparably exposed to MPA during the window visits. Patients in both treatment groups were also similarly exposed to Neoral® and steroids.*

In Study-B301, study medication was evaluated during each analytical visit window for the ITT population up to Month-12. There were 14 visit windows spanning the following periods:
Day 1-2
Day 3-4
Day 5-6
Day 7-11
Day 12-17
Day 18-24
Day 25-35
Day 36-49
Day 50-70
Day 71-99
Day 100-146
Day 147-226
Day 227-311
Day 312-450

Both treatment groups were comparable in duration of exposures to study medication in each analytical window. Similarly, the duration of exposure rates were comparable for Neoral® and for steroids respectively. A total of 151/213 (71%) patients in the ERL080 group and 158/210 (75%) patients in the MMF group were exposed to ERL080 or MMF respectively at the 12-Month window visit.

MO Comment: *A reasonable majority, 3/4 patients in the study, received study medication for at least 312 days. This provides a reasonable exposure time to evaluate safety issues related to ERL080. The rates for patients who had to discontinue study drug were comparable in both study groups and are expected in a de novo renal transplant study exposing patients to MPA, due to GI intolerance from MPA toxicity.*

Concomitant medications:

Immunosuppressive therapy other than study drugs, Neoral®, and steroids: A comparable rate of patients (41%) in both treatment groups received antibody induction therapy (basilixmab, daclizumab, muromonab-CD3, antilymphocyte, or thymocyte antibodies). Basilixmab was used in approximately half the population that received antibody therapy. Tacrolimus or MMF were commonly used for immunosuppression after study medications were discontinued.

Study-B302:

Extent of Exposure: The dosing schedule for Myfortic® was 720 mg po bid compared to MMF 1 gm po bid, with the intent to provide similar exposure to MPA in both treatment group of Study-B302. In addition, all patients in the study received Neoral® ± steroids (prednisone) as the immunosuppressive regimen.

Patient exposure was measured at each of the 9 visit windows:
Day 1-2
Day 3-21
Day 22-42
Day 43-70
Day 71-99
Day 100-146
Day 147-226 (Month-6)
Day 227-311
Day 312-450 (Month-12)

By the 6 months window visit, the majority of patients in the ERL080 group 148 (93%) and the MMF group 150 (92%) received study medication for 0-6 Months. At the 12-Month window visit the duration of exposure was 147 (89.9%) patients in the ERL080 group and 139 (87.7%) patients in the MMF group. The duration of exposure was comparable at all window visits.

MO Comment: *The majority of patients in the study were exposed to study medication up to the 12-Month window visit (PTT 8.1-1, Vol 149). This is a reasonable exposure period to evaluate the safety of ERL080 in a stable renal transplant population.*

The average daily dose of randomized study medication (expressed in fraction of nominal dose; nominal dose for ERL080 was 1440 mg and for MMF 2000 mg) in the ITT population from 0-12 Months was comparable in both treatment groups at all window visits [Day 1-226 mean fraction of nominal dose in the ERL080 0.974 vs. MMF 0.985, and Day 1-450 mean fraction of nominal dose in the ERL080 0.965 vs. MMF 0.977].

Dose of study medication was not reduced in the Month-0 to 6 period for 114 (71.7%) patients in the ERL080 group compared to 122 (74.8%) patients in the MMF group. At the 0-12 Months period, the rate for patients not reducing study dose medication was [ERL080 72 (45.3%) vs. MMF 71 (43.6%)]. The reasons for dose reductions were either due to an AE, dosing error or protocol related.

MO Comment: *A comparable number of patients had study medication reduced or interrupted at the 0-6 months or 0-12 months period.* The difference in rates for dose reductions for the two treatment groups was small.

Concomitant Medications:

Cyclosporine dose & whole blood trough levels: The average daily dose of cyclosporine for the 0-6 Month period was similar to the 0-12 Month period (ERL080 3 mg/kg vs. MMF 3.1 mg/kg). The average daily doses of cyclosporine were comparable at all window visits. Cyclosporine whole blood trough levels (ng/mL) during the visit windows at 0-6 Months and at the 0-12 Month were comparable across the two treatment groups.

Steroids: The average daily dose of corticosteroids in both treatment groups at all window visits (0-12 Months) was 0.1 mg/kg.

Other Immunosuppressive Medications: A comparable rate of patients in both treatment groups during the 0-12 Months received concomitant immunosuppressive therapy, mainly corticosteroid products [ERL080 138 (86.8%) vs. MMF 139 (85.3%)]. A few patients in the ERL080 and MMF groups received medication for rescue at the 0-12 Months [ERL080 6 (3.8%) vs. MMF 9 (5.5%)].

MO Comment: *The use of selective immunosuppressive agents was similar in both groups.*

Non-Immunosuppressive Medications: The most common concomitant non-immunosuppressive medications were used to treat or prevent the complications associated with the immunosuppressive regimen. These included but were not limited to HMG Co-A reductase inhibitors (to treat hypercholesterolemia), Sulfonamides (for PCP prophylaxis), and antihypertensives.

MO Comment: *The use of non-immunosuppressive medications was common in Study-B302. And the reported differences in the rates of non-immunosuppressive medication use were not clinically significant across the two treatment groups.*

C. Methods and Specific Findings of Safety Review

Study-B301 Safety

The safety population, defined as all randomized patients who received at least one dose of study medication and had at least one safety/tolerability assessment. All AEs were collected regardless of when they occurred after study drug was discontinued; however, safety data analyses were limited to those events that occurred up to 7 days after discontinuation of study medication. AE occurrences after 7 days of study drug

discontinuation were flagged in the database. This section will include AEs (clinical & laboratory), death, SAE, rejections, infections, malignancy.

MO Comment: *All patients in the ITT population were included in the safety analysis. Acute events were included in safety data analysis, including some AEs that may occur after study drug discontinuation, for example, diabetes mellitus, or infections, and malignancy may occur beyond the 7th day after discontinuing study medication. The Applicant used the MedDRA body system and preferred terms for tabulating and summarizing safety data in this study.*

The protocol included graft rejection as an AE, but was not considered a severe AE per se, since graft rejection was an expected event in transplantation and was analyzed as an efficacy variable. On the other hand, graft loss was counted as a severe AE.

MO Comment: *The MO concurs that graft loss should count as a severe AE, and that graft rejection be simply noted as an AE and not severe AE. AEs in the study included infections. Expected AEs in this study (also observed with CellCept®), include gastrointestinal (GI) and bone marrow suppression, in particular, GI intolerance to exposure from MPA and neutropenia.*

Adverse Events: By Month-12 most patients in Study-B301 experienced an AE [209/213 (98.1%) in the ERL080 group, and 206/210 (98.1%) in the MMF group]. The AEs that occurred at >10% for any of the two groups are listed in the next table.

Study-B301 Reported adverse events (>10% for any of the two treatment groups)
Source: Post-text table 10.1-2

AE	ERL080	MMF	ERL080-MMF
Gastrointestinal	170 (79.8%)	162 (77.1%)	
Infections	145 (68.1%)	154 (73.3%)	-5.3
Metabolism & Nutrition	136 (63.8%)	134 (63.8%)	
General & administrative site	117 (54.9%)	115 (54.8%)	
Blood & lymph	99 (46.5%)	88 (41.9%)	
Nervous system	90 (42.3%)	93 (44.3%)	
Renal & urinary	89 (41.8%)	83 (39.5%)	
Surgical & medical procedures	88 (41.3%)	68 (32.4%)	8.9
Investigations	84 (39.4%)	65 (31%)	8.5
Vascular	71 (33.3%)	72 (34.3%)	
Musculoskeletal	57 (26.8%)	61 (29%)	
Respiratory	56 (26.3%)	46 (21.9%)	
Skin	41 (19.2%)	53 (25.2%)	
Psychiatric	36 (16.9%)	42 (20%)	
Cardiac	33 (15.5%)	40 (19%)	
Injury & poisoning	37 (17.4%)	33 (15.7%)	
Endocrine	32 (15%)	22 (10.5%)	
Reproductive	27 (12.7%)	24 (11.4%)	

MO Comment: *In general the observed differences in rates of AEs across the two groups were comparable. There were slightly more GI, blood & lymph, procedures, investigations, respiratory, and endocrine AEs and slightly less infections, cardiac, and psychiatric AEs in the ERL080 group. The higher rate of procedures and investigations in the ERL080 group, was explained as a result of the high incidence of pain, post-transplant complications commonly encountered in this group of patients. There were no particular patterns identified in AEs between the two treatment groups. These differences in rates observed for AEs occurring in >10% of patients were small, and overall comparable across treatment groups.*

Gastrointestinal AEs: In Study-B301 the rates for any GI AE were comparable at most window visits (except for Days-25-49), and by Month-12, 81% and 80% of patients in the ERL080 and MMF groups respectively, had experienced a GI AE. Gastrointestinal AEs were reported for 170/213 (79.8%) patients in the ERL080 and for 162/210 (77.1%) patients in the MMF group. Common gastrointestinal AEs are listed in the table below.

Study-B301 Common GI AEs (Month-0 to 12)
Source: Post-Text Table 10.1-2

	ERL080	MMF
Constipation	81 (38%)	83 (39.5%)
Nausea	62 (29.1%)	57 (27.1%)
Diarrhea	50 (23.5%)	52 (24.8%)
Vomiting	49 (23%)	42 (20%)
Dyspepsia	48 (22.5%)	40 (19%)
Abdominal pain upper	30 (14.1%)	30 (14.3%)
Flatulence	21 (9.9%)	27 (12.9%)
Abdominal pain lower	17 (8%)	10 (4.8%)

The rate of GI AEs at the Month-12 visit was comparable across the two treatment groups. There were 43 (20.2%) patients with a GI AE at the Month-12 visit in the ERL080 compared to 36 (17.1%) patients in the MMF group. Rates for GI AEs (dyspepsia, nausea, vomiting, diarrhea, constipation, and upper abdominal pain) were comparable for both treatment groups.

The rate of discontinuing study drug due to a GI AE was comparable in both treatment groups at ~5% (see p:72 of this review). Also, a comparable proportion of patients (13.1% ERL080, and 17.1% MMF) experienced an interruption or dose reduction secondary to a GI AE.

On average, the proportion of days during the 12 month study period when a GI AE was experienced was 23% in the ERL080 group, and 19% in the MMF group (the rates were comparable). On a similar note, the average proportion of days with a serious GI AE was 3% in the ERL080 compared to 2% in the MMF group and for severe GI AEs was 2% in the ERL080 group compared to 1% in the MMF group. The majority of GI AEs

were moderate in nature, ERL080 38% compared to 31.4% MMF group. A small proportion of patients experienced severe GI AEs, 8.9% patients in the ERL080 compared to 11% in the MMF group.

MO Comment: *The rate for any GI AE was comparable across the treatment groups at all window visits; however, in the early post-transplant period especially the first week, slightly more patients in the ERL080 reported a GI AE [Day-5 & 6, ERL080 75 (35.2%) vs. MMF 64 (30.5%)]. Also for the two periods Day-25 to 35 and Day-36 to 49, the difference in (ERL080-MMF)* ***cumulative*** *rate for GI AEs was 6.1% & 7% respectively [ERL080 152 (71.4%) vs. MMF 137 (65.2%)]. ERL080 patients reported slightly more GI AEs than patients in the MMF group; when considering the totality of data the rates were comparable across the two treatment groups (Post-text table 10.5-2 & PTT 10.5-1). Symptoms of nausea, vomiting, dyspepsia, and lower abdominal pain were usually experienced in the first two weeks after transplantation (the differences in rates between the two treatment groups were not significant). Severe GI AEs were infrequent and the rates were comparable in both treatment groups. GI causes for D/C study medication were primarily due to diarrhea, nausea, and vomiting and the rates were comparable across the two treatment groups.*

Infections & Infestations: A total of 148/213 (69.5%) patients in the ERL080 group and 154 (73.3%) patients in the MMF group had at least 1 infection. Urinary tract infections and cytomegalovirus (CMV) infections were the two most common reported infections.

There were 62/213 (29.1%) patients in the ERL080 and 70/210 (33.3%) patients in the MMF group with a urinary tract infection. The observed differences in rates for urinary tract infections rates between the two treatment groups were not significant.

The rates for common viral infections were: cytomegalovirus 43/213 (20.2%) , herpes simplex 17/213 (8%), and herpes zoster 10/213 (4.7%) patient infections in the ERL080 compared to the MMF group 38/210 (18.1%), 13/210 (6.2%), and 8 (3.8%) respectively. The differences observed in the rates for viral infection across both treatment groups were small and not clinically significant.

Of the 148 patients with an infection in the ERL080 group, 85 (39.9%) patients were missing an etiologic organism, and of the 154 patients in the MMF group 87 (41.4%) were missing an etiologic organism. Bacterial infections accounted for the majority of infections [ERL080 74 (37.7%) vs. MMF 75 (35.7%)]. Fungal infections were comparable in both treatment groups [ERL080 23 (10.8%) vs. MMF 25 (11.9%)], and the majority of these infections were caused by *Candida* species.

MO Comment: *Although, the rate of urinary infections is slightly higher in the MMF group, the difference is not meaningful due to the small number of cases. Also, when one looks at the breakdown into specific anatomical sites for urinary tract infection , the numbers are too small to detect any specific patterns or meaningful differences. This is*

a renal transplant study where the urinary tract is surgically manipulated, and urinary tract infections are expected to be the most common site of infection.

MO Comment: *The rates for CMV infection were comparable for the two treatment groups. The study was not designed to study subgroup populations (GI, Respiratory, serostatus) of CMV. There were multiple confounding factors that would limit performing such an analysis (although, the Applicant did provide that data, which essentially showed no significant differences for the two treatment groups, there were no patterns and the numbers were too small to draw conclusions). Some of these confounding factors include study design (the study was not designed to make inferences from subpopulations of CMV infection), the use of antiviral agents for CMV was dependent on local practice (non-randomized), there were no restrictions on donor status.*

Metabolic & Nutrition: Rates for hypocalcaemia, hyperuricemia, hyperlipidemia, hypokalemia, and hypophosphatemia were comparable across treatment groups. A total of 8 patients in the ERL080 reported a diabetic related event (diabetes mellitus insulin dependent 3 patients, non-insulin dependent 3 patients, and glucose intolerance in 2 patients), none of the patients in the MMF group reported a diabetic related event.

MO Comment*: Hyperglycemia is expected in this population. The reason why few patients in this study developed diabetes may be related to the demographic characteristics of the population studied (~10% of patients in the study who were transplanted were diabetics compared to the general population of renal transplants in the United States ~20-25%), which suggests that patients with known glucose intolerance or diabetes mellitus may have been steered away from participating in the study. Also, the confounding use of steroids has to be taken into consideration as well. Therefore, the inferences that may be drawn from the difference in numbers for patients developing diabetes mellitus are limited.*

General disorders & administrative site conditions: There were 27/213 (12.7%) patients in the ERL080 group, and 39/210 (18.6%) patients in the MMF group who experienced pyrexia. Other events with noted differences in rates include pain NOS, reported in 29/213 (13.6%) patients in the ERL080 and 18/210 (8.6%) patients in the MMF group. The rates for other events were comparable in both groups.

MO Comment: *The slightly higher rate of elevated temperature observed in the MMF group may be related to many confounding factors, such as medication, infections, or surgically complications. The differences were too small to permit one to draw conclusions.*

Blood and lymph disorders: The rates of anemia, leukopenia, thrombocytopenia, were comparable in both treatment groups. All events related to bone marrow suppression occurred at a similar rate in both treatment groups. The rates for anemia in Study-B301 were similar in both groups (ERL080 22% vs. MMF 22%).

The majority of hematological laboratory abnormalities occurred during the first 6 months of the study. Hematocrit and hemoglobin rates increased significantly from baseline to Month-12 window visit, and the values were comparable for both treatment groups. Two patients in the ERL080 compared to one patient in the MMF group had a low hemoglobin level (<60 g/L) (table below).

Study-B301 Abnormal Hematology Laboratory Rates (Month-0 to 12) Source: PTT 10.3-5

Laboratory Parameter	Value code	ERL080	MMF
WBC < 4 10E9 /L	Low	56 (26.3%)	57 (27.1%)
WBC >16 10E9 /L	High	40 (18.8%)	50 (23.8%)
Neutrophils <1.5 10E9 /L	Low	11 (5.2%)	10 (4.8%)
Platelets <75 10E9 /L	Low	8 (3.8%)	7 (3.3%)
Hemoglobin <60 g/L	Low	2 (0.9%)	1 (0.5%)

With immunosuppression, leukocyte counts predictably decreased during treatment with study medication. The mean values were comparable across the two treatment groups at all points of examination. Similarly, the mean values for absolute neutrophil counts were comparable across the two groups (Figures: PTF 10.3.2a & PTF 10.3.2b); One patient in each treatment group reported neutropenia, these two patients did not have to discontinue study medication. Leukopenia resulted in discontinuation of study medications in 3 patients in the ERL080 group and 2 patients in the MMF group. After transplantation, platelet counts initially improved, and then were steady, so that at Month-12 evaluation, the mean platelet count in both treatment groups was ~235x 10^9/L. The rates for venous thrombosis were comparable for both treatment groups [ERL080 4 (1.9%) vs. MMF 6 (2.9%)].

MO Comment: *Administration of ERL080 and MMF in Study-B301 produced predictable and comparable bone marrow suppression in both treatment groups. There were no unusual trends or patterns observed. The MO concurs that abnormal hematology laboratory values were comparable between the two treatment groups. ESRD is associated with anemia despite the use of recombinant human hemapoeitin. After successful renal transplantation, it is normal for the hemoglobin levels to increase, which is what was observed in Study-B301.*

The MO concurs that the mean neutrophil counts were comparable across the two treatment groups. No patient in either treatment arm had to discontinue study medication because of neutropenia. In the 120-Day Safety Update report, the Applicant reported severe neutropenia in a few cases observed with the use of Myfortic® in the ongoing European transplant program. There is no reason to believe that ERL080's potential for causing neutropenia is different from MMF. Bone marrow suppression leading to anemia, leukopenia, and thrombocytopenia are known hazards of systemic MPA exposure based on the Cellcept® label, and from published literature and postmarketing safety. The WARNINGS section of the label correctly recommends monitoring for neutropenia in patients receiving Myfortic®. Platelet counts improved after transplantation, the rates were comparable in both treatment groups. Venous

thrombosis, as a potential consequence of improved platelet function and surgery was not observed with an increased frequency in this study.

Surgical and Medical procedures: A total of 88/213 (41.3%) patients in the ERL080 group, and 68/210 (32.4%) patients in the MMF group experienced an AE related to a procedure inclusive of post-operative pain. The AE listed as post-operative pain was reported for 51/213 (23.9%) patients in the ERL080 group, and 39/210 (18.6%) patients in the MMF group. Selected differences between the two groups are listed below.

Study-B301 Selected Post-operative AEs

	ERL080	MMF
Complications of transplant surgery	18 (8.5%)	14 (6.7%)
Post-operative complications NOS	14 (6.6%)	10 (4.8%)
Post-operative wound complication NOS	11 (5.2%)	5 (2.4%)
Post operative wound infection	5 (2.3%)	3 (1.4%)
Seroma	6 (2.8%)	2 (1%)
Wounds dehiscence	5 (2.3%)	2 (1%)

MO Comment: *The observed difference in the rate of pain between the two treatment groups is small, and may be related to the nature of the study (de novo renal transplant), where every patient undergoes a major abdominal operation and the majority of patients if not all patients are expected to experience pain. Study-B301 was not designed to evaluate pain, a symptom that is very difficult to quantify in the first place or to account for the potential confounding factors associated with quantitatively or qualitatively evaluating pain. The post-operative wound infection rates are comparable across both treatment groups. Overall, the rates for surgical and medical procedures were comparable for both treatment groups respectively.*

Musculoskeletal & bone disorders: The rates of AEs reported for this category were comparable in both groups, except for a slightly higher reported rate of back pain in the ERL080 group 25 (11.7%) vs. 13 (6.2%) in the MMF group.

Eye disorders: A total of 21 (9.9%) patients in the ERL080 group vs. 11 (5.2%) patients in the MMF group experienced an AE related to vision. In the ERL080 group there was a higher rate of blurred vision 10 (4.7%), eye pain 4 (1.9%) compared to 3 (1.4%), and 0 in the MMF group respectively.

MO Comment: *Back pain is multifactorial in this population (surgical, underlying disease, osteoporosis, other), and therefore it is unlikely that the observed difference in the rates can be attributed to the study medication. The difference in the rates is small*

to draw conclusions. The difference in rates for eye disorder related AEs is not clinically significant for both treatment groups..

Deaths: A total of 7 patients died during the Month 0-12 period. In the ERL080 group there were 2 deaths, the remaining 5 patients were in the MMF group (table below).

Study-B301 Deaths
Source: Modified Table 10.2-3

Treatment group	Patient #	Demographics	Day of Death	Cause of Death
ERL080	0002_00009	50 years, ♀, C	92	CHF
	0513_00016	52 years, ♀, Bl	343	Infection, treated for sepsis with multiantibiotics. Death occurred >6 months after transplantation.
MMF	0001_000024	56 years, ♂, C	303	Cerebral hemorrhage
	0012_00009	45 years, ♀, C	328	Myocardial infarction
	0063_00003	21 years, ♀, C	294	Cardiac insufficiency
	0513_00005	54 years, ♀, C	110	Ischemic bowel, atherosclerosis
	0514_00004	59 years, ♀, C	20	Pneumonia, respiratory arrest

C= Caucasian, Bl= Black
All deaths were prior to the cutoff date

MO Comment: *Cardiovascular causes and infection are the leading causes of death in renal transplantation. One year survival rate in renal transplant patients is in the 95% range (UNOS Data). Review of CRFs and the clinical summaries of patients who died during the study did not reveal any suspicious pattern. The number of patients who died in the study is within the expected frequency. At the time of death, all 7 patients had a functioning graft.*

Serious AEs (SAE): In Study-B301, the most frequent SAE were infections, GI, and renal AEs. In general, the rates for infections reported as SAE were comparable in both treatment groups. Other SAE related to different body systems were comparable. Table 10-8 provides rates for selected AEs. Overall, the differences in rates for serious bacterial, viral, and fungal infections were comparable between the two treatment groups. The MMF group had one case of *Pneumocystis carinii* infection.

The total number of patients who had to discontinue (D/C) study drug due to an AE was 39 (18.3%) patients in the ERL080 and 35 (16.7%) patients in the MMF group (0-12 Month safety population (see D/C study drug section p:72 of this review).

MO Comment: *In table-10.8 below, pneumonia as a SAE, was reported more frequently in the MMF group 8 patients compared to 1 patient in the ERL080 group. However, one has to consider that probably all cases of pneumonia in an immunocompromised population like the one studied would be classified as serious AEs regardless of the grade of severity or etiology, because pneumonia in such a population would be more likely to require or prolong hospitalization. In addition, the study was not designed to evaluate subcategories of pneumonia. Therefore, the observed difference in the rates for pneumonia as a SAE does not allow one to draw meaningful comparative conclusions. Overall, the rates reported for all SAEs were comparable across the two treatment groups. These rates as noted in table-10.8 were expected for a de novo renal transplant population; there were no concerns for trends or patterns observed in the study. The rates for D/C study medication were comparable across both treatment groups, there were no specific trends or patterns of concern.*

The rates for CMV infection listed in table-10.8 are rates for serious CMV infection and are therefore a subset of rates for total CMV infection (see Infections & Infestations p:65 of review). In the table, a patient was counted only once per body system and term.

Table 10-8. Number (%) of patients reporting SAEs by body system (≥3% in any group) (safety population, 0-12 months)

Body system affected Preferred term	ERL080 1.44g/day (N=213)	MMF 2g/day (N=210)	Difference in event rate (ERL-MMF)
Any SAE	117 (54.9%)	113 (53.8%)	1.1%
Infections and infestations	42 (19.7%)	55 (26.2%)	-6.5%
• CMV infection	20 (9.4%)	13 (6.2%)	3.2%
• Urinary tract infection	4 (1.9%)	13 (6.2%)	-4.3%
• Pneumonia NOS	1 (0.5%)	8 (3.8%)	-3.3%
Gastrointestinal system disorders	30 (14.1%)	24 (11.4%)	2.7%
• Diarrhea NOS	6 (2.8%)	7 (3.3%)	-0.5%
• Vomiting NOS	6 (2.8%)	7 (3.3%)	-0.5%
• Nausea	2 (0.9%)	7 (3.3%)	-2.4%
Renal and urinary disorders	23 (10.8%)	30 (14.3%)	-3.5%
• Renal impairment NOS	7 (3.3%)	5 (2.4%)	0.9%
Blood and lymphatic system disorders	16 (7.5%)	16 (7.6%)	-0.1%
• Lymphocele	11 (5.2%)	8 (3.8%)	1.4%
• Leukopenia NOS	2 (0.9%)	7 (3.3%)	-2.4%
General and administrative site disorders	14 (6.6%)	18 (8.6%)	-2.0%
• Pyrexia	11 (5.2%)	9 (4.3%)	0.9%
Surgical and medical procedures	11 (5.2%)	13 (6.2%)	-1.0%
Investigations	13 (6.1%)	9 (4.3%)	1.8%
• Blood creatinine increased	9 (4.2%)	7 (3.3%)	0.9%

Source: Post-text table 10.2-2b

Severe AEs: The ERL080 group had a total of 81/213 (38%) patients report a severe AE vs. 86/210 (41%) patients in the MMF group. Severity rates were comparable for most disorders. Moderate AE rates in the ERL080 group were 107 (50.2%) patients vs. 96 (45.7%) in the MMF group. Lastly, mild AEs were infrequent [ERL080 20 (9.4%) vs. MMF 24 (11.5%)].

MO Comment: *The rates for severe AEs were comparable in the study. When there were differences in the rates, these differences were small. Given the nature of the study, a de novo renal transplant study where patients are exposed to many stressors, and their immune system is compromised, the observed severity rates in the study were expected. There were no unusual trends or patterns observed for the two treatment groups.*

Discontinuation (D/C) of study medication due to AE: The rate for D/C study medication secondary to an AE was 36/213 (16.9%) ERL080 vs. 29/210 (13.8%) MMF group. Of note is the comparable rates in D/C study medication secondary to an AE in all categories between the two treatment groups. The most common cause for drug discontinuation due to an AE was related to a GI AE [ERL080 10 (4.7%) vs. MMF 11 (5.2%)], followed by renal disorder [ERL080 6 (2.8%) vs. MMF 7 (3.3%)], and immune system disorder namely graft loss [ERL080 5 (2.3%) vs. MMF 6 (2.9%)]. Other causes for D/C study medication due to an AE and >1% in any group include, infections, blood and lymph disorders, investigations, general disorders and administration site disorders, neoplasms, and nervous system disorders; the rates for study drug discontinuation for these groups were comparable across the two treatment groups.

MO Comment: *In Study-B301, the causes of D/C study medication from AEs were expected and comparable for both treatment groups. There were no unusual trends or patterns observed leading to D/C study medications. GI causes for D/C study medication were primarily due to diarrhea, nausea, and vomiting and were comparable between the two treatment groups. Three patients in the ERL080 and two patients in the MMF group had leukopenia that led to study medication discontinuation. Bone marrow suppression, GI intolerance, and renal causes were the main causes for D/C study drug; these causes were similar to D/C MMF reported in the Cellcept® Clinical Review by Dr. Joyce Korvick NDA #50,722.*

Malignancies: The rates of malignancies were comparable in both treatment groups [ERL080 5 (2.3%) vs. MMF 5 (2.4%)] (table below).00000000000.

Study-B301 Malignancies (Source: Table 10.1-1)

	Patient #	Brief narrative
ERL080	0045_00004	*PTLD. Started Day-336 (on Rx). D/C study medication, recovered Day-368
	0031_00001	*36 year Caucasian male with hypertension from Norway. D+/R+ CMV status. Cutaneous T-cell lymphoma. Started Day-9 (on Rx). D/C study medication, recovered Day-122. This patient did not receive antibody therapy.
	0023_00009	Basal cell skin. Started Day-53 (on Rx), surgically resected. Recovered
	0516_00005	Basal cell Left canthus. Started Day-324 (on Rx).
	0023_00028	Kaposi sarcoma. Started Day-196 (on Rx). D/C study medication, recovered Day-457
MMF	0502_00008	PTLD. Started Day-90. Study medication D/C & switched to tacrolimus
	0514_00019	Basal cell. Started Day-178 (on Rx)
	0514_00009	Squamous cell Rt. cheek. Started Day-359 (on Rx)
	0001_00024	Prostate cancer. Started Day-26 (on Rx, dose reduced)
	0516_00011	Skin carcinoma. Started Day-62 (on Rx) excised. Lt forearm squamous cell. Started Day-284 (on Rx), excised Day-732. Rt. forearm Squamous cell. Started Day-313 (on Rx) excised Day-340

* Indicates PTLD/Lymphoma
on Rx: On treatment

MO Comment: *Malignancies are a known hazard of immunosuppressive therapy in solid organ transplantation, and are probably related to the level of immunosuppression and not to the particular regimen used. The T-cell lymphoma in one of the patients on the ERL080 was diagnosed by Day-9 on treatment. The rate of malignancies reported in this study is comparable in both treatment groups, and is what one is expected to find in patients receiving immunosuppressive therapy [2].The range of malignancies is also within expected range, mostly PTLD and non-melanoma skin cancers. A black warning box at the front of the label states the risk of lymphoma and other neoplasms as a result of immunosuppression. This is addressed in more detail in the WARNINGS and ADVERSE REACTIONS sections of the label, including warnings for patients to limit exposure to sunlight though protective clothing and use of sunscreens. These labeling sections are consistent with the Cellcept® label and are appropriate given the risks associated with the systemic exposure to MPA.*

[2] Organ Procurement & Transplantation Network (UNOS).
http://www.optn.org/data/annualreport.asp?url/Data/ar2002/ar02_table_1406_tum.htm Last accessed November, 18, 2003.

Laboratory evaluation: The Applicant's analyses for laboratory data focused on comparisons between the two treatment groups rather than comparisons relative to baseline since most patients had many abnormal baseline laboratory values. Liver function tests, hemoglobin, platelets, WBC, creatinine, glucose, cholesterol, and electrolyte rates were comparable at the Month-0 to 6 and Month-0 to 12 periods.

Hematology: The rates for leukopenia, thrombocytopenia, and anemia were comparable in both treatment groups (see p:67 of this review for details) respectively.

MO Comment: *Administration of ERL080 and MMF in Study-B301 produced predictable and comparable bone marrow suppression in both treatment groups. There were no unusual trends or patterns observed.*

Biochemistry:

Renal Function: Mean creatinine values declined after transplantation in both groups. Creatinine values were comparable across the two treatment groups at most window visits, but were reported to be slightly above the normal range at Month-12 for both groups. Mean urea values correspondingly exhibited comparable changes in both treatment groups to the creatinine changes. Fifty five percent of (118) patients in the ERL080 and fifty three percent (111) of patients in the MMF group experienced a 30% increase in creatinine value from baseline.

MO Comment*: After renal transplantation, renal function predictably improves due to the functioning implanted organ. However, the half life of a cadaveric kidney is ~11 years, implying that over time, many kidneys fail over relatively short periods of time. Therefore, renal function is expected to gradually decline with time. The cause for the shortened half life of a transplanted kidney is multifactorial (acute & chronic rejection, drug toxicity, recurrence of original renal disease, other factors). In Study-B301, mean creatinine and urea values improved after transplantation and were comparable in both treatment groups. The mild increase of serum creatinine values from baseline is expected, especially that the majority of donor kidneys were cadaveric. There were no unusual trends for renal function for the two treatment groups. The fact that there is little difference in rates across the two treatment groups is reassuring and consistent with the fact that rejections rates were comparable.*

The Month-0 to 12 biochemistry data was comparable to the Month-0 to 6 data. Most biochemistry laboratory abnormalities occurred during the first 6 months of the study. The table below lists selected abnormal biochemistry values.

Study-B301 Abnormal Biochemistry Laboratory Rates (Month-0 to 12)
Source: Modified PTT 10.3-5

Laboratory Parameter	Value code	ERL080	MMF
Uric acid umol/L	High	53 (24.9%)	40 (19%)
Bilirubin ≥2X ULN umol/L	High	6 (2.8%)	3 (1.4%)
AST ≥3X ULN U/L	High	16 (7.5%)	8 (3.8%)
ALT ≥3X ULN U/L	High	35 (16.4%)	31 (14.8%)
Alkaline phosphatase ≥3X ULN U/L	High	8 (3.8%)	9 (4.3%)
Gamma Glutamyltransferase ≥3X ULN U/L	High	20 (9.4%)	21 (10%)
Cholesterol >9.1 mmol/L	High	17 (8%)	25 (11.9%)
Amylase ≥2X ULN U/L	High	28 (13.1%)	27 (12.9%)
Glucose < 2.5 mmol/L	Low	9 (4.2%)	7 (3.3%)
Glucose >13.9 mmol/L	High	25 (11.7%)	33 (15.7%)
Potassium >6 mmol/L	High	35 (16.4%)	27 (12.9%)
Magnesium < 0.4 mmol/L	Low	6 (2.8%)	11 (5.2%)
Magnesium >1.5 mmol/L	High	4 (1.9%)	1 (0.5%)
Calcium <1.5 mmol/L	Low	4 (1.9%)	6 (2.9%)
Calcium >3.2 mmol/L	High	3 (1.4%)	4 (1.9%)

Bold lines indicate a difference of ≥5% between treatment groups

Liver function tests: The average AST values were within the normal range and were comparable in both treatment groups during the Month-0 to 12 period. Patients with AST elevations aggregated in the early post-transplant period, and mean AST values were at baseline by Week-1 of the study. In the case of ALT, mean ALT levels increased slightly to reach a maximum at 1-2 weeks post-transplant, but were still within the normal range [ERL080 53 U/L vs. 46 U/L MMF]. During the window visits, changes from baseline were comparable between the two treatment groups.

Similarly, mean gamma-GT values were comparable between groups, although mean gamma-GT values were higher than at baseline. A few patients had elevated bilirubin level [ERL080 6 (2.8%) vs. MMF 3 (1.4%)], these also tended to occur early in the perioperative period. The mean bilirubin values for the two groups were normal and comparable at window visits. Due to secondary hyperparathyroidism after renal transplantation, mean alkaline phosphatase values were elevated comparably in both treatment groups. The ERL080 group had mean alkaline phosphatase values that were consistently higher at window visits compared to the MMF group, but the differences in mean values were comparable in both treatment groups.

MO Comment: *Transplanted patients are expected to develop liver enzyme elevations around the perioperative period as a result of their surgery, anesthesia, infection, and other medications administered. Therefore, the mild changes in liver enzymes observed in the study are expected. Dosage*

adjustment for Myfortic® in patients with parenchymal liver disease is not needed. The differences in rates for liver function changes were comparable for the two treatment groups. There were no unusual trends or patterns identified for liver function abnormalities.

Lipids: Mean cholesterol levels were elevated after renal transplantation in both groups comparably. At Month-12, the mean cholesterol values were 5.8 mmol/L in the ERL080 group and 5.6 mmol/L in the MMF group. The average increase in cholesterol values from baseline to Month-12 was 35% in both groups. The mean triglyceride values increased 40% from baseline in both treatment groups. Mean triglyceride levels were comparable at most visit windows.

MO Comment: *It is common for lipid levels to increase after transplantation secondary to underlying disease, metabolic abnormalities, drugs administered especially cyclosporine and steroids. The difference in rates for lipid levels were comparable for both treatment groups.*

Amylase: At baseline, patients in both treatment groups had an elevated amylase level (~100 U.L), soon after transplantation levels declined in both groups and at Month-12, amylase values in the ERL080 and MMF groups were 79 U/L and 80 U/L respectively. Incidence rates of elevated amylase values during the study was 13% for both treatment groups. Elevated amylase values were noted early in the post-transplant period. There differences were comparable across the two treatment groups.

MO Comment: *There were 3 patients in the ERL080 reported with pancreatitis compared to none in the MMF group. Although, the observed difference in the number of cases of pancreatitis is small, a class effect reference to the potential for Myfortic® to cause pancreatitis is made in the ADVERSE EVENTS section of the label.*

Urinalysis: Baseline rates for positive urine findings (protein and glucose) were comparable for both treatment groups. The rate for pathological urine findings at each window visit was comparable most of the time.

Study-B301 extension phase: Rates for safety events (18 month extension phase) are listed in the table. the rates were comparable to rates for the core Study-B302.

Study-B301 Extension Safety rates (18-Months extension phase)
Source: PTT 17.1-3, Vol 166.

	Study-B302 MMF (0-12 Months) N=163	ERL080 N=99 (12-30 Months)	exMMF N=103 (12-30 Months)
Adverse events	92.6	85.9%	90.3%
Severe AEs	20.1%	25.3%	24.3%
Serious AEs	30.1	41.4%	38.8%
Infections	58.9%	57.6%	55.3%
Severe infections	6.1%	7.1%	9.7%
Serious infections	16%	20.2%	19.4%

MO Comment: *The extension phase component for Study-B301 was optional and therefore the study was an open-label, non-randomized study in a selected subpopulation. This sets limitations on data interpretation due to the potential for selection bias in the study. Nevertheless, it is reassuring that the observed safety rates were comparable to the safety rates reported in the core Study-B302, a study conducted in stable renal transplant recipients who were at more than 6 months after transplantation.*

Study-B302: Study-B302 was a multicenter, randomized, double-blind, parallel study designed to evaluate the safety and efficacy of ERL080 720 mg po bid compared to MMF 1 gm po bid, in combination with Neoral® ± corticosteroids for the prophylaxis of organ rejection in stable renal transplant recipients. This study was primarily a safety study. Because ERL080 and MMF are similar drugs, the focus of this study was based on expected AEs identified from the use of MMF, namely: GI AEs, neutropenia, and infection. Therefore, the primary safety variables in the study were the incidence and severity of GI AE, and neutropenia at 3 months. These primary safety variables were also supported by the 6 & 12-Month visit windows for events related to GI AEs and neutropenia. There were several secondary safety variables identified: incidence and severity of GI AEs at 12 month, incidence and severity of neutropenia within 12 months, incidence and severity of AEs at 3 & 12 months, incidence and severity of infections (CMV in particular) within 3 & 12 months, discontinuations due to AEs and serious AEs within 3 & 12 months, and discontinuations due to GI AEs and serious AEs within 3 & 12 months, and hematology variables (WBC counts, neutrophil counts, and hemoglobin).

MO Comment*: The double-blind, randomized design of the study is one of its main strengths. A potential limitation of the study was that patients had prior experience with prolonged exposure to MMF before enrollment and represented a selected population that would be expected to be less sensitive to the GI AEs associated with exposure to MMF or MPA.*

The Applicant assigned the 3, 6, months cutoff dates for the safety analysis at Day-146, and Day-226. The 12-month safety analysis was not assigned a cutoff date. Adverse events incidence rates for the safety variables were compared between the two treatment groups in the study and a 2-sided 95% CI was generated for the difference in rates.

Infections were analyzed separately and as a whole under AEs analysis. AE tables for the 3- & 6-month included events that occurred up to 7 days after discontinuation of study medication or before the cutoff date (the earlier date was used). Whereas the 12-month AE tables included events that occurred up to 7 days after discontinuation of study medication or end of therapy. All AEs are included in the 12-Month database.

MO Comment: *The slight variation in the collected analysis at the cutoff dates should not affect the results of the study.*

AEs in the study report are shown relative to the day when the patient was randomized (first dose administered). The 6-month listings of AEs use "on treatment" variable to indicate that the events occurred after the cutoff date of 7 days after the last dose of study medication, a "no" in the "on treatment" column indicates AEs that occurred after the last dose of study medication plus the 7 day cutoff date. Whereas the 12-month AE listing uses the "on treatment" to identify that the AE occurred while on treatment, and uses a number to identify how many days after the last dose the AE occurred.

MO Comment: *During the course of this study, the Applicant updated the MedDRA dictionary from version 3.3 to 4.0, which lead to some AEs being mapped out to different organ classes or preferred terms in the 6 and 12-month analysis; for example, PTT 10.1-5 & 10.1-6 present AEs for the 6-month analysis that are mapped to another preferred term in the 12-month analysis. The MedDRA update did not affect the overall interpretation of the results of the study, the changes were mostly minor.*

Laboratory Data: The tables provided by the Applicant for the 3- & 6-month analyses of laboratory data represent values while on study medication. While the 12-month analysis, all laboratory values were included up to the day after the last dose of study medication.

MO Comment: *Flagged values in laboratory tables, indicate values after one day of permanent discontinuation of study medication. These values were not included in the analysis tables for the "on treatment" column.*

Safety Results: The safety population, was defined as all randomized patients who received at least one dose of study medication and had at least one safety/tolerability assessment. A total of 324 patients were randomized into the study; however, two patients from the ERL080 treatment group (patient # 0140008 & 5130008) withdrew consent prior to receiving study medication. Therefore, the safety population analyzed in the study was 322 patients [ERL080 159/322 compared to MMF 163/322].

MO Comment: *The cumulative long-term safety data for Study-B302 are represented in the 0-12 Month period analysis. Therefore, data from the 0-6 Month, and 0-3 Month periods are supportive, and may provide temporal relationships for AEs, for example, identifying if certain AEs were more frequent at the start of the trial or after the 6 months period.*

All Adverse Events

The overall experience of AEs is provided in the table below. At the 0-12 Month period there were 149 (93.7%) patients in the ERL080 group and 151 (92.6%) patients in the MMF group with at least one AE. The rates of AEs for the 0-3 Months period were [ERL080 135 (84.9%) vs. MMF 129 (79.1%). In the ERL080 group, diarrhea and nausea were the most common AEs, and in the MMF group diarrhea and nasopharyngitis were the commonest.

Table 10-4. Overall experience of adverse events including infections (safety population)

	Months 0 to 3		Months 0 to 6		Months 0 to 12	
	ERL (N=159) n (%)	MMF (N=163) n (%)	ERL (N=159) n (%)	MMF (N=163) n (%)	ERL (N=159) n (%)	MMF (N=163) n (%)
At least one AE	135 (84.9)	129 (79.1)	139 (87.4)	137 (84.0)	149 (93.7)	151 (92.6)
Any severe AE	15 (9.4)	18 (11.0)	20 (12.6)	24 (14.7)	34 (21.4)	34 (20.9)
Any serious AE	16 (10.1)	22 (13.5)	21 (13.2)	33 (20.2)	37 (23.3)	49 (30.1)
Any drug-related AE	37 (23.3)	38 (23.3)	41 (25.8)	42 (25.8)	47 (29.6)	48 (29.4)
Any infection	61 (38.4)	65 (39.9)	74 (46.5)	77 (47.2)	93 (58.5)	96 (58.9)
Any severe infection	1 (0.6)	5 (3.1)	3 (1.9)	8 (4.9)	9 (5.7)	10 (6.1)
Any serious infection	6 (3.8)	12 (7.4)	9 (5.7)	18 (11.0)	14 (8.8)	26 (16.0)[1]

Source: Post-text tables 10.1-1, 10.1-12, and 10.1-15.

MO Comment: *The Applicant's report for the overall experience of AEs shows comparable rates of AEs between the two treatment groups for each of the three analyzed periods (0-3 Months, 0-6 Months, and 0-12 Months). A possible exception was the apparent difference in the rates between the two treatment groups for serious infection (table above). However, considering the totality of the data, the rate for infections in the two treatment groups appeared similar for all study periods, and the rate of severe infection in the study is much smaller and comparable across treatment groups, which is a reassuring finding. In addition, the study was not designed to detect differences in subpopulations of the AE infections, in this instance the number of patients reported is small. One should be careful about interpretation of multiple comparisons. In a study where rates of acute rejection were comparable across treatment groups, and where there is similar exposure to the active moiety MPA, one would not expect to see a difference in risk for infection.*

The term "serious AE" was defined in the study as AEs that result in death, life threatening, incapacity, disability, prolongation of existing hospitalization, or requires hospitalization). Therefore, the significant difference reported by the Applicant for serious infections is potentially confounded by many variables that the study was not designed to evaluate (for example, what prophylactic regimens were used, by which centers, and for what populations; some patients could have had their hospitalization prolonged for a brief period for administrative purposes (such as waiting for blood culture results) and therefore be counted as a serious AE). The investigator blinded to study drug made the determination for serious AEs. AEs in the study were graded as mild, moderate, or severe; therefore, providing a qualitative assessment of the intensity of the AE and does not necessarily confer clinical seriousness or relationship to study drug. In this study serious and severe AEs were not mutually exclusive.

***MO Comment:** At all three periods the rates for AEs were comparable across the two treatment groups. There were no unusual trends or patterns observed for the two treatment groups. This study provides additional reassurances that exposure to MPA in Myfortic® provides a comparable safety profile to MMF.*

Incidence of common AEs (≥10%) in either group for the 0-12 month period are listed in the table below.

Table 10-5. Incidence of common adverse events (≥ 10% in either group) by MedDRA system organ class and preferred term (safety population – Months 0 to 12)

MedDRA system organ class Preferred term	ERL (N=159) n (%)	MMF (N=163) n (%)
At least one adverse event	149 (93.7)	151 (92.6)
Gastrointestinal disorders	90 (56.6)	93 (57.1)
Nausea	39 (24.5)	31 (19.0)
Diarrhea NOS	34 (21.4)	40 (24.5)
Vomiting NOS	24 (15.1)	21 (12.9)
Dyspepsia	22 (13.8)	24 (14.7)
Infections & infestations	89 (56.0)	92 (56.4)
Nasopharyngitis	26 (16.4)	32 (19.6)
Upper respiratory tract infection NOS	20 (12.6)	16 (9.8)
Urinary tract infection NOS	16 (10.1)	19 (11.7)
General disorders & administration site conditions	54 (34.0)	49 (30.1)
Edema peripheral	17 (10.7)	20 (12.3)
Musculoskeletal & connective tissue disorders	58 (36.5)	46 (28.2)
Arthralgia	22 (13.8)	16 (9.8)
Nervous system disorders	42 (26.4)	49 (30.1)
Headache NOS	28 (17.6)	27 (16.6)
Metabolism & nutrition disorders	43 (27.0)	44 (27.0)
Respiratory, thoracic & mediastinal disorders	41 (25.8)	40 (24.5)
Cough	18 (11.3)	13 (8.0)
Investigations	36 (22.6)	35 (21.5)
Injury, poisoning & procedural complications	25 (15.7)	20 (12.3)
Skin & subcutaneous tissue disorders	23 (14.5)	29 (17.8)
Vascular disorders	20 (12.6)	26 (16.0)
Renal & urinary disorders	18 (11.3)	25 (15.3)
Psychiatric disorders	16 (10.1)	20 (12.3)
Eye disorders	16 (10.1)	14 (8.6)

Source: Post-text tables 10.1-16 and 10.1-17.

MO Comment: *The rates for common AEs were comparable across the two treatment groups during the 0-12 Months period. There were no unusual trends or patterns observed.*

GI AEs (0-3 Months): The rates for GI AEs during the 0-3 Months period were comparable. The slightly higher rates for GI AEs in the ERL080 group were mainly attributable to the higher rates of nausea, vomiting, and loose stools. Two thirds of patients who experienced nausea or vomiting were reported in period 0-3 Months [ERL080 17.6%, 9.4% vs. MMF 10.4%, 6.1%]. During the 0-12 Months period, the rate for nausea and vomiting was [ERL080 24.5%, 15.1% vs. MMF 19%, 12.9%]. In addition, there were 5 (3.2%) patients in the ERL080 group who discontinued medication prematurely in the first 42 days after randomization due to a GI AE compared to 0 patients in the MMF group.

MO Comment: *The rates of GI AEs related to nausea and vomiting were comparable for the two treatment groups. Two patients in the ERL080 group prematurely discontinued study medication vs. zero patients in the MMF group due to a GI AE during the first 42 days after randomization, these numbers were small and expected. Despite the enteric coating of the ERL080 formulation, intended to minimize GI toxicity, the product does not appear to have been better tolerated compared to MMF.*

Study-B302 Selected GI AEs

	0-3 Months*		0-6 Months		0-12 Months	
	ERL080	MMF	ERL080	MMF	ERL080	MMF
GI AEs	76 (47.8%)	70 (42.9%)	81 (50.9%)	80 (49.1%)	90 (56.6%)	93 (57.1%)
Nausea	28 (17.6%)	17 (10.4%)	32 (20.1%)	24 (14.7%)	39 (24.5%)	31 (19%)
Vomiting	15 (9.4%)	10 (6.1%)	21 (13.2%)	16 (9.8%)	24 (15.1%)	21 (12.9%)
Loose stool	7 (4.4%)	3 (1.8%)	7 (4.4%)	4 (2.5%)	7 (4.4%)	3 (1.8%)
Diarrhea	8 (5%)	8 (4.9%)	26 (16.4%)	31 (19%)	34 (21.4%)	40 (24.5%)
Dyspepsia	13 (8.2%)	19 (11.7%)	17 (10.7%)	21 (12.9%)	22 (13.8%)	24 (14.7%)

Source: PTT: 10.1-2, 10.1-13, 10.1-16
*Diarrhea for 0-3 months rate is from Table 10-1 GI AEs at the 3 –months visit, where as diarrhea for 0-6 & 0-12 months is total rate of diarrhea for the time frame.

MO Comment: *The MO selected the GI AEs in the table above for their frequency, and because these are the AEs potentially related to GI intolerance from exposure to MPA. The rate for events in both treatment groups at 0-12 Months is generally better than the rates observed in de novo renal transplant recipients in Study-B301 (see page:64 for comparison). In assessing GI toxicity, one must consider that patients in the Myfortic® clinical program received the study drug on an empty stomach and not with food. In addition, these patients were taking a larger than usual load of tablets & capsules (study drug & matching dummy pills). Overall, the rates for these selected GI AEs were comparable for both treatment groups. There were no unusual trends or patterns observed. The overall rate of observed GI events appears a little higher than expected, and higher than the ones used to justify the study sample size for this study (for details please see page:49 of this review).*

GI AEs (0-12 Months): Common GI AEs during this period were diarrhea, nausea, dyspepsia, and vomiting in that respective disorder (table above). The rates were comparable across the two treatment groups. Overall, the incidence and types of serious GI AEs were comparable across the two treatment groups for the 0-12 Months period. There was a total of 6 (3.8%) patients in the ERL080 and 8 (4.9%) patients in the MMF group with a serious GI AE for the 0-12 Month period. The rates for serious GI AEs were comparable between the two treatment groups. A total of 3 patients in each treatment group discontinued study medication for the 0-12 Months period due to a GI AE.

MO Comment: *Overall, the rates for GI AEs were comparable for the two treatment groups, and no unusual patterns or trends emerged.*

Neutropenia: A low absolute neutrophil count was defined as <1.5x 10^9/L cells. For the 0-3 Months 1 patient in the ERL080 group and 5 patients in the MMF group had a low absolute neutrophil count.

Study-B302 Neutropenia
Source: PTT 10.3-5, 10.3-5, 10.3.12, 10.1-16

		ERL080	MMF
Neutropenia	0-3 Months	1 (0.6%)	5 (3.1%)
	0-6 Months	1 (0.6%)	5 (3.1%)
*Neutropenia reported as an AE	0-12 Months	0	1

Neutropenia = <1.5x 10^9/L
*Patient # 501_00002 : 36-year-old male, absolute neutrophil count of 0.29x10^9/L on Day 22-42 on MMF treatment (resolved).

MO Comment: *The difference in rates observed for neutropenia during the 0-12 Months period compared to the 0-6 Months period is related to the updated MedDRA database. Overall, although neutropenia is a potential hazard of systemic exposure to MPA, the observed rate is small and differences should be interpreted with caution as this population included by definition patients who were screened for MMF intolerance (not to mention that unstable patients, for example patients with neutropenia were excluded).*

Infections: During the 0-12 Months period, the rates for infections in both treatment groups were comparable [ERL080 93 (58.5%) vs. MMF 96 (58.9%)]. The most frequent infections (>10%) in either group and in descending order were nasopharyngitis (16.4% vs. 19.6%), urinary tract infection (10.1% vs. 11.7%), and upper respiratory tract infections (12.6% vs. 9.8%).

MO Comment: *Nasopharyngitis, is a common infection in the general population, and the observed rate in both treatment groups may be at or just above what one would expect to find in a healthy population. The rate for infections was comparable across the two treatment groups for the 0-12 Months period. There were no unexpected infectious events reported in the trial. One patient in the MMF group died from complications of pneumonia, and one patient in the ERL080 group died from cryptococcal meningitis/mass secondary to HIV infection. Therefore, the rate of death from infections was similar in both groups and within a reasonable range of what one would see in a transplant population. The one death from infection in the ERL080 group (patient with AIDS) died from an infection that is expected from the underlying disease, and probably has little or nothing to do with study medication.*

Bacteria were the most common pathogens identified during the 0-12 Month period [ERL080 16 (10.1%) vs. MMF 19 (11.7%)] followed by viral infections [ERL080 6 (3.8%) vs. MMF 9 (5.5%)], and fungal infection rates were [ERL080 4 (2.5%) vs. MMF 3 (1.8%)]. Many patients in both treatment groups were diagnosed with an infection but were missing an organism [ERL080 79 (49.7%) vs. MMF 89 (54.6%)]. Fungal infections were uncommon for the 0-12 Months period [ERL080 4 vs. MMF 3].

MO Comment: *The high number of infections without identified microorganisms in the study is not unusual and is related to many factors for example different collection and culture techniques, the wide array of potential pathogens and the fastidious nature of the organism. The range of infections observed in the study was not unusual. More importantly, infection rates were comparable across both treatment groups, and there were no unusual trends or patterns identified. Labeling for Myfortic® identifies the risk for immunosuppression and the potential risk for infections as a result of exposure to Myfortic®.*

Malignancies: For the 0-12 Month period there were 9 (5.7%) patients in the ERL080 group and 10 (6.1%) patients in the MMF group with a malignancy. Three further patients were reported after the database was locked and were not included in PTT 10.1-16). Two of the three patients were in the ERL080 group (pt# 001_0013 had a B-cell lymphoma, pt# 516_0021 had an AIDS-related lymphoma), and the remaining third patient was in the MMF group (pt# 015_0024 had a basal cell carcinoma). These 3 additional patients were reported as serious neoplasms. Therefore a total of 6/22 patients were reported with a serious neoplasm (3 in each treatment group). Nine of the 22 patients had skin papillomas (ERL080 4 vs. MMF 5),

MO Comment: *The rates for malignancies in both treatment groups were comparable, and are consistent with the expected rates and types of malignancies (PTLD & non-melanoma skin cancers) observed in patients receiving immunosuppressive therapy for transplantation. This justifies the class labeling for malignancy and the recommendations to limit exposure to sunlight.*

Study-B302 Malignancies (0-12 Months)*

Study Medication	Patient #	Details
ERL080	015_0013	Urothelial carcinoma diagnosed on Day-374, pt had ureteral obstruction
	503_0019	History of acne & skin papillomas. Squamous cell carcinoma diagnosed on Day-298, excised
	503_0019	History of prior skin cancer. Squamous cell carcinoma diagnosed & excised on Day-238
	527_0001	Basal cell carcinoma diagnosed on Day-134, resolved on Day-531 without therapy
MMF	021_0003	Gastric carcinoma diagnosed on Day-326. Study medication D/C on Day-339

Study-B302 Malignancies (0-12 Months)*

Study Medication	Patient #	Details
	516_0020	Bladder tumor diagnosed on Day-30 (Grade II-III papillary transitional cell carcinoma). Study medication D/C on Day-72
Pts reported after database locked		
ERL080	001_0013	Polymorphic B-cell lymphoma: histology on Day-309
	516_0021	AIDS-related lymphoma, cryptococcal brain abscess diagnosed on Day-249-253. Expired Day-256 from AIDS
MMF	015_0024	History of lupus & alopecia. Basal cell carcinoma on Day-313 excised on Day-348

*The remainder of patients with malignancies include: 4 patients in the ERL080 group with skin papillomas, 5 patients in the MMF group with skin papillomas, 1 patient in each treatment group with a breast lump NOS, and one patient in the ERL080 group with Bowen's disease, and the remaining 1 patient had a benign skin neoplasm NOS.

MO Comment: *Pt# 516_0021 was reported to die from AIDS. The cause of death in this patient was secondary to the two CNS complications (cryptococcal brain abscess / meningitis & lymphoma). The patient cause of death does not appear to be related to the study drug.*

Treatment related AEs: A total of 37 (23.3%) patients in the ERL080 and 38 (23.3%) patients in the MMF group had a suspected drug-related AE for the 0-3 Month period. A total of 47 (29.6%) patients in the ERL080 and 48 (29.4%) patients in the MMF group had a suspected drug-related AE for the 0-12 Month period. Drug-related AEs reported in at least 5% of patients were diarrhea (ERL080 7% vs. MMF 10%), and dyspepsia (ERL080 0 vs. MMF 5%).

MO Comment: *It is difficult to identify the causality of common drug-related AEs like diarrhea or dyspepsia in this population because of the many confounding factors. Therefore, one has to use caution in interpreting the data. At best, in Study-B302 one can say that drug-related AEs were comparable, and that there were no unusual trends or patterns identified.*

Serious AE: For the 0-3 Months period, the rate for serious AEs was 10.1% in the ERL080 group and 13.5% in the MMF group. And for the 0-12 Months period, the rate was 23.3% 37/159 in the ERL080 group and 30.1% 49/163 in the MMF group. The most common SAEs were dehydration in the ERL080 group and pneumonia NOS in the MMF group. The differences in rates across the treatment groups for these reported events were not clinically significant.

MO Comment: *The rates for serious AEs were comparable across the two treatment populations. The common SAE were mainly related to infection [ERL080 14 (8.8%) vs. MMF 25 (15.3%)], metabolism and nutrition disorders [ERL080 10 (6.3%) vs. MMF 7 (4.3%)], and GI related [ERL080 6 (3.8%) vs. MMF 8 (4.9%). The observed differences in rates were comparable across treatment groups. Examination of the individual SAEs did not reveal suspicious trends or patterns.*

Severe AEs: During the 0-6 Months, severe AEs experienced by >2% of patients in either group included 3 patients with dehydration in the ERL080 group and 3 patients with diarrhea in the MMF group. The rates for severe AEs were comparable for each of the three periods. For the 0-12 Months period there were 72 (45.3%) patients in the ERL080 group and 70 (42.9%) patients in the MMF group reported with a moderate AE, and 43 (27%) patients in the ERL080 group and 47 (28.8%) patients in the MMF group reported with a mild AE.

Study-B302 Severe AEs
Source: PTT 10.1-24, 10.1-12, 10.1-10

Period	ERL080	MMF
0-3 Months	15 (9.4%)	18 (11%)
0-6 Months	20 (12.6%)	24 (14.7%)
0-12 Months	34 (21.4%)	34 (20.9%)

MO Comment: *Common severe AEs included the GI system [ERL080 10 (6%) vs. MMF 9 (5%)], infections [ERL080 8 (5%) vs. MMF 9 (5%)], and metabolism/nutritional [ERL080 6 (4%) vs. MMF 6 (4%)]. The rates for severe adverse events were comparable across treatment groups. There were no unusual trends or patterns identified. The rates for severe AEs are half the rates that were observed in Study-B301, which is what one would expect for a stable transplant population.*

Premature D/C of study medication: The reasons for premature discontinuation of study medication secondary to an AEs or laboratory abnormality for ERL080 are listed in the table below.

Study-B302 D/C Study Medication Secondary to an AE & Reason
Source: PTT 10.1-8, CRFs, narratives

		ERL080	MMF
D/C study medication due to AE	0-3 Months	3 (1.9%)	2 (1.2%)
	0-6 Months	7 (4.4%)	2 (1.2%)
	0-12 Months	9 (5.7%)	6 (4%)
Reasons for D/C study medication			
	Death	2	1
	Leukopenia	2	
	↑ creatinine	1	1
	Infection	2	
	Diarrhea	2	2
	Malignancy		2

MO Comment: *The rates for D/C study medication secondary to an AE were comparable for the two treatment groups. The MO reviewed the patient narratives and raw tables in the study and available CRFs and concur with the Applicant's assessment.*

Deaths: In the 0-6 Month period, 1 patient died (MMF) from a hemorrhagic stroke. For the 0-12 Months period, a total of 7 patients died (2 deaths ERL080 group and 5 deaths in the MMF group).

Study-B302 Deaths
Source: Modified PTT 10.2-7

	Patient #	Cause of death	
ERL080	0015_00002	Multiorgan failure	*24 year ♀ Caucasian, death Day-350. Bowel perforation, fungal pneumonia
	0516_00021	AIDS, cryptococcal brain abscess	35 ♂ Black, CNS lymphoma, death Day-266
MMF	0011_00004	Cerebral bleed	46 ♀ Caucasian, death Day-84
	0512_00005	Hypoglycemia, heart attack	56 ♂ Caucasian, death Day369
	0512_00016	Cardiac arrest	70 ♂ Black, death Day-272
	0527_00016	Pneumonia	49 ♀ Black, death Day-300
	0511_00013	Myasthenia gravis, pulmonary HTN	This death occurred post-study. Patient withdrew consent on Day-273 and was D/C. Died on Day-290 flare up of M. gravis.

*The only study-medication related death in Study-B302
All of the deaths occurred prior to the cut-off date.

MO Comment: *Patient #0511_00013 expired off study drug from a flare up of myasthenia gravis. It is unlikely that this event is related to study drug. A study drug relation was suspected by the investigator's assessing patient #0015_00002; however, the attribution for the cause of death is difficult to ascertain in this patient due to confounding by the patient's complicated history of medical and surgical problems. Therefore, one cannot reliably exclude a potential role for the study drug in this fatal outcome. The rates for death were comparable for the two treatment groups. These death rates are within the expected rate for deaths in a renal transplant population. Common causes of death in a renal transplant population include infection and cardiovascular etiologies. Review of patient narratives and available CRFs did not identify any suspicious patterns.*

Laboratory

Hematology: During the 0-12 Months period there were 6 (3.8%) patients in the ERL080 group and 4 (2.5%) patients in the MMF group with a low hemoglobin. At 0-12

Month period the rate for hemoglobin shift was essentially unchanged (ERL080 4, vs. MMF 2). Thrombocytopenia (<75 x 10^9/L) was not reported in either group.

White Cell Counts (WBC) (<4 x 10^9/L): The rates for a low WBC count were comparable for the three study periods. For the 0-12 Months period, a total 14 (8.8%) patients in the ERL080 group and 15 (9.2%) patients in the MMF group had a low WBC count.

A low absolute neutrophil count, defined as (<1.5 x 10^9 /L), occurred in 1 patient in the ERL080 group and in 5 patients in the MMF group. The rates remained similar for the three study periods. In addition, all of these 6 patients were shifts from normal to low. By study end none of the patients in the ERL080 and 2 patients in the MMF group had a neutrophil count <1.5 x 10^9 /L (secondary to improvement in neutrophil count).

MO Comment: *The studied population, consisted of renal transplant recipients who had been screened for their ability to tolerate exposure to MPA and were already on immunosuppressive therapy. Therefore, the rates for anemia, thrombocytopenia, and leukopenia are expected to be much lower that those rates observed in the de novo renal transplant study. In addition, any patient with evidence of bone marrow suppression on a screening blood test was excluded from the study. The rates for hematologic events were comparable for the two treatment groups. Two patients in the ERL080 were prematurely D/C from the study due to leukopenia (patient # 517_0004 54-year-old female, WBC 2.3 x10^9/L visit Day 71-99 on treatment, absolute neutrophil count not available; & patient # 531_0003 36-year-old female, WBC 3.6 x10^9/L visit Day 71-99).*

Biochemistry:

Renal Function: For the 0-12 Month period, the mean creatinine, urea, and uric acid values were comparable to baseline. Shifts in creatinine values for the 0-12 Months period defined as a 30% increase from baseline or >265 µmol/L in creatinine occurred in 22 (13.8%) patients in the ERL080 group and 19 (17.7%) patients in the MMF group; these rates were comparable.

MO Comment: *In total 4 patients were prematurely D/C from the study due to a lab abnormality: two patients in the ERL080 had leukopenia, and one patient in both groups had an elevated creatinine (ERL080 pt# 014_0010 & MMF pt# 516_0016).*

Hepatic Function: For the 0-12 Months period, patients in both treatment groups had a low rate of liver test abnormalities. The rates were comparable for both treatment groups. A high bilirubin level (≥2X ULN) for the 0-12 Month period was observed in 1 patient in the MMF group. An elevated AST level (≥3X ULN) was reported in 1 patient in the ERL080 group and 2 patients in the MMF group. An elevated ALT level (≥3X ULN) was reported in 2 patients in the ERL080 group and none in the MMF group. Two patients in each group had an elevated alkaline

phosphatase level (≥3X ULN). Elevated GGT levels (≥3X ULN) were reported for 3 patients in the ERL080 group and for 10 patients in the MMF group.

MO Comment: *This was a stable renal transplant population. Liver function abnormalities are expected to be low, since these patients were already on immunosuppressive regimens, and were not expected to change their medications. The elevated alkaline phosphatase and GGT levels occurred early in the study and suggest cholestatic liver disease which may be multifactorial. Shifts from normal → high in liver tests were comparable in both treatment groups. Of the 10 patients in the MMF group with an elevated GGT, 4/10 had an elevated GGT at baseline. Therefore, the observed shift in GGT level for patients with a normal GGT level at baseline was comparable for both treatment groups.*

Metabolites & Electrolytes: For the 0-12 Month period, the mean values for metabolites and electrolytes were comparable. A few patients in either group had shifts that were essentially comparable for both treatment groups (PTT 10.3-10).

MO Comment: *Shifts in glucose values in this population (4 patients in each treatment group) are expected secondary to multifactorial causes (steroid use, other immunosuppressive medications, and kidney function). The rates for glucose shifts were comparable and expected. There were no unexpected electrolyte or metabolic abnormalities values reported in the study.*

Urinalysis: For the 0-12 Months period, the rate of patients who had an abnormal post-baseline urinary protein (baseline urine dipstick negative for protein) was similar for both treatment groups [ERL080 8 (5%) vs. MMF 16 (10%)].

MO Comment: *The rates for urine analysis abnormalities were comparable for both treatment groups (PTT 10.3-11). No clinically meaningful abnormal patterns were detected.*

Study-B302 Extension Phase: This phase of Study-B302, was an open-label, non-randomized extension for patients agreeing to participate and continue treatment with ERL080. The weaknesses of this extension phase of the study were the small number of patients enrolled and the potential for selection bias. Therefore, the results of the extension phase study should be interpreted with caution. The rates for safety events during the extension phase were comparable to the rate of events from the core Study-B302 (table). No new risks from the administration of ERL080 were identified.

Study-B302 Extension Safety rates (18-Months extension phase)
Source: PTT 17.1-4, Vol 169.

	Study-B302 MMF (0-12 Months) N=163	ERL080 N=77 (12-30 Months)	exMMF N=75 (12-30 Months)
Adverse events	92.6	89.6%	86.7%
Severe AEs	20.1%	22.1%	30.7%
Serious AEs	30.1	28.6%	38.7%
Infections	58.9%	57.1%	50.7%
Severe infections	6.1%	6.5%	2.7%
Serious infections	16%	13%	14.7%

D. Adequacy of Safety Testing

The 720 mg Myfortic® dose delivers 720 mg of MPA, and the 1000 mg CellCept® dose delivers 739 mg of MPA. Therefore in NDA 50-791, patients in the Myfortic® group studied at 720 mg po bid received a comparable amount of drug substance compared to the CellCept® 1000 mg po bid dosed group. Patients in the Myfortic® group were similarly exposed in duration to patients in the CellCept® group. CellCept® used in combination with cyclosporine and corticosteroids is an approved agent for prophylaxis of organ rejection in renal transplant patients.

E. Summary of Critical Safety Findings and Limitations of Data

Novartis is relying on FDA's determination that mycophenolate mofetil, the active comparator in studies B301 & B302, is safe and effective in preventing rejection in renal transplantation. The active moiety is mycophenolic acid. Myfortic® (mycophenolic acid) delayed release tablets were designed to deliver a similar amount of MPA, 720 mg, to that delivered by 1000 mg of MMF. Safety studies were required to evaluate whether potential differences in the rate of absorption and extent of GI exposure to MPA could lead to a different safety profile compared to MMF. Adequate numbers of *de novo* and stable renal transplant recipients have been evaluated in Studies B301 & B302, conducted by Novartis to characterize the safety profile of Myfortic® (mycophenolic acid) delayed release tablets, and assure that the safety of Myfortic® was comparable to that of mycophenolate mofetil.

Patients exposed to immunosuppressive regimens involving combinations of drugs, including Myfortic® to prevent organ rejection after transplantation are at an increased risk of developing malignancies particularly, PTLD and non-melanoma skin cancers. In addition, these patients have an increased susceptibility to infection and bone marrow suppression.

Safety data from the two clinical studies B301 & B302 showed that Myfortic® has a comparable safety profile to MMF. Overall, adverse event rates for malignancies, infection, gastrointestinal system, and bone marrow suppression were comparable between the two treatment groups for each study. These adverse events were reproduced in the two clinical studies, which characterize the class adverse events for precursors of MPA. In general, the adverse event rates in Study-B302 were lower than those in Study-B301. This is expected, and provides reassurances relating to the safety of Myfortic®, because Study-B301 was a *de novo* renal transplant population, whereas Study-B302 was a stable renal transplant population. Data beyond the 12-Month study period is limited in quality and quantity due to the design of the extension phases of both studies (open-label, non-randomized, potential for selection bias, small number of subjects enrolled). Therefore, long term data to characterize the safety of Myfortic® is limited.

Because of Myfortic®'s potential for inhibiting the *de novo* pathway of guanosine nucleotide synthesis, Myfortic® should be avoided in patients with the rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (Kesch-Nyhan and Kelley-Seegmiller syndrome).

Myfortic® use in *de novo* or stable renal transplant populations provides an alternative formulation for delivery of systemic MPA. However, this new formulation does not provide the flexibility with dosing as the approved MMF product, which is available in capsule, solution, and intravenous formulations. The enteric coated delayed release formulation of Myfortic® was intended to improve GI tolerance of exposure to mycophenolic acid. However, no improvement compared to Cellcept® was observed in two double-blind, randomized studies. Overall, the safety profile of Myfortic® was similar to the approved product, Cellcept®. Therefore, the risk/benefit profile for Myfortic® is acceptable to permit regulatory approval of the product.

VIII. Dosing, Regimen, and Administration Issues

The Applicant recommends the administration of Myfortic® 720 mg po bid for the prevention of organ rejection in *de novo* and stable renal transplant recipients. In the clinical studies reviewed in NDA 50-791, Myfortic® was evaluated in combination with

Neoral® and corticosteroids and therefore should not be used as a single agent for immunosuppression.

The proposed dosing for Myfortic® is 720 mg po bid. Myfortic® is supplied as 360 mg and 180 mg tablets. No dosing adjustments are required in patients with renal or hepatic impairment. Myfortic® tablets should not be crushed, chewed, or cut prior to ingesting; and tablets should be administered on an empty stomach (1 hour before or two hours after food intake). Myfortic® is indicated for prophylaxis of organ rejection in renal transplant recipients.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

In Study-B301, gender distribution in the ERL080 group was 137 (64%) male and 76 (36%) female patients. Whereas in the MMF group there were 142 (68%) male and 68 (32%) female patients. For males in Study-B301 the rate of AEs, severe AEs, serious AEs, infections, severe infections, serious infections, and drug related AEs were comparable across the two treatment groups [PTT 12.1-13a]. Within subgroups, the rate of Escherichia coli infections was higher among females compared to males in both treatment groups [ERL080 ♂5% vs. ERL080 ♀ 15%; and MMF ♂5% vs. MMF ♀16%].

MO Comment: *Although gender distribution favored men in this study, an adequate and comparable number of females were enrolled in the two treatment groups. The difference in E. coli infections between men and women may be related to an expected difference in frequency of urinary tract infections between the two genders.*

Similarly, females in Study-B301 the rate of AEs, severe AEs, serious AEs, infections, severe infections, serious infections, and drug-related AEs were comparable across the two treatment groups. In the ERL080 group, the rates for AEs between males and females were comparable

MO Comment: *In Study-B301 the number of female participants was reasonable in size in both treatment arms. There were no instances of significant differences in rates for adverse events in gender across the two treatment groups. Also, in the ERL080 group the rates for AEs were comparable for males and females. Therefore, it is reasonably safe to conclude that females are not at increased risk of AEs when compared to males in this study.*

Study-B302

Study-B302 gender distribution included 97 (61%) males and 62 (39%) females in the ERL080 group, and 115 (71%) males and 48 (29%) females in the MMF group. For male patients the rates for AEs, severe AEs, an infections were comparable between the two treatment groups. For female patients, the rates for AEs, severe AEs, and serious AEs were comparable between the two treatment groups. The rates for infections was higher in the ERL080 group compared to the MMF group(ERL080 66.1% vs. MMF 56.3%). This difference is almost totally accounted for by the difference in rates for nasopharyngitis [ERL080 15 (24%) vs. MMF 8 (17%)], and upper respiratory infections [ERL080 13 (21%) vs. MMF (5 (10%)].

MO Comment: *Like Study-B301, in Study-B302 there were no clinically meaningful differences between treatment groups to suggest an increased risk of infection in females. Overall, the rates were comparable between the two treatment groups. The significance of the higher rate of infections is questionable because, nasopharyngitis and upper respiratory tract infections are common in the general healthy population.*

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Age

Clinical studies of Myfortic® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant or other drug therapy. In Study-B301 there were 14 geriatric patients in the ERL080 group and 10 geriatric patients in the MMF group. Similarly, Study-B302 included 11 geriatric patients in the ERL080 group and 8 geriatric patients in the MMF group.

Race

Study-B301

Study-B301 had 17 and 13 Black patients in the ERL080 and MMF groups respectively. The rates for AEs, severe AEs, serious AEs, and in infections, severe infections, and serious infections were comparable across the two treatment groups.

MO Comment: *The small number of Black patients enrolled in the study makes it difficult to draw meaningful conclusions.*

Study-B302

In Study-B302 there were a total of 28 (18%) and 34 (21%) Black patients in the ERL080 and MMF groups respectively. The rates for AEs, severe AEs, serious infections, and drug related AEs were comparable across the two treatment groups.

MO Comment: *Similar to Study-B301, the small number of Black patients enrolled in the study makes it difficult to draw meaningful conclusions.*

C. Evaluation of Pediatric Program

The Applicant submitted one pediatric Study-0106 designed to evaluate the pharmacokinetics of ERL080 following a single dose in stable pediatric renal transplant patients (n=24) on Neoral®. There were no pediatric efficacy and safety studies in NDA 50-791. The safety and effectiveness of Myfortic® have been established in the age group 5-16 years in stable pediatric renal transplant patients. Use of Myfortic® in this age group is supported by evidence from adequate and well controlled studies of Myfortic® in stable adult renal transplant patients. Pediatric doses for patients with body surface area <1.19 m^2 cannot be accurately administered using currently available formulations of Myfortic® tablets. There are no pharmacokinetic data available for pediatric patients < 5 years.

D. Comments on Data Available or Needed in Other Populations

Pregnancy: There are no adequate and well controlled studies in pregnant women, Myfortic® should be used in pregnant women only if the potential benefit outweighs the potential risk to the fetus. Myfortic® is a Pregnancy Category C drug.

MMF is listed as a Pregnancy category C drug. In a recent report from the National Transplantation Pregnancy Registry [3], pregnancy outcomes were reported for 10 women with 14 pregnancies exposed to MMF. Regimens used in these 14 pregnant women included prednisone and either tacrolimus or cyclosporine. Of the 14 children, 8 were live births born between 31 & 39 weeks gestation, the remaining 6 were spontaneous abortions.

There were a total of 4 pregnancies reported in NDA 50-791, all were in partners of patients treated with ERL080. One of the four pregnancies was from Study-B301 (Patient# 512_0002: This patient was ex-MMF on ERL080 treatment for 6 months, his wife gave birth to a healthy female, normal delivery). Two pregnancies were reported from Study-B302Ext (Patient# 519_0005 an ex-MMF, his wife gave birth to a healthy male, normal delivery. Patient# 511_0008, ERL080 group, his wife gave birth to a

[3] Armenti VT et al. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation.. Eds Cecka & Terasaki, Clinical Transplants 2002:121-130. UCLA Immunogenetics.

healthy baby girl, normal delivery). The fourth patient#6109 was from Study-2302 MMF group. This patients partner experienced a spontaneous abortion (5-weeks gestation); pregnancy was reported 8 days after the end of study.

In the 120-Day Safety Update, the partner of patient #510_0009 from Study-B301Ext, ex-MMF group reported 1 pregnancy. The outcome was a healthy boy delivered by caesarian section.

Lung Fibrosis: There were no cases of pulmonary fibrosis reported in the submission or in the 120-Day Safety Update.

Pancreatitis: In Study-B301, there were 3 cases of pancreatitis in the ERL080 group and 1 case in the MMF group. In Study-B302, 1 patient in the ERL080 group developed pancreatitis. Four additional cases of pancreatitis were reported in patients treated with ERL080, one from Study 0107Ext, one from a clinical pharmacology study, and two from MYPROMS. The total number of patients with pancreatitis as of the cut-off date of January 17, 2003 was 8/1782 (0.4%) patients in the ERL080 group and 1/445 (0.2%) in the MMF group. There were no new cases of pancreatitis in the 120-Day Safety Update.

MO Comment: *Pancreatitis in renal transplant patients may be multifactorial. The Applicant performed an excellent analysis for pancreatitis, and provided relevant literature and AERS data to support their findings of low incidence of pancreatitis of <0.5% in patients on ERL080. Pancreatitis may develop as a result of exposure to systemic MPA, which justifies the class effect in the ADVERSE EVENTS section of the label.*

Diabetes mellitus (DM): Study-B301 included 34 and 42 diabetic patients (N=76/423, 18%) in the ERL080 and MMF groups respectively. Diabetics in both treatment groups had comparable rates for AEs, severe AEs, serious AEs, infections, severe & serious and drug-related AEs. Similarly, non-diabetics had comparable rates for AEs, severe AEs, serious AEs, infections, severe & serious and drug-related AEs. Of note is the higher rate of post-operative wound complications and infection in the ERL080-DM group 11/34 (32.4%) vs. MMF-DM group 3/42 (7%) [Non-DM patients experienced a ~3% rate of post-operative wound complications and infection]. GI AEs were reported more frequently in patients with DM in the ERL080 group 91.2% vs. MMF 73.8%. In particular nausea, diarrhea, vomiting, and abdominal pain were more common in the ERL080 group.

MO Comment: *The discussion in this section pertains to all patients in the study who had a diagnostic category of diabetes mellitus for the 0-12 Month (in contrast, at enrollment in the study there were 15 (10%) patients with diabetes mellitus at enrollment). The high rate of post-operative related infections in the ERL080-DM group is of concern. However, the number of patients in the study is small. Therefore, these potential limitations do not allow one to make reliable conclusions. Evaluation of post-marketing adverse event reports may provide further insights. At enrollment in the*

study, there were more patients with DM in the MMF group 15% compared to 10% in the ERL080 group, also, one would expect that diabetic gastroparesis would affect patients after several years of overt diabetes. Therefore, the MO is reasonably confident that the observed difference in rates for GI symptoms may be related to the small number of patients and potential confounding factors.

Study-B302: There were 89/322 (28%) diabetic patients in Study-B302 [ERL080 41 vs. MMF 48 patients] (for the 0-12 Month period). The overall rate of AEs was comparable in both treatment groups [ERL080 group 41/41 (100%) vs. MMF 44/48 (91.7%)]. The rate for leukopenia between the two treatment groups was comparable (ERL080 2% vs. MMF 4%). The overall rate for GI AEs was similar (57%) for the two treatment groups.

MO Comment: *The rates for AEs were comparable for the two treatment groups. In both studies, the rate for common GI AEs (nausea, diarrhea, vomiting, abdominal pain) is slightly higher in patients with DM compared to the core populations. Because of the small number of patients and the potential for multiple confounding factors a reliable conclusion is not possible based on the data analyzed.*

X. Conclusions and Recommendations

A. Conclusions

The reviewing Medical Officer (MO) recommends an action of **Approval** for NDA 50-791; use of Myfortic® (mycophenolic acid) for the prophylaxis of organ rejection in allogeneic *de novo* and stable renal transplant recipients.

The approval of Myfortic® for the prevention of rejection in renal transplantation was supported by two adequate and well controlled studies in *de novo* and stable renal transplant recipients, conducted by Novartis and reported in NDA 50-791. The Myfortic dose used in these studies was based on the amount of mycophenolic acid that is delivered by the approved dose of Cellcept® (mycophenolate mofetil) for prevention of rejection in renal transplantation, and supported by pharmacokinetic studies conducted by Novartis, comparing the systemic exposure to mycophenolic acid when delivered by oral doses of mycophenolate sodium or mycophenolate mofetil.

The safety of Myfortic® (mycophenolic acid) Delayed Release Tablets was found to be comparable to that of Cellcept® (mycophenolate mofetil) in renal transplantation patients. Although Myfortic® (mycophenolic acid) Delayed Release Tablets were formulated with an enteric coating intended to minimize the gastrointestinal toxicities associated with MPA, the product was not better tolerated than Cellcept®.

The safety of Myfortic® is supported by information from two 12-Month, randomized, double-blind, controlled studies comparing ERL080 to MMF in *de novo* and stable renal transplant recipients, respectively. The most common potential hazards associated with ERL080 are similar to those of MMF and include increased susceptibility to infection and the possible development of lymphoma and other neoplasms as a result from immunosuppression. Other common hazards include the gastrointestinal system (intolerance to the drug, gastrointestinal bleeding, peptic ulcers, intestinal perforation), and bone marrow suppression (neutropenia). These hazards are well reflected in the WARNINGS and PRECAUTIONS sections of the approved labeling, dated February 27, 2004.

B. Labeling

The primary changes requested in the proposed label were mainly to remove particular claims in the efficacy or safety section of the label that were not substantiated by the data in the submission. The following text reflects important changes that were communicated to the Applicant and accepted by the Agency and the Applicant during labeling negotiations.

Some sections of the label for Myfortic®, namely parts of the Drug Interaction section and parts of the Safety related sections were based on the Cellcept® label, because these pertained to exposure to mycophenolic acid, the same active moiety.

TRADEMARK

Applicant's version: Myfortic® (mycophenolate sodium)

FDA proposed changes: Myfortic® (mycophenolic acid).

Rationale for change: This change is based on the Agency's policy to classify free acids and free bases under a single established name (namely, the active moiety, in this instance that is the acid rather than the salt of mycophenolate). The Agency's policy allows health care providers to make uniform dosing comparisons among products that are chemically different but deliver the same active moiety in the human body.

CLINICAL PHARMACOLOGY

Food Effect

Applicant's version: Compared to the fasting state, administration of Myfortic 720 mg with a high fat meal (55g fat, 1000 calories) had no effect on the systemic exposure (AUC) of MPA . However, there was a 33% decrease in the maximal concentration (Cmax), a 3.5-hr delay in the

T_{lag} (range, -6 to 18 hr), and 5.0-hr delay in the T_{max} (range, -9 to 20 hr) of MPA. To avoid the variability in MPA absorption between doses, Myfortic should be taken on an empty stomach.

FDA proposed changes: Compared to the fasting state, administration of Myfortic 720 mg with a high fat meal (55g fat, 1000 calories) had no effect on the systemic exposure (AUC) of MPA . However, there was a 33% decrease in the maximal concentration (Cmax), a 3.5-hr delay in the T_{lag} (range, -6 to 18 hr), and 5.0-hr delay in the T_{max} (range, -9 to 20 hr) of MPA. [

]

Rationale for change: The safety and efficacy of Myfortic® has not been adequately studied in the fed state. Health care providers may falsely assume that exposure to MPA would be similar in the fed and fasting states. In addition, Myfortic® and Cellcept® exposure kinetics are different in the fed and fasting state, therefore, substitution of one product for the other should not be attempted without physician supervision.

PRECAUTIONS

General

Applicant's version: Gastrointestinal bleeding (requiring hospitalization) has been reported in de novo renal transplant patients (1.0%) or maintenance patients (1.3%) treated with Myfortic (up to 12 months) . Intestinal perforations, gastrointestinal hemorrhage, gastric ulcers and duodenal ulcers have rarely been observed

FDA proposed changes: Accepted

Rationale for change: Edited from the original label text for clarity.

Drug Interactions

Applicant's version: [

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FDA proposed changes: The simultaneous use of Myfortic and magnesium aluminum containing antacids should be avoided

Rationale for change: The Applicant would need to conduct a drug interaction study to determine the appropriate timing of the administration of Myfortic and antacids to avoid the drug interaction.

ADVERSE REACTIONS

Applicant's version: Novartis proposed changing the Adverse Event table from — to >20% events to reflect consistency with the reference drug, Cellcept®.

FDA proposed changes: Change accepted by Agency.

DOSAGE AND ADMINISTRATION

Applicant's version: [

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FDA proposed changes: The recommended dose of Myfortic is 720 mg administered twice daily (1440 mg total daily dose) on an empty stomach, one hour before or two hours after food intake (see CLINICAL PHARMACOLOGY: Food effect).

Myfortic delayed release tablets and mycophenolate mofetil tablets and capsules should not be used interchangeably without physician supervision because the rate of absorption following the administration of these two products is not equivalent.

Rationale for change: All phase III clinical studies, including *de novo* and stable transplantation, were conducted with the administration of Myfortic on an empty stomach (1 hour before or two hours after meals). Therefore, the efficacy and safety of Myfortic were not assessed under fed conditions.

Pediatric

Applicant's version: Pediatric: [

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FDA proposed changes: Based on a pharmacokinetic study conducted in pediatric patients, the recommended dose of Myfortic in pediatric patients is 400 mg/m^2 administered twice daily (up to a maximum dose of 720 mg administered twice daily). Patients with a body surface area (BSA) of 1.19 to 1.58 m^2 may be dosed either with three Myfortic 180 mg or one 180 mg plus one 360 mg twice daily (1080 mg daily dose). Patients with a BSA of > 1.58 m^2 may be dosed either with four Myfortic 180 mg or two Myfortic 360 mg twice daily (1440 mg daily dose). Pediatric doses for patients with BSA

< 1.19 m^2 cannot be accurately administered using currently available formulations of Myfortic tablets.

Rationale for change: Please refer to the Biopharmaceutical Review by Dr. Jang-Ik Lee for details.

Geriatric

Applicant's version: ***Elderly:*** Pharmacokinetics in the elderly have not formally been studied.
[redacted]

FDA proposed changes: Geriatric Use: Patients ≥65 years may generally be at increased risk of adverse drug reactions due to immunosuppression. Clinical studies of Myfortic did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Rationale for change: The reader is referred to 21 CFR 201.57 subsection 10 Geriatric use.

C. Recommendations

The MO recommends **Approval** of Myfortic® for prophylaxis of organ rejection in *de novo* and maintenance patients in renal transplant recipients in combination with Neoral® and corticosteroids.

Labeling changes are provided in the review. In brief, the changes recommended by the Agency were to ensure that any claims of a difference in the label in efficacy or safety for Myfortic® and MMF are those supported by data from the two adequate and well controlled clinical studies in the submission. Secondly, Myfortic® and MMF are not interchangeable products. Myfortic® is formulated as an enteric coated, delayed-release tablet, and is characterized by variability in its pharmacokinetic profile compared to MMF's (delayed T_{max}, T_{lag}, AUC) when studied under fast and fed states. Therefore, Myfortic® should be administered to patients on an empty stomach (1 hour before or 2 hours after food). Myfortic® label includes sections that address the risk / benefit profile related to immunosuppression, for example, the risk for malignancy, infection, and neutropenia. Labeling also provides recommendations to monitor patients for bone marrow suppression and to limit exposure to sunlight. The pediatric section of the label provides information related to dosing for stable pediatric renal transplant recipients.

The MO concurs with the recommendation made by the Pharmacology & Toxicology Reviewer, requesting that the Applicant conduct a Segment III prenatal/postnatal developmental toxicity study in pregnant female rates with Myfortic® as a phase IV post

marketing commitment. The Agency is requesting the study, because the 505 (b)(2) submission does not contain a reference to this study that can be used to address the requirements for a Segment III developmental toxicity study.

XI. Appendix

A. Proposed Label

B. Individual More Detailed Study Reviews (If performed)

Appears This Way
On Original

/S/

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HFD-590/Chem/RSood
HFD-590/Chen/NSchmuff
HFD-590/PharmT/SHundley
HFD-590/Stat/KLee
HFD-590/Stat/KHiggins
HFD-590/Micro/SBala
HFD-590/Biopharm/JILee
HFD-590/Biopharm/PColangelo
HFD-590/CPMS/EMolinaro
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/s/

Sary Beidas
3/18/04 02:52:25 PM
MEDICAL OFFICER

Marc Cavaille Coll
3/18/04 04:23:31 PM
MEDICAL OFFICER
I concur with the MO's conclusions and recommendations in the review of NDA 50-791, Myforticfi (Mycophenolic acid) DELAYED RELEASE TABLETS for teh preventio of graft rejection in renal transplantation.

Renata Albrecht
3/18/04 05:57:59 PM
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