# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPROVAL PACKAGE FOR:

## APPLICATION NUMBER

## 50-791

## Statistical Review(s)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

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| **NDA/Serial Number:** | N50-791 |
| **Drug Name:** | Myfortic (mycophenolate sodium) delayed-release tablets 180/360 mg |
| **Indication(s):** | Prophylaxis of organ rejection in patients receiving renal transplants |
| **Applicant:** | Novartis Pharmaceuticals Corporation |
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**Keywords:** Clinical Studies, NDA review

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# 1. EXECUTIVE SUMMARY

## 1.1 Conclusions and Recommendations

This review mainly focuses on the results of two controlled clinical trials, Study B301 and Study B302, in support of the efficacy and safety of Myfortic (ERL080) delayed-release tablet. Myfortic is given as a prophylaxis of organ rejection in patients receiving allogeneic renal transplants, administered in combination with cyclosporine, USP (MODIFIED) and corticosteroids. The clinical studies, Study B301 and Study B302, were conducted to show the therapeutic equivalence of ERL080 compared to CellCept (MMF) in *de novo* and in maintenance renal transplant patients, respectively. In addition, this review includes efficacy and safety analyses of the supportive safety Study 0170 of ERL080 in maintenance renal transplant patients.

The primary efficacy objectives were to show efficacy as measured by the incidence of biopsy-proven acute allograft rejection, graft loss, death, or lost to follow-up in the first 6 and 12 months of treatment in *de novo* (Study B301) and in maintenance (Study B302) renal transplant recipients. In Study B301 and Study B302, ERL080 was non-inferior to MMF for this endpoint. However, in a modified composite endpoint measured premature treatment discontinuation as additional failures, ERL080 was not non-inferior to MMF because of the disproportionately higher premature treatment discontinuation in the ERL080 group in Study B301, but ERL080 was non-inferior to MMF in Study B302. In general, in all efficacy analyses with the one exception of the analysis of Study B301where discontinuations were considered failures indicated that ERL080 was non-inferior to MMF and this was consistent across studies.

The safety analyses showed that the ERL080 group had almost the same incidence of gastrointestinal system adverse events (GI AEs) within 12 months and at Month 12 visit in Study B301, and no statistically significant differences were observed between the two treatment groups. In Study B302, the incidence of any GI AEs at Month 3 visit showed a slightly higher incidence in the ERL080 group compared to that of the MMF group. It was mainly due to higher incidence of non-upper GI AEs in the ERL080 group as compared to the MMF group. However, no statistically significant difference was observed between the two groups. The safety analyses results of Study 0107 and Study 0107Ext showed that the incidence of GI AEs was similar between the two groups. The core studies, Study B301 and Study B302, and a supportive Study 0107 do not show that there was statistically significant improvement of GI adverse events and tolerability.

The incidence of patients with clinically low absolute neutrophils ($<1.5 \times 10^9/L$ ) values was similar between the two treatment groups from Month 0 to Month 12 and no statistically significant differences were observed.

## 1.2 Brief Overview of Clinical Studies

Myfortic (ERL080 180 mg and 360 mg) administered in combination with Neoral and corticosteroids, was studied for the prophylaxis of organ rejection in patients receiving allogenic renal transplant. Myfortic delivers the same active moiety as CellCept (MMF) and is formulated as a delayed-release tablet whereas CellCept is formulated as an immediate release tablet.

The sponsor conducted two large international, multi-center, randomized, double blind, double dummy 1-year clinical trials, one in the *de novo* patients (Study B301) and one in maintenance

renal transplant patients (Study B302), comparing efficacy and safety of ERL080 versus MMF when administered in combination with Neoral and corticosteroids. In addition, a five week study, Study 0107, was conducted to assess the GI tolerability of ERL080 versus MMF in maintenance renal transplant patients. After completing these three double-blind, double-dummy clinical trials, all patients were eligible to receive continuous treatment with ERL080 in an open label manner in the context of long-term extension protocols.

The primary objective of Study B301 was to show therapeutic equivalence of ERL080 compared with MMF as measured by the composite incidence rate of biopsy-proven acute rejection, graft loss, death or loss to follow-up in the first 6 months of treatment in *de novo* renal transplant recipients. A total of 423 patients were randomized and treated, 213 in the ERL080 (1.44 g/day) group and 210 in the MMF (2 g/day) group.

The primary objective of Study B302 was to evaluate the incidence and severity of GI adverse events at 3 months after administration of study medication and neutropenia within the first 3 months of treatment in maintenance renal transplant patients treated with ERL080 or MMF. A total of 322 patients were randomized and treated, 159 in the ERL080 group and 163 in the MMF group. A secondary objective of this trial was to confirm non-inferior efficacy of ERL080 compared to MMF.

The Study 0107 was the additional safety study to support a GI tolerability labeling claim. In the 5-week core phase Study 0107, 74 and 75 patients were treated with ERL080 and MMF.

### 1.3 Statistical Issues and Findings

Study B301 and Study B302 showed that the ERL080 180 mg and 360 mg tablets given for prophylaxis of organ rejection in patients receiving allogeneic renal transplants administered in combination with cyclosporine was non-inferior to MMF at 6 and 12 months in preventing the incidence of biopsy-proven acute rejection, graft loss, or lost to follow-up measured as the composite primary efficacy endpoint. The main reason for failure was biopsy-proven acute rejection in both treatment groups. No statistically significant differences were observed in the incidence of the composite primary efficacy endpoint or in the separate components between the two groups. The primary and the secondary efficacy analyses indicated that ERL080 was non-inferior to MMF in both Study B301 and Study B302.

The ERL080 group was not non-inferior to MMF at 6 and 12 months in Study B301 when considering premature treatment discontinuation as an efficacy failure. The modified composite efficacy analysis measures the incidence of biopsy-proven acute rejection, graft loss, lost to follow-up or premature treatment discontinuation as a failure. The patients in the ERL080 group showed higher premature treatment discontinuation rate as compared to the MMF group. The primary reason for premature treatment discontinuation was adverse events for both groups. However, there were no statistically significant differences between the two groups for the modified composite efficacy endpoint for both Study B301 and Study B302.

Study B302 was conducted to evaluate the incidence and severity of gastrointestinal adverse events (GI AEs) at 3 months after administration of study medication and neutropenia within the first 3 months of treatment in maintenance renal transplant patients treated with ERL080 or MMF. The endpoint of any GI AEs at Month 3 visit showed slightly higher incidence in the ERL080 group compared to that of MMF. This was mainly due to the higher non-upper

gastrointestinal disorders incidence. However, no statistically significant difference was observed.

Study 0107 and its extension, Study 0107Ext showed that the incidence of overall adverse events and GI events were similar between the two groups during the core study period, but it increased over time during the extension period. The incidences of abnormal distension and upper abdominal pain in Study 0107 were higher than that in Study B302 because Study 0107 enrolled patients who were GI intolerant to MMF. Overall, there was no statistically significant difference between the two groups.

The core studies, Study B301 and Study B302, and a supportive Study 0107 do not show that there was statistically significant improvement of GI adverse events and tolerability. The efficacy analysis using only biopsy-proven rejection, graft loss, death, or lost to follow-up indicates that ERL080 was non-inferior to MMF. However, the premature treatment discontinuation rate was higher in the ERL080 group compared to the MMF group in Study B301 and the reason for premature treatment discontinuation was mostly due to adverse events. The patients in the ERL080 group had a higher incidence of GI events compared to the MMF group in the early period in Study B301. The ERL080 was not non-inferior to MMF in the modified efficacy endpoint which included treatment discontinuation as an efficacy failure in Study B301.

## 2. INTRODUCTION

### 2.1 Overview

This review focuses on the statistical review of the two controlled clinical trials (Study B301 and Study B302) of the immunosuppressive drug ERL080 (Myfortic), which is an enteric-coated formulation of mycophenolate sodium (EC-MPS) tablets.

The ERL080 is given as a prophylaxis of organ rejection in patients receiving allogeneic renal transplants. This medication is administered in combination with cyclosporine, USP (MODIFIED) and corticosteroids. ERL080 has the same active moiety as the approved prodrug Mycophenolate mofetil (MMF) as drug substance, CellCept ® from Roche.

The sponsor developed the solid oral ERL080 tablets (180 mg and 360 mg) to show similar pharmacokinetic behavior as MMF (CellCept ®), but obviated the need to use a prodrug concept and avoided release of drug substance in the stomach, thus offering a potential for improved gastrointestinal tolerability.

The sponsor performed a Phase III clinical program to show that ERL080 had equivalent efficacy as MMF, and to evaluate the safety profile of the two products in *de novo* and in maintenance renal transplant patients. Study B301was controlled, randomized, double-blind Phase III studies to show therapeutic equivalence of ERL080 compared to MMF. Study B302 and a supportive Study 0107 were controlled, randomized, double-blind Phase III studies to show tolerability, safety and efficacy of ERL080 compared to MMF. In addition, the extension studies of B301, B302 and Study 0107 were conducted to evaluate the long term safety of ERL080.

In Study B301, the sponsor conducted a randomized, double-blind and controlled trial with MMF as a comparator to show the efficacy and safety of ERL080 for the treatment in *de novo* renal transplant recipients. There were a total of 423 randomized and treated patients, 213 in the

ERL080 group and 210 in the MMF group. The primary and secondary objectives were to show therapeutic equivalence of ERL080 compared with MMF.

In Study B302, the sponsor conducted a randomized, double-blind and controlled trial with MMF as a comparator to show the efficacy and to evaluate gastrointestinal (GI) adverse events and neutropenia after initial administration of study medication in maintenance renal transplant patients. A total of 322 patients were randomized and treated, 159 in the ERL080 group and 163 in the MMF group. The primary objective was to evaluate the incidence and severity of GI adverse events at 3 months after administration of study medication and neutropenia within the first 3 months of treatment in maintenance renal transplant patients treated with ERL080 or MMF. Secondary objectives were to evaluate the efficacy and other safety variables of ERL080 compared with MMF in maintenance renal transplant patients.

The extension phases of the key renal studies, Study B301Ext and Study B302Ext, are uncontrolled and open-label. Two hundred thirty seven and 178 patients who were initially treated to MMF for 12 months in Study B301 and Study B302 were switched to ERL080, and followed for a total of 12 and 18 months, respectively. Two hundred thirty two and 176 patients who were continuously treated with ERL080 for 12 months (12 months of cohort) and 18 months (18 months of cohort) were followed for 24 and 30 months, respectively.

In the 5-week core phase of Study 0107, 74 and 75 patients were initially treated with ERL080 and MMF, respectively in a double-blind manner. The extension phase of Study 0107, Study 0107Ext, added 65 patients with 8+ months exposure to ERL080, as well as 63 patients whose therapy was switched from MMF to ERL080 and continued ERL080 for 7 months (7 months of cohort). Thirty two patients who were switched from MMF to ERL080 after 5 weeks core study and 33 patients who were continuously treated with ERL080 for 18 months (18 month of cohort) were followed.

This statistical review focuses mainly on two large core studies, Study B301 and Study B302. We briefly summarized the extension studies of B301and B302, Study B301Ext and Study B302Ext, and a supportive safety Study 0107.

## 2.2 Data Sources

The sponsor provided electronic datasets for the Phase III studies, Study B301 and Study B302. The datasets utilized for the review are as follows;

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There were differences in the numbers of lost to follow-up for the primary efficacy analysis in Study 302 between our analysis and sponsor's analysis. The sponsor calculated the endpoint using specifically the 6 month locked data set for the 6-month composite endpoint. In the 12-month B302 clinical study report (Date: June 5, 2002), the calculation of the 6-month composite endpoint was based on this 6-month dataset and was not recalculated using a 6-month subset of the 12-month dataset. The difference between the 6-month and 12-month databases is explained by two patients (ERL080 patient 0531/00003 and MMF patient 0506/00002). The sponsor agreed with the numbers that we presented.

The sponsor stated in the 120 day safety update dated 8/28/03 that it was determined that patient 513/023 in study B301 had been misclassified as not having had a graft loss for the 12 month analysis. This patient is considered as having a graft loss by the 12 month analysis in this review.

The Study 0107 data were not submitted because Study 0107 was terminated early. The study did not achieve its objective for "superiority", and the Division informed the sponsor early on that we would not accept the gastrointestinal tool results because the instrument they were using is not validated.

# 3. STATISTICAL EVALUATION

## 3.1 Evaluation of Efficacy

### 3.1.1 Study design and endpoints

**Study B301**

The study design was a multi-center, double-blind, double-dummy, randomized, parallel-group study. The study consisted of a screening period which is within seven days of randomization, a baseline period which is within 2 hours of randomization and a double-blind treatment period of 12 months during which ERL080 or MMF was administered bid. Both ERL080 and MMF were administered in combination with cyclosporine, USP (MODIFIED) and corticosteroids. The patients were evaluated on Days 1, 3, 5, and 8, at Weeks 2, 3, 4, 6, 8, and at Months 4, 6, 9, and 12. Discontinuations from study medication were to be followed for up to 1 year post-randomization.

After completion of the double-blind treatment for 12 months, all patients were to be given the option to continue on ERL080 treatment (open-label). Further safety information arising during open-label ERL080 treatment was collected and summarized in Study B301Ext.

The primary objective of Study B301 was to show therapeutic equivalence of ERL080 compared with MMF as measured by the composite incidence rate of biopsy-proven acute rejection, graft loss, death or loss to follow-up in the first 6 months of treatment in *de novo* renal transplant recipients.

The secondary objectives were to show therapeutic equivalence of ERL080 compared with MMF as measured by the incidence of biopsy-proven acute rejection, graft loss, death, loss to follow-up, clinically-diagnosed rejections, rejections requiring antibody treatment, all treated rejections, and biopsy-proven chronic rejections, all at Month 6. In addition, 12-month data of all variables were obtained.

The key inclusion criteria consisted of male and female patients 18-75 years of age who were undergoing primary cadaveric, living unrelated, human leukocyte antigen mismatched, or living related donor renal transplant recipients.

Study B301 was conducted at 30 centers in nine countries; Austria (3), Canada (2), Germany (6), Hungary (4), Italy (2), Norway (1), Spain (4), UK (2), and USA (6). A total of 423 patients were randomized and treated, 213 in the ERL080 (1.44 g/day) group and 210 in the MMF (2 g/day)

group. Seven centers had more than ten patients in each group, 14 centers had five to ten patients in each group and nine centers had five or less than five patients in each group.

Physical examination, vital signs, safety laboratory evaluation (hematology, urinalysis, biochemistry), adverse events (AEs), including infections were observed. Gastrointestinal AEs and infections were also evaluated separately.

Efficacy was analyzed in the intent-to-treat population (ITT) using all patients who were randomized to the two treatment groups and who had at least one assessment after use of study medication and per protocol populations (PP) including patients who completed the study without any major deviations from the protocol procedures. The safety was analyzed in the safety population using all patients who received at least one dose and had at least one assessment. Twelve patients randomized into the ERL080 group and eight patients randomized into the MMF group were identified as having protocol violations leading to exclusions from the per protocol population. A total of 403 patients were used for per protocol population, 201 in the ERL080 group and 202 in the MMF group.

Primary efficacy was assessed by the 2-sided 95% confidence intervals (CIs) of the difference in event rates (ERL080-MMF), which had to be entirely within the interval (-12%, +12%) to conclude equivalence. The Division typically uses a non-inferiority margin of 10% (upper bound) for the primary endpoint at 6 months and a non-inferiority margin of 5 to 10% (upper bound) for graft loss and death at 12 months. Furthermore, z-test statistics, Cochran-Mantel-Haenszel test, Breslow-Day test, log-rank test and Kaplan-Meier methodology were used. Efficacy was generally evaluated including all events recorded during study as well as after exclusion of all events following permanent discontinuation of study medication. Safety variables were evaluated by using descriptive statistics. Continuous laboratory variables were analyzed by the Wilcoxon rank-sum test.

**Study B302**

This study design was a one-year randomized, double-blind, double-dummy, multi-center, and parallel-group study of the tolerability, safety, and efficacy of ERL080 vs. MMF in maintenance renal transplant patients. The ERL080 and MMF were administered in combination with cyclosporine, USP (MODIFIED) and corticosteroids. The study consisted of a screening visit, an open-label run-in period, and a double-blind treatment period. During the run-in period, all patients received open-label MMF capsules for two weeks prior to randomization. Upon successful completion of the run-in period, patients who fulfilled the inclusion/exclusion criteria were randomized equally into one of the two treatment groups: 2 g/day MMF (1 g twice daily (bid)) or 1.44 g/day ERL080 (720 mg bid) for one year of treatment.

After completion of the double-blind treatment for 12 months, all patients were to be given the option to continue on the ERL080 treatment for 24 months open-label extension period until it is marketed in the country where their particular study site is located. Information from this open-label ERL080 treatment phase was collected and summarized in Study B302Ext.

The primary objective was to evaluate the incidence and severity of GI adverse events at 3 months after administration of study medication and neutropenia within the first 3 months of treatment in maintenance renal transplant patients treated with ERL080 or MMF. Physical examination, vital signs, safety laboratory evaluation (hematology, urinalysis, biochemistry),

adverse events (AEs), including infections were observed for safety variables. Gastrointestinal AEs and infections were also evaluated separately.

Secondary objectives were to evaluate the efficacy and other safety variables of ERL080 compared with MMF in maintenance renal transplant patients. The efficacy variables, which were secondary endpoints in this study, included the incidence rate of the composite variable biopsy-proven acute rejection, graft loss, death or loss to follower-up at 6 and 12 months as well as the incidence rate of biopsy-proven acute rejection, graft loss, death or loss to follow-up separately, the incidence of acute rejection, treated acute rejections, and acute rejections requiring antibody therapy at 6 and 12 months.

The key inclusion criteria consisted of male and female patients 18-75 years of age who were undergoing post-renal transplantation and had undergone primary or secondary cadaveric or living donor kidney transplantation.

Study B302 was conducted at 34 centers in 7 countries; Austria (2), Belgium (2), Canada (5), Germany (3), Italy (1), Spain (2), and USA (19). A total of 322 patients were randomized and treated, 159 in the ERL080 (1.44 g/day) group and 163 in the MMF (2 g/day) group. Three centers had more than ten patients in each group, ten centers had five to ten patients in each group, and 21 centers had five or less than five patients in each group.

Efficacy was analyzed in the intent-to-treat population using all patients who were randomized and received at least one dose of study medication, and safety was analyzed in the safety population using all patients who received at least one dose and had at least one assessment. The incidence rates of efficacy events were assessed by the 2-sided 95% confidence intervals (CIs) of the difference in event rates (ERL080-MMF). Safety variables were evaluated by means of frequency distributions and descriptive statistics. Continuous laboratory variables were analyzed by the Wilcoxon rank-sum test, and categorical variables were tested using the Chi-square or Fisher's exact tests.

**Study 0107**

This study was a randomized, 5-week double blind, double dummy and 2-year open-label, multi-center, parallel-group study of the safety and efficacy of ERL080 compared with MMF as part of a triple immunosuppressive therapy regimen with Neoral® and steroids in maintenance renal transplant patients with upper GI intolerance to MMF. A total of 159 patients entered the run-in period, and 149 were randomized: 74 in the ERL080 group and 75 in the MMF group. The efficacy and safety results were summarized in the secondary efficacy results and overall safety assessment section, respectively.

Study 0107 was terminated early because: it did not achieve its objective for "superiority", and because the Division informed the sponsor early on that we would not accept the gastrointestinal tool results (the instrument they were using is not validated).

### 3.1.2 Patient Demographic and Baseline Characteristics

All patients who were randomized and received at least one dose of study medication (ITT) and patients who did not have any major protocol violations (PP) were included in the analyses of Study B301. Only one patient randomized to MMF who did not receive any study treatment was excluded from the ITT population. The exclusion rates of subjects from the per-protocol (PP)

analysis were low and fairly balanced; 5.6 % and 4.3 % for ERL080 and MMF, respectively in the Study B301. Only ITT results are presented for Study B301 here. Because the primary objective of the Study B302 is safety, this review reports only the ITT results for this study as well.

**Study B301**

Table 1 shows demographic and baseline characteristics for 423 randomized patients. The categorical variables were evaluated using CMH tests stratified by center. The continuous variables were evaluated using ANOVA with treatment and center as factors.

Table 1. Patient Baseline Demographic and Background Characteristics (B301)

| **Variable** | | **ERL080 N=213** | **MMF N=210** | **P-value** |
|---|---|---|---|---|
| Age | Mean (± SD) | 47.1 (± 11.8) | 47.2 (± 11.6) | 0.8827 |
| Age group | < 20 years | 0 | 1 (0.5) | 0.8362 |
| | 20-35 years | 38 (17.8) | 34 (16.2) | |
| | 36-50 years | 87 (40.8) | 89 (42.4) | |
| | 51-65 years | 76 (35.7) | 78 (37.1) | |
| | > 65 years | 12 (5.6) | 8 (3.8) | |
| Gender, n (%) | Male | 137 (64.3) | 142 (67.6) | 0.4388 |
| | Female | 76 (35.7) | 68 (32.4) | |
| Race, n (%) | Caucasian | 187 (87.8) | 187 (89.0) | 0.5790 |
| | Black | 17 (8.0) | 13 (6.2) | |
| | Oriental | 3 (1.4) | 2 (1.0) | |
| | Other | 6 (2.8) | 8 (3.8) | |
| Weight (kg) | Mean (± SD) | 75.8 (± 15.1) | 76.5 (± 16.2) | 0.5931 |
| Height (cm) | Mean (± SD) | 171 (± 9.9) | 171 (± 10.4) | 0.7738 |
| Donor source, n (%) | Cadaveric heart beating | 180 (84.5) | 173 (82.4) | 0.3298 |
| | Cadaveric non-heart beating | 1 (0.5) | 0 | |
| | Living related | 23 (10.8) | 26 (12.4) | |
| | Living unrelated | 9 (4.2) | 11 (5.2) | |
| Country, n (%) | USA | 59 (27.7) | 57 (27.0) | 0.8742 |
| | Europe | 154 (72.3) | 154 (73.0) | |
| Panel reactive antibodies | 0% | 173 (81.2) | 183 (87.1) | 0.0277 |
| | > 0% | 40 (18.7) | 25 (11.9) | |
| Positive viral serology | CMV: donor +/recipient + | 90 (42.3) | 115 (54.8) | 0.1340* |
| | CMV: donor +/recipient – | 36 (16.9) | 26 (12.4) | 0.1887*[1] |
| | CMV: donor -/recipient + | 48 (22.5) | 29 (13.8) | |
| | CMV: donor -/recipient – | 26 (12.2) | 32 (15.2) | |
| | EBV: donor + | 24 (11.3) | 27 (12.9) | 0.6159# |
| Cold ischemia time (hrs) | Mean (±SD) | 17.0 (9.2) | 15.6( 8.8) | 0.0784## |
| | More than ≥ 24 hours (N, %) | 44 (20.7) | 28 ( 13.3) | 0.5067 |

* : CMH stratified by center p-value of difference between treatment groups in terms of the distribution of CMV matches of donors and recipients (4 groups).

*[1]: Chi-square p-value of difference between the two groups in CMV negative patients having a graft of donor CMV positive vs. the other group (Don_CMV+/Rec_CMV+, Don_CMV-/Rec_CMV+, and Don_CMV-/Rec_CMV-).

# : 2-sided Fishers Exact test p-value of difference between the two groups in EBV positive donor vs. other group

##: ANOVA p-value adjusted for center

Demographic characteristics were similar between the two treatment groups. Male, Caucasian, and age of less than 50 years old were the majority among patients for both groups. Over 80% of donors were from cadaveric donors in the two treatment groups. Over 72% of patients were from Europe for both groups. There were no statistically significant differences in age, gender, race, weight, height, donor source, and country origin between the treatment groups after adjusting for center.

Nineteen percent patients in the ERL080 group had panel reactive antibodies (PRA) > 0% as compared to 13% of the MMF group and there was statistically significant difference in PRA 0% vs. PRA > 0 % between the two groups after adjusting for center (p=0.0277). There were no statistical differences between the two groups in terms of the distribution of CMV matches of donors and recipients after adjusting the center (p=0.1340). The incidence of CMV-negative patients having received a graft from CMV-positive donors vs. the other group was not statistically different between the two groups (p=0.1887). This population is considered clinically as a high risk population for developing CMV infection. The positive donor EBV viral serology values were 11% and 13%, for ERL080 and MMF, respectively with no statistically significant difference between the two groups (p=0.6169). More patients in the ERL080 group had renal allografts with a prolonged cold ischemia time of ≥ 24 hours than that of the MMF patients with no statistical difference after adjusting for center (p=0.5067). Subgroup efficacy analyses were conducted for these baseline characteristics in the other special subgroup population section.

Tables 2 and 3 show the patient disposition at 6 and 12 month analyses. The cutoff days for 6 and 12 months are 226 and 450 days from the first dose date to discontinuation date.

Table 2. Premature Treatment or Study Discontinuation with ITT Population at 6 months (B301)

| | **ERL080** (N=213) n (%) | **MMF** (N=210) n (%) |
|---|---|---|
| **Prematurely discontinued Treatment** | **58 (27.2)** | **46 (21.9)** |
| Adverse events | 35 (16.4) | 29 (13.8) |
| Abnormal lab values | 1 (0.5) | 0 (0.0) |
| Unsatisfactory therapeutic effect | 10 (4.7) | 5 (2.4) |
| Protocol violation | 5 (2.3) | 4 (1.9) |
| Withdrawal of consent | 2 (0.9) | 0 (0.0) |
| Lost to follow-up | 0 (0.0) | 0 (0.0) |
| Death | 0 (0.0) | 2 (0.9) |
| Graft loss | 5 (2.3) | 6 (2.9) |
| **Prematurely discontinued Study** | **9 (4.2)** | **7 (3.3)** |
| Lost to follow-up | 5 (2.3) | 3 (1.4) |
| Withdrawal of consent | 3 (1.4) | 2 (1.0) |
| Death | 1 (0.5) | 2 (1.0) |

Table 3. Premature Treatment or Study Discontinuation with ITT Population at 12 months (B301)

| | **ERL080** (N=213) n, (%) | **MMF** (N=210) n, (%) |
|---|---|---|
| **Prematurely discontinued Treatment** | **62 (29.1)** | **52 (24.8)** |
| Adverse events | 36 (16.9) | 29 (13.8) |
| Abnormal lab values | 1 (0.5) | 0 (0.0) |

| | | |
|---|---|---|
| Unsatisfactory therapeutic effect | 11 (5.2) | 8 (3.8) |
| Protocol violation | 5 (2.3) | 5 (2.4) |
| Withdrawal of consent | 2 (1.0) | 0 (0.0) |
| Lost to follow-up | 1 (0.5) | 0 (0.0) |
| Death | 1 (0.0) | 4 (1.9) |
| Graft loss | 5 (2.3) | 6 (2.9) |
| **Prematurely discontinued Study** | **13 (6.2)** | **13 (6.3)** |
| Lost to follow-up | 7 (3.3) | 5 (2.4) |
| Withdrawal of consent | 4 (1.9) | 3 (1.4) |
| Death | 2 (1.0) | 5 (2.4) |

Approximately, 27% of ERL080 and 22% of the MMF patients discontinued treatment during the study period of 6 months and 29% of ERL080 and 25% of the MMF patients discontinued treatment during the study period of 12 months. More patients in the ERL080 group discontinued treatment during the 6 and 12 months study periods compared to the MMF group, but no statistically significant difference was observed. The most common reason for the treatment discontinuation during the 6 and 12 months study periods was adverse events for both groups. The ERL080 group had higher treatment discontinuation rate due to adverse events compared to that of MMF, but with no statistically significant difference.

The incidences of premature discontinuation of the study were 4.2% and 3.3% at 6 months and 6.2% and 6.3% at 12 months, for ERL080 and MMF, respectively. The incidence of premature discontinuation of the study was not statistically significantly different between the ERL080 and the MMF group for the 6 months and 12 months study periods.

**Study B302**

Table 4 shows demographic characteristics for all randomized patients. The categorical variables were evaluated using CMH tests stratified by center. The continuous variables were evaluated using ANOVA with treatment and center as factors.

Table 4. Patient Demographic Characteristics (B302)

| **Variable** | | **ERL080 (N=159)** | **MMF (N=163)** | **P-value** |
|---|---|---|---|---|
| Age | Mean (± SD) | 48.6 (± 11.4) | 46.8 (± 12.1) | 0.2517 |
| Age group | < 20 years | 0 | 0 | 0.1731 |
| | 20-35 years | 20 (12.6) | 31 (19.0) | |
| | 36-50 years | 68 (42.8) | 68 (41.7) | |
| | 51-65 years | 62 (39.0) | 57 (35.0) | |
| | > 65 years | 9 (5.7) | 7 (4.3) | |
| Gender, n (%) | Male | 97 (61.0) | 115 (70.6) | 0.1392 |
| | Female | 62 (39.0) | 48 (29.4) | |
| Race, n (%) | Caucasian | 118 (74.2) | 119 (73.0) | 0.6694 |
| | Black | 28 (17.6) | 34 (20.9) | |
| | Oriental | 5 (3.1) | 4 (2.5) | |
| | Other | 8 (5.0) | 6 (3.7) | |
| Weight (kg) | Mean (± SD) | 83.0 (± 18.8) | 82.7 (± 19.0) | 0.6490 |
| Height (cm) | Mean (± SD) | 169.3 (± 10.2) | 170.9 (± 10.6) | 0.1454 |
| Country, n (%) | USA | 90 (56.6) | 57 (56.4) | 0.9766 |
| | Europe | 69 (43.4) | 106 (43.6) | |

The demographic characteristics were similar between the two treatment groups. Male, Caucasian, and age of less than 50 years were the majority among patients. Over 56% were from the USA for both groups. There were no statistically significant differences in age, gender, race, weight, height, and country between the treatment groups after adjusting for center.

Tables 5 and 6 show the incidence of patients who permanently discontinued study medication at 6 months and 12 months. The cutoffs for 6 months and 12 months were day 226 and day 450, respectively.

Table 5. Premature Treatment or Study Discontinuation with ITT population at 6 Months (B302)

| | **ERL080** (N=159) n (%) | **MMF** (N=163) n (%) |
|---|---|---|
| **Prematurely discontinued Treatment** | **11 ( 6.9)** | **13 ( 8.0)** |
| Adverse events | 6 (3.8) | 3 (1.8) |
| Protocol violation | 1 (0.6) | 1 (0.6) |
| Withdrawal of consent | 3 (1.9) | 7 (4.3) |
| Lost to follow-up | 0 | 1 (0.6) |
| Administrative problems | 1 (0.6) | 0 |
| Death | 0 | 1 (0.6) |
| **Prematurely discontinued Study** | **5 (3.1)** | **9 (5.5)** |
| Lost to follow-up | 4 (2.5) | 7 (4.3) |
| Withdrawal of consent | 1 (0.6) | 1 (0.6) |
| Death | 0 | 1 (0.6) |

Table 6: Premature Treatment or Study Discontinuation with ITT Population at 12 Months (B302)

| | **ERL080** (N=159) n (%) | **MMF** (N=163) n (%) |
|---|---|---|
| **Prematurely discontinued Treatment** | **16 (10.1)** | **19 (11.7)** |
| Adverse events | 9 (5.3) | 4 (2.5) |
| Abnormal lab values | 1 (0.6) | 1 (0.6) |
| Protocol violation | 1 (0.6) | 2 (1.2) |
| Withdrawal of consent | 3 (1.9) | 9 (5.5) |
| Lost to follow-up | 1 (0.6) | 1 (0.6) |
| Administrative reason | 1 (0.6) | 0 |
| Death | 0 | 2 (1.2) |
| **Prematurely discontinued Study** | **10 (6.3)** | **14 (8.6)** |
| Lost to follow-up | 5 (3.1) | 8 (4.9) |
| Withdrawal of consent | 3 (1.9) | 3 (1.8) |
| Death | 2 (1.3) | 3 (1.8) |

Approximately, 7% of ERL080 and 8% of MMF patients discontinued treatment during the study period of 6 months and 10% of ERL080 and 12% of MMF patients discontinued treatment during the study period of 12 months with no statistically significant differences between the two groups. The most common reason for the treatment discontinuation was adverse events for the ERL080 group, but it was withdrawal of consent for the MMF group during the 6 and 12 months study periods. The incidences of premature discontinuation of the study were not statistically significantly different between the two groups for the 6 and 12 months study periods.

**Study B301Ext and Study B302Ext**

During the extension studies, discontinuation of treatment implies discontinuation from the studies. The reasons for the premature discontinuation from the studies are summarized in Table 7.

Table 7. Premature Treatment or Study Discontinuation with ITT Population at Month 12 and 18 (B301Ext and B302Ext)

| | Study B301 Ext | | | | Study B302Ext | | | |
|---|---|---|---|---|---|---|---|---|
| | Month 12 visit* | | Month 18 visit* | | Month 12 visit | | Month 18 visit | |
| | Ex-MMF (N=125) n, (%) | ERL080 (N=122) n, (%) | Ex-MMF (N=125) n, (%) | ERL080 (N=122) n, (%) | Ex-MMF (N=130) n, (%) | ERL080 (N=130) n, (%) | Ex-MMF (N=130) n, (%) | ERL080 (N=130) n, (%) |
| **Discontinued treatment Prematurely:** | **17(13.6)** | **18(14.8)** | **20(16.0)** | **21(17.2)** | **12 (9.2)** | **9 (6.9)** | **14(10.8)** | **13(13.0)** |
| Adverse events | 11 (8.8) | 10 (8.2) | 12 (9.6) | 12 (9.8) | 6 (4.6) | 2 (1.5) | 6 (4.6) | 3 (2.3) |
| Abnormal lab values | 0 | 0 | 0 | 0 | 1 (0.8) | 0 | 1 (0.8) | 0 |
| Unsatisfactory therapeutic Effect | 0 | 0 | 0 | 0 | 0 | 1 (0.8) | 0 | 1 (0.8) |
| Abnormal test procedure results | 0 | 1 (0.8) | 0 | 1 (0.8) | 1 (0.8) | 1 (0.8) | 1 (0.8) | 1 (0.8) |
| Protocol violation | 1 (0.8) | 0 | 2 (1.6) | 0 | 0 | 3 (2.3) | 0 | 3 (2.3) |
| Patients withdrew consent | 3 (2.4) | 2 (1.6) | 3 (2.4) | 2 (1.6) | 3 (2.3) | 1 (0.8) | 4 (3.1) | 2 (1.5) |
| Lost to follow-up | 1 (0.8) | 1 (0.8) | 1 (0.8) | 2 (1.6) | 0 | 0 | 0 | 0 |
| Administrative problems | 0 | 1 (0.8) | 0 | 1 (0.8) | 0 | 0 | 1 (0.8) | 0 |
| Death | 1 (0.8) | 2 (1.6) | 2 (1.6) | 2 (1.6) | 0 | 1 (0.8) | 0 | 3 (2.3) |
| Graft Loss | 0 | 1 (0.8) | 0 | 1 (0.8) | 1 (0.8) | 0 | 1 (0.8) | 0 |

*: The cutoffs for month 12 and month 18 are 404 and 584 days, respectively.

The incidences of discontinuations of study medication in patients newly exposed to ERL080 after switching from MMF were not statistically significantly different compared to the patients who remained on ERL080 continuously for both studies Study B301Ext and Study B302Ext at Month 12 and 18.

### 3.1.3 Primary Efficacy Results

**Study B301**

The results of the primary endpoints, efficacy failure (biopsy-proven acute rejection, graft loss, death, or lost follow-up) for treatment groups at 6 and 12 months were summarized in Table 8. The table includes the following:

1. The overall rates of efficacy failure using the composite endpoints for each treatment group.

2. The p-value of the Breslow-Day statistic used to test homogeneity of the treatment effect across strata (centers).

3. The overall rate difference of efficacy failure adjusted for center and the 95% confidence interval.

Table 8. Analysis of Primary Efficacy Endpoints at 6 and 12 Months (B301)

| | **ERL 080 (N=213)** | **MMF (N=210)** |
|---|---|---|
| **Efficacy Failure Rate Within 6 months, n (%)** | **55 (25.8)** | **55 (26.2)** |
| Biopsy-proven acute rejection | 46 (21.6) | 48 (22.9) |
| Graft loss | 7 (3.3) | 9 (4.3) |
| Death | 1 (0.5) | 2 (1.0) |
| Loss to follow-up | 3 (1.4) | 0 (0.0) |
| **Breslow-Day p-value** | **0.0904** | |
| **Center adjusted rate difference (ERL080-MMF), %** | **-0.42 (-8.6, 7.8)** | |
| **Efficacy Failure Rate Within 12 months, n (%)** | **61 (28.6)** | **59 (28.1)** |
| Biopsy-proven acute rejection | 48 (22.5) | 51 (24.3) |
| Graft loss | 9 (4.2) | 9 (4.3) |
| Death | 2 (0.9) | 5 (2.4) |
| Loss to follow-up | 5 (2.3) | 0 (0.0) |
| **Breslow-Day p-value** | **0.1035** | |
| **Center adjusted rate difference (ERL080-MMF), %** | **0.67 (-7.7, 9.0)** | |

The Breslow-Day p-value indicates that there were borderline statistically significant overall efficacy failure differences across centers at 6 months and 12 months between the two groups using a significance level of 0.1. However, in further assessing this interaction it was found that small centers had the more extreme results, while results from the larger centers were very consistent with the overall results. The overall rate difference between ERL080 and MMF of efficacy failure was -0.4 % at 6 months and 0.7 % at 12 months and the 95 % confidence intervals were (-8.6 %, 7.8 %) at 6 month and (-7.7 %, 9.0 %) at 12 months after adjusting for center. These results indicated that the rates of efficacy failure for ERL080 at 6 and 12 months were non-inferior to that of MMF using a non-inferiority margin of 10%, because the upper limits of the 95% confidence intervals for ERL080 minus MMF were less than 10 %.

The sponsor did not adjust for center in the primary analysis, however, the results were very consistent with the results given in Table 8 above. The observed rate and sponsor's 95% confidence interval for the primary endpoint at 6 months (ERL080-MMF) were 0.4 % and (-8.7%, 8.0%) and at 12 months were 0.5% and (-8.1%, 9.2%).

**Study B302**

The results of the efficacy endpoints, efficacy failures (biopsy-proven acute rejection, graft loss, death, or lost follow-up) at 6 and 12 months, were summarized in Table 9. The table includes the following:

1. The overall rates of efficacy failure using the composite endpoints for each treatment group.

2. The p-value of the Breslow-Day statistic used to test homogeneity of the treatment effect across strata (centers).

3. The overall rate difference of efficacy failure adjusted for center and the 95% confidence interval.

Table 9. Analysis of Primary Efficacy Endpoints at 6 and 12 Months (B302)

| | **ERL080 (N=159)** | **MMF (N=163)** |
|---|---|---|
| **Efficacy Failure Rate within 6 Months, n,%** | **7 (4.4)** | **11 (6.7)** |
| Biopsy-proven acute rejection | 2 (1.3) | 2 (1.2) |
| Graft loss | 0 (0.0) | 1 (0.6) |
| Death | 0 (0.0) | 1 (0.6) |
| Loss to follow-up | 5 (3.1) | 7 (4.3) |
| **Breslow-Day p-value** | **0.3157** | |
| **Center adjusted rate difference (ERL-MMF), %** | **-2.35 (-7.4, 2.7)** | |
| **Efficacy Failure Rate within 12 Months, n ,%** | **12 (7.5)** | **20 (12.3)** |
| Biopsy-proven acute rejection | 2 (1.3) | 5 (3.1) |
| Graft loss | 0 (0.0) | 1 (0.6) |
| Death | 2 (1.3) | 4 (2.5) |
| Loss to follow-up | 8 (5.0) | 10 (6.1) |
| **Breslow-Day p-value** | **0.1263** | |
| **Center adjusted rate difference (ERL-MMF), %** | **-4.22 (-10.7, 2.2)** | |

The Breslow-Day p-value indicated that there were no overall efficacy failure differences across centers at 6 and 12 months between the two groups using a significant level of 0.1. The overall rate difference between ERL080 and MMF of efficacy failure was -2.4 % at 6 months and -4.2 % at 12 months and the 95 % confidence intervals were (-7.4 %, 2.6 %) at 6 month and (-10.7 %, 2.2 %) at 12 months after adjusting for center. These results indicated that the rates of efficacy failure for ERL080 at 6 and 12 months were non-inferior to that of MMF using a non-inferiority margin of 10%, because the upper limits of the 95% confidence intervals for ERL080 minus MMF are less than 10%.

The sponsor did not adjust for center in the primary analysis, however, the results were very consistent with the results given in Table 9 above. The observed rate and sponsor's 95% confidence interval for the endpoint at 6 months (ERL080-MMF) were 2.4% and (-7.4%, 2.7%) and at 12 months were 4.2% and (-11.3%, 1.8%).

The efficacy failure rates at 6 and 12 months were much lower than those of study B301 because study 302 enrolled maintenance renal transplant patients as opposed to the *de novo* renal transplant patients in study 301. The majority of rejections are experienced within the first six months of transplant.

### 3.1.4 Sponsor's Secondary Efficacy Results

The sponsor's analyses of the selected secondary efficacy results for Study B301 and Study B302 separately were summarized in this section. In addition, the efficacy results for extension studies B301Ext and B302Ext, and a supportive Study 0107 and Study 0107Ext were summarized.

**Study B301**

The secondary efficacy was the incidence rates of rejection-related secondary efficacy variables other than biopsy-proven acute rejection. The secondary efficacy endpoint at 6 and 12 months were summarized in Table 10.

Table 10. Analysis of Secondary Efficacy Endpoints at 6 and 12 Months (B301)

| Secondary Efficacy Endpoint | ERL080 (N=213) n (%) | MMF (N=210) n (%) | Difference (ERL-MMF) (%) | 95% CI (ERL-MMF) (%) |
|---|---|---|---|---|
| **End Point at 6 Months** | | | | |
| Any acute rejection | 52(24.4) | 55 (26.2) | -1.8 | (-10.1, 6.5) |
| Treated acute rejection | 51(23.9) | 52 (24.8) | -0.8 | ( -9.0, 7.4) |
| Antibody-treated acute rejection | 11( 5.2) | 10 ( 4.8) | 0.4 | ( -3.7, 4.5) |
| Biopsy-proven chronic rejection | 8( 3.8) | 12 ( 5.7) | -2.0 | ( -6.0, 2.1) |
| **End Point at 12 Months** | | | | |
| Any acute rejection | 54(25.4) | 58 (27.6) | -2.3 | (-10.7, 6.1) |
| Treated acute rejection | 52(24.4) | 54 (25.7) | -1.3 | ( -9.6, 7.0) |
| Antibody-treated acute rejection | 11( 5.2) | 10 ( 4.8) | 0.4 | ( -3.7, 4.5) |
| Biopsy-proven chronic rejection | 12( 5.6) | 16 ( 7.6) | -2.0 | ( -6.7, 2.8) |

The ERL080 group showed slightly smaller incidences in any acute rejections, treated acute rejections, biopsy-proven chronic rejections as compared to those of the MMF group. However, no statistically significant differences were observed for both at 6 and 12 months.

**Study B302**

The secondary efficacy was the incidence rates of rejection-related secondary efficacy variables other than biopsy-proven acute rejection. The secondary efficacy endpoint at 6 and 12 months were summarized in Table 11.

Table 11. Analysis of Secondary Efficacy Endpoints at 6 and 12 Months (B302)

| Secondary Efficacy Endpoint | ERL080 (N=159) n (%) | MMF (N=163) n (%) | Rate Difference (ERL080-MMF) (%) |
|---|---|---|---|
| **End Point at 6 Months** | | | |
| Any acute rejection | 2(1.3) | 2(1.2) | 0.1 |
| Treated acute rejection | 2(1.3) | 2(1.2) | 0.1 |
| Antibody-treated acute rejection | 0 | 0 | 0 |
| Biopsy-proven chronic rejection | 4(2.5) | 4(2.5) | 0 (-3.4, 3.5)* |
| **End Point at 12 Months** | | | |
| Any acute rejection | 2(1.3) | 6(3.7) | -2.4 |
| Treated acute rejection | 2(1.3) | 3(1.8) | -0.5 |
| Antibody-treated acute rejection | 0 | 0 | 1.3 |
| Biopsy-proven chronic rejection | 6(3.8) | 8(4.9) | -1.1 (-6.4, 2.9)* |

*CI was calculated for Biopsy proven chronic rejection.

The two groups showed small incidences in any acute rejections, treated acute rejections, and biopsy-proven chronic rejections and no incidence in the treated acute rejection for both at 6 and 12 months.

**Study B301Ext and Study B302Ext**

The incidences of efficacy related events for extension studies of Study B301Ext and Study B302Ext were summarized for the initial 12 months, an extension of 12 months, and the total 24 months as the 12-month cohort in Tables 12 and 13. They are also summarized for the initial 12 months, an extension of 18 months and the total 30 months as the 18-months cohort in these same tables. In the 12 months and 18 months cohorts, patients were treated with ERL080 for 12 months and 18 months, respectively. The subset of patients who entered the extension phase was used. The patients of the Ex-MMF group were treated with MMF from 0 to 12 months, but switched from MMF to ERL080 after 12 months.

Table 12. Analysis of Efficacy Endpoints for Extension Phase-Study B301Ext

| | **Month 12 cohort** | | | | | |
|---|---|---|---|---|---|---|
| | **0 to12 months** | | **Extension 12 months** | | **Total 24 months** | |
| **Group** | **Ex-MMF* (N=125)** | **ERL080 (N=122)** | **Ex-MMF (N=125)** | **ERL080 (N=122)** | **Ex-MMF (N=125)** | **ERL080 (N=122)** |
| **Treatment** | **MMF** | **ERL080** | **ERL080** | **ERL080** | **MMF/ ERL080** | **ERL080** |
| **Composite Variables** | | | | | | |
| BPAR, GL or death | 21(16.8) | 19(15.6) | 5(4.0) | 4(3.3) | 26(20.8) | 22(18.0) |
| BPAR, CR, GL or death | 23(18.4) | 19(15.6) | 6(4.8) | 7(5.7) | 29(23.2) | 24(19.7) |
| **Secondary variables** | | | | | | |
| BPAR | 21(16.8) | 19(15.6) | 4(3.2) | 1(0.8) | 25(20.0) | 20(16.4) |
| Acute rejection | 23(18.4) | 21(17.2) | 5(4.0) | 1(0.8) | 28(22.4) | 21(17.2) |
| Biopsy & clinically confirmed CR | 2(1.6) | 1(0.8) | 2(1.6) | 5(4.1) | 4(3.2) | 6(4.9) |
| GL | 0 | 0 | 0 | 1(0.8) | 0 | 1(0.8) |
| Death | 0 | 0 | 1(0.8) | 2(1.6) | 1(0.8) | 2(1.6) |
| | **Month 18 cohort** | | | | | |
| | **0 - 12 months** | | **Extension 18 months** | | **Total 30 months** | |
| **Group** | **Ex-MMF* (N=103)** | **ERL080 (N=99)** | **Ex-MMF (N=103)** | **ERL080 (N=99)** | **Ex-MMF (N=103)** | **ERL080 (N=99)** |
| **Treatment** | **MMF** | **ERL080** | **ERL080** | **ERL080** | **MMF/ ERL080** | **ERL080** |
| **Composite Variables** | | | | | | |
| BPAR, GL or death | 18(17.5) | 17(17.2) | 7(6.8) | 5(5.1) | 24(23.3) | 21(21.2) |
| BPAR, CR, GL or death | 19(18.4) | 17(17.2) | 9(8.7) | 8(8.1) | 27(26.2) | 23(23.2) |
| **Secondary variables** | | | | | | |
| BPAR | 18(17.5) | 17(17.2) | 5(4.0) | 2(2.0) | 23(22.3) | 19(19.2) |
| Acute rejection | 20(19.4) | 17(17.2) | 6(5.8) | 2(2.0) | 26(25.2) | 19(19.2) |
| Biopsy & clinically confirmed CR | 1(1.0) | 0 | 4(3.9) | 6(6.1) | 5(4.9) | 6(6.1) |
| GL | 0 | 0 | 0 | 2(2.0) | 0 | 2(2.0) |
| Death | 0 | 0 | 2(1.9) | 2(1.6) | 2(1.9) | 2(2.0) |

*: This period represents MMF exposure in the core phase of the study prior to entering the extension phase on ERL080 treatment.

Note:

1. All events up to the defined cutoffs at day 404 (12 months) and Day 584 (18 months) are included.
2. Events included in the column '0-12 months' represent only those events that occurred during the core phase of the

study in patients who also entered the extension phase of the study.

The incidences of efficacy-related events were similar and there was no difference between the patients who continued to receive ERL080 for a total of 24 months and the patients who switched from MMF to ERL080 after receiving MMF for 12 months and then received ERL080 for 12 months in the Month 12 cohort. There was also no difference seen in 18 months cohort.

Table 13. The analysis of Efficacy Endpoints for Extension Phase-Study B302Ext

| | **Month 12 cohort** | | | | | |
|---|---|---|---|---|---|---|
| | **0 to12 months** | | **Extension 12 months** | | **Total 24 months** | |
| **Group** | **Ex-MMF* (N=112)** | **ERL080 (N=110)** | **Ex-MMF (N=112)** | **ERL080 (N=110)** | **Ex-MMF* (N=112)** | **ERL080 (N=110)** |
| **Treatment** | **MMF** | **ERL080** | **ERL080** | **ERL080** | **MMF/ERL** | **ERL080** |
| **Composite Variables** | | | | | | |
| BPAR, GL or death | 2(1.8) | 1(0.9) | 2(1.8) | 2(1.8) | 4(3.6) | 3(2.7) |
| BPAR, CR, GL or death | 4(3.6) | 2(1.8) | 2(1.8) | 6(5.5) | 6(5.4) | 7(6.4) |
| **Secondary Variables** | | | | | | |
| BPAR | 2(1.8) | 1 (0.9) | 2(1.8) | 1(0.9) | 4(3.6) | 2 (1.8) |
| Acute rejection | 2(1.8) | 1 (0.9) | 2(1.8) | 1(0.9) | 4(3.6) | 2 (1.8) |
| Biopsy & clinically confirmed CR | 3(2.7) | 1(0.9) | 2(1.8) | 5(4.5) | 5(4.5) | 6(5.5) |
| GL | 0 | 0 | 1(0.9) | 0 | 1(0.9) | 0 |
| Death | 0 | 0 | 0 | 1(0.9) | 0 | 1(0.9) |
| | **Month 18 cohort** | | | | | |
| | **0 - 12 months** | | **Extension 18 months** | | **Total 30 months** | |
| **Group** | **Ex-MMF* (N=75)** | **ERL080 (N=77)** | **Ex-MMF (N=77)** | **ERL080 (N=75)** | **Ex-MMF* (N=77)** | **ERL080 (N=75)** |
| **Treatment** | **MMF** | **ERL080** | **ERL080** | **ERL080** | **MMF/ERL** | **ERL080** |
| **Composite Variables** | | | | | | |
| BPAR, GL or death | 1(1.3) | 1 (1.3) | 2(2.7) | 5(6.5) | 3(4.0) | 6(7.8) |
| BPAR, CR, GL or death | 2(2.7) | 2 (2.6) | 2(2.7) | 8(10.4) | 4(5.3) | 9(11.7) |
| **Secondary variables** | | | | | | |
| BPAR | 1(1.3) | 1 (1.3) | 2(2.7) | 2(2.6) | 3(4.0) | 3(3.9) |
| Acute rejection | 1(1.3) | 1 (1.3) | 2(2.7) | 2(2.6) | 3(4.0) | 3(3.9) |
| Biopsy & clinically confirmed CR | 1(1.3) | 1(1.3) | 2(2.7) | 4(5.2) | 3(4.0) | 5(6.5) |
| GL | 0 | 0 | 1(1.3) | 1(1.3) | 1(1.3) | 1(1.3) |
| Death | 0 | 0 | 0 | 3(3.9) | 0 | 3(3.9) |

*: This period represents MMF exposure in the core phase of the study prior to entering the extension phase on ERL080 treatment.

Note:

1. All events up to the defined cutoffs at day 404 (12 months) and Day 584 (18 months) are included.
2. Events included in the column '0-12 months' represent only those events that occurred during the core phase of the study in patients who also entered the extension phase of the study.

The incidences of efficacy-related events were less than ten and there was no difference between the patients who continued to receive ERL080 for 12 or 18 months and the patients who switched from MMF to ERL080 after receiving MMF for 12 months and then received ERL080 for 12 or 18 months for Study B302Ext.

**Study 0107 and Study 0107Ext**

The incidences of efficacy related events were summarized in core and extension phases of the study 0107 in Table 14. In the 7 months and 18 months cohorts, patients were treated with ERL080 for 7 months and 18 months, respectively. The subset of patients who entered the extension phase was used.

Table 14. Analysis of Efficacy Endpoints-Study 0107 and Study 0107Ext

| | **Study 0107** | | **Study 0107Ext** | | | |
|---|---|---|---|---|---|---|
| | **Core** | | **Months 7 cohort** | | **Month 18 cohort** | |
| **Group** | **MMF (N=74)** | **ERL080 (N=75)** | **Ex-MMF (N=63)** | **ERL080 (N=65)** | **Ex-MMF (N=32)** | **ERL080 (N=33)** |
| **Treatment Duration of ERL080** | **MMF** | **ERL080 0 to 5 wk.** | **ERL080 0 to 7mo.** | **ERL080 5wk to 8+ mo** | **MMF/ ERL080 0 to 18mo** | **ERL080 5wk to 19+ mo** |
| **Composite Variables** | | | | | | |
| BPAR, GL, death or lost to follow-up | 2(2.7) | 2 (2.7) | N/A | N/A | N/A | N/A |
| BPAR, GL or death | N/A | N/A | 2(3.2) | 1(1.5) | 2(6.3) | 1(3.0) |
| BPAR, CR, GL or death | N/A | N/A | 3(4.8) | 1(1.5) | 3(9.4) | 1(3.0) |
| **Secondary variables** | | | | | | |
| BPAR | 1 (1.3) | 2(2.7) | 2(3.2) | 1(1.5) | 2(6.3) | 1(3.0) |
| Acute rejection | 2(2.7) | 2(2.7) | 2(3.2) | 2(3.1) | 2(6.3) | 2(6.1) |
| Treated acute rejection | 2(2.7) | 1(1.4) | N/A | N/A | N/A | N/A |
| Biopsy & clinically confirmed CR | N/A | N/A | 2(3.2) | 1(1.5) | 2(6.3) | 1(3.0) |
| Lost to follow-up | 1(1.3) | 0 | N/A | N/A | N/A | N/A |

The incidences of other efficacy-related events were less than five in all the treatment groups through 18 or 19 + months of the ERL080 treatment in Study 0107 and Study 0107Ext. The sponsor did not submit the data because Study 0107 was terminated early. The study objective of superiority of ERL080 compared to MMF was not achieved and the Division decided not to accept the results.

### 3.1.5 Reviewer's Additional Analyses

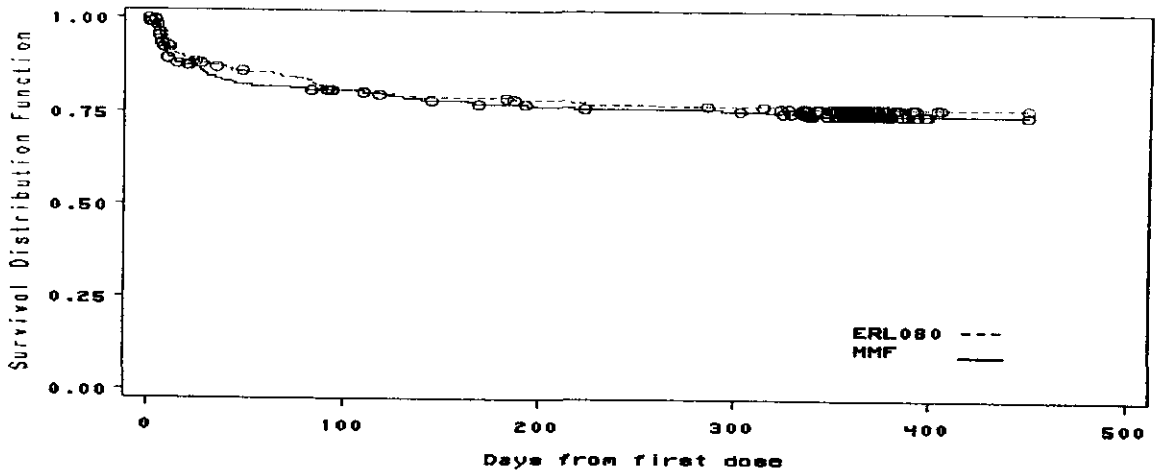
The incidence of biopsy-proven acute rejection was the most common reason for efficacy failure among the composite endpoints in Study B301. The time to failure of the first biopsy-proven acute rejection during 12 months was analyzed using a Kaplan-Meier Survival analysis. The survival curves up to 12 months are shown in Figure 1 and the Kaplan-Meier mean time estimates are presented in Table 15.

Table 15. Kaplan-Meier Mean time Estimates of time to failure of BPAR at 12 Months (B301)

| | N/Total, (%) | Mean days to 1st BPAR (SD) | Log rank p-value |
|---|---|---|---|
| ERL080 | 48/213(22.5) | 267.74 (9.082) | 0.6303 |
| MMF | 51/210(24.3) | 261.93 (8.291) | |

Data censored on day 450.

Figure 1. Survival Curves of Time to the First Biopsy-Proven Acute Rejection at 12 Months (B301)




There was no statistically significant difference in the mean time to failure to the first biopsy-proven acute rejection between ERL080 and MMF for Study B301.

The time to failure of graft loss, death, or lost to follow-up during 12 months for Study B301 was analyzed using a Kaplan-Meier Survival analysis. The lost follow-up patients were lost to follow up to prior to graft loss or death but after having BPAR in this analysis of graft loss, death, or lost to follow-up endpoint during 6 and 12 months. The survival curves up to 12 months are shown in Figure 2 and the Kaplan-Meier mean time estimates are presented in Table 16.

Figure 2. Survival Curves of Time to Failure of Graft Loss, Death, and Lost to Follow-Up at 12 Months (B301).

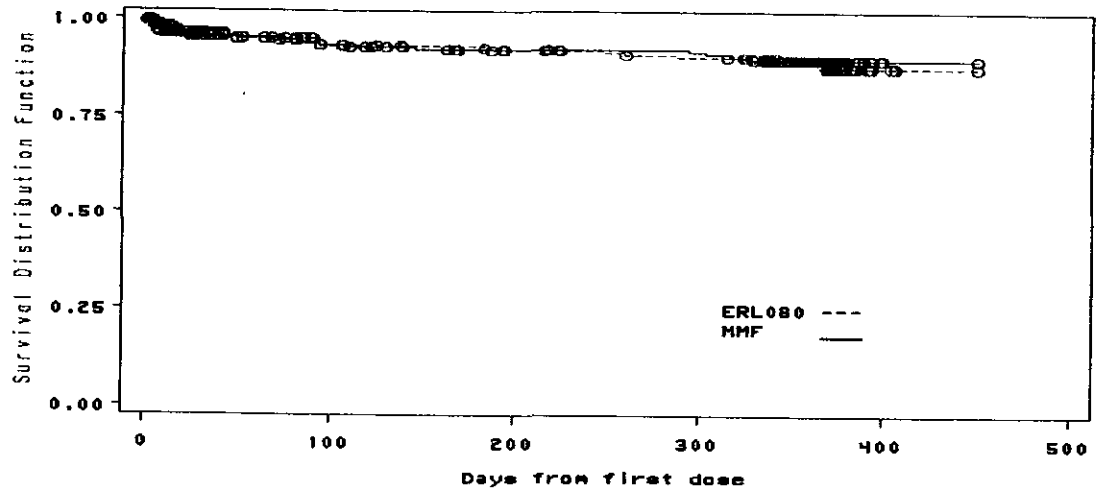


Table 16. Kaplan-Meier Mean Time Estimates of Time to Failure of Graft Loss, Death, and Lost to Follow-up at 12 Months (B301)

| | N/Total, (%) | Mean days to graft loss, deaths or lost-to-follow-up (SD) | Log rank p-value |
|---|---|---|---|
| ERL080 | 20/213(9.4) | 342.47 (6.350) | 0.8145 |
| MMF | 18/210(8.6) | 306.29 (5.659) | |

Data censored on day 450.

There was no statistically significant difference in the mean time to failure to the graft loss, death, or lost to follow-up between ERL080 and MMF at 12 months for Study B301.

The number of Graft loss, Death, or lost to follow-up at 6 and 12 months and their 95% confidence intervals were presented in Table 17.

Table 17. Analysis of Graft Loss, Death and Lost to Follow-up at 6 and 12 Months.

| | **ERL080 (N=213) n (%)** | **MMF (N=210) n (%)** | **Difference (ERL-MMF) (%)** | **95% CI (ERL-MMF) (%)** |
|---|---|---|---|---|
| **Graft Loss, Death or Lost to Follow-up at 6 Months** | 15 (7.0) | 14 (6.7) | 0.3 | ( -4.4, 5.3) |
| Graft loss | 7 (3.3) | 9 (4.3) | -1.0 | ( -4.6, 2.7) |
| Death | 1 (0.5) | 2 (1.0) | -0.5 | |
| Loss to follow-up | 6 (2.8) | 4 (1.9) | 0.9 | |
| **Graft Loss, Death or Lost to Follow-up at 12 Months** | 20 (9.4) | 18 (8.6) | 0.8 | ( -4.5, 6.4) |
| Graft loss | 9 (4.2) | 9 (4.3) | -0.1 | ( -3.8, 3.9) |
| Death | 2 (0.9) | 5 (2.4) | -1.5 | |
| Loss to follow-up | 9 (4.2) | 4 (1.9) | 2.3 | |

A 95% confidence interval is calculated if there are at least 5 patients experiencing the event in each group

The graft loss, death, or lost to follow-up endpoint of the ERL080 group at 6 and 12 months were non-inferior to that of MMF because the upper limits of 95% confidence intervals are within 5-10 % that the Division uses for non-inferiority margin for graft loss and death.

The time to the first occurrence of efficacy failure was analyzed using a Kaplan-Meier survival analysis for Study B301 and Study B302. The survival curves up to 12 months are shown in Figures 3 (Study B301) and 4 (Study B302) and the Kaplan-Meier time estimates are presented in Table 18 for both Study B301 and Study B302.

Table 18: Kaplan-Meier Mean Time Estimates of Time to the First Primary Efficacy Failure at 12 months (Study B301 and Study B302).

| B301 | N/Total, (%) | Mean days to primary efficacy (SD) | Log rank p-value |
|---|---|---|---|
| ERL080 | 61/213(28.6) | 283.79 (9.911) | 0.9905 |
| MMF | 59/210(28.1) | 258.98 (9.334) | |
| B302 | N/Total, (%) | Mean days to primary efficacy (SD) | Log rank p-value |
| ERL080 | 17/159(10.7) | 344.41 (5.902) | 0.4457 |
| MMF | 22/163(13.5) | 338.40 (5.883) | |

Figure 3. Survival Curves of Time to the First Primary Efficacy Failure up to 12 Months (B301)

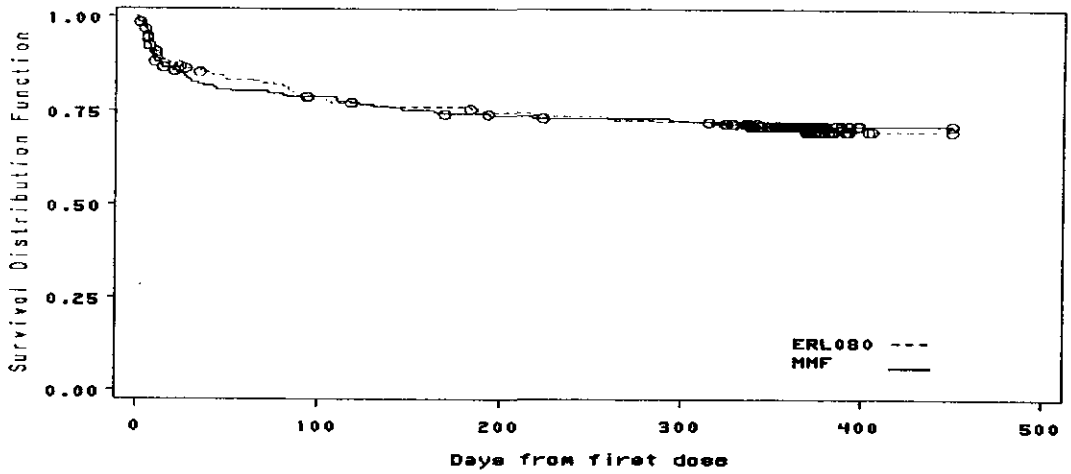
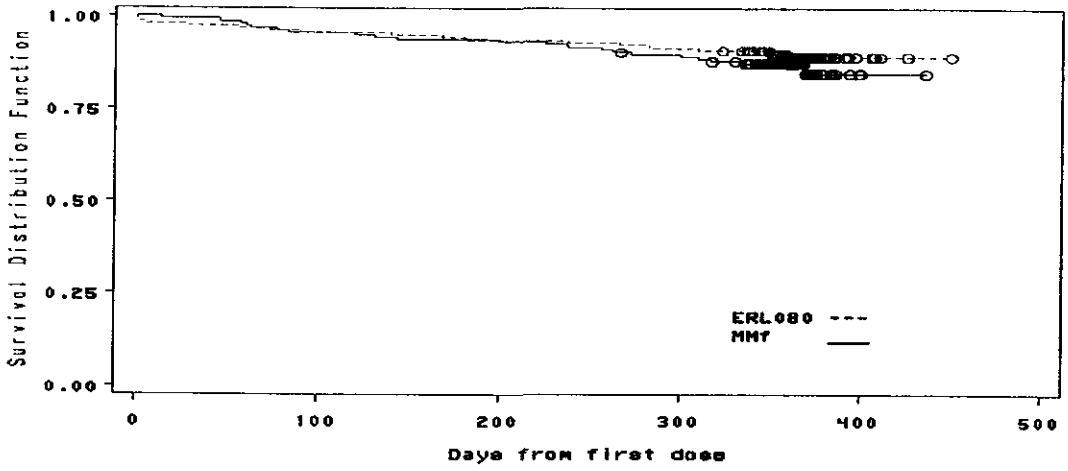



Figure 4. Survival Curves of Time to the First Primary Efficacy Failure up to 12 Months (B302)




There were no statistically significant differences in the mean time to the first primary efficacy failures between the ERL080 and the MMF groups for both Study B301 and Study B302.

An analysis considering treatment discontinuation as a failure within the efficacy composite endpoint is presented in Table 19.

Table 19. Primary Efficacy Endpoints with Premature Treatment Discontinuation Considered as a Failure at 12 Months (ITT Population-Study B301 and Study B302).

| | **Study B301** | | **Study B302** | |
|---|---|---|---|---|
| | ERL080 (N=213) n, (%) | MMF (N=210) n, (%) | ERL080 (N=159) n, (%) | MMF (N=163) n, (%) |
| Efficacy Failure or Premature Discontinuation at 6 Months | 84 (39.4) | 73 (34.8) | 18 (11.3) | 15 (9.2) |
| 95% CI (ERL080-MMF) | 4.6 (-4.6, 13.9) | | 2.1 (-4.5, 8.8) | |
| Efficacy Failure or Premature Discontinuation at 12 Months | 87 (40.9) | 77 (36.7) | 23 (14.5) | 21 (12.9) |
| 95% CI (ERL080-MMF) | 4.2 (-5.1, 13.5) | | 1.6 (-6.0, 9.1) | |

The rates of the first occurrence of efficacy failure or treatment discontinuation within 6 and 12 months for the ERL080 group were not non-inferior to that of MMF for Study B301, even though the primary efficacy endpoint at 6 and 12 months of the ERL080 group was non-inferior to MMF using a 10% non-inferiority margin. The reason is that the graft loss, death, and lost to follow-up events at 6 and 12 months for Study B301 were low relative to premature treatment discontinuation and a larger proportion of the ERL080 patients discontinued treatment. However, there were no statistically significant differences in the co-primary efficacy endpoints with premature treatment discontinuation considered as a failure between the two treatment groups in both Study B301 and Study B302.

The rates of the first occurrence of efficacy failure or treatment discontinuation with 6 and 12 months for the ERL080 group were non-inferior to that of MMF for Study B302 and the results were consistent with the primary efficacy endpoint analysis.

The Kaplan-Meier survival curves are presented in Figures 5 and 6, Study B301 and Study B302, respectively, using the co-primary efficacy endpoints with premature treatment discontinuation considered as a failure. Table 20 shows the mean time to this event.

Table 20. Mean Time to the First Occurrence of Efficacy Failure or Treatment Discontinuation at 12 Months for Study B301 and Study B302.

| B301 | N/Total, (%) | Mean days to primary efficacy (SD) | Log rank p-value |
|---|---|---|---|
| ERL080 | 87/213(40.9) | 236.95 (9.619) | 0.4047 |
| MMF | 77/210(36.7) | 245.45 (9.454) | |
| B302 | N/Total, (%) | Mean days to primary efficacy (SD) | Log rank p-value |
| ERL080 | 21/159(10.7) | 306.08 (6.048) | 0.9495 |
| MMF | 23/163(14.5) | 341.05 (6.326) | |

There were no statistically significant differences in the mean time to the first occurrence of primary efficacy failure or treatment discontinuation within 12 months between the ERL080 and MMF groups for both Study B301 and Study B302.

Figure 5. Survival Curve for Efficacy Endpoints with Treatment Discontinuation as a Failure at 12 Months for Study B301

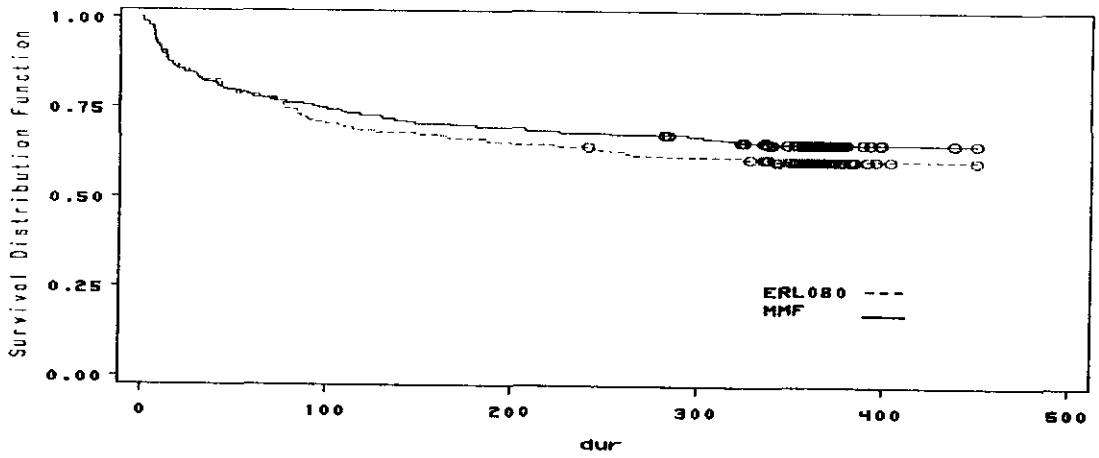



Figure 6. Survival Curve for Efficacy Endpoints with Treatment Discontinuation as a Failure at 12 Months for Study B302

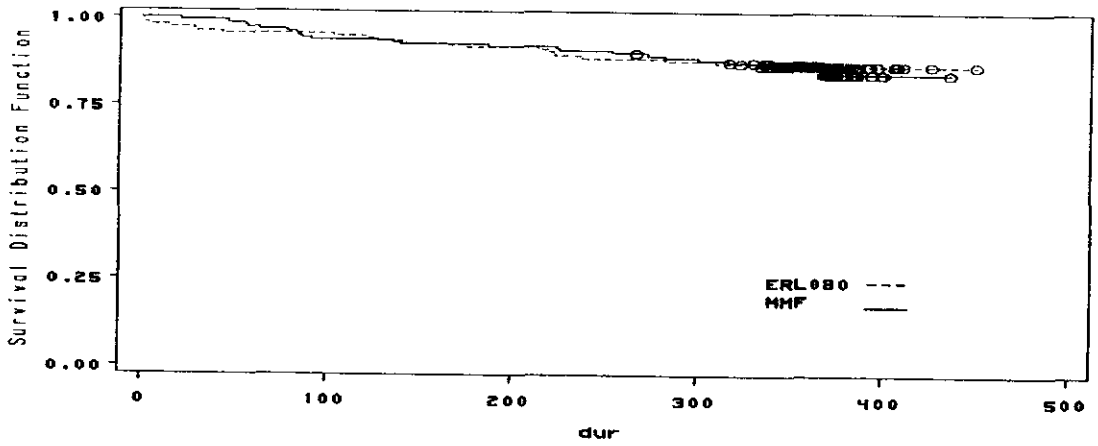



Figure 5 shows that the ERL080 group had a slightly higher rate of the efficacy failure when primary efficacy failure or treatment discontinuation were treated as a failure than that of MMF within 12 months, but there was no statistically significant difference between the two treatment groups in Study B301. Figure 6 shows that the ERL080 group and the MMF group had almost the same rate of efficacy failure when the primary efficacy or treatment discontinuation were treated as a failure at 12 months in Study B302.

## 3.2 Evaluation of Safety

The sponsor developed ERL080 to show a potential for improved gastrointestinal tolerability compared to MMF. The focus of this section is gastrointestinal system (GI) adverse events reported during the 12 months of the study and neutrophils values during the study period.

### Study B301

Any incidence of GI AEs that occurred in five or more cases within 12 months of randomization was summarized in Table 21.

Table 21. Number and Percent with GI Adverse Events (≥ 5 patients in any group) within 12 Months of Randomization (B301)

| Gastrointestinal adverse event | ERL080 N=213 n, (%) | MMF N=210 n, (%) | Difference in event rate ( %) | 95% CI (ERL-MMF) (%) |
|---|---|---|---|---|
| **Any GI AE** | **172 (80.8)** | **168 (80.0)** | **0.8** | **( -6.8, 8.3)** |
| **Upper GI adverse event** | 114 (53.5) | 114 (54.3) | -0.8 | (-10.3, 8.7) |
| **Gastrointestinal disorder** | 111 (52.1) | 111 (52.9) | -0.7 | (-10.3, 8.8) |
| Nausea | 62 (29.1) | 57 (27.1) | 2.0 | ( -6.6, 10.5) |
| Vomiting | 49 (23.0) | 42 (20.0) | 3.0 | ( -4.8, 10.8) |
| Dyspepsia | 48 (22.5) | 40 (19.0) | 3.5 | ( -4.2, 11.2) |
| Abdominal pain upper | 30 (14.1) | 30 (14.3) | -0.2 | ( -6.9, 6.4) |
| Eructation | 1 ( 0.5) | 5 ( 2.4) | -1.9 | |
| **Metabolic & nutrition disorders** | 6 ( 2.8) | 10 ( 4.8) | -1.9 | ( -5.6, 1.7) |
| Anorexia | 5 ( 2.3) | 4 ( 1.9) | 0.4 | |
| **Non-upper GI adverse events** | 146 (68.5) | 143 (68.1) | 0.4 | ( -8.4, 9.3) |
| **Gastrointestinal disorders** | 140 (65.7) | 136 (64.8) | 1.0 | ( -8.1, 10.0) |
| Constipation | 81 (38.0) | 83 (39.5) | -3.2 | (-10.8, 7.8) |
| Diarrhea NOS | 50 (23.5) | 52 (24.8) | -1.5 | ( -9.4, 6.9) |
| Flatulence | 21 ( 9.9) | 27 (12.9) | -3.0 | ( -9.0, 3.0) |
| Abdominal distension | 16 ( 7.5) | 15 ( 7.1) | 0.4 | ( -4.6, 5.3) |
| Sore throat NOS | 16 ( 7.5) | 13 ( 6.2) | 1.3 | ( -3.5, 6.1) |
| Abdominal pain lower | 17 ( 8.0) | 10 ( 4.8) | 3.2 | ( -1.4, 7.9) |
| Abdominal pain NOS | 15 ( 7.0) | 11 ( 5.2) | 1.8 | ( -2.8, 6.4) |
| Gingival hyperplasia | 8 ( 3.8) | 14 ( 6.7) | -2.9 | ( -7.1, 1.3) |
| Loose stools | 12 ( 5.6) | 9 ( 4.3) | 1.3 | ( -2.8, 5.5) |

Include GI adverse events and infections ≥ 5 using only once per body system and term.
A 95% confidence interval is calculated if there are at least 5 patients experiencing the event in each group (Table 10.5-4 vol 142, page 8-222)

The ERL080 group showed slightly higher incidences of any GI AEs compared to MMF, but there was no statistically significant difference between the two groups.

The incidence of patients with GI AEs by body system and preferred term observed at the 12 months visit (window from Day 312 to 450) is shown in Table 22.

Table 22. Number of Patients with Gastrointestinal Adverse Events (≥ 2 patients in any group) at Month 12 Visit (safety population, 0-12 months-Study B301)

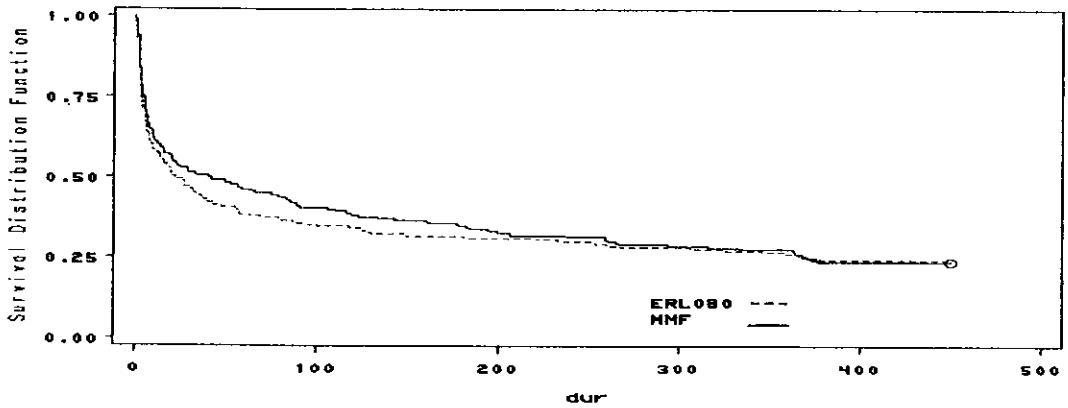
| Gastrointestinal adverse event | ERL080 N=213 n, (%) | MMF N=210 n, (%) | Difference in event rate ( %) | 95% CI (ERL-MMF) (%) |
|---|---|---|---|---|
| **Any GI AE** | **43 (20.2)** | **36 (17.1)** | **3.0** | **( -4.4, 10.5)** |
| **Upper GI adverse event** | 17 ( 8.0) | 13 ( 6.2) | 1.8 | ( -3.1, 6.7) |
| Dyspepsia | 10 ( 4.7) | 6 ( 2.9) | 1.8 | ( -1.8, 5.5) |
| Nausea | 3 ( 1.4) | 4 ( 1.9) | -0.5 | |
| Vomiting | 3 ( 1.4) | 2 ( 1.0) | 0.5 | |
| Abdominal pain upper | 2 ( 0.9) | 1 ( 0.5) | 0.5 | |
| **Non-upper GI adverse events (any body system)** | 35 (16.4) | 30 (14.3) | 2.1 | ( -4.7, 9.0) |
| **Lower GI adverse events:** | | | | |
| Diarrhea NOS | 6 ( 2.8) | 4 ( 1.9) | 0.9 | |
| Constipation | 5 ( 2.3) | 4 ( 1.9) | 0.4 | |
| Abdominal pain (not specified) | 4 ( 1.9) | 1 ( 0.5) | 1.4 | |
| Abdominal pain lower | 2 ( 0.9) | 2 ( 1.0) | 0 | |
| Abdominal distension | 2 ( 0.9) | 0 | 0.9 | |
| Constitution aggravated | 0 | 2 ( 1.0) | -1.0 | |

Includes events during the Month 12 visit window (between Days 312 to 450)
A 95% confidence interval is calculated if there are at least 5 patients experiencing the event in each group (Table 10-4, Vol 140 page 8-113)

The incidences of GI AEs, upper GI AEs, and non-upper GI AEs within the Month 12 window appeared a little higher for the ERL080 group compared to the MMF group, but there were no statistically significant differences between the two groups.

Because the main reason for premature treatment discontinuation was adverse events in Study B301 and GI AEs was the main safety concerns in the safety studies, the time to the first occurrence of GI AEs during 12 months was analyzed by this reviewer using a Kaplan-Meier survival analysis. The survival curves up to month 12 are shown in Figure 7 for Study B301.

Figure 7. Survival Curve for the First GI AEs at 12 Months for Study B301



As shown in Figure 7, the ERL080 group had slightly higher incidences of GI AEs in the earlier period as compared to MMF in Study B301.

The mean absolute neutrophil values were summarized for the Month 3, 6, and 12 windows in Table 23.

Table 23. The Mean Absolute Neutrophil (10E9/L) Value for 3, 6, 12 Month Windows (B301)

| | **ERL080 N=213** | **MMF N=210** |
|---|---|---|
| **Baseline** | 10.7 (n=163) | 10.7 (n=151) |
| **Month 3** | 5.3 (n=133) | 5.0 (n=134) |
| **Month 6** | 4.5 (n=134) | 4.7 (n=131) |
| **Month 12** | 4.7 (n=80) | 5.0 (n=89) |

(Post-test Table 10.3-1, vol 142, page 8-105)
Month 3 window is Day 71 to 99
Month 6 window is Day 147 to 226
Month 12 window is Day 312 to 450

The incidence of patients with clinically low absolute neutrophils (<1.5 x $10^9$/L) was similar between the ERL080 group and the MMF group during Months 3 to 12 and no statistical difference was observed. The baseline incidence of low absolute neutrophils (<1.5 x $10^9$/L) was higher than that of Months 3, 6, and 12, but the values were similar between the two groups with no statistically significant difference.

**Study B302**

The incidence of GI adverse events at the 3 months after administration of study medication is shown in Table 24. The incidences of patients with GI AEs by body system and preferred term observed within the 12 months of randomization are shown in Table 25. The neutropenia values with the first 3, 6 and 12 months of treatment in maintenance renal transplant patients treated with ERL080 or MMF were summarized in Table 26.

Table 24. Number of Patients with Gastrointestinal Adverse Events (≥ 2patients in any group) at Month 3 Visit (safety population, 1-12 months-Study B302)

| **Gastrointestinal adverse event** | **ERL080 N=159 n, (%)** | **MMF N=163 n, (%)** | **Difference in event rate ( %)** | **95% CI (ERL-MMF) (%)** |
|---|---|---|---|---|
| **Any GI AE** | **42 (26.4)** | **34 (20.9)** | **5.6** | **(- 3.7, 14.8)** |
| **Upper GI adverse event** | 21 (13.2) | 22 (13.5) | -0.3 | ( -7.7, 7.1) |
| **Gastrointestinal disorder** | 20 (12.6) | 21 (12.9) | -0.3 | ( -7.6, 7.0) |
| Nausea | 10 ( 6.3) | 6 ( 3.7) | 2.6 | ( -2.1, 7.4) |
| Dyspepsia | 5 ( 3.1) | 5 ( 3.1) | 0.1 | ( -3.7, 3.9) |
| Abdominal pain upper | 2 ( 1.3) | 5 ( 3.1) | -1.8 | |
| Gastro-oesophageal reflux disease | 3 ( 1.9) | 2 ( 1.2) | 0.7 | |
| Oesophageal reflux | 2 ( 1.3) | 5 ( 3.1) | 0.6 | |
| Gastritis NOS | 0 | 2 ( 1.2) | -1.2 | |
| **Metabolic & nutrition disorders** | 2 ( 1.3) | 2 ( 1.2) | 0.1 | |
| Anorexia | 1 ( 0.6) | 2 ( 1.2) | -0.6 | |
| **Non-upper GI adverse events** | 29 (18.2) | 21 (12.9) | 5.4 | ( -2.5, 13.3) |

| | | | | |
|---|---|---|---|---|
| **Gastrointestinal disorders** | 29 (18.2) | 21 (12.9) | 5.4 | ( -2.5, 13.3) |
| Diarrhea NOS | 8 ( 5.0) | 8 ( 4.9) | 0.1 | ( -4.6, 4.9) |
| Abdominal pain NOS | 2 ( 1.3) | 3 ( 1.8) | -0.6 | |
| Dry mouth | 2 ( 1.3) | 3 ( 1.8) | -0.6 | |
| Loose stools | 4 ( 2.5) | 1 ( 0.6) | 1.9 | |
| Abdominal distension | 0 | 3 ( 1.8) | -1.8 | |
| Constipation | 2 ( 1.3) | 1 ( 0.6) | 0.6 | |
| Flatulence | 3 ( 1.9) | 0 | 1.9 | |
| Dry throat | 2 ( 1.3) | 0 | 1.3 | |
| Gingival hyperplasia | 2 ( 1.3) | 0 | 1.3 | |

A 95% confidence interval is calculated if there are at least 5 patients experiencing the event in each group

The incidences of GI AEs and non-upper GI AEs within Month 3 window appeared a little higher for the ERL080 group compared to MMF, but there were no statistically significantly differences between the two groups.

Table 25. Number and Percent with GI Adverse Events (≥ 5 patients in any group) within the 12 Months of Randomization (B302)

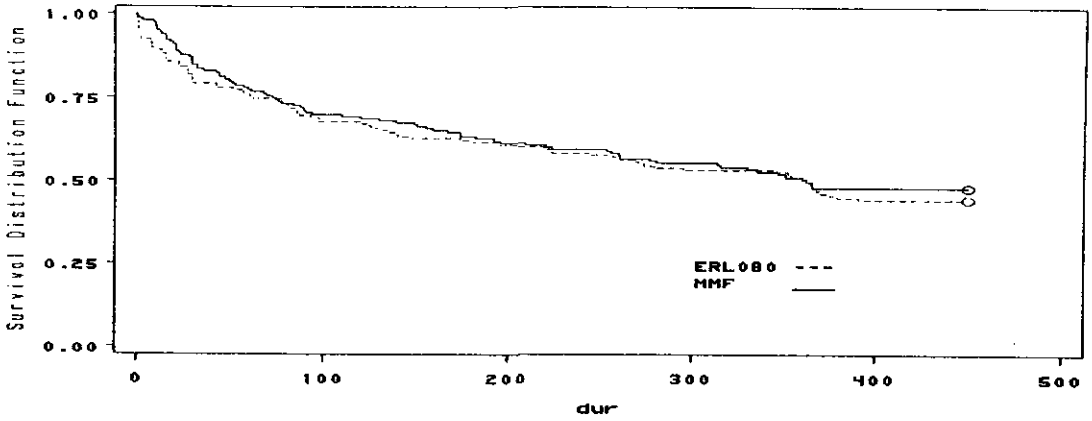
| **Gastrointestinal adverse event** | **ERL080 N=159 n, (%)** | **MMF N=163 n, (%)** | **Difference in event rate ( %)** | **95% CI (ERL-MMF) (%)** |
|---|---|---|---|---|
| **Any GI AE** | **96 (60.4)** | **100 (61.3)** | **-1.0** | **(-11.6, 9.7)** |
| **Upper GI adverse event** | 69 (43.4) | 67 (41.1) | 2.3 | ( -8.5, 13.1) |
| **Gastrointestinal disorder** | 67 (42.1) | 66 (40.5) | 1.6 | ( -9.1, 12.4) |
| Nausea | 39 (24.5) | 31 (19.0) | 5.5 | ( -3.5, 14.5) |
| Dyspepsia | 22 (13.8) | 24 (14.7) | -0.9 | ( -8.5, 6.8) |
| Vomiting NOS | 24 (13.8) | 21 (12.9) | 2.2 | ( -5.4, 9.8) |
| Abdominal pain upper | 11 ( 6.9) | 7 ( 4.3) | 2.6 | ( -2.4, 7.6) |
| Gastro-oesophageal reflux disease | 7 ( 4.4) | 7 ( 4.3) | 0.1 | ( -4.3, 4.6) |
| **Metabolic & nutrition disorders** | 4 ( 2.5) | 5 ( 3.1) | -0.6 | |
| **Non-upper GI adverse events** | 72 (45.3) | 74 (45.4) | -0.1 | ( -11.0,10.8) |
| **Gastrointestinal disorders** | 62 (39.0) | 66 (40.5) | -1.5 | ( -12.2, 9.2) |
| Diarrhea NOS | 34 (21.4) | 40 (24.5) | -3.2 | ( -12.3, 6.0) |
| Abdominal pain NOS | 11 ( 6.9) | 15 ( 9.2) | -2.3 | ( -8.2, 3.7) |
| Constipation | 10 ( 6.3) | 10 ( 6.1) | 0.2 | ( -5.1, 5.4) |
| Loose stools | 7 ( 4.4) | 3 ( 1.8) | 2.6 | |
| Abdominal distension | 3 ( 1.9) | 6 ( 3.7) | -1.8 | |
| Flatulence | 5 ( 3.1) | 4 ( 2.5) | 0.7 | |

A 95% confidence interval is calculated if there are at least 5 patients experiencing the event in each group

The incidences of GI AEs observed within 12 months appeared the same with no statistically significant differences between two groups.

The time to the first occurrence of GI AEs during 12 months was analyzed using a Kaplan-Meier survival analysis. The survival curves up to the 12 months are shown in Figure 8 for Study B302.

Figure 8. Survival Curve for first GI AEs at the 12 Months for Study B302




As shown in Figure 8, there was no difference in the time to the first GI AEs between the two groups in Study B302.

The mean absolute neutrophils values were summarized within Month 3, 6, and 12 windows in Table 26.

Table 26. The Mean Absolute Neutrophil (10E9/L) Values of the 3, 6, 12 Month Windows (B302)

| | **ERL080 N=159** | **MMF N=163** |
|---|---|---|
| **Baseline** | 5.2 (n=113) | 4.9 (n=127) |
| **Month 3** | 5.3 (n=130) | 5.0 (n=133) |
| **Month 6** | 5.2 (n=126) | 5.2 (n=130) |
| **Month 12** | 5.1 (n=123) | 5.0 (n=117) |

(Post-test Table 10.3-8, vol 151, page 8-53)
Month 3 window is Day 71 to 99
Month 6 window is Day 147 to 226
Month 12 window is Day 312 to 450

The incidence of patients with clinically low absolute neutrophils (<1.5 x $10^9$/L ) was similar between the ERL080 group and the MMF group during Months 0 to 12 and no statistically significant differences were observed.

**Study 0107 and Study 0107Ext**

The overall incidence of GI adverse events was summarized in Table 27. In the 5-week core phase of Study 0107, 74 and 75 patients were treated with ERL080 and MMF, respectively. The patients in the Ex-MMF group in the Months 7 or 18 cohorts were treated with MMF in the 5-week core phase period and were switched to ERL080 treatment for 7 or 18 months. The patients in the ERL080 group in the Months 7 or 18 cohorts were treated with ERL080 in the 5-week core phase period and treated with ERL080 continuously during the 7 or 18 months extension.

Table 27. Number and Percent of Common GI Adverse Events (≥ 5 patients in any group)-Safety Population-Core and Extension Phases (0107 and 0107Ext)

| | Study 0107 | | Study 0107Ext | | | |
|---|---|---|---|---|---|---|
| | Core | | Months 7 cohort | | Month 18 cohort | |
| **Group** | **MMF (N=74)** | **ERL080 (N=75)** | **Ex-MMF (N=63)** | **ERL080 (N=65)** | **Ex-MMF (N=32)** | **ERL080 (N=33)** |
| **Treatment Duration of ERL080** | **MMF** | **ERL080 0 to 5 wk.** | **ERL080 0 to 7 mos.** | **ERL080 5wk to 8+ mo** | **MMF/ ERL080 0 to 18mo** | **ERL080 5wk to 19+ mo** |
| | **n, (%)** | **n, (%)** | **n, (%)** | **n, (%)** | **n, (%)** | **n, (%)** |
| **At least one adverse event** | **55(74.3)** | **55 (73.3)** | **40 (63.5)** | **34 (52.3)** | **20 (62.5)** | **20 (60.6)** |
| **Gastrointestinal disorder** | **50(67.6)** | **49 (65.3)** | **20 (31.7)** | **20 (30.8)** | **11 (34.4)** | **14 (42.4)** |
| Abdominal distention | 15(20.3) | 20 (26.7) | 5 (7.9) | 3 (4.6) | 2 (6.3) | 0 |
| Abdominal pain upper | 17(23.0) | 18 (24.0) | 5 (7.9) | 2 (3.1) | 4 (12.5) | 2(6.1) |
| Dyspepsia | 13(17.6) | 14(18.7) | 6 (9.5) | 2 (3.1) | 4 (12.5) | 3(9.1) |
| Diarrhea NOS | 14(18.9) | 12(16.0) | 5 (7.9) | 5 (7.7) | 4 (12.5) | 3(9.1) |
| Nausea | 11(14.9) | 7 (9.3) | 4 (6.3) | 4 (6.2) | 3 (9.4) | 4(12.1) |
| Gastroesophageal reflux | 5( 6.8) | 9(12.0) | 1(1.6) | 0 | 1 (3.1) | 0 |
| Flatulence | 7( 9.5) | 6 (8.0) | 1(1.5) | 2(3.1) | 0 | 2(3.1) |
| Abdominal pain NOS | 5(6.8) | 5 (6.7) | 2(3.2) | 3(4.6) | 1(3.1) | 1(3.0) |
| Eructation | 6(8.1) | 4 (5.3) | 2(3.2) | 3(4.6) | 0 | 3(9.1) |
| Constipation | 7(9.5) | 2 (2.7) | 1(1.6) | 2(3.1) | 0 | 1(3.0) |
| **Metabolism & nutrition disorders** | **7(9.5)** | **7(9.3)** | **5( 7.9)** | **6( 9.2)** | **3( 9.4)** | **5(15.2)** |

Include GI adverse events and infections ≥ 5 using only one once per body system and term.
(Table 10.1-2 vol 159, page 8-3, Table 16.1-3 vol. 162, page 8-120, Table 16.1-4 vol 162, page 8-131)

The incidence of overall adverse events and GI events were similar between the two groups during the core study period. The incidence of abnormal distension and upper abdominal pain was observed higher than that of Study B302 because Study 0107 enrolled patients who were GI intolerant to MMF. Overall, there was no statistically significant difference between the two groups.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race and Age

**Study B301**

The incidence rates of efficacy failure at 12 months stratified by recipient sex, recipient race of Caucasian vs. non-Caucasian, recipient age of less than or equal to 50 vs. greater than 50, and patients in the USA vs. Europe are summarized in Table 28.

Table 28. Analysis of Primary Efficacy Endpoints at Months 12 Stratified by Recipient Sex, Race, Age, and Country (B301)

| | **ERL080 (N=213) n, (%)** | **MMF (N=210) n, (%)** |
|---|---|---|
| **Overall rate of efficacy failure** | 61/213 (28.6) | 59/210 (28.1) |
| **Male** | 39/137 (28.5) | 38/142 (26.8) |
| **Female** | 22/76 (29.0) | 21/76 (30.9) |
| **Caucasian** | 53/187 (28.3) | 53/187 (28.3) |
| **Non-Caucasian** | 8/26 (30.8) | 6/26 (26.1) |
| **age ≤ 50 years** | 36/125 (28.8) | 37/124 (19.8) |
| **age > 50 years** | 25/88 (28.4) | 22/86 (25.6) |
| **USA** | 16/59 (27.1) | 14/56 (25.0) |
| **Europe** | 45/154 (29.2) | 45/154 (29.2) |

The rates of primary efficacy failure of ERL080 were not statistically significantly different for Caucasian and non-Caucasian, male and female, patients of age less than an equal to 50 years old and patients of age greater than 50 years, and patients in the USA and Europe as compared with that of MMF.

**Study B302**

The incidence rates of primary efficacy failure at the 12 months stratified by recipient sex, recipient race of Caucasian vs. non-Caucasian, recipient age of less than or equal to 50 vs. greater than 50 and patients in the USA vs. in Europe are summarized in Table 29.

Table 29. Analysis of Primary Efficacy Endpoints at the 12 Months Stratified by Recipient Sex, Race, Age, and Country (B302)

| | **ERL080 (N=159) n, (%)** | **MMF (N=163) n, (%)** |
|---|---|---|
| **Overall rate of efficacy failure** | 12/159 (7.6) | 20/163 (12.3) |
| **Male** | 5/97 ( 5.2) | 14/115(12.2) |
| **Female** | 7/62 (11.3) | 6/48 (12.5) |
| **Caucasian** | 4/118 (3.4) | 9/119 (7.6) |
| **Non-Caucasian** | 8/41 (19.5) | 11/44 (25.0) |
| **age ≤ 50 years** | 6/88 (6.8) | 10/99 (10.1) |
| **age > 50 years** | 6/71 (8.5) | 10/64 (15.6) |
| **USA** | 11/90 (12.2) | 17/92 (18.5) |
| **Europe** | 1/69 (1.5) | 3/71 (4.2) |

The rates of efficacy failure of the ERL080 were not statistically significantly different for Caucasian and non-Caucasian, for male and female, patients for age less than or equal to 50 years old and for greater than 50 years, and patients in the USA and Europe as compared to that of MMF.

## 4.2 Other Special/Subgroup Populations

The sponsor stated that the ERL080 group had numerically more patients who were CMV – and who were matched with a CMV+ donor, who had prolonged cold ischemia time of ≥ 24 hours and who had panel reactive antibodies (PRA) > 0%. They stated that these factors should be considered in the overall judgment of the efficacy outcome. In the baseline analysis of Study B301, CMV-negative patients having received a graft from CMV-positive donor vs. the other group (Don_CMV+/Rec_CMV+, Don_CMV-/Rec_CMV+, and Don_CMV-/Rec_CMV-) and a prolonged cold ischemia time of ≥ 24 hours vs. a prolonged cold ischemia time of < 24 hours were not statistically significantly different between the two groups, but the panel reactive antibodies, PRA > 0% vs. PRA 0% was statistically significantly different between the two groups.

Subgroup analyses of efficacy failure by PRA of 0 % vs. PRA > 0%, positive viral serology CMV: donor+/ recipient – vs. the other group, and cold ischemia time more than ≥ 24 hours vs. < 24 hours were examined in Table 30.

Table 30. Efficacy Subgroup Analyses of PRA, CMV, and Cold Ischemia (B301) Using the 12 Month Endpoint.

| | **ERL080 N=213** | **MMF N=210** | **p-values Chi-square*** | **CMH**** |
|---|---|---|---|---|
| **PRA 0%** | 49/173 (28.3) | 52/183 (28.4) | 0.9847 | 0.8725 |
| **> 0%** | 12/40 (30.0) | 7/25 (28.0) | 0.8631 | |
| **Don_CMV+/Rec_CMV- Other[#1]** | 14/36 (38.9) | 6/26 (23.1) | 0.1888 | 0.4493 |
| | 47/177 (26.6) | 53/184 (28.8) | 0.6329 | |
| **Cold ischemia time < 24 hrs.** | 51/169 (30.2) | 52/182 (28.6) | 0.7413 | 0.5067 |
| **Cold ischemia time ≥ 24 hrs.** | 10/44 (22.7) | 7/28 (25.0) | 0.8248 | |

*: Chi-square p-value of the difference between the two groups
**: CMH stratified by center p-value of difference between the two groups
[#1]: Other group includes Don_CMV+/Rec_CMV+, Don_CMV-/Rec_CMV+, and Don_CMV-/Rec_CMV-.

In the baseline analysis, the proportion of patients with PRA > 0% was higher in the ERL080 group (18.7 %) than the MMF group (11.9 %) with statistically significant difference (p=0.0277) in the PRA 0% vs. PRA > 0% between the two groups. The efficacy failures of PRA 0% vs. PRA > 0% between the two groups were not statistically different after adjusting for center (p=0.8725). In addition, there was not statistically significant differences in the efficacy failure between the two treatment groups in the PRA 0% and PRA > 0% groups (p=0.9847 and 0.8631, respectively). There was no clear indication that patients in this study with PRA > 0% had worse outcomes than patients with PRA 0%. Therefore, the imbalance seen at baseline would not have greatly influenced the overall study results.

The incidence of efficacy failure of CMV-negative patients having received a graft from CMV-positive donors was higher in the ERL080 group (38.9%) than that of the MMF group (23.1%), but no statistical difference was observed between the two groups (p=0.1888). There was no overall statistical difference of the efficacy failure in CMV-negative patients having received a graft from CMV-positive donors vs. other patients group after adjusting for center (p=0.4493).

The incidence of cold ischemia time ≥ 24 hours was higher for the ERL080 group (20.7%) compare to the MMF group (13.3%), but no statistically significant difference was observed in

the baseline analysis. The efficacy failure of cold ischemia time ≥ 24 hours was not statistically different between the two treatment groups. There is no indication that patients in this study with cold ischemia time ≥ 24 hours had worse outcome than those with cold ischemia time of less than 24 hours. In both treatment arms, patients with cold ischemia time of less than 24 hours had higher failure rates than those with cold ischemia time of ≥ 24 hours.

# 5. SUMMARY AND CONCLUSIONS

## 5.1 Statistical Issues and Collective Evidence

A statistical concern is that the number of patients who discontinued treatment prematurely was higher in the ERL080 group compared to the MMF group in Study B301 for both the 6 and 12 month periods. Moreover, the primary reason for treatment discontinuation was adverse events. These rates of premature treatment discontinuation were inconsistent across studies. Premature treatment discontinuation rates were similar between the two treatment groups for both the 6 and 12 month periods in Study B302. The premature treatment discontinuation rate of Study B301 was three times more than that of Study B302. This could be due to the fact that only patients who could tolerate MMF based on a two weeks run-in period were enrolled in Study B302. The premature treatment discontinuation rates of Study 0107 were very low in both treatment groups.

In the efficacy analysis of the first occurrence of efficacy failure or treatment discontinuation within 6 and 12 months when considering premature treatment discontinuation as a failure, the incidence rates for the ERL080 group were not non-inferior to MMF using a 10% non-inferiority margin because of the higher premature treatment discontinuation rate of the ERL080 group relative to those of the MMF group in Study B301. However, no statistically significant differences were observed between the two groups.

## 5.2 Conclusions and Recommendations

The primary efficacy objectives were to show efficacy as measured by the incidence of biopsy-proven acute allograft rejection, graft loss, death, or lost to follow-up in the first 6 and 12 months of treatment in *de novo* (Study B301) and in maintenance (Study B302) renal transplant recipients. In Study B301 and Study B302, ERL080 was non-inferior to MMF for this endpoint. However, in a modified composite endpoint measured premature treatment discontinuation as additional failures, ERL080 was not non-inferior to MMF because of the disproportionately higher premature treatment discontinuation in the ERL080 group in Study B301, but ERL080 was non-inferior to MMF in Study B302. In general, in all efficacy analyses with the one exception of the analysis of Study B301where discontinuations were considered failures indicated that ERL080 was non-inferior to MMF and this was consistent across studies.

The safety analyses showed that the ERL080 group had almost the same incidence of GI AEs within 12 months and at the Month 12 visit in Study B301, and no statistically significant differences were observed between the two treatment groups. In Study B302, the incidence of any GI AEs at Month 3 visit showed a slightly higher incidence in the ERL080 group compared to that of the MMF group. It was mainly due to higher incidence of non-upper GI AEs in the ERL080 group as compared to the MMF group. However, no statistically significant difference was observed between the two groups. The safety analyses results of Study 0107 and Study 0107Ext showed that the incidence of GI AEs was similar between the two groups. The core studies, Study B301 and Study B302, and a supportive Study 0107 do not show that there was statistically significant improvement of GI adverse events and tolerability.

The incidence of patients with clinically low absolute neutrophils (<1.5 x $10^9$/L ) values was similar between the two treatment groups from Month 0 to Month 12 and no statistically significant differences were observed.

**SIGNATURES/DISTRIBUTION LIST PAGE**

**Primary Statistical Reviewer: Kyung Yul Lee, Ph.D.**
**Date: February 23, 2004**

**Concurring Reviewer(s):**

**Statistical Team Leader: Karen Higgins, Sc.D.**

**Biometrics Division Director: Mohammed Huque, Ph.D.**

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**HFD-590/Project Manager**
**HFD-590/Medical Officer**
**HFD-590r/Medical Team Leader**
**HFD-725/Primary Statistical Reviewer**
**HFD-725/Statistical Team Leader**
**HFD-725/Biometrics Deputy Division Director**
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**HFD-700/Office of Biostatistics Deputy Director**

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Mohammad Huque
2/24/04 02:33:30 PM
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Statistical Review and Evaluation

| | |
|---|---|
| IND: | 57-005 |
| Applicant: | Novartis Pharmaceutical Corp. |
| Name of Drug: | SDZ ERL 080 |
| Document Reviewed: | Vol. 11-15 |
| Reviewing Pharmacologist: | Steve Hundley, Ph.D. |
| Reviewing Biostatistician: | Qian Li, Sc.D. |

## Background

SDZ ERL 080 is an immuosuppressant. A rat study was conducted to evaluate the potential carcinogenicity of the test substance, SDZ ERL 080, following daily oral administration (gavage) to rats for 104 weeks. The study was conducted at [redacted] in compliance with the requirements of Good Laboratory Practices guidance from many nations including US.

## Study Design

Four treated groups, each composed of 50 male and 50 female rats of the Wistar Han strain received the test substance daily by gavage at dose-level of 1, 3, 6 and 9 mg/kg/day for 104 to 105 weeks. Two groups of 50 males and 50 females received the vehicle, carboxymethylcellulose aqueous solution at 1%. The Wistar Han strain was selected because background data from previous studies are available.

Morbidity and mortality were checked twice daily; clinical signs were checked once daily. After 6 months of treatment, palpation of possible masses was carried out at four-weekly intervals. On completion of 104 or 105 weeks of treatment all surviving animals were sacrificed. A macroscopic postmortem examination was performed on all animals, including descendants.

Statistical methods for analyses: The sponsor used Chi-square tests for the survival rates and using Peto's test to compare the number of neoplasms.

*Reviewer's comments: In addition to sponsor's analyses, based on the Manual of Policies and Procedures (MAPP)[1] "Methods and Procedures for Statistical Review and Evaluation of Animal Carcinogenicity Studies", this reviewer performed some standard statistical analyses for regular two-year carcinogenicity study for each sex. These analyses included:*

*1) Mortality: Cox's proportional hazard model and the Generalized Wilcoxon tests were used to perform both dose-mortality trend and homogeneity tests. The weight used to*

[1] Draft MAPP (8/29/01), "Methods and Procedures for Statistical Review and Evaluation of Animal Carcinogenicity Studies", Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, Maryland.

*perform the trend test was the actual dose levels for the six dose groups, i.e., (0, 0, 1, 3, 6, 9). The homogeneity tests were used to assess the consistency of death rates among different dose groups. To assess the homogeneity, trend tests using weight (1,1,1,1,1,1) for the dose groups were performed.*

2) *Tumor incidence: Survival-adjusted tests for dose-response tumor incidence rates (Peto's method[2]) by organs and tumor types were performed for each sex. In this review, the weight for trend test was also the actual dose level for the six dose groups. The death rate method was used for the type of tumors that "caused death" (fatal) and the prevalence method for the type of tumor that "did not cause death" (incidental). When a tumor type was classified to be both fatal and incidental, the death rate method and prevalence method were applied to fatal and incidental respectively for the tumor type. The results of the two methods were then combined for the tumor type. The p-values from exact test were used since the tumor incidence rates for most tumor type was low. The time intervals used were 0-50, 51-78, 79-91, 92-103, 104-termal (110 for male and 105 for female) weeks.*
3) *Combining tumors: Suggested by Dr. Hundley, the pharmacologist reviewer for this study, the tumor type of "Hemangiosarcoma" across organs should be combined to evaluate.*

*Since tests for trend or difference were performed on all the tumor/tissue and combinations, the decision rule for testing positive trend was different for "rare" and "common" tumor. Currently, the decision rule for "rare" tumor (the published spontaneous tumor rate or the tumor rate in control group is less than 1%) is 0.025, while the decision rule for common tumor is 0.005 based on the recommendation by Lin and Rahman[3]. For pairwise comparison tests, the decision rule for "rare" tumor is 0.05 and the decision rule for "common" tumor is 0.01 based on Haseman's[4] recommandation.*

## Sponsor's Analysis Results

Mortality:

The mortality rate in all groups was low. A total of 12 and 9, and 12, 6, 6, and 10 male animals died in control groups 1 and 2, and the groups given 1, 3, 6, and 9 mg/kg/day of the test substance respectively, among male groups. The distribution of death among the female groups was 7 and 16, and 14, 15, 6, 11 in control groups 1 and 2, and the groups given 1, 3, 6, 9 mg/kg/day. The distribution and timing of deaths in the different groups were similar. At study termination (Week 104), the group mean survival rates ranged

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[2] Peto,R., etc. (1980) "Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-term Animal Experiments," In Long-term and Short-term Screening Assays for Carcinogens: An Critical Appraisal, World Health Organization.

[3] Lin, K.K. and M.A. Rahman (1998), "Overall False Positive Rates in Tests for Linear Trend in Tumor Incidence in Animal Carcinogenicity Studies of New Drugs," Journal of Biopharmaceutical Statistics, Vol. 8, No. 1, 1998.

[4] Haseman, J.K. (1983). "A Reexamination of False-Positive Rates for Carcinogenesis Studies," Fundamental and Applied Toxicology, 3, 334-339.

from 76 to 88% in the males and from 68 to 88% in the females. The sponsor concluded that the cause of death was similar in all groups and did not show any indication of treatment or dose relationship.

Palpable masses:

The sponsor's tests suggested that treatment with the test substance had no effect on the onset time or the incidence of palpable masses.

Macroscopic post-mortem examination:

The sponsor noted that no treatment-related necropsy findings were noted. The masses and nodules found in some organs and tissues were equally distributed between control and treated animals and showed no indication of treatment or dose-relationship either in size or number.

Microscopic examination:

The sponsor concluded that treatment with ERL 080 for 104 weeks in rats by oral administration was without any carcinogenic and toxicological effect. Although there was a higher incidence of benign thymomas in females at the dose-levels of 6 and 9 mg/kg/day, they did not reach a level of statistical significance when compared with the incidence in control females from a parallel study performed under the same conditions and using the same strain of rats.

## Reviewer's analysis:

*Survival analyses: The survival curves for the 6 dose groups were presented in Figures 1F and 1M for female and male rats, respectively. The dose-mortality trend and homogeneity tests among dose groups for male and female rats were presented in Table 1M and 1F, respectively. Both Cox proportional hazard model and the Generalized Wilcoxon test provided consistent test results for both trend and homogeneity tests in both male and female rats.*

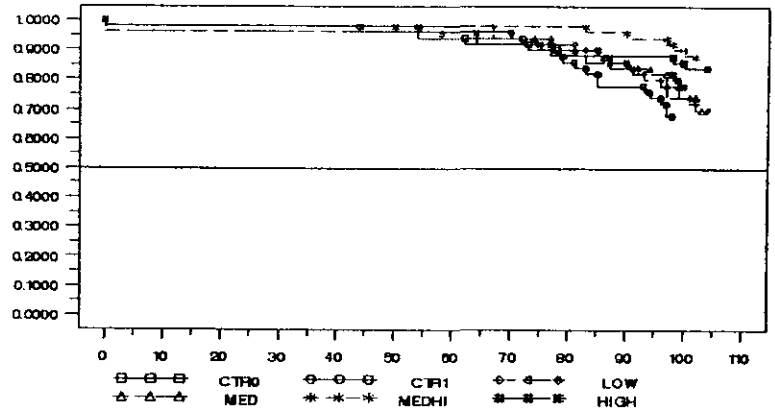



*Figure 1F: Survival curves for female rats*

*Table 1F: Dose-mortality trend test results for female rats.*

| | *Method* | | | |
|---|---|---|---|---|
| | *Cox* | | *Kruskal-Wallis* | |
| | *Statistics* | *P-Value* | *Statistics* | *P-Value* |
| *Time-Adjusted Trend Test* | | | | |
| *Depart from Trend* | *8.8353* | *0.0654* | *8.6590* | *0.0702* |
| *Dose-Mortality Trend* | *1.1221* | *0.2895* | *1.2207* | *0.2692* |
| *Homogeneity* | *9.9573* | *0.0765* | *9.8797* | *0.0787* |

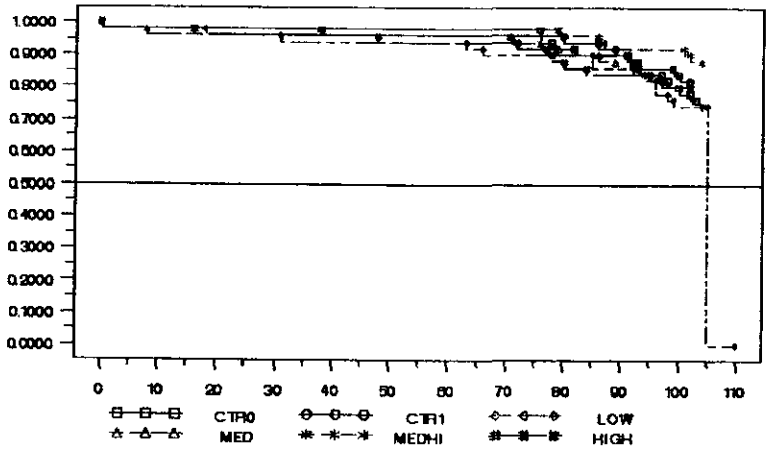



*Figure 1M: Survival curves for male rats*

*Table 1M: Dose-mortality trend test results for female rats.*

| | Method | | | |
|---|---|---|---|---|
| | Cox | | Kruskal-Wallis | |
| | Statistics | P-Value | Statistics | P-Value |
| Time-Adjusted Trend Test | | | | |
| Depart from Trend | 5.5839 | 0.2324 | 5.5174 | 0.2382 |
| Dose-Mortality Trend | 0.8973 | 0.3435 | 0.7303 | 0.3928 |
| Homogeneity | 6.4812 | 0.2622 | 6.2476 | 0.2829 |

*For female rats, the homogeneity tests detected inconsistency in mortality rates among dose groups, the p-values of the test results were marginal significant (about 0.077). Although the trend tests did not show statistical significant results, the tests for the departure from the trend showed marginal significant results. The results for the departure of the trend tests suggested that the weight of actual dose levels used for the trend tests was not appropriate. The inconsistency of mortality rates was mainly due to the large difference in mortality rates in the two control groups, 86% and 68% respectively.*

*For male rats, the test results suggested that the mortality rates were consistent among dose groups and there was no positive linear trend detected.*

*Tumor data:*

*All the test results for dose-response positive trends of tumor rates in female rats were provided in Table 2F. Statistical significant positive trend (p-value=0.0021) was observed in the benign thymoma tumor in thymus. This tumor type was classified as both fatal and incidental by the sponsor. The series of 2x6 tables by study period were presented in Table 2F-1. As can be seen from this table, the tumor rates in the two highest dose groups were higher than the rest of dose groups. Consistent with the sponsor's finding, the tests for pairwise comparisons did not reach statistical significance.*

*In the male rat group, the results are provided in Table 2M. No significant positive dose-response trend was detected. However, in pairwise comparison, statistically significant result (p-value=0.005) was observed between the control groups and the low dose group in the benign thymoma tumor in thymus. The 2x3 tables (2 control groups+low dose group) were presented in Table 2M-1. The total tumor rates for the combined control groups and the low dose group were 3% (3/100) and 16% (8/50), respectively.*

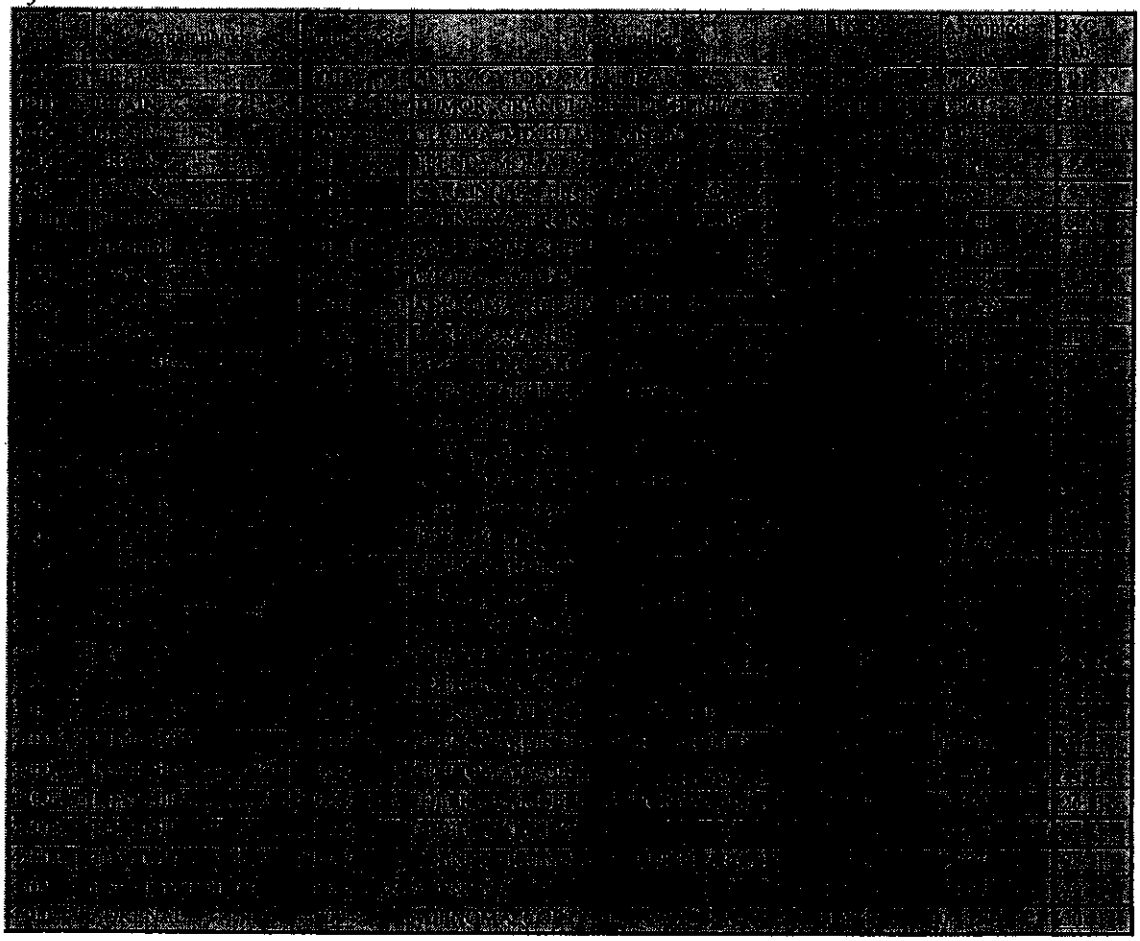
*Combining tumor type "Hemangiosarcoma" across organs: Overall hemangiosarcoma tumor occurrence rates were low for both female and male rats. For the female rats, there were only 4 benign hemangiosarcoma tumors, 2 in control group and 2 in the medium dose (3mg/kg /day) group across organs. For male rats, there were 3, 0, 1, 2, 1, 0 hemangiosarcoma tumors in the two control groups, and dose groups 1, 3, 6, and 9 mg/kg /day, respectively.*

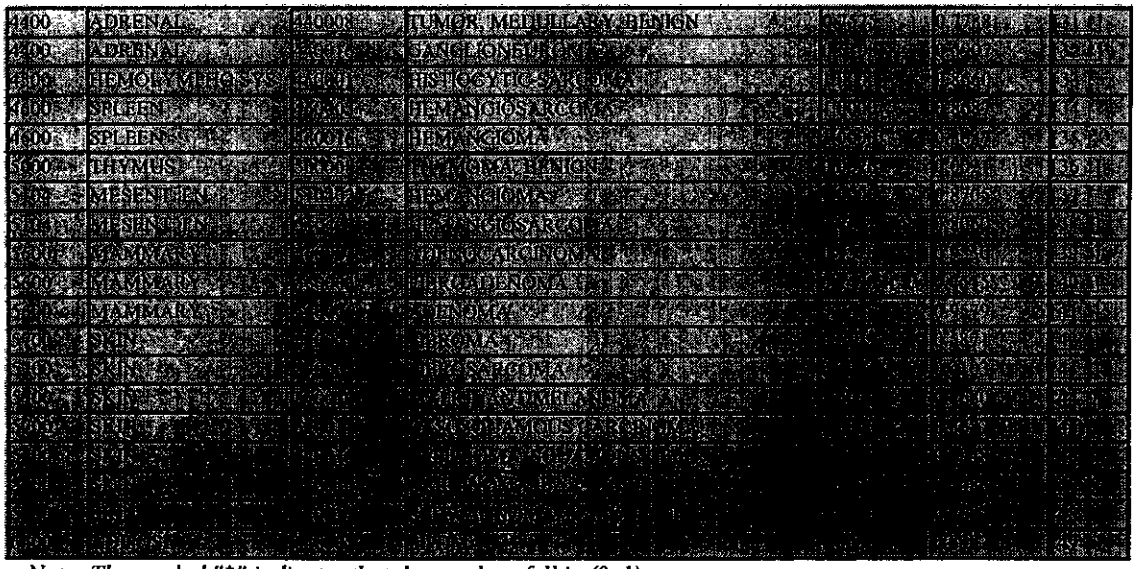
*Study validity: Dr. Hundley raised serious concerns regarding the validity of the type of animal carcinogenicity studies for immunologic suppressive drug products. He pointed out that since the study was not conducted in bacterial free environment, the level of dose studied had to be compromised at low levels to reduce the potential confounding factor, the increased infection and tumor rate due to weakened immune systems. Because of the dose levels of the test substance that the rats received in the study, it was impossible to assess the carcinogenicity potential of the test substance.*

## Conclusion:

No statistically significant dose-mortality trend was observed in either female or male rats in this two-year carcinogenicity study. Positive dose-response trend was observed in the benign thymoma tumor in thymus in female rats. Pariwise comparisons also detected statistically significant difference in the benign thymoma tumor in thymus between the control and low dose groups in male rats. Overall, the validity of detecting the carcinogenicity potential of the test substance was compromised in this study due to insufficient dose levels.

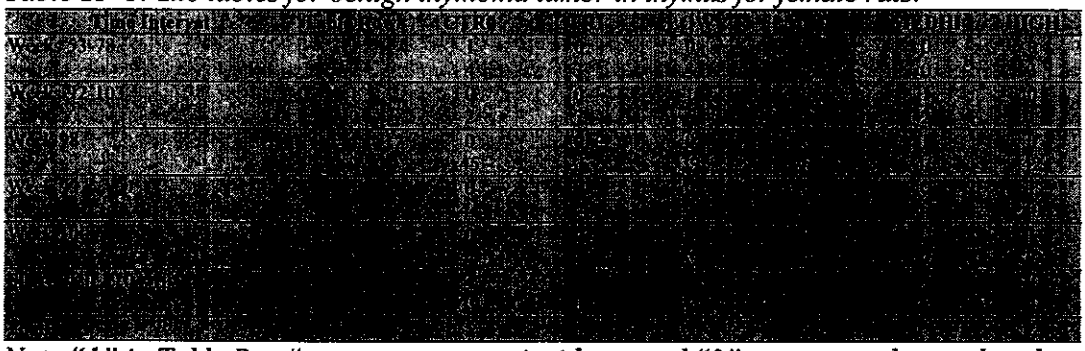
*Table 2F: Test results for dose-response positive trend by organ and tumor type for female rats.*





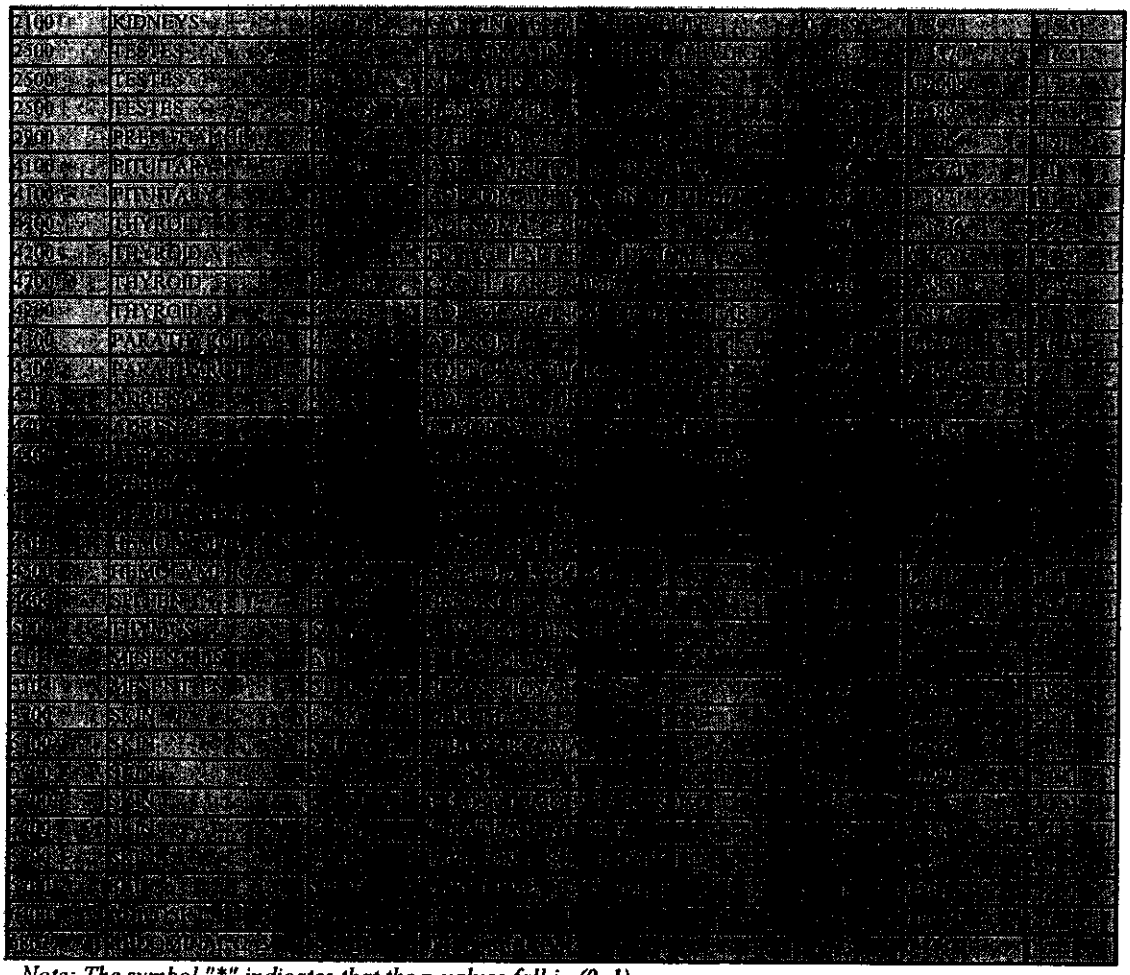
*Note: The symbol "*" indicates that the p-values fall in (0, 1).*

*Table 2F-1: 2x6 tables for benign thymoma tumor in thymus for female rats.*



*Note "1" in Table Row# represents tumor incidence and "2" represents the number that were tumor free.*

*Table 2M:* Test results for dose-response positive trend by organ and tumor type for male rats.



*Note: The symbol "*" indicates that the p-values fall in (0, 1).*

*Table 2M-1: Pairwise comparison 2x3 tables for bengign thymoma tumor in thymus for male rats.*

*Note "1" in Table Row# represents tumor incidence and "2" represents the number that were tumor free.*

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