CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-708/S027

50-709/S021

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	SE8
Submission Number	50-708 and 50-709
Submission Code	S-027 and S-021 (Amended)
Letter Date	February 13, 2006 and March 31, 2008
Reviewer Name	Patrick Archdeacon, M.D.
Review Completion Date	April 14, 2009
Established Name	Tacrolimus
(Proposed) Trade Name	Prograf
Therapeutic Class	Immunosuppressive
Applicant	Astellas Pharma US, Inc.
Priority Designation	S
Formulation	Capsule
Dosing Regimen	Tac/MMF/CS/Daclizumab
Indication	Prophylaxis of Acute Rejection in Kidney Transplantation
Intended Population	Adult

Table of Contents

1 Recommendations/Risk Benefit Assessment

Introduction:

Fujisawa initially sought the addition of MMF to the Prograf labeling as an adjunct therapy during a Type C meeting with the Agency on January 24, 2000. At that time, the Agency indicated that insufficient evidence existed to support such a labeling claim. Astellas Pharma US Inc ("Astellas"), the successor in interest to Fujisawa, proposed adding MMF to the Prograf labeling at a Type C meeing on March 18, 2002 based on a summary and meta-analysis of three prospective randomized trials involving 418 patients and an analysis of United Network for Organ Sharing (UNOS) data from 3,074 patients. The Agency again found the data insufficient for fileability and recommended that Astellas conduct a phase III study of Prograf and MMF versus cyclosporine and MMF, appropriately powered for safety and efficacy.

In response, Astellas designed and conducted Study 02-0-158; the findings of that study were submitted to NDA 50-708/S-027 (Prograf capsules) and NDA 50-709/S-021 (Prograf injection) as sNDAs 027 and 021, respectively, on February 13, 2006. The Division of Special Pathogens and Transplant Products completed its review of Study 02-0-158 on March 14, 2007: the Division concluded that Study 02-0-158 failed to provide sufficient evidence to support adding MMF to the Prograf labeling. In fact, due to an imbalance in the numbers of deaths between study groups considered to be related to overimmunosuppression, the review recommended an addition to the Prograf WARNING section.

While the Division found that Study 02-0-158 failed to demonstrate that the tacrolimus/MMF regimen evaluated in the study was safe and effective, DSPTP acknowledged that the transplant community remained interested in elucidating a tacrolimus/MMF regimen appropriate for use as an active comparator in kidney transplant trials. In addition, DSPTP believed that identifying such a regimen would serve the public health interest. Consequently, in August of 2007, the Division requested of several industry sponsors all available data from trials evaluating combinations of tacrolimus and MMF; the sponsors contacted included Hoffmann-La Roche Inc., Novartis Pharmaceuticals Corporation, Astellas Pharma US, Inc., and (b) (4) These companies responded by sending a summary of studies they had conducted or supported.

Among the trials submitted, the Roche Symphony-ELiTE trial stood out due to its size, its four arm design, availability of patient level data, and its robust results. Astellas subsequently amended its sNDA application with right of reference to Symphony-ELiTE. A complete review of Symphony-ELiTE and another independent review of Study 02-0-158 led to the conclusions that tacrolimus and MMF may be used in conjunction safely and effectively (see **Recommendation on Regulatory Action** for details regarding regimens).

1.1 Recommendation on Regulatory Action

Kidney Transplantation:

As noted above, the Division of Special Pathogens and Transplant Products (DSPTP) received the complete study report and data for the Symphony-ELiTE study from Roche. DSPTP customarily reviews submissions prepared by applicants for the purpose of evaluating specific claims requested by the applicant. The present submission of the Symphony-ELiTE study is somewhat different because it was submitted to FDA by Roche in response to an FDA letter to companies requesting clinical trial data that could be used to evaluate and identify a safe and effective way to use tacrolimus in conjunction with mycophenolate mofetil in the management of kidney transplant patients. The request was motivated by the Division's awareness both of the previous failed attempts (2000, 2002, 2007) to gather adequate data to support such labeling for these products and also the continued interest in using these products together in managing patients and in clinical trials. The present review, therefore, involves a submission requested from a sponsor for the purpose of investigating a specific concern of the Division. DSPTP reviewed in detail the patient level data provided to elucidate safety and efficacy issues pertaining to the use of Prograf (tacrolimus) in conjunction with Cellcept (MMF).

The use of tacrolimus in conjunction with MMF has become commonplace in kidney transplantation: over 60% of new kidney transplant patients in the US are maintained on some combination of the two drugs.[3] To date, however, the Agency has judged as insufficient the data submitted to show that such approaches are safe and effective. In the absence of such submitted data, immunosuppressive regimens using combinations of tacrolimus and MMF have been disallowed as active comparators in clinical trials.

Much of the transplant community, meanwhile, has become concerned that continued reliance on cyclosporine-based immunosuppressive regimens (the active comparators recommended by the FDA based on labeling) may not be ethical due to a growing belief within the community that the tacrolimus-based immunosuppressive regimens provide superior prophylaxis against rejection. Their concerns mirror the findings of the Cochrane Collaboration: its meta-analysis of 30 randomized clinical trials (4102 patients) concluded that "treating 100 recipients with tacrolimus instead of cyclosporine would avoid 12 suffering acute rejection, two losing their graft but cause an extra five to become insulin-requiring diabetics."[17]

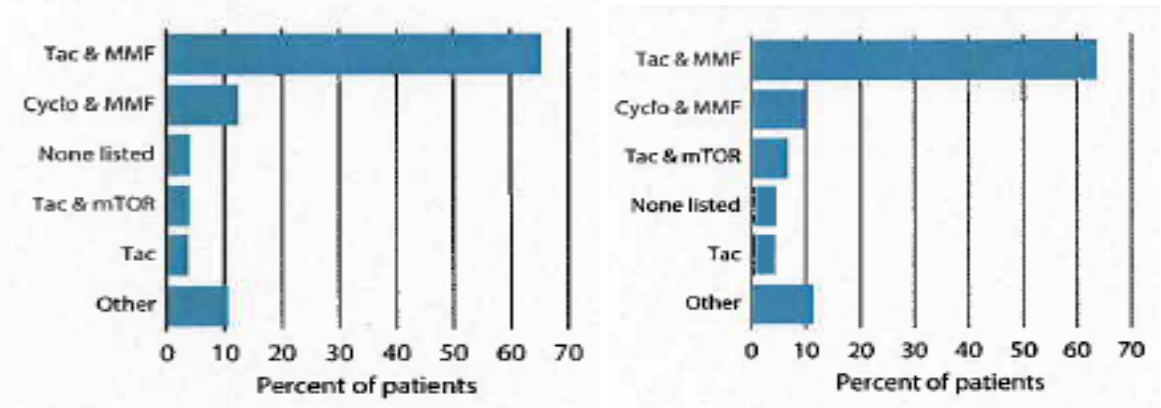


Figure 1.1A: Most common immunosuppression regimens at time of kidney transplant, 2002-06
On left: patient age 18+; on right: patient age 0-17
(Adapted from 2008 USRDS Annual Report)

While the Agency has been aware of such sentiments within the transplant community, it has identified a specific concern regarding the use of tacrolimus in conjunction with MMF. Several years after the introduction of MMF, it was appreciated that cyclosporine interferes with the enterohepatic recirculation of MPA (the active metabolite of MMF) causing a fixed oral dose of MMF to result in greater MPA exposure for patients on tacrolimus than patients on cyclosporine.[36, 37] MMF was approved on the basis of three clinical trials (the US Renal Transplantation MMF Study Group, The European MMF Cooperative Study Group, and the Tri-continental MMF Renal Transplant Study Group) which all used cyclosporine based immunosuppressive regimens.[5, 6, 7] The dosages determined safe and effective by those studies, therefore, could conceivably represent toxic dosages in the context of a tacrolimus based immunosuppressive regimen. For that reason, the Agency has attempted to identify adequate and well-controlled trials that would address the safety and efficacy of tacrolimus in conjunction with MMF compared to cyclosporine in conjunction with MMF.

A PubMed search was performed using the keywords "tacrolimus" and "cyclosporine" and the limit "randomized controlled trial". The search returned 344 results which were inspected individually. All single organ kidney transplant trials which randomized to tacrolimus in combination with MMF versus cyclosporine in combination with MMF were reviewed. In addition, the Division requested of several industry sponsors (Roche, Astellas, Novartis, and (b) (4)) all available data from trials evaluating combinations of tacrolimus and MMF. Through this search, the following pertinent trials were identified: Symphony-ELiTE[18], Study 02-0-158[19], DIRECT[2], Johnson et al 2000[20] (with follow-up data in Ahsan et al 2001[28]), Hernandez et al 2007[21], the CRAF[23] study, OPTIMA[24], and others.[27, 29, 30, 31, 32, 44]

The Symphony-ELiTE study was a Phase 3 study designed to investigate the safety and efficacy of four immunosuppressive regimens: Group A received MMF, "standard-dose" cyclosporine, and corticosteroids; Group B received MMF, "low-dose" cyclosporine, corticosteroids, and daclizumab; Group C received MMF, "low-dose" tacrolimus, corticosteroids, and daclizumab; Group D received MMF, "low-dose" sirolimus, corticosteroids, and daclizumab. Symphony-ELiTE was conducted entirely outside of the United States. The trial was not performed under any IND or NDA; the protocol was not reviewed by the Division prior to the conduct of the study. Prof. Henrik Ekberg, Lund University, Malmö, Sweden, and Prof. Philip Halloran, University of Alberta, Edmonton, Canada sponsored and F. Hoffman-La Roche, Basel, Switzerland supported the ELiTE-Symphony trial. Its size (n = 1645 patients) and scope (with 12 months of follow-up) make it a uniquely powerful study in the field of transplantation. Though nominally designed as "low-dose", the exposures to tacrolimus (and to MMF) achieved among the patients randomized to Group C reflect current clinical practices. In addition, the symmetric design of Group B to Group C allowed a demonstration of the efficacy of tacrolimus in conjunction with MMF for the indication of prophylaxis of acute rejection through a straightforward and statistically convincing superiority analysis. The Agency therefore selected the Symphony-ELiTE study as the primary focus of the investigation, though the results of the other studies also instructed its review of the use of tacrolimus in conjunction with MMF.

The Division has previously reviewed Study 02-0-158 (submitted to Astellas NDA 50-708/S-027 and NDA 50-709/S-021). With regards to the primary efficacy endpoint, the tacrolimus/MMF group of Study 02-0-158 met its pre-specified non-inferiority margin when compared to the

cyclosporine/MMF group. Due to safety concerns related to an imbalance in deaths between the two groups, however, the Division did not approve labeling for the use of tacrolimus in conjunction with MMF at that time. Rather, the following language was added to the Prograf WARNINGS section, "In one randomized, open-label, multi-center trial… There was an imbalance in mortality at 12 months in those patients receiving Prograf/MMF (4.2%) compared to those receiving cyclosporine/MMF (2.4%)." While the Division acknowledged that this imbalance was not statistically significant, it judged that the applicant had failed to provide "substantial evidence… consisting of adequate and well-controlled investigations" in support of the safety of tacrolimus used in conjunction with MMF, as required under section 505 of the Food Drug and Cosmetic Act of 1962. During the clinical review of the Symphony-ELiTE trial, the Division thoroughly revisited the primary data, the sponsor's clinical study report, and the 2007 DSPTP review of Study 02-0-158.

The DIRECT study, while large (n = 690 patients), was a 6 month trial primarily designed to elucidate whether tacrolimus is more likely to induce new onset diabetes after transplantation (NODAT) than cyclosporine; given its focus and shorter duration, it was deemed potentially less informative than Symphony-ELiTE, although it may merit additional attention in the future. The primary data from the DIRECT study has not yet been submitted to the FDA, but its clinical study report was available to assist the review of Symphony-ELiTE. In terms of all-cause mortality, 8 deaths occurred among the 339 patients randomized to cyclosporine (2.4%) and 8 deaths occurred among the 351 patients randomized to tacrolimus (2.3%) – suggesting the lack of a safety signal that would preclude the approval of tacrolimus in conjunction with MMF as used in the Symphony-ELiTE trial.

The CRAF and OPTIMA trials were conversion studies, rather than trials of *de novo* transplant patients. All of the other cited trials were relatively small. While primary data were not available from these trials, the Division examined the related published literature to supplement further its review of Symphony-ELiTE. Each suggested that the efficacy of tacrolimus with MMF was, at least, equivalent to cyclosporine with MMF. In their totality, no evidence of a difference in terms of all-cause mortality between the two combinations was detected (see section **1.2, Table 6**).

While the 2007 DSPTP review of Study 02-0-158 found that its data did not adequately support the safety of the combined use of Prograf and Cellcept, its results are considered along with the findings of the current review of Symphony-ELiTE in reaching the following recommendation on regulatory action. Given the demonstrated safety and efficacy of the combined use of Prograf (tacrolimus) and Cellcept (MMF) as used in Symphony-ELiTE, the Prograf labeling should be amended as detailed in Section **8.2** (Labeling Recommendations).

> *Reviewer Comment: Submissions for future trials in kidney transplantation using active comparators that include the combined use of Prograf and Cellcept may be considered acceptable. Similar to cyclosporine-based immunosuppressive regimens used as active comparators in the past, proposed tacrolimus-based immunosuppressive regimens should adhere to dosing parameters established within the framework of adequate and well-controlled clinical trials. Acceptance of an active comparator as an appropriate control remains an issue that will be addressed during the review of each and every proposed clinical trial.*

1.2 Risk Benefit Assessment

Risk-benefit analysis of immunosuppression in kidney transplantation represents an extremely challenging task. Inadequate immunosuppression leads to acute rejection episodes and/or graft loss. The interventions necessary to manage such events carry additional morbidity (and occasionally mortality) for the affected patient. Over-immunosuppression, on the other hand, may result in a range of infectious complications of varying significance. Quantifying the long-term costs of episodes of over- or under-immunosuppresion relative to one another inevitably requires subjective judgments. Moreover, unlike many other recipients of solid organ transplants (e.g., heart, liver, and lung), end stage renal disease patients do not have an absolute and immediate need of transplantation in order to survive. The option to support ESRD patients with dialysis, however, does not imply that the risks associated with transplantation and immunosuppresion are not justified.

A common misperception (and one which was specifically applied to the original review of Study 02-0-158) is that the benefits of kidney transplantation relate to quality of life: in discussing an imbalance in the number of deaths which occurred between groups in that study, the reviewer comments noted that "the higher mortality rate in the Prograf arm is extremely troubling because kidney transplantation would have been primarily life-enhancing, not life-saving, for these study subjects" (p.38 from the clinical review). The data clearly shows, however, that successful kidney transplantation represents a life-saving intervention. A longitudinal study published in the New England Journal of Medicine analyzed outcomes of 46,164 patients who were placed on a waiting list for deceased donor kidney transplantation. The study compared the mortality of those patients who received a transplant to those who remained on the waiting list: at 18 months, the relative risk of death for those who had received a transplant was 0.32 (95% confidence interval, 0.30 to 0.35, p-value<0.001). Further analysis of the data led to the conclusion that "the projected years of life remaining were 10 for patients who remained on the waiting list and 20 for those who received a transplant. The greatest difference in long-term survival was found among patients who were 20 to 39 years old at the time of placement on the waiting list: those who underwent transplantation were projected to live almost 17 years longer than those who remained on the waiting list."[4]

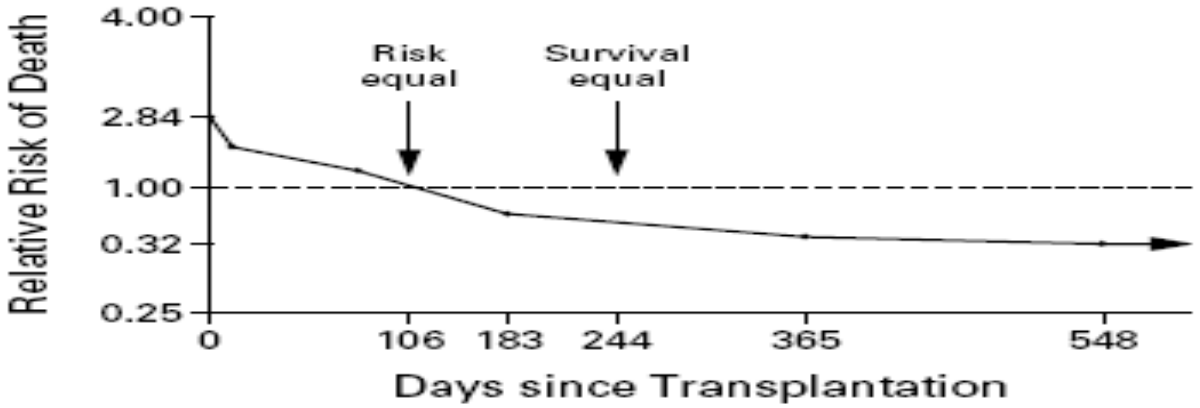


Figure 1.2A: Adjusted Relative Risk of Death among 23,275 Recipient of a First Deceased Donor Transplant (adapted from NEJM 1999; 341(23): p. 1727)

Table 1.2A: Outcomes Among Recipients of First Deceased Donor Renal Transplants

Group	Relative Risk 18 Mo after Transplantation (95% CI)†	P Value	Time at Which Risk of Death Equals That in Reference Group	Time at Which Likelihood of Survival Equals That in Reference Group	Projected Years of Life (in Reference Group) without Transplantation†‡	Projected Years of Life with Transplantation‡
			days after transplantation			
All recipients of first cadaveric transplants	0.32 (0.30–0.35)	<0.001	106	244	10	20
Age						
0–19 yr	0.33 (0.12–0.87)	0.03	3	5	26	39
20–39 yr	0.24 (0.20–0.29)	<0.001	11	57	14	31
40–59 yr	0.33 (0.29–0.37)	<0.001	95	251	11	22
60–74 yr	0.39 (0.33–0.47)	<0.001	148	369	6	10

(Adapted from NEJM 1999; 341(23): p. 1728)

Note that this comparison included only recipients of deceased donor kidneys. Patients who receive a transplant from a living donor enjoy significantly improved outcomes relative to patients who receive deceased donor kidneys. Such patients were necessarily excluded from the study because (as patients who had an identified living donor) they were never placed on the waiting list. Approximately 35% of kidney transplantations performed in the United States involve living donors[16]; the inclusion of such patients in the analysis would have demonstrated even more extreme differences. As an observational study, some potential for bias exists: the group of patients who did not receive a kidney may not have been otherwise identical to the group of patients who did. The findings of the study are sufficiently robust, however, to conclude that the benefits of successful kidney transplantation extend well beyond quality of life issues.

Figure 1.2A and **Table 1.2A** capture a guiding principle in renal transplantation: certain risks assumed in the transplantation may result in long term benefits. While the study by Wolfe et al elegantly proves that kidney transplantation translates to increased patient survival, not all risk-benefit analyses lend themselves so well to quantification. The most preferable transplant strategy, of course, is that approach which leads to the most years of additional life. Conducting trials using this endpoint, however, is not feasible.

Relative to most other solid organ transplant recipient populations, the one-year mortality of kidney transplant patients is low – less than 4%, according to USRDS data.[33] Due to the rarity of the outcome, clinical trials lack the power to detect any differences in all-cause mortality associated with various immunosuppressive regimens. Moreover, renal allograft loss does not inevitably require immediate re-transplantation to circumvent death – unlike in liver and heart transplantation, graft loss does not directly cause mortality (though the indirect contribution is clearly significant: the adjusted annual mortality of patients who suffer graft loss far exceeds that

of patients on the transplant waitlist: 145.0 deaths versus 87.6 deaths per 1,000 patient years at risk[39]). Higher graft function (as measured by glomerular filtration rate or GFR) at one year post transplantation and avoidance of rejection are both associated with longer graft survival.[34, 35] While the established benefits of transplantation and risks of graft loss imply that shorter graft survival will ultimately translate to years of life lost, however, the magnitude of that loss is not readily calculated. A survival benefit clearly should accrue to patients on immunosuppressive regimens associated with improved GFR, less acute rejection, and longer graft survival. Insufficient data exist, however, to quantify that benefit precisely.

The data from Symphony show that its tacrolimus/MMF immunosuppressive regimen (Group C) resulted in higher glomerular filtration rates (GFR) and lower rates of acute rejection than either cyclosporine regimen studied (Group A and Group B). The data further showed a trend in favor of greater graft survival among patients in the tacrolimus group (see **Table 1,2B**, **1.2C**, and **1.2D**). For greater details, please refer to sections **6.1.4** and **6.1.5**.

Table 1.2B: Efficacy Outcomes at 12 Months

	Group A N=390	Group B N=399	Group C N=401	Group D N=399	P value
Estimated GFR at Month 12					
All patients mean ± SD median	N=390 57.07±25.10 57.04	N=399 59.39±25.05 60.94	N=401 65.40±27.03 66.18	N=399 56.68±26.88 57.45	<0.0001
Rate of BPAR					
All patients	113/390 (29%)	106/399 (27%)	60/401 (15%)	152/399 (38%)	<0.0001
Rate of Graft Loss Excluding Death					
All patients	28/390 (7.2%)	20/399 (5.0%)	12/401 (3.0%)	30/399 (7.5%)	0.0193

(adapted from Biometrics Review)

Table 1.2C: Summary Statistics for Estimated GFR at Month 12 with Sponsor's Imputation, ITT

Group	GFR [ml/min] at Month 12							
	N	MEAN	SD	MIN	Q1	MEDIAN	Q3	MAX
A	390	57.07	25.10	8.60	43.49	57.04	73.67	126.62
B	399	59.39	25.05	4.89	44.89	60.94	75.36	143.25
C	401	65.40	27.03	8.40	49.33	66.18	83.50	160.52
D	399	56.68	26.88	8.40	39.11	57.45	73.63	143.56
Total	1589	59.66	26.25	4.89	44.06	60.59	77.05	160.52
Pairwise Comparisons between the Groups								
	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D		
95% CI	(-5.83,1.18)	(-11.98,-4.69)	(-3.25,4.02)	(-9.63,-2.40)	(-0.90,6.32)	(4.98,12.47)		
99.2% CI	(-7.05,2.40)	(-13.25,-3.43)	(-4.52,5.29)	(-10.89,-1.14)	(-2.16,7.58)	(3.68,13.77)		
P value*	0.1658	0.0001	0.8087	0.0011	0.1171	0.0001		

*Wilcoxon rank-sum test; (adapted from Biometrics Review)

Table 1.2D: Pairwise Comparisons of Overall Failure, BPAR, and Graft Loss

	A - B	A - C	A – D	B – C	B – D	C - D
Overall Failure						
95% CI	(-2.3,11.4)	(9.3,22.1)	(-17.3,-3.1)	(4.8,17.4)	(-21.7,-7.8)	(-32.5,-19.4)
99.2% CI	(-4.6,13.8)	(7.1,24.3)	(-19.7,-0.7)	(2.7,19.5)	(-24.1.,-5.5)	(-34.7,-17.2)
P value	0.1996	<0.0001	0.0046	0.0005	<0.0001	<0.0001
BPAR						
95% CI	(-4.1, 8.9)	(8.1, 20.0)	(-15.9,-2.3)	(5.8, 17.4)	(-18.2,-4.8)	(-29.3,-17.0)
99.2% CI	(-6.3, 11.1)	(6.0, 22.0)	(-18.2, 0.0)	(3.8, 19.4)	(-20.5,-2.6)	(-31.4,-14.9)
P value	0.4993	<0.0001	0.0084	<0.0001	0.0007	<0.0001
Graft loss excluding death						
95% CI	(-1.4, 5.8)	(0.9, 7.5)	(-4.2, 3.6)	(-0.9, 5.0)	(-6.1, 1.1)	(-7.9, -1.2)
99.2% CI	(-2.6, 6.9)	(-0.2,8.6)	(-5.5, 4.8)	(-1.9, 5.9)	(-7.3, 2.3)	(-8.9, -0.1)
P value	0.2609	0.0116	0.9632	0.2015	0.1886	0.0067

(adapted from Biometrics Review)

One can therefore deduce qualitatively that benefits in terms of additional years of life should accrue to those patients who received the tacrolimus/MMF. As long as this regimen is not associated with greater risks, then, those data demonstrate that the risk-benefit analysis favors the tacrolimus group in the Symphony-ELiTE trial.

Quantifying the risks associated with an immunosuppressive regimen is as difficult as calculating the benefits. Again, one cannot simply conduct randomized clinical trials to determine which immunosuppresion regimen confers the most years of additional life. One may, however, examine safety endpoints that impact on that critical outcome: deaths, graft loss, graft function, rejection rates, opportunistic infections, overall infections, malignancies, cardiovascular events, and hospitalizations represent some of the events which must be considered. Some transplant strategies may declare themselves failures through clear statistical inferiority in one or more of these important endpoints. In the Symphony-ELiTE study, for instance, the sirolimus/MMF arm (Group D) showed clear inferiority in terms of pre-determined safety endpoints compared to the cyclosporine treated groups. Those same safety endpoints, however, either favored the tacrolimus arm (graft function, rejection rates, CMV infection) or failed to show a difference between the tacrolimus and the cyclosporine arms (all of the others) except with regards to incidence of diarrhea and new onset diabetes after transplantation. Please refer to sections **6.1.4**, **6.1.5**, and **7.3** for details.

Two explanations exist for failing to show a difference between groups for an endpoint of interest: either no difference exists or the study lacked sufficient power to detect a difference. Due to the knowledge that (when using identical oral doses of MMF) tacrolimus regimens result in higher MPA exposure, a hypothesis exists that the use of tacrolimus in conjunction with MMF may lead to over-immunosuppression and excess mortality. Given that one cannot precisely quantify the long-term benefit conferred by tacrolimus/MMF regimens over cyclosporine/MMF regimens in units of additional years of life gained, it has been suggested that any detectable

increase in early all-cause mortality for a given regimen of tacrolimus and MMF should dissuade one from the use of tacrolimus in conjunction with that dose of MMF. Less clear, however, are the mechanisms by which one can examine whether the use of tacrolimus with MMF leads to a difference in mortality. The size limits on transplant trials and the relative rarity of death in kidney transplant populations precludes relying on a single randomized clinical trial to determine whether all-cause mortality is affected by their combined use because ruling out a risk difference of 1% between patients assigned to a tacrolimus/MMF based regimen and patients assigned to an active comparator would require a trial of approximately 15,000 patients randomized 1:1.

To address this crucial concern, the risk-benefit analysis of the Symphony-ELiTE trial was supplemented with an overview of the published literature. A meta-analysis by the Cochrane Collaboration published in 2005 show no increased risk of all-cause death for tacrolimus-based immunosuppressive regimens relative to cyclosporine-based immunosuppressive regimens.[17] In fact the data collected by the Cochrane review trended in favor of tacrolimus-based regimens in terms of all-cause death.

Table 1.2E: All-cause Death for Tacrolimus-based IS Compared To Cyclosporine-based IS from Cochrane Collaboration Review

	No of Trials	No of Patients	Relative Risk (95% CI)*	P-value
Death (all cause)				
Six months	8	1702	0.68 (0.36 to 1.31)	0.92
One year	14	2604	1.05 (0.66 to 1.68)	0.31
Two years	4	1262	0.78 (0.48 to 1.27)	0.45
Three years	6	1290	0.91 (0.59 to 1.40)	0.91
Five years	2	827	1.00 (0.75 to 1.33)	0.47

*Relative risk values <1 favor treatment with tacrolimus; Adapted from BMJ 2005; 331:810

The Cochrane meta-analysis included many trials that used azathioprine rather than MMF; in addition, the meta-analysis did not include several large trials conducted after 2003. For those reasons, an independent global review of the literature was performed to determine whether evidence exists to suggest that the combination of tacrolimus and MMF leads to increased mortality in kidney transplantation. The global review included all trials cited in the Cochrane review that used MMF and all additional studies identified through a PubMed search for randomized trials comparing tacrolimus and cyclosporine. As described earlier, the search was performed using the keywords "tacrolimus" and "cyclosporine" and the limit "randomized controlled trial". The search returned 344 results which were inspected individually. All single organ kidney transplant trials which randomized to tacrolimus in combination with MMF versus cyclosporine in combination with MMF were included in the global review. A total of 13 studies with 3707 patients were identified.

Table 1.2F: All-cause Death for Tacrolimus/MMF Compared To Cyclosporine/MMF in Global Literature Review

Study	F/U	Design	Tac/MMF	CYA/MMF	Diff (Tac-CYA) 95% CI (exact test)
Busque et al[27]	6 months	*De novo*	0/23	0/21	0, (-14.8, 16.2)
Ahsan et al[28]	2 years	*De novo*	4/72	9/75	-6.4, (-16.7, 3.1)

Liu et al[29]	6 months	*De novo*	0/15	0/12	0, (-26.5, 23.9)
Wang et al[30]	1 year	*De novo*	0/25	0/32	0, (-11.2, 13.7)
Yang et al[31]	1 year	*De novo*	3/30	0/30	10.0, (-2.4, 26.5)
Yu et al[32]	6-12 months	*De novo*	0/40	0/50	0, (-7.2, 8.9)
Vincenti et al[2] (DIRECT)	1 year (for death)	*De novo*	8/351	8/339	-0.08, (-2.6, 2.4)
Ekberg et al[18] (SYMPHONY)	1 year	*De novo*	11/401	7/399	-0.59, (-3.2, 2.0)
"	"	"	11/401	13/390	0.99, (-1.3, 3.3)
Silva et al[19] (Study 02-0-158)	1 year	*De novo*	9/214	6/212*	1.38, (-2.4, 5.3)
"	"	"	3/212	6/212	-1.42, (-4.8, 1.6)
Hernandez et al[21]	2 years	*De novo*	8/80	4/80	5.0, (-3.6, 14.3)
Anil Kumar et al[44]	5 years	*De novo*	9/50	8/50	2 (-13.5, 17.6)
Bolin et al[27] (OPTIMA)	1 year	Conversion	0/100	2/111	(-1.9, 6.4)
"	"	"	1/112	2/111	(-3.2, 5.5)
Shihab et al[23] (CRAF)	5 years	Conversion	12/131	8/60	(-5.2, 15.8)

* The publication reports 5 deaths, but review of Study 02-0-158 revealed an additional death in the ITT group not included in the safety analysis

Inspection of Table 3 suggests that no increase in absolute mortality is observed with use of tacrolimus and MMF compared to cyclosporine and MMF. The three largest trials (DIRECT, Symphony, and Study 158) show essentially equivalent mortality associated with tacrolimus and cyclosporine immunosuppressive regimens each studied. Among the smaller trials, three (Ahsan et al, Bolin et al, Shihab et al) appeared to trend in favor of tacrolimus, two appeared to trend in favor of cyclosporine (Yang et al, Hernandez et al), while five showed no difference (Busque et al, Liu et al, Wang et al, Yu et al, Anil Kumar et al). While one cannot decisively conclude that tacrolimus-MMF regimens are not associated with a higher mortality than cyclosporine-MMF regimens, neither can one conclude that cyclosporine-MMF regimens are not associated with a higher mortality than tacrolimus-MMF regimens.

The Food and Drug Cosmetic Act of 1962 requires that the Agency base its regulatory decisions on "evidence consisting of adequate and well-controlled investigations". In addition to the data from Symphony-ELiTE and the other randomized controlled trials in **Table 1.2F**, however, it may be reasonable to consider the observational data available from US transplant registries. **Figure 1.2B** depicts the shift in clinical practice towards the tacrolimus/MMF based immunosuppressive regimens since 1995. **Table 1.2G** suggests that mortality rates have not been adversely impacted by that shift. Even the unadjusted mortality rates have remained stable throughout that same time period, despite pronounced shifts towards transplanting older patients, more patients with co-morbidities, and more patients with extended criteria donor kidneys (see

Table 1.2H). The association of tacrolimus/MMF combination regimens with improved adjusted mortality does not prove that tacrolimus/MMF regimens offer a benefit in terms of mortality over cyclosporine/MMF combination regimens: during that same period, other changes were introduced into kidney transplantation (including approaches to induction, to diagnosis and management of infectious complications, and to treatment of acute rejection episodes). Nonetheless, such data provide additional support to the analysis of the randomized controlled trials which found no clear evidence of a difference in early mortality between groups receiving cyclosporine/MMF and groups receiving tacrolimus/MMF.

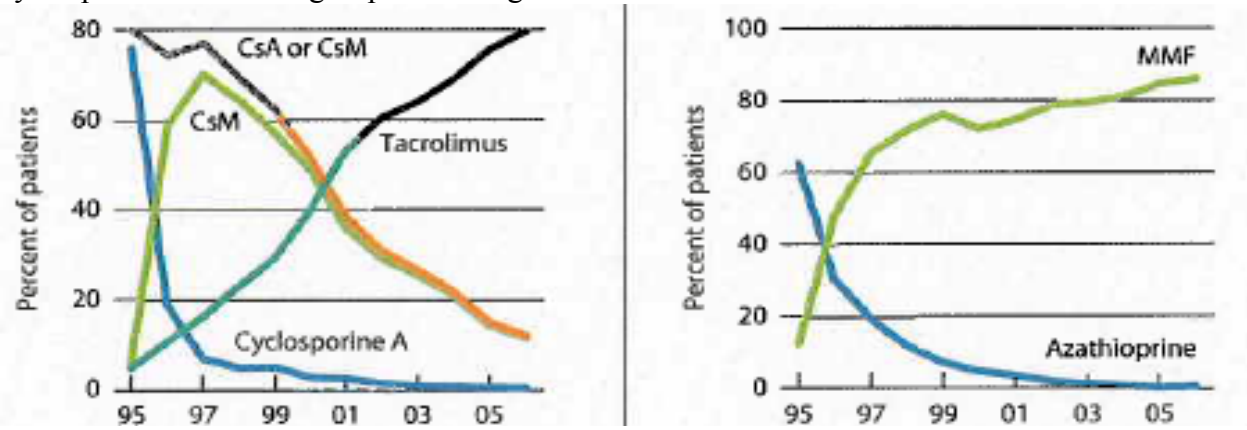


Figure 1.2B: Trends in Use of Tacrolimus, Cyclosporine, and MMF from 1995-2006
(Adapted from 2008 USRDS Annual Report, Fig 7.17 and 7.18)

Table 1.2G: Adjusted Annual Mortality Rates by Year per 1,000 Patient Years at Risk

1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
58.7	54.6	50.9	49.2	50.1	48.7	49.8	47.3	47.3	44.1	44.1	40.8

(Adapted from 2008 USRDS Annual Report, Table H.28, p.205)

Table 1.2H: Unadjusted Annual Mortality Rates by Year per 1,000 Patient Years at Risk

1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
33.9	33.9	33.9	33.9	34.3	34.5	35.6	33.9	34.5	33.1	33.8	33.2

(Adapted from 2008 USRDS Annual Report, Table H.28, p.205)

The best data available, then, suggests the following conclusions. Kidney transplantation is a life-saving intervention.[4] Immunosuppressive regimens which yield lower rates of rejection and higher graft function will result in longer graft life (and therefore increased years of additional life).[34, 35] The Symphony-ELiTE study demonstrates that lower rates of rejection and higher graft function are achieved with its tacrolimus/MMF regimen than with either of its cyclosporine/MMF regimens (see sections **6.1.4** and **6.1.5** for details). While some have hypothesized that increased MPA exposures could result in increased mortality among recipients of tacrolimus/MMF regimens compared to cyclosporine/MMF regimens, the evidence does not convincingly support this contention. In fact, as much evidence exists to suggest that cyclosporine/MMF regimens result in increased mortality compared to tacrolimus/MMF regimens. Consideration of all these conclusions leads to the following risk-benefit analysis: tacrolimus and MMF, as used in the Symphony-ELiTE trial, are at least as safe and efficacious as cyclosporine and MMF, as used in the Symphony-ELiTE trial.

1.3 Recommendations for Postmarketing Risk Management Activities

Each of the drugs used in the Symphony-ELiTE study has been lawfully marketed for indications related to kidney transplantation for many years. DSPTP, however, remains interested in further elucidating issues pertaining to the combined use of tacrolimus and MMF. Additional studies available for review include FDCC, OPTICEPT, and DIRECT. Consideration of these (and other) studies may further inform the current recommendations. Additional trials to elucidate proper use of lytic induction agents such as thymoglobulin and campath are needed. It is not clear that the use of tacrolimus in conjunction with MMF (or cyclosporine in conjunction with MMF, for that matter) would remain appropriate in the context of such powerful induction without adjustment of the dosages of the concomitant immunosuppressants.

2 Introduction and Regulatory Background

Astellas Pharma US Inc had submitted supplemental applications for Prograf (NDA 50-708/S-027 and NDA 50-709/S-021) seeking approval of the use of MMF in conjunction with Prograf for the indication of prophylaxis of (b) (4) rejection in kidney transplant on February 13, 2006. After completing the review of the submission, the FDA issued an approvable letter on March 14, 2007 which stated its finding that "a safe and effective dosage regimen of mycophenolate mofetil (MMF) as an adjunct therapy with Prograf® has not been established in this study… Although you met the primary non-inferiority efficacy endpoint in Study 02-0-158, the risk/benefit analysis did not support inclusion of this study in the CLINICAL STUDIES section of the Prograf® package insert because of more adverse events known to be associated with the use of MMF as well as an increase in deaths considered to be related to over immunosuppresion and infections in the Prograf® and MMF arm." The approvable letter further informed the Sponsor that "under 21 CFR 314.102(d), you may request a meeting or telephone conference with the Division of Special Pathogen and Transplant Products to discuss what further steps need to be taken before the application may be approved."

Astellas submitted a request for a Type A meeting on March 22, 2007 which was subsequently held on May 30, 2007. At that meeting, the Sponsor presented additional data from the Symphony-ELiTE trial to supplement their responses to the issues raised by DSPTP. Astellas stated its intention to obtain right of reference to that trial, which it subsequently did. The Sponsor has since amended NDA 50-708/S-027 and NDA 50-709/S-021 to include data from the Symphony-ELiTE trial. Independently, as previously described in this review, a literature search and request for industry data was performed by DSPTP: those efforts also identified Symphony-ELiTE as a uniquely powerful study that compare the use of tacrolimus in conjunction with MMF to the use of cyclosporine in conjunction with MMF.

Prof. Henrik Ekberg, Lund University, Malmö, Sweden, and Prof. Philip Halloran, University of Alberta, Edmonton, Canada sponsored and F. Hoffman-La Roche, Basel, Switzerland supported the ELiTE-Symphony trial. The principal investigator was Prof. Henrik Ekberg. The nominal investigational drug of the study was daclizumab (Zenapax®), a Roche product. Identification of an efficacious regimen or regimens with less toxicity than the nominal comparator regimen (Group A) constituted the underlying goal of the study. A traditional approach to

immunosuppression, as represented by that comparator regimen, relies on relatively high doses of cyclosporine. The investigators therefore hypothesized that the traditional approach will carry a significant burden of calcineurin inhibitor related toxicities including nephrotoxicity, hypertension, hyperlipidemia, infection, and malignancy. They further hypothesized that the traditional approach limits mean graft survival both directly through increased cumulative non-immunologic renal insults and indirectly through an increased incidence of deaths with a functioning graft (DWFG). The ELiTE-Symphony trial tested the hypothesis that alternate regimens with either less exposure or no exposure to calcineurin inhibitors would provide efficacious prophylaxis against rejection while limiting toxicity. Identifying and adopting such regimens could theoretically improve graft survival.

With the exception of corticosteroids, each of the drugs used in the ELiTE-Symphony trial has a labeled indication for renal transplantation: cyclosporine received FDA approval in 1983; tacrolimus received FDA approval in 1997; mycophenolate mofetil received FDA approval in 1995; sirolimus received FDA approval in 1999; daclizumab received FDA approval in 1997. Based on the clinical trials on which it approved mycophenolate mofetil, the FDA labels states that MMF should be used in conjunction with cyclosporine and corticosteroids. To date, the FDA has not concluded that any clinical trials have shown that MMF may be used safely and effectively in conjunction with daclizumab, tacrolimus, or sirolimus.

The Symphony-ELiTE clinical study report and datasets were submitted by Roche at the specific request of the FDA; the FDA had requested of Roche (as well as other industry leaders in transplantation) all trial information regarding the use of tacrolimus in combination with mycophenolate mofetil. Roche noted at the time of its submission that it regarded the Symphony-ELiTE as an investigator-driven trial: while Roche provided significant financial backing to conduct the study, it did not ensure that the data were compiled with the rigor and precision Roche would demand of a trial intended for submission to the FDA.

2.1 Product Information

Products: Zenapax, Cellcept, Neoral, Prograf, Rapamune, Corticosteroids

Zenapax (daclizumab) is a humanized IgG1 monoclonal antibody that binds CD25 (IL-2R) on activated lymphocytes. It is approved for the prophylaxis of acute organ rejection in renal transplant recipients, as part of an immunosuppressive regimen including cyclosporine and corticosteroids. Its labeling includes a warning that "in a randomized, double-blind, placebo-controlled trial of ZENAPAX in cardiac transplant recipients (n=434) receiving concomitant cyclosporine, mycophenolate mofetil, and corticosteroids, mortality was increased in patients randomized to receive ZENAPAX compared with those randomized to receive placebo."

Cellcept (mycophenolate mofetil, MMF) is the precursor of MPA (mycophenolic acid), a selective, uncompetitive, and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH). MPA inhibits the proliferative responses of both B and T lymphocytes. It is approved for the prophylaxis of organ rejection in patients receiving renal, cardiac, or hepatic transplants. Its labeling instructs that it should be used concomitantly with cyclosporine and corticosteroids. MMF was approved on the basis of three clinical trials: the US Renal Transplantation MMF

Study Group, The European MMF Cooperative Study Group, and the Tri-continental MMF Renal Transplant Study Group. The USA study regimen included cyclosporine, corticosteroids, and ATGAM induction; the European and Tri-continental study regimens included cyclosporine and corticosteroids (but did not use induction). Cyclosporine was used according to local practices, not targeted to protocol specified levels; the limited information available suggests that the cyclosporine levels achieved in those trials were higher than levels targeted in present day trials and clinical practice. Based on those same three trials, the following recommendation was included in the labeling: "A dose of 1 g … twice a day (daily dose of 2g) is recommended for use in renal transplant patients. Although a dose of 1.5 g administered twice daily (daily dose of 3g) was used in clinical trials and was shown to be safe and effective, no efficacy advantage could be established for renal transplant patients." In practice, the Agency has subsequently allowed the use of immunosuppressive regimens that combine approved induction agents, cyclosporine dosed to a range of target troughs, MMF started at 2 g/day, corticosteroids dosed according to local practice as active comparators in renal transplant clinical trials. Since the approval of MMF, it has been appreciated that cyclosporine interferes with the enterohepatic recirculation of MMF, resulting in lower MPA levels. Recommendations for the dosing of MMF in conjunction with tacrolimus (or any non-cyclosporine based immunosuppressive regimen) have not been established by the Agency.

Recently, several groups have attempted to apply therapeutic dose monitoring (TDM) to the use of MMF.[40-43] The results of some clinical studies by at least two of those groups have suggested that dosing MMF at 2 g/day in conjunction with cyclosporine will result in sub-therapeutic MPA levels.[41, 42] One group proposed "that clinical outcomes might be improved if the starting dose of MMF is 1 g twice daily when co-administered with tacrolimus and 1.5 g twice daily with cyclosporine."[41]

Neoral (cyclosporine) is cyclic nonribosomal peptide produced by *Tolypocladium inflatum*. It is a member of the calcineurin inhibitor class of immunosuppressants. It is approved for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants. Its labeling states that it has been used in combination with azathioprine and corticosteroids; it contains no instructions regarding its use with MMF. With regards to therapeutic dose monitoring (TDM), the labeling states only that "While no fixed relationship has been established, blood concentration monitoring may assist in the clinical evaluation of rejection and toxicity, dose adjustments, and the assessment of compliance". In practice, the Agency has allowed the use of immunosuppressive regimens that combine approved induction agents, cyclosporine dosed to a range of target troughs, MMF started at 2 g/day, corticosteroids dosed according to local practice as active comparators in renal transplant clinical trials.

Prograf (tacrolimus) is a macrolide lactone produced by *Streptomyces tsukubaensis*. Like cyclosporine, its immunosuppressant effects result from its inhibitor of calcineurin (a protein phosphatase). It is approved for the prophylaxis of organ rejection in patients receiving renal, cardiac, or hepatic transplants. Its current labeling states that "A safe and effective dosing regimen of MMF in combination with Prograf has not been established in kidney transplantation". With regards to therapeutic dose monitoring (TDM), the labeling states that "During the first three months, 80% of the patients maintained trough concentrations between 7-20 ng/mL, and then between 5-15 mg/mL, through 1 year. The relative risk of toxicity is

increased with higher trough concentrations." Those data derive from the Phase 3 study in kidney transplantation; the full immunosuppressive regimen in that study included an antilymphocyte antibody preparation, corticosteroids, and azathioprine.

Rapamune (sirolimus) is a macrolide lactone produced by *Streptomyces hygroscopicus*. It is not a member of the calcineurin inhibitor class; its immunosuppressant effect derives from inhibiting the activation of the mTOR, a regulator kinase, thereby inhibiting progression from the G_1 to the S phase of the cell cycle. While the use of sirolimus has the putative advantage of avoiding the nephrotoxicity associated with calcineurin inhibitors, evidence is accumulating that it may worsen proteinuria. It is approved for the prophylaxis of organ rejection in patients receiving renal transplants. Its labeling states that "it is recommended that Rapamune be used initially in a regimen with cyclosporine and corticosteroids." In clinical practice, sirolimus has not commonly been combined with MMF in kidney transplant patients.

Corticosteroids, including methylprednisolone and prednisone, remain a common component of immunosuppressive regimens. The use of corticosteroids in the Symphony-ELiTE study was consistent with usual clinical practices.

2.2 Tables of Currently Available Treatments for Proposed Indications

For kidney transplantation (based on the labeling):

1) Cellcept/MMF (with corticosteroids + cyclosporine)
2) Neoral/Cyclosporine (with corticosteroids + azathioprine)
3) Prograf/Tacrolimus (with corticosteroids + azathioprine)
4) Rapamune/Sirolimus (with cyclosporine and corticosteroids; cyclosporine may be withdrawn)
5) Myfortic/Mycophenolic Sodium (with cyclosporine)
6) Zenapax/Daclizumab for induction (with cyclosporine and CS)
7) Simulect/Basiliximab for induction (with cyclosporine and CS)
8) Thymoglobulin for acute rejection

The relevant package inserts include a variable amount of information regarding the target dosages of each of these drugs: the Prograf labeling recommends maintaining a trough level of 5-20 ng/mL; the Rapamune labeling includes data that suggests a range 4.5-14 ng/mL when used with cyclosporine and a range of 12-24 ng/mL when used without cyclosporine; the Cellcept label recommends a fixed dose of 2 (or 3) grams by mouth per day in divided doses; the Neoral label states that "while no fixed relationship has been established, blood concentration monitoring may assist in the clinical evaluation of rejection and toxicity…". Of note, as evident from inspection of the list, the FDA has approved several of these drugs to be used in combination with one another. The FDA has not, however, established "gold-standard" regimens with detailed dosing instructions for optimized combinations of three or more drugs. It is further worth noting that clinicians in the field of transplantation view the recommended dosing on the package inserts as antiquated: the upper range levels recommended by the Prograf and Rapamune labeling, for instance, are currently seen as supra-therapeutic.

2.3 Availability of Proposed Active Ingredient in the United States

All of the products in 2.2 are lawfully marketed in the US.

2.4 Important Safety Issues with Consideration to Related Drugs

All of the drugs used in Symphony-ELiTE are lawfully marketed products. Many have known safety issues well-documented in the literature and their respective labeling. These issues include (but are not limited to) hypertension, new onset diabetes after transplantation (NODAT), infection (including BK nephropathy and CMV), and malignancy (including post transplant lymphoproliferative disorder and skin cancer). Because the review was undertaken to elucidate safety of using tacrolimus in conjunction with MMF, particular attention was given to these issues during the evaluation of Symphony-ELiTE.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Fujisawa initially sought the addition of MMF to the Prograf labeling as an adjunct therapy during a Type C meeting with the Agency on January 24, 2000. At that time, the Agency indicated that insufficient evidence existed to support such a labeling claim. Astellas Pharma US Inc ("Astellas"), the successor in interest to Fujisawa, proposed adding MMF to the Prograf labeling at a Type C meeing on March 18, 2002 based on a summary and meta-analysis of three prospective randomized trials involving 418 patients and an analysis of United Network for Organ Sharing (UNOS) data from 3,074 patients. The Agency again found the data insufficient for fileability and recommended that Astellas conduct a phase III study of Prograf and MMF versus cyclosporine and MMF, appropriately powered for safety and efficacy.

In response, Astellas designed and conducted Study 02-0-158; the findings of that study were submitted to NDA 50-708 (Prograf capsules) and NDA 50-709 (Prograf injection) as sNDAs 027 and 021, respectively, on February 13, 2006. The Division of Special Pathogens and Transplant Products completed its review of Study 02-0-158 on March 14, 2007: the Division concluded that Study 02-0-158 failed to provide sufficient evidence to support adding MMF to the Prograf labeling. In fact, due to an imbalance in the numbers of deaths between study groups, the review recommended an addition to the Prograf WARNING section.

While the Division found that Study 02-0-158 failed to demonstrate that its tacrolimus/MMF regimen was safe and effective, DSPTP acknowledged that the transplant community remained interested in elucidating a tacrolimus/MMF regimen appropriate for use as an active comparator in kidney transplant trials. In addition, DSPTP believed that identifying such a regimen would serve the public health interest. Consequently, in August of 2007, the Division requested of several industry sponsors all available data from trials evaluating combinations of tacrolimus and MMF; the sponsors contacted included Hoffmann-La Roche Inc., Novartis Pharmaceuticals Corporation, Astellas Pharma US, Inc., and (b) (4).

Among the trials submitted, the Roche Symphony-ELiTE trial stood out due to its size, its four arm design, and its robust results. Astellas subsequently amended its sNDA application with right of reference to Symphony-ELiTE. A complete review of Symphony-ELiTE and another

independent review of Study 02-0-158 led to the conclusions that tacrolimus and MMF may be used in conjunction safely and effectively (see **Recommendation on Regulatory Action** for details regarding regimens).

2.6 Other Relevant Background Information

Transplantation medicine has rapidly evolved since the introduction of cyclosporine in the 1980s. Clinicians have refined their practices to reflect a growing familiarity with the use of immunomodulators gained not only through randomized clinical trials but also through inspection of registry data and review of local experiences. Given the relatively limited size of the field, practitioners in transplantation medicine have been able to disseminate information and opinions to one another quickly and efficiently. As a result, current approaches to immunosuppression for the purpose of prophylaxis of organ rejection do not adhere closely to product labeling. For instance, over 60% of new kidney transplant patients in the US are now maintained on regimens which use tacrolimus in conjunction with MMF.[3] Furthermore, even those patients maintained on cyclosporine-based immunosuppression do not use regimens similar to those used in the clinical trials which provided the basis for the approval of MMF in conjunction with cyclosporine.

The rapid evolution of immunosuppressive regimens in transplantation medicine has posed certain challenges to the FDA: the Agency has needed to balance its mandate to make regulatory decisions based on the review of adequate and well-controlled clinical trials with its requirement to ensure the ethical integrity of those same trials. Expert opinion has held that strict adherence to regulatory practices would result in substandard patient care by requiring on outmoded comparators with unnecessary toxicities. Dilemmas of this nature are not unknown to the Agency or unique to the arena of transplantation medicine, but they do require individual analysis and occasional action.

At present, the Agency has allowed the use of some active comparators that reflect current practices but which have not been rigorously assessed in reviewed clinical trials. For instance, the Phase 2 and Phase 3 trials conducted in support of the BLA application for Belatacept used as their active comparator basiliximab induction, cyclosporine troughs of 100-250 ng/mL after the first month, MMF starting at 2 grams per day, and corticosteroids. Similarly, a recent Astellas Phase 3 trial (Study 02-0-158) use as its active comparator basiliximab induction, cyclosporine troughs of 125-400 ng/mL for days 0 through 90 and 100-300 ng/mL thereafter, MMF starting at 2 grams per day, and corticosteroids. Such approaches to prophylaxis of renal transplant rejection are consistent with both current standard-of-care and with product labeling. It does not, however, reflect the precise approach to immunosuppression of any clinical trial in renal transplantation reviewed by the FDA. Specifically, the Agency has not determined that basiliximab is safe and effective when used in combination with MMF and the Agency has not determined that cyclosporine is safe and effective when dosed to achieve troughs between 100-250 ng/mL (or 125-400 ng/mL or 100-300 ng/mL).

The Symphony-ELiTE study similarly uses regimens that reflect current practices but do not replicate approaches previously studied by the FDA. The lack, then, of a defined “gold-standard”

regimen both complicates the review itself and restricts the conclusions that should be made. Despite those limitations, however, the study provides considerable information regarding the use of tacrolimus in conjunction with MMF. Certainly the observations are most valid in the context of the Symphony-ELiTE trial – which included the use of an induction agent, studied a largely Caucasian study population, and excluded US transplant centers. Parallel objections, however, could be made regarding our trials-based information regarding the use of cyclosporine in conjunction with MMF – that those data do not inform the use of induction agents, do not meaningfully direct the dosing of cyclosporine, and do not correspond to current expert opinion.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Symphony-ELiTE was an investigator-driven study designed to elucidate approaches to reduced calcineurin inhibitor exposures in renal transplantation. Roche supported the trial but had not intended to submit it in support of any application and/or labeling. The quality of the datasets, consequently, does not entirely meet the usual standards of an industry study submitted under an NDA in the area of transplantation medicine. Roche provided the datasets and the clinical study report (CSR) at the request of the Agency, but openly conveyed its own reservations at that time. Inspection of the datasets has indeed revealed multiple deficits consistent with data entry errors – primarily in the concomitant medication components of the records. The submission also lacks case report forms and complete patient narratives. For instance, the CSR includes death narratives (in Appendix 8.4) for only 34 of the 43 total reported patient deaths at 12 months. In comparison, for instance, the data from Astellas Study 02-0-158 were more complete and easier to analyze. On the other hand, despite those shortcomings, the submission provides a wealth of data from 1,589 renal transplant patients randomized to one of four treatment groups (all of which used MMF). The information captured includes baseline demographic and transplant characteristics (including gender, ethnicity, HLA matches, PRA levels, cross-match results, cold ischemia times, donor and recipient CMV and EBV serologies, etc.); details from 793 acute rejection episodes (biopsy results, treatment intervention, and change in serum creatinines), 11,263 adverse events organized by MedDRA System Organ Class (SOC) and Preferred Term (PT), and 650 opportunistic infections including isolated pathogens and patient outcomes; physical exam data from over 15,000 clinic visits; 291,813 individual laboratory results (including full chemistries and complete blood counts and iothalamate GFRs); 11,099 therapeutic drug monitoring levels (including 5,732 cyclosporine, 3,859 tacrolimus, and 1,508 sirolimus troughs); 7,517 daclizumab dosing records; 83,185 concomitant medication dosage adjustments (including all changes to MMF dosages); and details related to 106 graft losses, 49 deaths, and 592 premature withdrawals. The quality of the data was deemed more than sufficient to review the primary endpoints and major safety issues.

Reviewer comment: The robustness of the Symphony-ELiTE study findings largely mitigates any deficits in the quality of the data recording. While occasional data entry errors can be identified, they remain relatively rare. As suggested by the results of the Biometrics Review sensitivity analyses, those rare errors do not substantially affect the conclusions of the trial.

3.2 Compliance with Good Clinical Practices

Symphony-ELiTE was designed and conducted with full awareness of the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP). There did not appear to be any violation of ethical standards for research. At one meeting of the Data Safety Monitoring Board (DSMB) on November 5, 2004, the DSMB noted that the patient data were not up to date for greater than 30% of patients. The DSMB therefore requested that the study participants immediately update their study records. At the following meeting the DSMB noted "a gratifying improvement in reporting quality and completeness". A total of 434 separate protocol violations were logged: they included 147 events of incorrect daclizumab dosing; 14 events of incorrect initial dosing of other immunosuppressive drugs; 13 events of incorrect maintenance dosing; 88 exclusion criteria violations (6 related to history of malignancy, 54 related to PRA level, and 28 "other"); 1 exemption; 122 "other violations"; and 49 events determined not to be protocol violations.

Reviewer Comment: Given the size and duration of the Symphony-ELiTE trial, the number of protocol violations appears reasonable.

3.3 Financial Disclosures

No financial disclosures were made in the submitted study reports or datasets. Over 80 investigators working at 83 sites were involved with the Symphony-ELiTE trial; many of these investigators are known by DSPTP to have relationships with the pharmaceutical industry and have participated in trials of various immunosuppressive drugs and regimens.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Clinical Pharmacology

According to the Cellcept Package Insert, mycophenolate mofetil undergoes complete metabolism to mycophenolic acid (MPA), the active metabolite. Metabolism to MPA occurs presystemically after oral dosing. MPA is metabolized principally by glucuronyl transferase to for the phenolic glucuronide of MPA (MPAG) which is not pharmacologically active. In vivo, MPAG is converted to MPA via enterohepatic circulation. Cyclosporine is known to interrupt the enterohepatic recirculation of MPA, leading to a reduction in systemic MPA exposure when a fixed dose of MMF is used in conjunction with cyclosporine rather than tacrolimus.[37]

5 Sources of Clinical Data

5.1 Related Clinical Studies

The review focuses on the Symphony-ELiTE trial. Additional trials that helped inform the analysis, however, include Study 02-0-158, CRAF, and OPTIMA (Astellas), DIRECT and

CAESAR (Novartis), OPTICEPT, FDCC, and APOMYGRE (Roche), IM103008 and IM103027 (Bristol-Myers Squibb) among others. In addition, an extensive literature review was performed to examine the use of tacrolimus in conjunction with MMF, especially with regard to its impact on mortality (see section **1.2**)[20-23, 27-32, 41-44]. Study 02-0-158 and DIRECT also represent large randomized clinical trials that compared the use of Prograf and MMF together with cyclosporine and MMF together. The precise regimens in Study 02-0-158 and DIRECT, however, differed from those in the Symphony trial: the study arms used basiliximab as an induction agent, followed different target trough levels for the respective calcineurin inhibitors, and exhibited slightly different patterns of MMF use. These trials afford additional insight into the correlation between regimen dosages and study outcomes. The CAESAR study was a randomized clinical trial comparing "low dose" and "standard dose" cyclosporine regimens (as well as CNI withdrawal); the trial included arms identical in design to two of the Symphony-ELiTE groups ("standard dose" cyclosporine + MMF + CS and daclizumab + "low dose" cyclosporine + MMF + CS); the CAESAR trial allows some degree of insight into the variance associated with these data. OPTICEPT, FDCC, and APOMYGRE were clinical trials that compared outcomes for patients randomized to fixed dose MMF or concentration controlled MPA levels; OPTICEPT and FDCC enrolled patients on both tacrolimus and cyclosporine, but did not randomize patients to tacrolimus or cyclosporine (all patients in APOMYGRE used cyclosporine-based regimens). They provide additional insight into MPA pharmacokinetics and pharmacodynamics in the presence and absence of cyclosporine. IM103008 and IM103027 were phase 3 clinical trials comparing novel immunosuppressive regimens based on Belatacept to a cyclosporine based control regimen. The control regimen also included basiliximab, MMF, and corticosteroids. They provide insight into current practices for determining active comparator regimens.

5.2 Review Strategy

The ELiTE-Symphony study was designed to investigate the safety and efficacy of four immunosuppressive regimens: Group A received MMF, "standard-dose" cyclosporine, and corticosteroids; Group B received MMF, "low-dose" cyclosporine, corticosteroids, and daclizumab; Group C received MMF, "low-dose" tacrolimus, corticosteroids, and daclizumab; Group D received MMF, "low-dose"sirolimus, corticosteroids, and daclizumab. Given the goal of the review – the identification of a safe and effective dosing regimen of tacrolimus in combination with MMF – the study design presents a challenge: three of the regimens included an induction agent, daclizumab, not present in Group A (the "standard-dose" cyclosporine arm). An additional challenge derives from the use of MMF in all arms and cyclosporine in some arms: due to the interruption of enterohepatic recirculation by cyclosporine, one cannot easily compare fixed dose regimens of MMF across all four arms (some of which use cyclosporine, some of which do not) in the absence of MPA levels -- which the Symphony-ELiTE data did not capture. A non-inferiority approach is, in practice, impossible to apply rigorously to groups that contain such asymmetries. Traditional superiority approaches would allow for comparisons across arms of the Symphony-EliTE study, although the asymmetries would still affect the nature of the conclusions drawn.

Trials in transplantation have evolved towards a reliance on non-inferiority comparisons; the high efficacy of the active comparators have led to a belief that demonstrating the superiority of new regimens might no longer be feasible. The investigators of Symphony-ELiTE, however,

always intended to analyze the data to establish the superiority of group(s). As presented in the Roche clinical study report (and as analyzed by the Agency), the data from the Symphony-ELiTE trial are sufficiently robust to demonstrate a significant difference for both the endpoint of eGFR and the endpoint of biopsy-confirmed acute rejection (BCAR) + death + graft loss between Group C (daclizumab + "low-dose" tacrolimus + MMF + CS) and any other group.

The conclusions of such comparisons would necessarily depend on which groups were compared. Demonstrating the superiority of Group C (daclizumab + "low-dose" tacrolimus + MMF + CS) to Group A ("standard-dose" cyclosporine + MMF + CS), for instance, does not result in a single interpretation: one might either conclude that the addition of daclizumab or the substitution of tacrolimus (or both) led to the improved outcomes. Comparisons of Group B (daclizumab + "low-dose" cyclosporine + MMF + CS) to Group A are somewhat more straightforward, but remain limited by the asymmetries inherent in the study: superiority of Group B would most logically result from the addition of daclizumab, but could still conceivably derive from the differences in cyclosporine dosing (i.e. the levels achieved in Group B provided adequate immunosuppression without as much associated toxicities). The simplest comparison, which would allow the strongest conclusions, is between Group B and Group C: the symmetry between these two arms allow direct comparison between the use of cyclosporine and MMF in Group B with the use of tacrolimus and MMF in Group C. Such a comparison could provide the basis for elucidating a safe and effective use of MMF in combination with tacrolimus. The conclusions of that comparison are broadened by the additional comparison of Group B and Group D: while one might otherwise hypothesize that the increased MPA exposure in Group C entirely accounted for the efficacy of that regimen, the clear inferiority of Group D (whose patients experience similar MPA exposure) allows one to discard that theory.

In order to approve the use of MMF in conjunction with tacrolimus, the FDA would have to review clinical trial data demonstrating the safety and efficacy of the combination in comparison to an accepted comparator. MMF currently is approved for use in conjunction with cyclosporine. It is worth noting, however, that inspection of the Cellcept and Neoral labeling suggests that the FDA has not rigorously defined complete cyclosporine/MMF comparator regimen(s). While the Cellcept labeling states that, for the prophylaxis of organ rejection, MMF should be used at 1 gram BID concomitantly with cyclosporine and corticosteroids, the Neoral labeling omits any similar reference to Cellcept. In addition, the Neoral labeling makes no specific recommendations regarding target trough levels -- it only states that "transplant centers have found blood concentration monitoring of cyclosporine to be an essential component of patient management… while no fixed relationship has been established, blood concentration monitoring may assist in the clinical evaluation of rejection and toxicity, dose adjustments, and the assessment of compliance". The FDA approved the use of Cellcept in conjunction with cyclosporine and corticosteroids based on three trials performed in the early-to-mid 1990s.[5,6,7] The study protocols stated only that cyclosporine should be used according to the local practice of the participating trial sites – which, reflecting the era of the studies, reflected dosages that would be considered high by present standards. Since that approval, the FDA has accepted for review numerous trials in renal transplantation which relied on a comparator immunosuppression regimen including the combination of MMF and cyclosporine. Over the years, however, common practices have changed: clinicians now use lower doses of cyclosporine in conjunction with MMF. For instance, Bristol Myers Squibb recently conducted trials IM103008 and

IM103027 using a cyclosporine/MMF comparator with target CSA troughs of 150-300 ng/mL for the first month, then 100-200 ng/mL thereafter. While rigorous stepwise trials justifying the shifts in comparator regimens have not been performed, the comparator regimens have been consistent with the Cellcept and Neoral labeling.

The design of the Symphony-ELiTE study implied that Group A, the "standard-dose" cyclosporine arm, constituted the intended comparator. However, Group B, the "low-dose" cyclosporine arm, could also represent an acceptable comparator. Neither of these arms follows a protocol identical to a regimen derived from the Cellcept approval. Both of these arms have strong similarities (though neither are identical) to other comparators that have been recently accepted by the FDA. The Agency has undertaken the current review of Symphony-ELiTE in order to compare the safety and efficacy of tacrolimus and MMF in combination to that of cyclosporine in conjunction with MMF. Due to the symmetry between Group B and Group C (which both included the use of daclizumab as an induction agent), comparisons between those groups are more interpretable. Accordingly, the designation of Group B as the primary comparator for the purpose of this review is both logical and expedient. Because a superiority analysis is employed to compare Group B and Group C, the possibility that cyclosporine exposures in Group B are suboptimal does not invalidate the conclusion that tacrolimus provides some contribution to the Group C regimen (though such an argument would be valid if a non-inferiority analysis were used). The review will therefore focus on a comparison of Group B and Group C, but will also make use of Group A as a secondary comparator (especially for purposes of evaluating safety outcomes). Symphony-EliTE was designed to identify a superior treatment arm based on the primary endpoint of estimated glomerular filtration rate (eGFR) at 12 months after transplantation, determined from serum creatinine using the Cockcroft-Gault formula. Secondary endpoints included eGFR based on the MDRD formula, measured GFR, biopsy confirmed acute rejection, treatment failure, and patient death and/or graft loss at 12 months post-transplant.

Given that the review will examine whether Group C proved superior to Group B, the statistical issues associated with non-inferiority will not pertain to the analysis of the primary endpoint (eGFR as determined by creatinine clearance using the Cockcroft-Gault formula). Several other secondary endpoints are also candidates for similar comparisons: events of rejection, for instance, are sufficiently common to detect statistically significant differences between the rates of the two groups with a 95% confidence interval. Comparisons of patient death and graft loss (both as separate and combined endpoints), however, do not lend themselves well to statistical methods of either superiority analyses or non-inferiority analyses. Given the rarity of such events and the size of the clinical study, one cannot reasonably expect to detect differences between the two groups with a 95% confidence interval. Non-inferiority approaches for evaluation of important (but rare) safety issues are also unsatisfactory: while the data would very likely allow one to conclude with 95% certainty that the groups are mutually non-inferior with a 5% margin, a risk difference for 1-year mortality of 5% is arguably unacceptable. A risk difference that more reasonably meets the standard of clinical indifference would be 1%, but inadequate numbers of transplant patients exist to conduct clinical trials with the power to support such a conclusion with 95% certainty. For certain safety issues (like all-cause mortality), therefore, the analyses were augmented by comparisons between rates observed in the Symphony-ELiTE study and

rates predicted by registry data; the analysis of all-cause mortality was also augmented by a global review of the literature (see **Section 1.2**: Risk-Benefit Analysis).

6 Review of Efficacy

Efficacy Summary

6.1 Indication

Roche submitted the ELiTE-Symphony study in response to the FDA request for kidney transplant trials that used tacrolimus in combination with mycophenolate mofetil; Astellas has obtained right of reference to the trial and amended NDA 50-708/S-027 and NDA 50-709/S-021 to include its data. Both tacrolimus and mycophenolate mofetil are currently approved for the indication of prophylaxis of organ rejection in patients receiving allogenic kidney transplants. To date, however, the FDA has not approved the use of tacrolimus in combination with mycophenolate mofetil in kidney transplantation. The FDA has proposed to review the ELiTE-Symphony trial to determine whether it provides data that may identify a safe and effective dosing regimen of tacrolimus in combination with mycophenolate mofetil in kidney transplantation.

6.1.1 Methods

In accordance with the strategy described in section **5.2**, data from Symphony-ELiTE were reviewed by members of the clinical, clinical pharmacology, and statistical teams. The findings presented in the Roche clinical study report were investigated. Additional subgroup and exposure analyses were performed.

6.1.1.1 Study Design

The Symphony-ELiTE trial was conducted as a prospective, open-label, randomized multicenter investigation of four immunosuppressive regimens administered to four parallel patient groups. Individual patients were treated for 12 months. Group A received no induction therapy and cyclosporine adjusted to a target trough levels of 150-300 ng/ml for the first three months and 100-200 ng/thereafter; Group B received daclizumab at 2 mg/kg within 24 hours pre-transplant followed by 4 additional doses of 1 mg/kg every two weeks and cyclosporine adjusted to a target trough levels of 50-100 ng/ml; Group C received daclizumab at 2 mg/kg within 24 hours pre-transplant followed by 4 additional doses of 1 mg/kg every two weeks and tacrolimus adjusted to achieve target trough levels of 3-7 ng/ml; Group D received daclizumab at 2 mg/kg within 24 hours pre-transplant followed by 4 additional doses of 1 mg/kg every two weeks and sirolimus adjusted to achieve target trough levels of 4-8 ng/ml. All groups received MMF with a starting dose of 1 g twice daily and intra-operative and maintenance corticosteroids according to center practice.

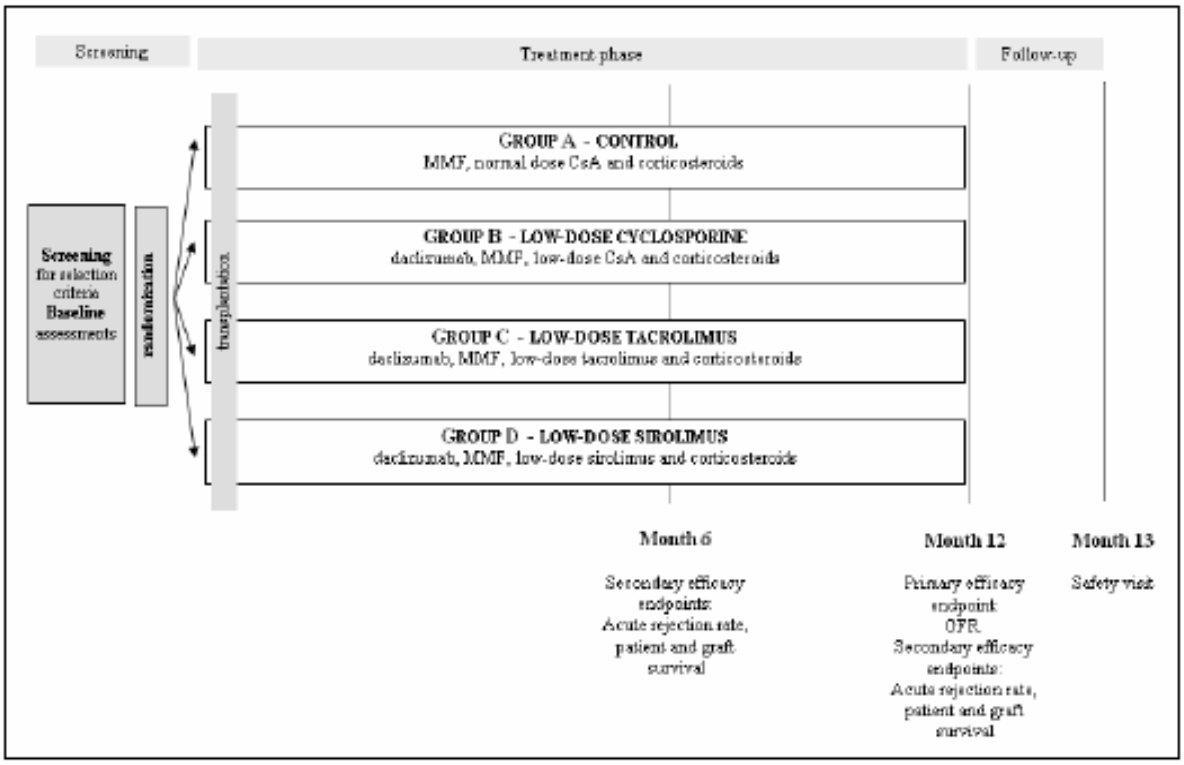


Figure 6.1.1.1A: Study Design (Taken from the Roche CSR)

The Symphony-ELiTE study protocol was amended three times. The first amendment, made October 1, 2002 (prior to the enrollment of the first patient), changed the stratification parameter for randomization from donor age to expanded donor criteria (EDC). In addition, new pre-transplant assessments were introduced, exclusion criteria were changed, the initial loading dose of sirolimus was increased, and a new analysis population ("strict third drug – STD") was introduced. The second amendment, made September 22, 2003, increased the target enrollment from 1300 to 1760 patients. The third enrollment, made January 18, 2005, stated that sub-analyses may be performed after submission of a substudy protocol to the Steering Committee.

6.1.2 Demographics

The Symphony-ELiTE study was conducted at 83 sites in 15 countries (Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Germany, Greece, Israel, Mexico, Poland, Spain, Sweden, Turkey, and United Kingdom). Of the 1645 patients randomized to treatment, 19.2% of were from Germany, 16.7% from Spain, 15.7% from Turkey, 10.9% from Brazil, and 7.5% from Czech Republic. Significant dissimilarities exist between the Symphony-ELiTE patient population and the US renal transplant patient population. Despite drawing the study population from centers around the world, the Symphony-ELiTE trial demonstrated a striking lack of racial diversity. Attributable in part to the demographics of the participating counties and, perhaps, also to local inequalities in access to transplantation, the study population was 93% Caucasian, 2% Black, 1% Asian, and 4% "other". By comparison, for the year 2007, the United Network for Organ Sharing (UNOS) database reports that 54% of kidney transplant recipients in the US were

Caucasian.[9] The causes of end-stage renal disease (ESRD) among the Symphony-ELiTE patient population were also dissimilar to those among the US kidney transplant population. Glomerulonephritis (at 28%) was the most common cause of ESRD in the Symphony-ELiTE patient population; diabetes was responsible for only 8% of cases. In sharp contrast, the United States Renal Data System reports that diabetes causes five times as many cases of ESRD as glomerulonephitis in the US (and that hypertension causes three times as many cases as glomerulonephritis).[10] The median age of patients in the Symphony-ELiTE study was 47 – considerably younger than the typical transplant recipient in the US. The median BMI of patients in the Symphony-ELiTE study was 24 – considerably lower than the typical transplant recipient in the US.[9] Further, the exclusion criteria for enrollment into Symphony-ELiTE included infection with hepatitis C (United Network for Organ Sharing data from January 2004 suggest 5.2% of US renal transplant patients are HCV positive).[8] The gender distribution (65% male recipients) seen in the Symphony-ELiTE study did grossly correspond to the distribution recorded among the US transplant population (61% male recipients in 2007 according to UNOS).[8]

The differences between the Symphony-ELiTE study population and the US kidney transplant population are not only readily perceivable but also clinically relevant. On average, Caucasians have better outcomes after renal transplant (fewer rejection episodes, longer graft survival, less diabetes).[11-13] Patients with a history of ESRD secondary to diabetes typically fare worse than those with a history of glomerulonephritis.[14] Patients with hepatitis C have higher rates of new onset of diabetes after transplantation – particularly, according to some studies, in the setting of immunosuppression with Prograf.[15] The study population also excluded patients with a Panel Reactive Antibody (PRA) greater than 20% or cold ischemia time (CIT) longer than 30 hours. Applying the conclusions drawn from the Symphony-ELiTE study to the US kidney transplant patient population, therefore, should be done judiciously.

The distribution of baseline parameters (race, age, gender, BMI, cause of ESRD) among the arms of the Symphony-ELiTE study proved less concerning. Inspection of Table 9 shows that the four study groups were comprised of similar kidney recipients. In addition, inspection of Table 10 (adapted from the Roche CSR) shows that the four groups were allocated donor kidneys of similar quality. Donor age, CMV status, and serum creatinine appeared comparable across study groups. No discrepancies relating to allocation of deceased versus living donor kidneys or standard versus extended criteria donor kidneys were detected.

Table 6.1.2A: Recipient Demographic Information at Entry

	Group A N=390	Group B N=399	Group C N=401	Group D N=399
Gender				
Male	243 (62.3%)	265 (66.4%)	264 (65.8%)	266 (66.7%)
Female	147 (37.7%)	134 (33.6%)	137 (34.2%)	133 (33.3%)
Age				
mean±SD	45.9±13.8	47.2±13.5	45.4±14.7	44.9±14.5
median	47.1	47.7	46.2	45.8
Min – Max	18.2 - 72.5	18.4 - 75.8	18.1 - 75.1	18.1 - 74.6

Race				
Caucasian	359(92.1%)	368(92.2%)	377(94.0%)	376(94.2%)
Black	8(2.1%)	9(2.3%)	4(1.0%)	5(1.3%)
Asian	5(1.3%)	3(0.8%)	3(0.8%)	2(0.5%)
other	18(4.6%)	19(4.8%)	17(4.2%)	16(4.0%)
Weight (kg)				
mean±SD	69.7±13.3	70.1±15.0	70.0±15.1	70.8±15.6
median	70	70	68.5	69
Min – Max	36 - 105	38 - 126	37 - 120	40 - 137

(adapted from Biometrics Review)

Table 6.1.2B: Donor Demographic Information at Entry

ITT Population		Group A N=390	Group B N=399	Group C N=401	Group D N=399
Type of Donor	Living related	111(28.5%)	107(26.8%)	127(31.7%)	120(30.1%)
	Living unrelated	23(5.9%)	35(8.8%)	21(5.2%)	23(5.8%)
	Deceased	256(65.6%)	256(64.2%)	252(62.8%)	256(64.2%)
Donor Age	Median	46	48	47	48
	Min – Max	1 to 82	7 to 80	4 to 77	4 to 80
CMV of Donor	Positive	255 (65.4%)	258 (64.7%)	251 (62.6%)	256 (64.2%)
	Negative	110 (28.2%)	119 (29.8%)	129 (32.2%)	125 (31.3%)
Expanded Donor Criteria	Yes	155 (40%)	163 (41%)	165 (41%)	162 (41%)
	No	235 (60%)	236 (59%)	236 (59%)	236 (59%)
History of Donor Hypertension	Yes	61 (15.6%)	54 (13.5%)	63 (15.7%)	64 (16%)
	No	281 (72.2%)	302 (75.7%)	290 (72.3%)	280 (70.2%)
Serum Creatinine of Donor	> 1.5 mg/dL	29 (7.4%)	31 (7.8%)	23 (5.7%)	31 (7.8%)
	≤ 1.5 mg/dL	345 (88.5%)	344 (86.2%)	355 (88.5%)	345 (86.5%)

(adapted from Roche CSR)

6.1.3 Patient Disposition

Of 2,072 patient screened for eligibility, 1,645 were randomized into the four treatment groups. The study lasted from November 28, 2002 (first patient enrolled) to December 9, 2005 (last patient complete). A total of 501 (31.5%) patients in the ITT population were prematurely withdrawn: the highest proportion of withdrawals was observed in Group D (48.9%), followed by Group A (29.7%), then Group B (27.6%), then Group C (20%). The main reason for premature withdrawal was treatment failure (53.1% of all discontinuations). See also section **7.2.3**

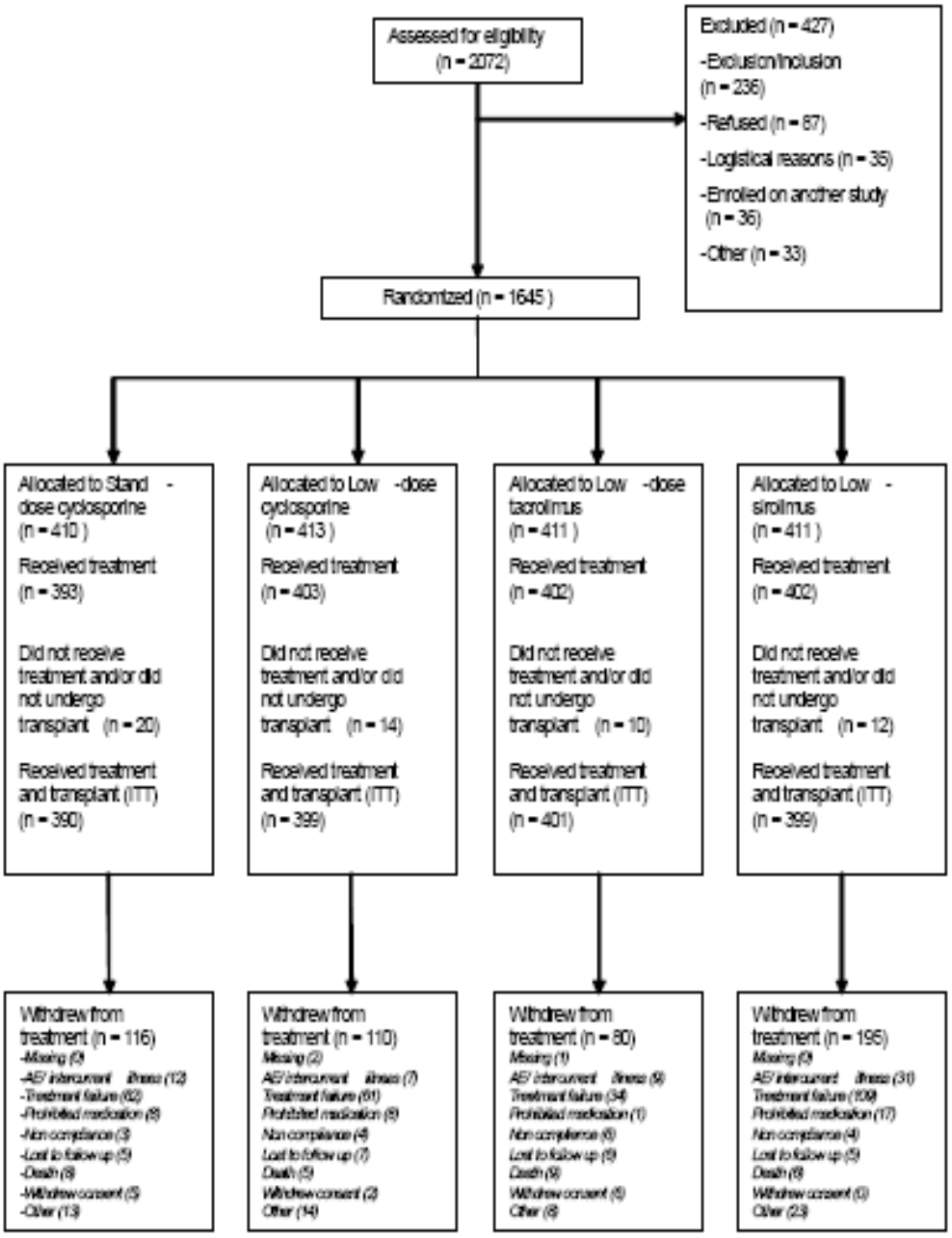


Figure 6.1.3A: Patient Disposition (adapted from Roche CSR)

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint of the Symphony-ELiTE trial was estimated glomerular filtration rate (GFR) measured at 12 months after transplantation determined from serum creatinine using Cockcroft-Gault formula to calculate the creatinine clearance:

- In men:

$$\text{Creatinine Clearance } [ml/min] = \frac{(140 - \text{Age } [years]) \times \text{Body Weight } [kg]}{\text{Serum Creatinine } [mg/dl] \times 72}$$

- In women:

$$\text{Creatinine Clearance } [ml/min] = \frac{(140 - \text{Age } [years]) \times \text{Body Weight } [kg]}{\text{Serum Creatinine } [mg/dl] \times 72} \times 0.85$$

Reference to the formulas above illustrates that calculating a patient's creatinine clearance requires several data points: the serum creatinine, the body weight, the age, and the gender of the patient. While the age and gender for all patients were known, some data were missing for some patients at the 12 month and earlier time points. Some missing data were unavoidable: in the case of graft loss (and return to dialysis), obtaining a serum creatinine and calculating a creatinine clearance would have been inappropriate; in the case of death, it obviously would have been impossible. Other missing data were theoretically avoidable, but still unobtainable (for instance, patients who were lost to follow up because they withdrew from the study). Yet other missing data were not obtained due to a missed clinic visit.

Given the spectrum of causes behind the missing data, no single methodology for handling the missing data is without flaw. Assigning a creatinine clearance of zero (or perhaps 10 ml/min) might be appropriate for patients who have returned to dialysis, but would clearly underestimates the GFR of a patient who has simply missed the appointment. Carrying forward the last serum creatinine available who missed the 12-month clinic appointment, but would clearly overestimates the GFR of a patient who had died during the study and would likely overestimate the GFR of a patient who had withdrawn from the protocol at month six due to adverse events and not returned to clinic. Similarly, objections could be made to carrying forward observations of patient's weight, though drastic changes in weight would be less likely.

Such data collection and handling issues might easily have rendered the primary endpoint of the Symphony-ELiTE trial uninterpretable. Fortunately, the results of the study proved remarkable robust: despite some missing data at the 12 month time point and despite uncertainty regarding how such missing data might be best handled, clear conclusions regarding the primary endpoint could still be reached. A variety of methods for handling the missing data all returned the same result: Group C proved superior to the other treatment groups studied. Sensitivity analysis, employing opposing imputation methods to explore the primary endpoint, supported that conclusion.

The Sponsor of the Symphony-ELiTE study handled the missing data by carrying forward last observations from the month 3 visit on. If the month 12 serum creatinine was available, but the weight was missing, the weight was imputed by the last observation carry forward (LOCF) method. In all other cases, a value of 10 ml/min was imputed. By this method, 91 patients with missing creatinines (including 23 in Group A, 22 in Group B, 19 in Group C, and 27 in Group D) and 162 patients with missing weights (including 43 in Group A, 40 in Group B, 34 in Group C, and 45 in Group D) were imputed with a GFR substantially greater than 10 ml/min whereas 124 patients with missing data (including 37 in Group A, 25 in Group B, 24 in Group C, and 38 in Group D) were imputed with a GFR of 10 ml/min. Following these rules resulted in the imputation of 38 patients (including 10 from Group A, 10 from Group B, 5 from Group C, and 13 from Group D) who had died or suffered graft loss with a GFR substantially greater than 10 ml/min. Despite those unfavorable and illogical assignments, Group C exhibited a statistically significantly higher GFR compared to each of the other groups.

Table 6.1.4A Estimated GFR at Month 12 with Sponsor's Imputation

Group	GFR [ml/min] at Month 12							
	N	MEAN	SD	MIN	Q1	MEDIAN	Q3	MAX
A	390	57.07	25.10	8.60	43.49	57.04	73.67	126.62
B	399	59.39	25.05	4.89	44.89	60.94	75.36	143.25
C	401	65.40	27.03	8.40	49.33	66.18	83.50	160.52
D	399	56.68	26.88	8.40	39.11	57.45	73.63	143.56
Total	1589	59.66	26.25	4.89	44.06	60.59	77.05	160.52
Pairwise Comparisons between the Groups								
	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D		
95% CI	(-5.83,1.18)	(-11.98,-4.69)	(-3.25,4.02)	(-9.63,-2.40)	(-0.90,6.32)	(4.98,12.47)		
99.2% CI	(-7.05,2.40)	(-13.25,-3.43)	(-4.52,5.29)	(-10.89,-1.14)	(-2.16,7.58)	(3.68,13.77)		
P value*	0.1658	0.0001	0.8087	0.0011	0.1171	0.0001		

*Wilcoxon rank-sum test

(adapted from Biometrics Review)

An alternate method was employed by the Biometrics Division at CDER to test the sensitivity of that conclusion. All patients who died or suffered graft loss (41 patients in Group A, 27 patients in Group B, 23 patients in Group C, and 42 patients in Group D) were imputed with a GFR of 10 ml/min. Patients without an available serum creatinine at or after the month 3 time point were also imputed with a GFR of 10 ml/min The LOCF method was once again employed for patients with an available serum creatinine at or after the month 3 time point (and imputing weight whenever necessary). With this imputation method, 57 patients were imputed with creatinine clearances substantially greater than 10 ml/min (11 patients from Group A, 12 from Group B, 15 from Group C, and 19 from Group D) and 35 patients were imputed with GFR of 10 ml/min (10 in Group A, 9 in Group B, 7 in Group C, and 9 in Group D). Again, Group C exhibited a statistically higher GFR compared to each of the other groups (see **Table 6.1.4B**).

Table 6.1.4B Estimated GFR at Month 12 with the Alternative Imputation Method

Group	GFR [ml/min] at Month 12							
	N	MEAN	SD	MIN	Q1	MEDIAN	Q3	MAX
A	390	56.45	25.79	8.60	43.39	56.90	73.60	126.62

B	399	58.94	25.65	4.89	43.75	60.94	75.36	143.25
C	401	65.14	27.42	8.40	49.33	66.18	83.50	160.52
D	399	56.17	27.37	10.00	38.66	57.28	73.63	143.56
Total	1589	59.20	26.80	4.89	43.56	60.48	77.04	160.52
Pairwise Comparisons between the Groups								
	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D		
95% CI	(-6.08,1.11)	(-12.41,-4.97)	(-3.43,4.01)	(-9.89,-2.52)	(-0.92,6.46)	(5.17,12.78)		
99.2% CI[#]	(-7.33,2.36)	(-13.7,-3.68)	(-4.73,5.30)	(-11.18,-1.24)	(-2.2,7.74)	(3.85,14.10)		
P value[*]	0.1499	<0.0001	0.8115	0.0010	0.1088	<0.0001		

[*] Wilcoxon rank-sum test
[#] Adjusted by multiple comparisons, 1-0.05/6=99.2%

(adapted from Biometrics Review)

To further investigate the strength of that conclusion, another sensitivity analysis was performed by imputing all missing estimated GFRs with a value of 40 ml/min (see Table 6.1.4C). As Group C had the fewest missing values, such a method would favor the other three groups. Note that the mean estimated GFR values for Groups A, B, and D are higher than the corresponding values in Table 6.1.4A but that the mean estimated GFR for Group C is lower than the corresponding value in Table 6.1.4A. With this imputation method, however, Group C is still superior to Groups A, B and D in terms of estimated GFR at month 12 post-transplantation.

Table 6.1.4C Estimated GFR at Month 12 Imputing GFR=40 ml/min for Missing Values

Group	GFR [ml/min] at Month 12							
	N	MEAN	SD	MIN	Q1	MEDIAN	Q3	MAX
A	390	58.74	20.55	8.60	40	54.40	72.26	126.62
B	399	60.28	21.81	8.74	40	59.71	74.25	143.25
C	401	64.80	23.78	9.21	42.82	62.57	82.13	160.52
D	399	58.41	22.14	11.50	40	54.59	72.93	143.56
Total	1589	60.57	22.24	8.60	40	57.60	75.61	160.52
Pairwise Comparisons between the Groups								
	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D		
95% CI	(-4.51,1.42)	(-9.16,-2.95)	(-2.65,3.32)	(-7.68,-1.35)	(-1.18,4.93)	(3.20, 9.58)		
99.2% CI[#]	(-5.54,2.45)	(-10.25,-1.87)	(-3.69,4.36)	(-8.79,-0.25)	(-2.24,5.99)	(2.09,10.69)		
P value[*]	0.2746	0.0004	0.5309	0.0092	0.1181	<0.0001		

[*] Wilcoxon rank-sum test
[#] Adjusted by multiple comparisons, 1-0.05/6=99.2%

Reviewer comment: Several additional sensitivity analyses were also performed by the Biometrics division which all confirmed the conclusion that Group C exhibited the highest GFR. Please see the review from the Biometrics division for further details.

6.1.5 Analysis of Secondary Endpoints(s)

The Symphony-ELiTE trial evaluated many secondary endpoints including other measurements of GFR (iohexol clearance or 24 hour urinary creatinine clearance, various measurements of

acute rejection (clinically suspected, biopsy proven, biopsy proven excluding borderline cases), patient death, graft loss including patient death, death censored graft loss, treatment failure, and delayed graft function. Previous applications for the indication of prophylaxis of acute rejection in kidney transplant have relied on the combined endpoint of biopsy proven acute rejection (BPAR), graft loss, and/or death to demonstrate efficacy. DSPTP, therefore, analyzed the patient level data to compare outcomes for the four treatment groups based on that precedent; Group C demonstrated statistically significant superiority to each of the other groups (see **Tables 6.1.5A** and **B**).

Table 6.1.5A Rate of BPAR, Graft Loss, Death or Loss to follow-up at 12 months

	A N=390	B N=399	C N=401	D N=399
Overall Failure	141 (36.2)	126 (31.6)	82 (20.4)	185 (46.4)
BPAR	113 (29.0)	106 (26.6)	60 (15.0)	152 (38.1)
Graft loss	28 (7.2)	20 (5.0)	12 (3.0)	30 (7.5)
Mortality	13 (3.3)	7 (1.8)	11 (2.7)	12 (3.0)
Loss to follow-up	5 (1.3)	7 (1.8)	5 (1.3)	6 (1.5)

(adapted from Biometrics Review)

Table 6.1.5B Pairwise Comparison of Overall Failure, BPAR, Graft Loss, and Mortality

	A - B	A - C	A – D	B – C	B – D	C - D
Overall Failure						
95% CI	(-2.3,11.4)	(9.3,22.1)	(-17.3,-3.1)	(4.8,17.4)	(-21.7,-7.8)	(-32.5,-19.4)
99.2% CI	(-4.6,13.8)	(7.1,24.3)	(-19.7,-0.7)	(2.7,19.5)	(-24.1.,-5.5)	(-34.7,-17.2)
P value	0.1996	<0.0001	0.0045	0.0005	<0.0001	<0.0001
BPAR						
95% CI	(-4.1, 8.9)	(8.1, 20.0)	(-15.9,-2.3)	(5.8, 17.4)	(-18.2,-4.8)	(-29.3,-17.0)
99.2% CI	(-6.3, 11.1)	(6.0, 22.0)	(-18.2, 0.0)	(3.8, 19.4)	(-20.5,-2.6)	(-31.4,-14.9)
P value	0.4993	<0.0001	0.0084	<0.0001	0.0007	<0.0001
Graft loss excluding death						
95% CI	(-1.4, 5.8)	(0.9, 7.5)	(-4.2, 3.6)	(-0.9, 5.0)	(-6.1, 1.1)	(-7.9, -1.2)
99.2% CI	(-2.6, 6.9)	(-0.2, 8.6)	(-5.5, 4.8)	(-1.9, 5.9)	(-7.3, 2.3)	(-8.9, -0.1)
P value	0.2609	0.0116	0.9632	0.2015	0.1886	0.0067
Mortality						
95% CI	(-0.9, 4.0)	(-2.1, 3.2)	(-2.4, 3.0)	(-3.3, 1.3)	(-3.6, 1.1)	(-2.8, 2.3)
99.2% CI	(-1.6, 4.8)	(-2.9, 4.1)	(-3.2, 3.9)	(-4.0, 2.0)	(-4.4, 1.9)	(-3.6, 3.1)
P value	0.2363	0.7822	0.9538	0.4811	0.3530	0.9903

(adapted from Biometrics Review)

The combined endpoint was driven primarily by the component of biopsy proven acute rejection (BPAR). Independently analyzed, BPAR was also shown to have a lower incidence for Group C than for each other treatment group in Symphony-ELiTE (see **Table 6.1.5C**). The other components of the combined endpoint (death and graft loss) are discussed in sections **7.2.1** and **7.2.1.1**)

Table 6.1.5C Number of BPAR by Groups (Rates by Kaplan-Meier Estimates)

Time	Group A N=390	Group B N=399	Group C N=401	Group D N=399
Week 4	75 (19.54%)	57 (14.44%)	35 (8.82%)	54 (13.80%)
Week 8	89 (23.28%)	65 (16.50%)	41 (10.37%)	79 (20.37%)
Month 3	96 (25.19%)	77 (19.59%)	44 (11.16%)	107 (27.87%)
Month 6	107 (28.25%)	97 (24.79%)	55 (14.07%)	145 (38.17%)
Month 9	110 (29.10%)	104 (26.63%)	58 (14.87%)	150 (39.56%)
Month 12	113 (29.98%)	106 (27.18%)	60 (15.42%)	152 (40.12%)

(adapted from Biometrics Review)

6.1.6 Subpopulations

Subpopulations of general interest in renal transplant clinical studies include those related to gender, age, race, diabetes, and hepatitis C status. Due to the demographics and the conduct of the Symphony-ELiTE study, meaningful subgroup analyses could not be conducted for all the usual subpopulations: Caucasians comprised the only substantial group according to race; instances of pre-transplant and new onset diabetes after transplant were both exceedingly rare;, and infection with hepatitis C constituted grounds for exclusion from the study. Subgroup analyses were conducted according to gender and age; both subgroup analyses supported the findings of the analyses of the primary population.

Table 6.1.6A Efficacy Outcome at 12 Months by Gender

	Group A N=390	Group B N=399	Group C N=401	Group D N=399	P value
Estimated GFR at Month 12					
Male mean ± SD median	N=243 60.15±24.38 59.26	N=265 61.35±24.96 63.32	N=264 68.46±27.24 69.50	N=266 58.09±27.46 59.61	<0.0001
Female mean ± SD median	N=147 51.97±25.53 52.54	N=134 55.50±24.86 55.72	N=137 59.51±25.72 59.97	N=133 53.86±25.54 53.46	0.0892
All patients mean ± SD median	N=390 57.07±25.10 57.04	N=399 59.39±25.05 60.94	N=401 65.40±27.03 66.18	N=399 56.68±26.88 57.45	<0.0001
Rate of BPAR/GL/Death/LTFU					
Male N=1038	86/243 (35.4%)	89/265 (33.6%)	52/264 (19.7%)	136/266 (51.1%)	<0.0001
Female N=551	55/147 (37.4%)	37/134 (27.6%)	30/137 (21.9%)	49/133 (36.8%)	0.0119
All patients N=1589	141/390 (36.2%)	126/399 (31.6%)	82/401 (20.5%)	185/399 (46.4%)	<0.0001
Rate of BPAR					
Male	74/243	77/265	39/264	111/266	<0.0001

N=1038	(30.5%)	(29.1%)	(14.8%)	(41.7%)	
Female N=551	39/147 (26.5%)	29/134 (21.6%)	21/137 (15.3%)	41/133 (30.8%)	0.0182
Rate of Graft Loss excluding Death					
Male N=1038	16/243 (6.6%)	13/265 (4.9%)	6/264 (2.3%)	23/266 (8.6%)	0.0122
Female N=551	12/147 (8.2%)	7/134 (5.2%)	6/137 (4.4%)	7/133 (5.3%)	0.5404
Mortality Rate					
Male N=1038	4/243 (1.7%)	6/265 (2.3%)	5/264 (1.9%)	10/266 (3.8%)	0.3936
Female N=551	9/147 (6.1%)	1/134 (0.8%)	6/137 (4.4%)	2/133 (1.5%)	0.0396

(adapted from Biometrics Review)

*Reviewer comment: Casual inspection of the p-values may suggest that the differences between Group C and the other treatment groups for the endpoint of GFR and the combined endpoint of BPAR, graft loss, and/or death are greater for males than females. While comparison of the raw data also suggests that the absolute differences tended to be larger among the male subpopulations, the smaller size of the female populations also contributed to the less impressive p-values. Moreover, though the superiority of Group C may have been less impressive among females than males, the identical patterns were repeated for both measurements of efficacy. The subgroup analysis of graft loss also exhibited trends that favored Group C for both genders. The subgroup analysis of death failed to provide any clear patter. The relatively high death rate of females in Group C was noted, but given the small size of that group (n=137), no clear conclusions were suggested: comparison to the two cyclosporine/MMF regimens reveals that females in Group A exhibited a higher death rate, while those in Group B exhibited a lower death rate (see section **7.2.1** for further discussion).*

Table 6.1.6B: Efficacy Outcome by Age Groups

	Group A N=390	Group B N=399	Group C N=401	Group D N=399	P value
Estimated GFR at month 12					
min - Q1	N=93	N=78	N=110	N=117	
mean ± SD	62.98±26.22	64.78±23.82	75.20±26.86	64.80±25.21	0.0007
median	67.22	66.42	77.63	67.98	
Q1 - median	N=101	N=111	N=95	N=90	
mean ± SD	65.33±23.47	66.83±26.24	70.30±24.68	59.61±27.08	0.0406
median	65.57	67.69	71.78	62.41	
Median – Q3	N=105	N=102	N=96	N=94	
mean ± SD	53.75±23.73	59.08±22.56	62.58±25.74	57.03±29.20	0.0826
median	54.44	61.88	65.35	57.75	
Q3 - Max	N=91	N=108	N=100	N=98	
mean ± SD	45.68±22.39	48.14±23.05	52.70±25.38	43.94±21.50	0.0749

median	47.71	48.47	51.00	43.02	
All patients mean ± SD median	N=390 57.07±25.10 57.04	N=399 59.39±25.05 60.94	N=401 65.40±27.03 66.18	N=399 56.68±26.88 57.45	<0.0001
Rate of BPAR/GL/Death/LTFU					
Min – Q1	27/93 (29.0%)	20/78 (25.6%)	20/110 (18.2%)	54/117 (46.2%)	<0.0001
Q1 - median	36/101 (35.6%)	41/111 (36.9%)	19/95 (20.0%)	48/90 (53.3%)	<0.0001
Median – Q3	43/105 (41.0%)	34/102 (33.3%)	19/96 (19.8%)	39/94 (41.5%)	0.0041
Q3 - max	35/91 (38.5%)	31/108 (28.7%)	24/100 (24%)	44/98 (44.9%)	0.0080
All Patients N=1589	141/390 (36.2%)	126/399 (31.6%)	82/401 (20.5%)	185/399 (46.4%)	<0.0001

(adapted from Biometrics Review)

Reviewer comment: The differences between treatment groups appear to have been greater among younger patients than older patients. This may reflect that the older patients are more likely to have a complicated post-operative course and worse graft function: they are more likely to receive extended criteria donor (ECD) kidneys and they are less likely to provide a healthy environment for their allograft. The decreased benefit detected, then, may reflect differences between the groups rather than a different response to the treatments. In any case, while the differences may have been smaller, the trends still favored Group C for both measures of efficacy.

Subpopulations were also defined according to various study criteria: a safety population, an intent-to-treat population, a per-protocol population, and a "strict third drug" population (patients who did not have two consecutive trough levels out of the protocol-defined target ranges). Evaluations of the per-protocol and strict third drug populations supported the findings of the intent-to-treat analysis (see Biometrics Review for details).

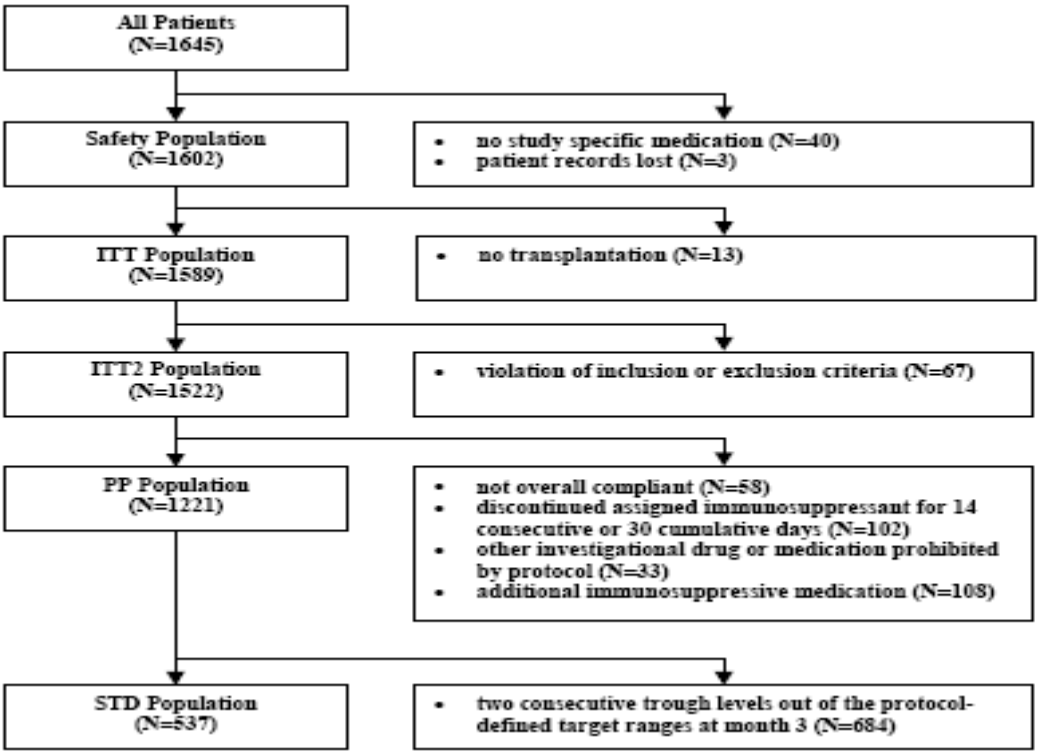


Figure 6.1.6A: Symphony-ELiTE Study Populations (Taken from the Roche CSR)

7 Review of Safety

Safety Summary

7.1 Safety Assessments

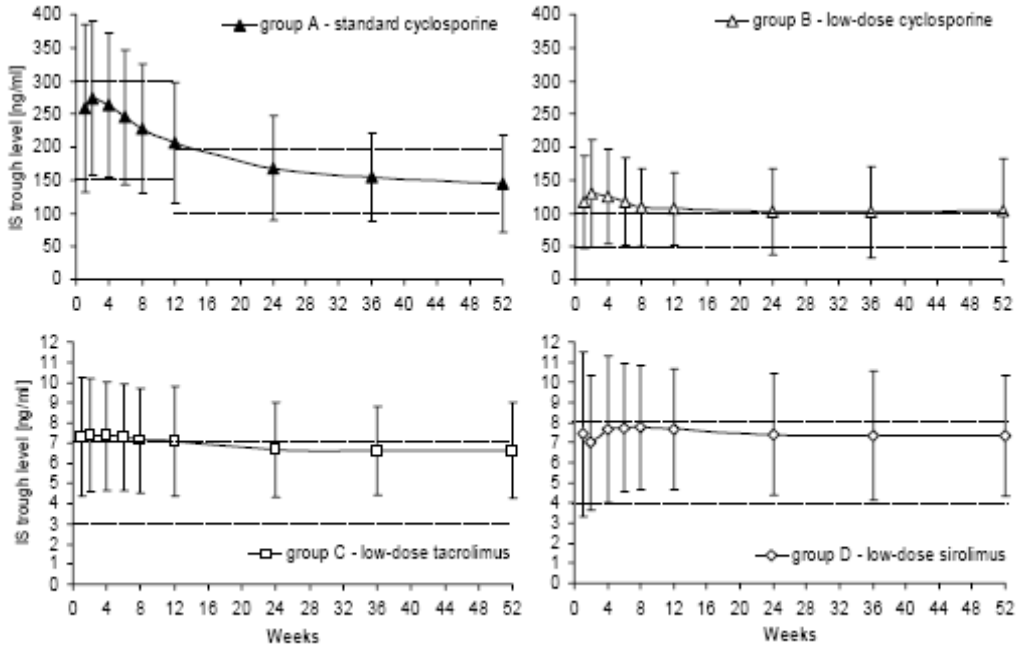
The Symphony-ELiTE study captured data regarding patient deaths and graft losses as part of its primary efficacy endpoint among the 1,589 patients who received kidney transplants (the "intent to treat population**").** The "safety population" included an additional 13 patients who were enrolled and received at least one dose of a study drug (daclizumab, cyclosporine, tacrolimus, sirolimus, and/or MMF) but who did not ultimately receive a transplant. The "safety population" has been organized according to actual treatment received by the patient rather than the treatment to which the patient was randomized; the "safety" population also includes a treatment "Group 0" for the 27 patients who receive at least one dose of a study drug but whose actual treatment did not correspond to any of the study specific treatment groups. As a result, the "intent to treat population" Groups A, B, C and D are not identical to the "safety population" Groups A, B, C, and D (except for the endpoints of death and graft loss). They are, however, very similar: safety population Group A (n=384) includes 383 patients randomized to Group A and a single patient randomized to Group D who was treated according to the Group A protocol; safety population Group (n=408) B includes 396 patients randomized to Group B, 7 patients randomized to Group

A, and 5 patients randomized to Group D who were treated according to the Group B protocol; safety population Group C (n=403) includes 397 patients randomized to Group C and 6 patients randomized to Group D who were treated according to the Group C protocol; safety population Group D (n=380) includes 378 patients randomized to Group D, 1 patient randomized to Group A, and 1 patients randomized to Group B. Safety population Group O (n=27) included 2 patients who were randomized to Group A, 6 patients who were randomized to Group B, 7 patients who were randomized to Group C, and 12 patients who were randomized to Group D, none of whom were treated according to all study specific treatment group. Of the 13 patients who did not actually receive a kidney transplant but were included in the safety analysis, two were in safety population Group A, two were in safety population Group B, and nine were in safety population Group O.

*Reviewer comment: The Sponsor elected to report the safety data according to the "safety" population rather than the "intent to treat" population allows the pairing of observed safety outcomes with the actual drug(s) to which the patient was exposed. That approach had the potential to introduce bias as patients appear to have been switched from their randomized treatments unevenly (most notably, more patients appear to have been diverted away from the sirolimus arm than from any of the other arms). The impact of such bias, however, would be quite limited as the "safety populations" and the "intent to treat" populations share a high degree of identity. The present clinical review continued the practice of reporting safety outcomes according to the Sponsor-defined "safety" population for two reasons: 1) as the safety outcomes (other than graft loss and death) represent secondary endpoints, the data should not be subjected to rigorous statistical interpretation under any circumstances due to issues pertaining to "multiple looks" and 2) some safety endpoints pertaining to opportunistic infections and diabetes were generated by the Sponsor from the electronic case report forms. As the eCRFs were not submitted, those analyses could not be independently performed during the clinical review process (see also Reviewer comments in sections **7.2.2** and **7.2.4**).*

7.1.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The study investigators demonstrated some unwillingness to follow the therapeutic drug monitoring guidelines given by the protocol. With the exception of Group A ("standard-dose" cyclosporine), patients at the treatment groups in the Symphony-ELiTE trial tended to receive exposures near or above the upper limit established by the protocol for the calcineurin inhibitor (Groups B and C) or mTOR inhibitor (Group D): the mean trough levels achieved for Groups B, C, and D essentially mirrored the upper limit allowed by the study protocol.



The figure presents mean drug levels with error bars representing standard deviations. The horizontal lines delimit the target ranges.

Figure 7.1.1A: Whole blood trough concentrations for all Symphony-ELiTE treament groups (adapted from Roche CSR)

MMF dosing in the Symphony-ELiTE trial followed a pattern rather similar to that observed in Study 02-0-158. As in that trial, patients across all treatment groups started MMF at 2 grams per day. While MMF dosage decreased throughout the study in every treatment group, the decrease was most pronounced in the tacrolimus and sirolimus arms (Group C and Group D).

Table 7.1.1A: MMF Dosage (mg) (taken from Roche CSR)

SAFETY POPULATION		Group A (N=384)	Group B (N=408)	Group C (N=403)	Group D (N=380)	Group O (N=27)	TOTAL (N=1602)
Baseline	n	242	246	236	225	4	953
	mean	1631	1601	1552	1604	1750	1598
	SD	542	596	586	544	500	567
Week 1	n	368	382	382	361	3	1496
	mean	1914	1910	1804	1870	1500	1873
	SD	483	429	529	534	866	497
Week 2	n	356	383	381	350	1	1471
	mean	1936	1893	1795	1836	1500	1864
	SD	432	458	523	543	-	493
Week 4	n	349	375	378	338	1	1441
	mean	1912	1860	1761	1815	1500	1836
	SD	491	501	562	569	-	534
Week 6	n	336	372	377	324	1	1410
	mean	1916	1863	1756	1820	1500	1837
	SD	466	500	601	536	-	532
Week 8	n	326	369	368	317	1	1381
	mean	1862	1840	1725	1771	1500	1798
	SD	519	523	602	630	-	572
Month 3	n	306	357	360	296	0	1319
	mean	1822	1773	1664	1701	0	1739
	SD	574	590	644	665	-	621
Month 6	n	338	370	371	338	4	1421
	mean	1679	1665	1553	1533	1688	1608
	SD	629	668	648	749	625	676
Month 9	n	282	316	334	246	0	1178
	mean	1779	1726	1545	1599	0	1661
	SD	533	584	642	672	-	616
Month 12	n	332	362	364	325	4	1387
	mean	1667	1662	1463	1492	1500	1570
	SD	637	639	684	738	1000	682

* doses >20 grams were divided by 1000 (error in data entry based on eCRF page design)

7.1.2 Explorations for Dose Response

The clinical pharmacology group detected a trend toward improved outcomes both in terms of increased glomerular filtration rate (GFR) and decreased biopsy-proven acute rejection (BPAR) at higher tacrolimus trough levels and higher MMF doses (see **Table 7.1.2A** and **Table 7.1.2B**).

Table 7.1.2A: GFR in ml/min at Month 12 in Group C

Mean $C_{trough,Tac}$ (ng/mL)	TA-MMF dose (g/Day)		
	<1	1-<2	2
≤6	53.9	63.6	69.5
6-≤9	56.9	65.8	74.5
>9	60.9	68.4	85

(adapted from Clinical Pharmacology Review)

Table 7.1.2B: Incidence of BPAR in Group C as a Function Of Tacrolimus Trough at 30 Days Post-Transplant

Tacrolimus Trough (ng/ml)	Incidence of BPAR [% (n/N)]
< 5.84	13.7% (13/95)
5.84 to 8	6.1% (10/164)
8 to 10	4.23% (3/71)
> 10	6% (3/50)

(adapted from Clinical Pharmacology Review)

Reviewer comment: Not surprisingly, rates of acute rejection appeared lower for those patients in Group C who experienced higher tacrolimus and MMF exposures (and, presumably, greater immunosuppression). They also exhibited higher glomerular filtration rates (GFR), on average, at 12 months post-transplantation. As calcineurin-inhibitor nephropathy is a cumulative injury, however, it is less clear that those same patients will continue to enjoy higher GFR further along their transplant course. In addition, the apparent tendency towards higher GFR for patients receiving MMF at 2g/day may be the result of bias: given that the starting dose of MMF was 2 g/day, patients doing well would tend to remain at a dose of 2 g/day. Similarly, populations less able to tolerate 2g/day (women, the elderly, recipients of ECD kidneys) tend towards lower GFRs independent of their MMF usage. Nonetheless, the findings of the clinical pharmacology group suggest that higher levels of immunosuppression could potentially lead to even better efficacy outcomes than those achieved in the Symphony-ELiTE trial.

7.2 Major Safety Results

7.2.1 Deaths

In light of the findings of the 2007 DSPTP review of Study 02-0-158, the Division approached the review of Symphony-ELiTE determined to elucidate whether the imbalance in deaths seen that study represented a true trend or a simple chance. As described in section **1.2** (Risk Benefit Assessment), a global review of the literature and an inspection of registry data did not offer substantial evidence to support a hypothesis that the use of MMF in combination with tacrolimus results in supra-therapeutic MPA exposure and increased death. In this section, the data from Symphony-ELiTE (and Study 02-0-158) are evaluated with respect to the same hypothesis. Statistical analyses often can offer only limited assurances when evaluating safety outcomes in trials in kidney transplantation. For rare events, the trials lack the power to detect differences between groups that would be considered clinically important. The literature will generally report such outcomes as "equivalent" so long as statistical analysis does not return a p-value less than 0.05 when interrogating a null hypothesis that no difference exists between the two groups for the outcome of all-cause mortality. Non-inferiority approaches are not helpful either: due to size constraints, trials in kidney transplantation lack sufficient power to exclude clinically significant risk differences between groups (as described in section **1.2**, a two-armed study would require 15,000 patients to detect a risk difference of 1% between the two groups for the endpoint of all-cause mortality). Conservative analyses, therefore, must occasionally err on the side of safety if a statistically insignificant trend in the data appears to support a plausible hypothesis.

Several years after the introduction of MMF, it was appreciated that cyclosporine interferes with the enterohepatic recirculation of MPA (the active metabolite of MMF) causing a fixed oral dose of MMF to result in greater MPA exposure for patients on tacrolimus than patients on cyclosporine.[36, 37] MMF was approved on the basis of three clinical trials (the US Renal Transplantation MMF Study Group, The European MMF Cooperative Study Group, and the Tri-continental MMF Renal Transplant Study Group) which all used cyclosporine based immunosuppressive regimens.[5, 6, 7] The dosages determined safe and effective by those studies, therefore, could conceivably represent supra-therapeutic dosages in the context of a tacrolimus based immunosuppressive regimen. While the imbalance in deaths between the tacrolimus arm and the cyclosporine arm of Study 02-0-158 was not statistically significant, the trend did appear to fit the hypothesis that increased MPA exposure could result in over-immunosuppression and increased deaths: in addition to the higher number of all-cause deaths in the tacrolimus arm compared to the cyclosporine arm (9 versus 5), the 2007 DSPTP review also suggested that more deaths in the tacrolimus arm were related to infectious causes (5 versus 1). Attribution of cause of death in kidney transplantation trials is notoriously difficult. The interpretation, however, was that the observed trend tended to support the pre-existing concerns of the Division.

A re-examination of the deaths in Study 02-0-158 demonstrates the difficulty in determining cause of death among transplant patients: among the patients who were randomized to cyclosporine, Patient 10212009 died of diverticulitis on day 222 after developing multiple episodes of CMV infections; Patient 10222001 died of "pulmonary edema" on day 45 after

requiring treatment with thymoglobulin for an early rejection episode; Patient 10931013 died of myocardial infarction on day 35 after being admitted to the hospital on day 34 with "life threatening cellulitis"; Patient 00321006 died of myocardial infarction on day 324; Patient 00712001 died of a pulmonary embolus in the hospital on day 55 in the setting of a wound infection, BK nephropathy, and CMV viremia. In addition, Patient 10222007 (who was randomized to the cyclosporine arm but never received the study drug due to critical illness from time of randomization) died of sepsis on day 19. One could very reasonably argue, then, that the cyclosporine group had six deaths and that at least four of those deaths were related to infection. A similar re-examination of the deaths in the tacrolimus study group reveals that one of the nine deaths was due to homicide, one was due to a due to a subdural bleed after a fall, one was due to "possible pulmonary embolus", one was due to cardiac arrest, and the others were more clearly related to infection. Study 02-0-158 also included a third study group which received Advagraf (an extended release formulation of tacrolimus), MMF, corticosteroids, and basiliximab; the hypothesis of increased MPA exposure leading to increased deaths, then, should have applied equally to that study group. Only three deaths, however, occurred in the equally sized Advagraf arm (only one of which was clearly related to infection).

A similar examination of all the deaths that occurred within the 12 month follow-up period of Symphony-ELiTE was conducted to determine whether the data supports a conclusion that the exposure to higher levels of MPA led to increased infectious deaths among patients randomized to Group C (tacrolimus and MMF). As reported in **Table 7.2.1A**, the incidence of all-cause mortality in Group C was greater than one of the cyclosporine study groups (Group B) and less than one of the other cyclosporine study groups (Group A) – though no statistically significant difference for all-cause mortality was detected among the groups. **Table 7.2.1B** lists the cause of death of each patient as inferred from the submitted death narratives. As noted in the table and stated previously in section **3.1**, the submission omitted death narratives for several patients (3 from Group A, 3 from Group B, 3 from Group C, and 6 from Group D). Given those limitations, however, no clear trend for an increase in infectious deaths was detected among patients assigned to Group C (see **Table 7.2.1C**).

Table 7.2.1A: Number of Deaths (and Mortality Rates)

	Group A	Group B	Group C	Group D
Week 4	1 (0.26%)	2 (0.51%)	2 (0.50%)	3 (0.77%)
Week 8	5 (1.32%)	3 (0.77%)	5 (1.27%)	6 (1.56%)
Month 3	7 (1.87%)	3 (0.77%)	7 (1.79%)	6 (1.56%)
Month 6	13 (3.53%)	5 (1.29%)	9 (2.31%)	10 (2.62%)
Month 9	13 (3.53%)	5 (1.29%)	10 (2.58%)	11 (2.89%)
Month 12	13 (3.53%)	7 (1.83%)	11 (2.85%)	12 (3.17%)
Total # of Death	14	8	12	15

(There is no statistically significant difference for mortality rate among the treatment groups, p=0.3448, log rank test)
(adapted from Biometrics Review)

Table 7.2.1B: Individual Patient Deaths in Symphony-ELiTE

PID	Group	Age	Gender	Cause of Death (Based on Death Narrative)

100140	A	67	Male	Ruptured aortic aneurysm
120308	A	68	Female	Sepsis, CMV
130112	A	54	Male	Sepsis, CMV
130904	A	53	Female	Sepsis, CMV
130915	A	33	Male	Sepsis, CMV, anaphylaxis
150207	A	64	Female	Post-op hemorrhage → cardiac failure
150421	A	65	Female	Mycotic arteritis and meningitis (probably asperillus)
161717	A	70	Female	ICH in setting of bleeding disorder → PNA
180505	A	59	Female	No narrative
220131	A	56	Female	No narrative
221016	A	69	Female	Cholecystitis
260216	A	43	Male	Ruptured aortic aneurysm
270409	A	55	Female	Asystolic arrest
161025	B	62	Male	No narrative
161108	B	46	Male	No narrative
161734	B	58	Male	Post biopsy hemorrhage
170107	B	65	Male	Endocarditis, septic shock
221103	B	48	Male	Myocardial infarction on POD#2
221812	B	65	Female	Perirenal abscess → sepsis
240117	B	68	Male	Pneumonia, septic shock (narrative unclear)
120326	C	71	Female	Suicide (narrative unclear)
150410	C	50	Male	Pulmonary embolism @ 2 months post-operative
160302	C	35	Female	Sigmoid necrosis, bowel perforation, sepsis
160323	C	53	Male	Fungal pneumonia, sepsis (aspergillus and candida)
160817	C	66	Female	No narrative
180504	C	53	Male	BK nephropathy, ACR → Tx'd, Sepsis
200108	C	43	Female	Pulmonary embolus @ 2 weeks post-operative
220135	C	72	Female	Cardiac insufficiency
221801	C	63	Female	Cardiac arrest, AV block, recent history of arrhythmias
230421	C	39	Male	Pulmonary embolus @ 1 week post-op (known DVT)
260239	C	74	Male	No narrative
130116	D	36	Male	No narrative
130510	D	63	Male	Sepsis 2/2 ureteral fisula
150213	D	68	Female	Cardiac failure, colon perforation → sepsis
161741	D	69	Male	No narrative
170204	D	59	Male	Pneumonia, CMV
200107	D	28	Male	Systemic candidiasis, giardia
230317	D	54	Female	PNA → septic shock on POD#10
230431	D	51	Male	Surgical site infection (pseudomonas) → sepsis POD #16
230438	D	34	Male	Pulmonary embolus on POD #7 (no autopsy)
230803	D	35	Male	Ureteral stenosis, lymphocele → sepsis

260106	D	50	Male	Cardiac arrest @ 1 month post-operative
270101	D	59	Male	No narrative

Table 7.2.1C: Summary of Patient Deaths by Group

	Group A (n=390)	Group B (n=399)	Group C (n=401)	Group D (n=399)
Infectious cause of death	6	3	2.5	5.5
Non-infectious cause of death	5	2	6.5	3.5
No narrative or unclear cause	2	2	2	3
Total	13	7	11	12

(Cause of death was inferred from the submitted death narrative by the DSPTP primary medical reviewer)

*Reviewer comment: No evidence of a true difference in total number of deaths or number of infectious deaths could be appreciated between the study groups of Symphony-ELiTE. An independent examination of the data from Study 02-0-158, including a review of the patient death narratives, did not find a strong safety signal supporting the hypothesis that the use of MMF in conjunction with tacrolimus resulted in a higher incidence of deaths due to infection. The most concerning finding from Study 02-0-158 was the relatively high rate of all-cause death in the tacrolimus/MMF arm (4.2%). That signal was not confirmed by either the Advagraf arm of Study 02-0-158 (which had an all-cause mortality rate of 1.4%) or the tacrolimus arm of larger Symphony-ELiTE trial (which had an all-cause morality rate of 3.0%). As noted in section **6.1.6 (Subpopulations)**, it was appreciated that Group C exhibited a high death rate of females (4.4%), but given the small size of that group (n=137), no clear conclusions were suggested: comparison to the two cyclosporine/MMF regimens reveals that females in Group A exhibited a higher death rate (6.1%, n=147), while those in Group B exhibited a lower death rate (0.8%, n=134). For that reason, particular attention was given to the death narratives of the females. In Group C, one of the six female deaths appeared related to infection (PID 160302; bowel perforation and sepsis), 4 others did not (1 suicide, 1 pulmonary embolus, and two cardiac cases), and one did not have a narrative. The single female death in Group B (PID 221812) was due to sepsis in the setting of a perirenal abscess. At least 4 deaths of female patients in Group A were clearly related to infection. The data, then, also did not suggest an increased rate of death due to infection in female patients.*

7.2.1.1 Graft Loss

The findings of the Cochrane Collaborative Review suggest that tacrolimus-based immunosuppressive regimens may result in superior graft survival compared to cyclosporine-based regimens. The data from Symphony-ELiTE appear consistent with those conclusions. Though the differences between study groups did not reach the level of statistical significance, a strong trend towards decreased graft loss (especially death-censored graft loss) favored the tacrolimus/MMF treatment group in Symphony-EliTE.

Table 7.2.1.1A: Graft Loss in Symphony-EliTE

	Group A (n=390)	Group B (n=399)	Group C (n=401)	Group D (n=399)
All Graft Loss	41 (10.5%)	27 (6.8%)	23 (5.7%)	42 (10.5%)
Death-Censored Graft Loss	28 (7.2%)	20 (5.0%)	12 (3.0%)	30 (7.5%)

Reviewer comment: The difference between Group C and the other groups were not statistically significant after the Bonferroni adjustment for multiple comparisons. A strong trend in favor of the Tac/MMF group over the other groups, however, is noted.

7.2.2 Nonfatal Serious Adverse Events

Predictable adverse events after renal transplantation related to the institution of various immunosuppression regimens include new onset diabetes after transplantation (and worsening of pre-existing diabetes), new onset or worsened hypertension, increased rates of malignancy (including post transplant lymphoproliferative disorders (PTLD)), increased rates of infection (including CMV, BK, PML and other opportunistic infections), decreased hematopoesis (including leucopenia and thrombocytopenia), and diarrhea.

Symphony-EliTE allowed the analysis of 1,580 serious adverse events organized by MedDRA System Organ Class (SOC) and Preferred Term (PT) distributed among 1,602 renal transplant recipients randomized to one of four study groups. For the purposes of the study, a serious adverse event was defined as "any adverse event that results in death, is life-threatening…, requires patient hospitalization or prolongation of existing hospitalization…, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, (or) is medically significant or requires intervention to prevent one or other of the outcomes listed above." The database generated by Symphony-EliTE represents a uniquely powerful tool to investigate the relative safety of tacrolimus in conjunction with MMF compared to cyclosporine or sirolimus in conjunction with MMF. Inspection of the serious adverse event profiles suggests that the safety profile for the use of tacrolimus in conjunction with MMF is largely similar to that for the use of cyclosporine in conjunction with MMF. Patients using tacrolimus in conjunction with MMF, however, appeared to experience more serious adverse events related to gastrointestinal disorders (including diarrhea) and nervous system disorders compared to patients following a cyclosporine-based regimen.

Table 7.2.2A: All Serious Adverse Events (Preferred Terms with Incidence ≥ 1%)

System Organ Class ***Preferred Term***		**Group A (N=384)**	**Group B (N=408)**	**Group C (N=403)**	**Group D (N=380)**	**Group O (N=27)**
Not coded	No. of Aes	1	4	1	1	0

	No. of Pat.	1 (0.3%)	3 (0.7%)	1 (0.2%)	1 (0.3%)	0 (0%)
Blood and lymphatic system disorders	No. of Aes	8	21	14	20	0
	No. of Pat.	7 (1.8%)	14 (3.4%)	12 (3.0%)	16 (4.2%)	0 (0%)
Anemia	No. of Aes	3	2	5	2	0
	No. of Pat.	3 (0.8%)	2 (0.5%)	4 (1.0%)	9 (2.4%)	0 (0%)
Leucopenia	No. of Aes	1	9	4	10	0
	No. of Pat.	1 (0.3%)	8 (2.0%)	4 (1.0%)	9 (2.4%)	0 (0%)
Cardiac disorders	No. of Aes	20	20	22	16	0
	No. of Pat.	15 (3.9%)	15 (3.7%)	13 (3.2%)	11 (2.9%)	0 (0%)
Atrial fibrillation	No. of Aes	5	2	2	0	0
	No. of Pat.	4 (1.0%)	2 (0.5%)	2 (0.5%)	0 (0%)	
Congenital, familial, and genetic disorders	No. of Aes	1	1	0	0	0
	No. of Pat.	1 (0.3%)	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)
Endocrine disorders	No. of Aes	1	3	2	1	0
	No. of Pat.	1 (0.3%)	3 (0.7%)	2 (0.5%)	1 (0.3%)	0 (0%)
Eye disorders	No. of Aes	1	0	2	0	0
	No. of Pat.	1 (0.5%)	0 (0%)	2 (0.5%)	0 (0%)	0 (0%)
Gastrointestinal Disorders	No. of Aes	18	27	41	37	0
	No. of Pat.	15 (3.9%)	23 (5.6%)	33 (8.2%)	29 (7.6%)	0 (0%)
Abdominal pain	No. of Aes	2	5	4	2	0
	No. of Pat.	2 (0.5%)	5 (1.2%)	3 (0.7%)	2 (0.5%)	0 (0%)
Diarrhea	No. of Aes	2	7	12	7	0
	No. of Pat.	2 (0.5%)	7 (1.7%)	11 (2.7%)	7 (1.8%)	0 (0%)

General disorders and administration site conditions	No. of Aes No. of Pat.	5 5 (1.3%)	11 10 (2.5%)	13 12 (3.0%)	20 20 (5.3%)	2 2 (7.4%)
Pyrexia	No. of Aes No. of Pat.	4 4 (1.0%)	7 7 (1.7%)	9 8 (2.0%)	14 14 (3.7%)	1 1 (3.7%)
Sudden death	No. of Aes No. of Pat.	0 0 (0%)	0 0 (0%)	0 0 (0%)	0 0 (0%)	1 1 (3.7%)
Hepatobiliary disorders	No. of Aes No. of Pat.	6 5 (1.3%)	4 3 (0.7%)	3 2 (0.5%)	0 0 (0%)	0 0 (0%)
Immune system Disorders	No. of Aes No. of Pat.	6 6 (1.6%)	13 11 (2.7%)	6 6 (1.5%)	13 13 (3.4%)	1 1 (3.7%)
*Kidney transplant rejection**	No. of Aes No. of Pat.	2 2 (0.5%)	10 9 (2.2%)	4 4 (1.0%)	10 10 (2.6%)	0 0 (0%)
*Transplant rejection**	No. of Aes No. of Pat.	4 4 (1.0%)	3 3 (0.7%)	2 2 (0.5%)	3 3 (0.8%)	1 1 (3.7%)
Infections and Infestations	No. of Aes No. of Pat.	86 58 (15.1%)	81 57 (14.0%)	84 60 (14.9%)	103 78 (20.5%)	3 2 (7.4%)
Gastroenteritis	No. of Aes No. of Pat.	3 3 (0.8%)	3 3 (0.7%)	4 2 (0.5%)	1 3 (0.8%)	0 1 (3.7%)
Infected lymphocele	No. of Aes No. of Pat.	1 1 (0.3%)	1 1 (0.2%)		5 5 (1.3%)	0 0 (0%)
Pneumonia	No. of Aes No. of Pat.	6 6 (1.6%)	1 1 (0.2%)	9 9 (2.2%)	17 14 (3.7%)	0 0 (0%)
Postoperative wound infection	No. of Aes No. of Pat.	2 2 (0.5%)	2 2 (0.5%)	5 5 (1.2%)	4 3 (0.8%)	2 1 (3.7%)
Pyelonephritis	No. of Aes No. of	5 5 (1.3%)	1 1 (0.2%)	4 4 (1.0%)	3 3 (0.8%)	0 0 (0%)

	Pat.					
Pyelonephritis	No. of Aes	2	1	5	1	0
Acute	No. of Pat.	2 (0.5%)	1 (0.2%)	5 (1.2%)	1 (0.3%)	0 (0%)
Sepsis	No. of Aes	7	2	5	6	1
	No. of Pat.	7 (1.8%)	2 (0.5%)	5 (1.2%)	6 (1.6%)	1 (3.7%)
Urinary tract	No. of Aes	19	26	12	12	0
Infection	No. of Pat.	14 (3.6%)	19 (4.7%)	11 (2.7%)	11 (2.9%)	0 (0%)
Urosepsis	No. of Aes	9	3	5	5	0
	No. of Pat.	6 (1.6%)	3 (0.7%)	5 (1.2%)	5 (1.3%)	0 (0%)
Wound infection	No. of Aes	0	2	1	4	0
	No. of Pat.	0 (0%)	2 (0.5%)	1 (0.2%)	4 (1.1%)	0 (0%)
Injury, poisoning, and	No. of Aes	49	45	43	55	0
procedural complications	No. of Pat.	43 (11.2%)	36 (8.8%)	39 (9.7%)	42 (11.1%)	0 (0%)
Complications of	No. of Aes	7	10	6	8	0
transplanted kidney	No. of Pat.	7 (1.8%)	8 (2.0%)	6 (1.5%)	6 (1.6%)	0 (0%)
Drug toxicity	No. of Aes	2	0	6	1	0
	No. of Pat.	1 (0.3%)	0 (0%)	5 (1.2%)	1 (0.3%)	0 (0%)
Graft dysfunction	No. of Aes	5	5	7	5	0
	No. of Pat.	5 (1.3%)	5 (1.2%)	7 (1.7%)	4 (1.1%)	0 (0%)
Post procedural	No. of Aes	3	1	4	5	0
hemorrhage	No. of Pat.	3 (0.8%)	1 (0.2%)	4 (1.0%)	3 (0.8%)	0 (0%)
Post procedural	No. of Aes	3	3	3	5	0
urine leak	No. of Pat.	3 (0.8%)	3 (0.7%)	3 (0.7%)	4 (1.1%)	0 (0%)
Therapeutic agent	No. of Aes	6	5	0	0	0
Toxicity	No. of Pat.	6 (1.6%)	5 (1.2%)	0 (0%)	0 (0%)	0 (0%)
Urinary anastomotic	No. of Aes	4	1	4	2	0
Leak	No. of Pat.	4 (1.0%)	1 (0.2%)	4 (1.0%)	2 (0.5%)	0 (0%)

Wound dehiscence	No. of Aes	1	1	0	5	0
	No. of Pat.	1 (0.3%)	1 (0.2%)	0 (0%)	5 (1.3%)	0 (0%)
Investigations	No. of Aes	17	19	29	24	0
	No. of Pat.	14 (3.6%)	12 (2.9%)	25 (6.2%)	21 (5.5%)	0 (0%)
Blood creatinine	No. of Aes	11	13	18	15	0
Increased	No. of Pat.	9 (2.3%)	9 (2.2%)	15 (3.7%)	14 (3.7%)	0 (0%)
Metabolism and nutrition	No. of Aes	9	10	18	15	0
Disorders	No. of Pat.	8 (2.1%)	10 (2.5%)	14 (3.5%)	14 (3.7%)	0 (0%)
Dehydration	No. of Aes	2	1	3	7	0
	No. of Pat.	1 (0.5%)	1 (0.2%)	3 (0.7%)	7 (1.8%)	0 (0%)
Diabetes mellitus	No. of Aes	2	1	4	0	0
	No. of Pat.	2 (0.5%)	1 (0.2%)	4 (1.0%)	0 (0%)	0 (0%)
Musculoskeletal and	No. of Aes	6	4	2	5	0
connective tissue disorders	No. of Pat.	5 (1.3%)	4 (1.0%)	2 (0.5%)	5 (1.3%)	0 (0%)
Nervous system	No. of Aes	4	3	13	4	0
Disorders	No. of Pat.	4 (1.0%)	3 (0.7%)	10 (2.5%)	3 (0.8%)	0 (0%)
Psychiatric disorders	No. of Aes	1	1	2	1	0
	No. of Pat.	1 (0.3%)	1 (0.2%)	2 (0.5%)	1 (0.3%)	0 (0%)
Renal and urinary	No. of Aes	59	75	62	36	3
Disorders	No. of Pat.	46 (12.0%)	53 (13.0%)	45 (11.2%)	30 (7.9%)	3 (11.1%)
Hydronephrosis	No. of Aes	8	5	1	2	1
	No. of Pat.	8 (2.1%)	5 (1.2%)	1 (0.2%)	1 (0.3%)	1 (3.7%)
Renal artery stenosis	No. of Aes	1	5	1	0	0
	No. of	1 (0.3%)	4 (1.0%)	1 (0.2%)	0 (0%)	0 (0%)

	Pat.					
Renal artery Thrombosis	No. of Aes No. of Pat.	4 4 (1.0%)	5 5 (1.0%)	2 2 (0.5%)	2 2 (0.5%)	1 1 (3.7%)
Renal failure acute	No. of Aes No. of Pat.	0 0 (0%)	5 4 (1.0%)	5 5 (1.2%)	0 0 (0%)	0 0 (0%)
Renal hemorrhage	No. of Aes No. of Pat.	2 2 (0.5%)	0 0 (0%)	0 0 (0%)	0 0 (0%)	1 1 (3.7)
Renal impairment	No. of Aes No. of Pat.	4 4 (1.0%)	4 4 (1.0%)	6 5 (1.2%)	6 6 (1.6%)	0 0 (0%)
Renal vein thrombosis	No. of Aes No. of Pat.	3 3 (0.8%)	0 0 (0%)	2 2 (0.5%)	4 4 (1.1%)	0 0 (0%)
Urethral necrosis	No. of Aes No. of Pat.	3 3 (0.8%)	4 4 (1.0%)	2 2 (0.5%)	2 2 (0.5%)	0 0 (0%)
Urethric fistula	No. of Aes No. of Pat.	3 3 (0.8%_	5 5 (1.2%)	2 2 (0.5%)	1 1 (0.3%)	0 0 (0%)
Urethric obstruction	No. of Aes No. of Pat.	4 4 (1.0%)	4 4 (1.0%)	0 0 (0%)	0 0 (0%)	0 0 (0%)
Urethric stenosis	No. of Aes No. of Pat.	5 5 (1.3%)	7 7 (1.7%)	5 5 (1.2%)	4 4 (1.1%)	0 0 (0%)
Urinary tract Obstruction	No. of Aes No. of Pat.	4 4 (1.0%)	4 4 (1.0%)	0 0 (0%)	0 0 (0%)	0 0 (0%)
Reproductive system and breast disoreders	No. of Aes No. of Pat.	2 2 (0.5%)	3 3 (0.7%)	1 1 (0.2%)	1 1 (0.3%)	0 0 (0%)
Respiratory, thoracic, and mediastinal disorders	No. of Aes No. of Pat.	9 9 (2.3%)	4 4 (1.0%)	10 7 (1.7%)	16 11 (2.9%)	2 2 (7.4%)
Dyspnea	No. of Aes No. of	4 4 (1.0%)	0 0 (0%)	1 1 (0.2%)	1 1 (0.3%)	0 0 (0%)

	Pat.					
Hypoxia	No. of Aes	0	0	0	0	1
	No. of Pat.	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3.7%)
Pulmonary embolism	No. of Aes	3	0	2	2	1
	No. of Pat.	3 (0.8%)	0 (0%)	2 (0.5%)	2 (0.5%)	1 (3.7%)
Skin and subcutaneous	No. of Aes	3	1	1	1	0
tissue disorders	No. of Pat.	3 (0.8%)	1 (0.2%)	1 (0.2%)	1 (0.3%)	0 (0%)
Surgical and medical	No. of Aes	5	11	14	9	2
Procedures	No. of Pat.	5 (1.3%)	10 (2.5%)	10 (2.5%)	9 (2.4%)	2 (7.4%)
Nephrectomy	No. of Aes	0	2	0	0	2
	No. of Pat.	0 (0%)	2 (0.5%)	0 (0%)	0 (0%)	2 (7.4%)
Vascular disorders	No. of Aes	23	19	18	46	1
	No. of Pat.	22 (5.7%)	16 (3.9%)	17 (4.2%)	39 (10.3%)	1 (3.7%)
Hemorrhage	No. of Aes	4	0	0	3	0
	No. of Pat.	4 (1.0%)	0 (0%)	0 (0%)	3 (0.8%)	0 (0%)
Lymphocele	No. of Aes	7	10	5	26	0
	No. of Pat.	7 (1.8%)	8 (2.0%)	5 (1.2%)	22 (5.8%)	0 (0%)
Venous thrombosis	No. of Aes	0	0	0	2	1
	No. of Pat.	0 (0%)	0 (0%)	0 (0%)	2 (0.5%)	1 (3.7%)
TOTAL	No. of Aes	343	385	407	431	14
	No. of Pat.	170 (44.3%)	177 (43.4%)	177 (43.9%)	202 (53.2%)	10 (37.0%)

(adapted from Roche CSR)

*The adverse event database includes some cases of rejection, though rejection was an endpoint and should not have been reported as an AE

Reviewer Comment 1: Other than slight signals for the severe adverse events of diarrhea (incidence of 2.7% for Group C, compared to 0.5% for Group A and 1.7% for Group B) and nervous system disorders (incidence of 2.5% for Group C, compared to 1.0% for Group A

and 0.7% for Group B), the regimen Group C appeared at least as well-tolerated as the other study regimens.

Serious Adverse Events of Special Interest

In addition to a review of all serious adverse with an incidence greater than 1%, specific investigations were performed to analyze safety concerns of particular interest to the patient population (kidney transplant patients on immunosuppresion) and/or previously identified as potentially worse for patients using a combination of tacrolimus and MMF. The serious adverse events of interest included malignancies, infections (including opportunistic infections), anemia, leucopenia, and diarrhea.

Malignancies:

The Sponsor performed a manual review of all 11,263 adverse events captured by the safety database. In addition to the cases reported under Systems Organ Class (SOC) *neoplasms benign, malignant, and unspecified*, additional cases were found under other SOC classifications. **Table 7.2.2B** includes all cases reported within 12 months post-transplant including prematurely withdrawn patients.

Table 7.2.2B: Malignancies Identified in Symphony-EliTE at 12 Months

SAFETY POPULATION	Group A (N=384)	Group B (N=408)	Group C (N=403)	Group D (N=380)	Group O (N=27)
Oral mucosa cancer	1	-	-	1	-
Kaposi's sarcoma	1	1	-	-	-
Prostate cancer	-	-	1	-	-
Transitional cell carcinoma	-	1	-	-	-
Renal cell carcinoma	-	1	2	1	-
Non-small cell lung cancer	-	-	-	1	-
Small cell lung cancer	-	-	-	1	-
Breast cancer	-	-	-	1	-
Colon cancer	-	-	-	-	1[o,sw]
Cerebral lymphoma *	-	-	1	-	-
Non-Hodgkin's T-cell lymphoma *	-	-	-	1[sw]	-
Non-Hodgkin's B-cell lymphoma *	-	-	-	1	-
Post-Tx lymphoproliferative disorder *	-	-	-	-	1[o,sw]
TOTAL patients with ≥1 „major' malignancy	**2 (0.5%)**	**3 (0.7%)**	**4 (1.0%)**	**7 (1.8%)**	**1 (3.7%)**
Basal cell carcinoma	2	1	3	-	-
Squamous cell carcinoma	1	-	1	-	-
Ovarian cancer (borderline)	-	-	-	1	-
TOTAL Patients with ≥1 malignancy	**5 (1.3%)**	**4 (1.0%)**	**8 (2.0%)**	**8 (2.1%)**	**1 (3.7%)**

sw = patient switched to tacrolimus or cyclosporine (1 case) several months before diagnosis.
o = multiple cases in the same patient; originally randomized to group D

(adapted from Roche CSR)

Reviewer comment: Not all of the predictable adverse events above lend themselves to study within the confines of a randomized controlled trial: for example, malignancies (including PTLD) are sufficiently rare events that one cannot meaningfully elucidate differences between regimens through studies limited in size to hundreds (or even thousands) of patients. Not unexpectedly, Symphony-EliTE fails to elucidate whether any difference with regards to this important group of adverse events exists between the tacrolimus/MMF arm and the cyclosporine/MMF arm. No significant evidence to support a hypothesis that a true difference does exist, however, was appreciated.

Serious Adverse Events due to Infection:

In addition to submitting serious adverse events captured under MedDRA SOC *Infections and infestations* (see **Table 7.2.2A** above), investigators reported details regarding opportunistic infections through electronic Case Report Forms (eCRFs). Renal transplant patients require routine monitoring for BK virus and cytomegalovirus (CMV), pathogens commonly responsible for significant morbidity in that patient population. **Table 7.2.2C** reports the incidence of serious BK, CMV, and other opportunistic infections in the Symphony-EliTE trial.

Table 7.2.2C: Serious Opportunistic Infections

PATHOGEN AS PER PROTOCOL		A (N=384)	B (N=408)	C (N=403)	D (N=380)	O (N=27)	TOTAL (N=1602)
Aspergillus	No. of AEs	2	2	2	1	0	7
	No. of Pat.	1 (0.3%)	2 (0.5%)	2 (0.5%)	1 (0.3%)	0 (0%)	6 (0.4%)
BK Polyoma virus	No. of AEs	2	1	4	1	0	8
	No. of Pat.	2 (0.5%)	1 (0.3%)	4 (1.0%)	1 (0.3%)	0 (0%)	8 (0.5%)
Candida	No. of AEs	2	2	0	6	0	10
	No. of Pat.	2 (0.5%)	2 (0.5%)	0 (0%)	6 (1.6%)	0 (0%)	10 (0.6%)
Cryptococcus	No. of AEs	0	0	3	0	0	3
	No. of Pat.	0 (0%)	0 (0%)	1 (0.3%)	0 (0%)	0 (0%)	1 (0.1%)
Cytomegalovirus (CMV)	No. of AEs	36	32	21	11	0	100
	No. of Pat.	30 (7.8%)	27 (6.6%)	20 (5.0%)	11 (2.9%)	0 (0%)	88 (5.5%)
Herpes simplex virus	No. of AEs	1	0	3	6	0	10
	No. of Pat.	1 (0.3%)	0 (0%)	3 (0.74%)	6 (1.6%)	0 (0%)	10 (0.6%)
Pneumocystis	No. of AEs	1	2	0	1	0	4
	No. of Pat.	1 (0.3%)	2 (0.5%)	0 (0%)	1 (0.3%)	0 (0%)	4 (0.2%)
Varicella-Zoster Virus (VZV)	No. of AEs	5	5	7	5	0	22
	No. of Pat.	5 (1.3%)	5 (1.2%)	7 (1.7%)	5 (1.3%)	0 (0%)	22 (1.4%)
TOTAL	No. of AEs	49	44	40	31	0	164
	No. of Pat.	41 (10.7%)	39 (9.6%)	34 (8.4%)	31 (8.2%)	0 (0%)	145 (9.1%)

(adapted from Roche CSR)

Reviewer comment 1: The Symphony-ELiTE study was notable for its low incidence of serious adverse events related to BK virus. Some literature exists to suggest that the incidence of BK nephropathy increased after the use of tacrolimus and MMF became commonplace. While the data in Symphony-EliTE are insufficient to refute the possibility of an association between tacrolimus/MMF use and BK disease, they suggest that the current monitoring strategies (primarily routine urine cytology looking for decoy cells) have been successful at mitigating of BK nephropathy in renal transplant patients.

Reviewer comment 2: An appreciable trend towards increased incidence of serious CMV infections is notable among the groups treated with cyclosporine and MMF combinations. Risk factors for CMV disease (i.e., donor and recipient CMV serum antibody status) were equally distributed among the groups. The occurrence of acute rejection episodes prior to CMV reactivation has been noted as a risk factor for CMV disease.[45] A plausible explanation for the trend, then, relates to the greater incidence of rejection episodes among the cyclosporine/MMF groups.

Reviewer comment 3: Table AAA derives from the Roche Clinical Study Report. It was generated from data from the eCRFs which were not submitted. Those data could not, therefore, be independently validated during the clinical review.

Serious Adverse Events related to diarrhea, anemia, and leucopenia

Side effects related to MPA exposure include anemia, leucopenia, and diarrhea. Given that the use of MMF in combination with tacrolimus may result in greater MPA exposure than the use of MMF in combination with cyclosporine, a comparison of serious adverse events related to anemia, leucopenia, or diarrhea has been reported in **Table 7.2.2D.**

Table 7.2.2D: Serious Adverse Events Related to Anemia, Leucopenia, or Diarrhea

Preferred Term		Group A (N=384)	Group B (N=408)	Group C (N=403)	Group D (N=380)	Group O (N=27)
Anemia	No. of Aes	3	2	5	2	0
	No. of Pat.	3 (0.8%)	2 (0.5%)	4 (1.0%)	9 (2.4%)	0 (0%)
Leucopenia	No. of Aes	1	9	4	10	0
	No. of Pat.	1 (0.3%)	8 (2.0%)	4 (1.0%)	9 (2.4%)	0 (0%)
Diarrhea	No. of Aes	2	7	12	7	0
	No. of Pat.	2 (0.5%)	7 (1.7%)	11 (2.7%)	7 (1.8%)	0 (0%)

Reviewer comment 1: The original clinical review of Study 02-0-158 focused on the finding that patients on the tacrolimus/MMF regimen experienced more days of leucopenia. Less clear, however, is the clinical significance of a laboratory result of leucopenia with total white blood cells less than 2,500 cells/ml (unlike, for instance, neutropenia with absolute neutrophil count less than 500 cells/ml – which does have quantifiable significance). Effective immunosuppression likely requires some impact on leucocyte production. While tacrolimus in combination with MMF may result more total days of low white blood cell counts, the data from Symphony-EliTE does not suggest that its tacrolimus-based regimen resulted in more frequent serious adverse events related to leucopenia.

Reviewer comment 2: While the differences observed were not statistically significant, the data from Symphony-EliTE suggests that the use of tacrolimus in combination with MMF

may result in a greater likelihood of serious adverse events related to diarrhea. The data further suggests, however, that such events were rare in all patient groups.

7.2.3 Dropouts and/or Discontinuations

As noted in section **6.1.3**, premature withdrawal represented the final patient disposition for 501 patients (31.5%) in the ITT population. Such discontinuations were unevenly distributed across the study groups: Group D accounted for the most (48.9% of enrolled patients withdrew prematurely) while Group C accounted for the least (20% of enrolled patients withdrew prematurely). Treatment failure represented the most common cause for premature withdrawal, followed by the use of additional maintenance immunosuppressive medication and discontinuation of any of the assigned immunosuppressants for greater than 14 consecutive days. Group C also had the fewest withdrawals among the 4 groups for each of those reasons.

Table 7.2.3A: Reasons for Premature Withdrawals

	Group A N=390	Group B N=399	Group C N=401	Group D N=399
Reason missing	0 (0.0%)	2 (0.5%)	1 (0.2%)	0 (0.0%)
Adverse event or intercurrent illness	12 (3.1%)	7 (1.8%)	9 (2.2%)	31 (7.8%)
Treatment failure	62 (15.9%)	61 (15.3%)	34 (8.5%)	109 (27.3%)
Use of additional maintenance immunosuppresion medication	27 (6.9%)	24 (6.0%)	6 (1.5%)	59 (14.8%)
Discontinuation of any of the assigned immunosuppressant > 14 consecutive days	20 (5.1%)	21 (5.3%)	18 (4.5%)	27 (6.8%)
Discontinuation of any of the assigned immunosuppressant > 30 cumulative days	4 (1.0%)	6 (1.5%)	2 (0.5%)	5(1.3%)
Graft loss (return to chronic dialysis)	11 (2.8%)	10 (2.5%)	8 (2.0%)	18 (4.5%)
Death of patient	8 (2.1%)	5 (1.3%)	9 (2.2%)	6 (1.5%)
Necessity for treatment with other investigational drug or other medications prohibited by protocol	8 (2.1%)	8 (2.0%)	1 (0.2%)	17 (4.3%)
Non-compliance with protocol schedule	3 (0.8%)	4 (1.1%)	6 (1.5%)	4 (1.0%)
Failure to return (lost to follow-up)	5 (1.3%)	7 (1.8%)	6 (1.5%)	5 (1.3%)

Patient withdrew consent	5 (1.3%)	2 (0.5%)	6 (1.5%)	0 (0.0%)
Other reason	13 (3.3%)	14 (3.5%)	8 (2.0%)	23 (5.8%)
Total	**116 (29.7%)**	**110 (27.6%)**	**80 (20.0%)**	**195 (48.9%)**

(Adapted from Roche CSR)

Reviewer comment 1: As an open-label study, a potential for bias existed in the Symphony-EliTE trial which may have contributed to the uneven distribution of premature withdrawals observed. It is worth noting, however, that the differences in premature withdrawals between the tacrolimus group and the cyclosporine groups were driven almost entirely by treatment failures and the use of additional maintenance immunosuppresion medications.

Reviewer comment 2: Please note that the data in the above table report pertain to causes for premature withdrawals only. They do not report totals of these events observed in the study. This accounts for the apparent discrepancy in graft losses, deaths, etc.

7.2.4 Significant Adverse Events

Predictable adverse events after renal transplantation related to the institution of various immunosuppression regimens include new onset diabetes after transplantation (and worsening of pre-existing diabetes), new onset or worsened hypertension, increased rates of malignancy (including post transplant lymphoproliferative disorders (PTLD)), increased rates of infection (including CMV, BK, PML and other opportunistic infections), decreased hematopoesis (including leucopenia and thrombocytopenia), and diarrhea.

Symphony-EliTE allowed the analysis of 11,263 adverse events organized by MedDRA System Organ Class (SOC) and Preferred Term (PT) among 1,602 renal transplant recipients randomized to one of four study groups. The database generated by Symphony-EliTE represents a uniquely powerful tool to investigate the relative safety of tacrolimus in conjunction with MMF compared to cyclosporine or sirolimus in conjunction with MMF. For the purposes of the study, an adverse event was defined as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment… Pre-existing conditions which worsened during a study were to be reported as adverse events." The database generated by Symphony-EliTE represents a uniquely powerful tool to investigate the relative safety of tacrolimus in conjunction with MMF compared to cyclosporine or sirolimus in conjunction with MMF. Inspection of the adverse event profiles suggests that the safety profile for the use of tacrolimus in conjunction with MMF is largely similar to that for the use of cyclosporine in conjunction with MMF. Patients using tacrolimus in conjunction with MMF, however, appeared to experience more serious adverse events related to gastrointestinal disorders (particularly diarrhea) and nervous system disorders but fewer lipid disorders compared to patients following a cyclosporine-based regimen.

Table 7.2.4A: Adverse Events (Preferred Terms with Incidence ≥ 5%)

System Organ Class ***Preferred Term***		**Group A (N=384)**	**Group B (N=408)**	**Group C (N=403)**	**Group D (N=380)**	**Group O (N=27)**
Blood and lymphatic system disorders	No. of Aes	190	205	217	193	2
	No. of Pat.	128 (33.3%)	137 (33.6%)	146 (36.2%)	137 (36.1%)	2 (7.4%)
Anemia	No. of Aes	79	79	79	102	2
	No. of Pat.	71 (18.5%)	71 (17.4%)	69 (17.1%)	95 (25.0%)	2 (7.4%)
Leucopenia	No. of Aes	48	47	59	42	0
	No. of Pat.	39 (10.2%)	41 (10.0%)	54 (13.4%)	39 (10.3%)	0 (0%)
Cardiac disorders	No. of Aes	43	44	42	40	1
	No. of Pat.	29 (7.6%)	33 (8.1%)	27 (6.7%)	30 (7.9%)	1 (3.7%)
Gastrointestinal disorders	No. of Aes	259	248	333	255	3
	No. of Pat.	128 (33.3%)	133 (32.6%)	167 (41.4%)	132 (34.7%)	2 (7.4%)
Abdominal pain	No. of Aes	16	19	34	11	0
	No. of Pat.	15 (3.9%)	17 (4.2%)	21 (5.2%)	10 (2.6%)	0 (0%)
Constipation	No. of Aes	34	21	30	26	1
	No. of Pat.	25 (6.5%)	21 (5.1%)	27 (6.7%)	23 (6.1%)	1 (3.7%)
Diarrhea	No. of Aes	73	64	136	96	0
	No. of Pat.	60 (15.6%)	53 (13.0%)	102 (25.4%)	74 (19.5%)	0 (0%)
Vomiting	No. of Aes	23	17	27	11	0
	No. of Pat.	18 (4.7%)	16 (3.9%)	22 (5.5%)	10 (2.6%)	0 (0%)
General disorders and administration site conditions	No. of Aes	111	131	129	162	3
	No. of Pat.	89 (23.2%)	92 (22.5%)	89 (22.1%)	104 (27.4%)	3 (11.1%)
Edema peripheral	No. of Aes	48	59	55	65	1
	No. of Pat.	46 (12.0%)	51 (12.5%)	45 (11.2%)	50 (13.2%)	1 (3.7%)

Pyrexia	No. of Aes	17	26	22	37	1
	No. of Pat.	17 (4.4%)	23 (5.6%)	20 (5.0%)	34 (8.9%)	1 (3.7%)
Immune system disorders	No. of Aes	13	19	16	20	1
	No. of Pat.	13 (3.4%)	14 (3.4%)	15 (3.7%)	20 (5.3%)	1 (3.7%)
Infections and infestations	No. of Aes	434	398	443	388	8
	No. of Pat.	208 (54.2%)	206 (50.5%)	211 (52.4%)	200 (52.6%)	5 (18.5%)
Nasopharyngitis	No. of Aes	25	36	35	20	0
	No. of Pat.	22 (5.7%)	32 (7.8%)	32 (7.9%)	15 (3.9%)	0 (0%)
Pneumonia	No. of Aes	18	5	13	25	0
	No. of Pat.	18 (4.7%)	5 (1.2%)	13 (3.2%)	19 (5.0%)	0 (0%)
Urinary tract infection	No. of Aes	165	141	149	117	0
	No. of Pat.	109 (28.4%)	97 (23.8%)	95 (23.6%)	88 (23.2%)	0 (0%)
Injury, poisoning, and procedural complications	No. of Aes	184	168	150	168	2
	No. of Pat.	125 (32.6%)	111 (27.2%)	108 (26.8%)	118 (31.1%)	2 (7.4%)
Complications of transplanted kidney	No. of Aes	25	30	22	19	0
	No. of Pat.	24 (6.3%)	27 (6.6%)	21 (5.2%)	17 (4.5%)	0 (0%)
Investigations	No. of Aes	175	188	219	163	2
	No. of Pat.	94 (24.5%)	101 (24.8%)	108 (26.8%)	97 (25.5%)	2 (7.4%)
Blood creatinine increased	No. of Aes	36	38	38	37	0
	No. of Pat.	30 (7.8%)	28 (6.9%)	33 (8.2%)	30 (7.9%)	0 (0%)
Metabolism and nutrition disorders	No. of Aes	293	262	277	316	1
	No. of Pat.	177 (46.1%)	156 (38.2%)	153 (38.0%)	179 (47.1%)	1 (3.7%)
Diabetes mellitus	No. of Aes	23	17	35	25	0
	No. of Pat.	23 (6.0%)	17 (4.2%)	34 (8.4%)	25 (6.6)	0 (0%)

Hypercholesterolemia	No. of Aes	40	42	18	40	0
	No. of Pat.	40 (10.4%)	42 (9.8%)	18 (4.5%)	39 (10.3%)	0 (0%)
Hyperglycemia	No. of Aes	17	12	23	23	0
	No. of Pat.	17 (4.4%)	12 (2.9%)	19 (4.7%)	19 (5.0%)	0 (0%)
Hyperlipidemia	No. of Aes	58	54	44	64	0
	No. of Pat.	57 (14.8%)	51 (12.5%)	40 (9.9%)	60 (15.8%)	0 (0%)
Hypertriglyceridemia	No. of Aes	17	15	14	28	0
	No. of Pat.	16 (4.2%)	14 (3.7%)	14 (3.5%)	26 (6.7%)	0 (0%)
Hyperuricemia	No. of Aes	25	27	18	7	0
	No. of Pat.	22 (5.7%)	23 (5.6%)	18 (4.5%)	6 (1.6%)	0 (0%)
Hypophosphatemia	No. of Aes	13	15	15	21	0
	No. of Pat.	12 (3.1%)	15 (3.7%)	14 (3.5%)	21 (5.5%)	0 (0%)
Musculoskeletal and connective tissue disorders	No. of Aes	83	73	85	75	1
	No. of Pat.	56 (14.6%)	57 (13.0%)	64 (15.9%)	52 (13.7%)	1 (3.7%)
Nervous system disorders	No. of Aes	69	56	78	44	2
	No. of Pat.	50 (13.0%)	40 (9.8%)	64 (15.9%)	34 (8.9%)	2 (7.4%)
Headache	No. of Aes	22	22	24	14	0
	No. of Pat.	19 (4.9%)	17 (4.2%)	22 (5.5%)	12 (3.2%)	0 (0%)
Psychiatric disorders	No. of Aes	21	29	36	23	0
	No. of Pat.	18 (4.7%)	26 (6.4%)	29 (7.2%)	18 (4.7%)	0 (0%)
Renal and urinary disorders	No. of Aes	172	179	186	153	4
	No. of Pat.	10 (28.6%)	114 (27.9%)	120 (29.8%)	110 (28.9%)	3 (11.1%)
Hematuria	No. of Aes	22	22	21	17	0
	No. of Pat.	20 (5.2%)	20 (4.9%)	21 (5.2%)	16 (4/2%)	0 (0%)
Proteinuria	No. of Aes	9	8	20	20	0

	No. of Pat.	9 (2.3%)	8 (2.0%)	20 (5.0%)	20 (5.3%)	0 (0%)
Reproductive system and breast disorders	No. of Aes	18	20	24	17	2
	No. of Pat.	17 (4.4%)	19 (4.7%)	22 (5.5%)	16 (4.2%)	1 (3.7%)
Respiratory, thoracic, and mediastinal disorders	No. of Aes	46	42	47	66	5
	No. of Pat.	34 (8.9%)	32 (7.8%)	38 (9.4%)	47 (12.4%)	4 (14.8%)
Skin and subcutaneous tissue disorders	No. of Aes	66	43	47	66	5
	No. of Pat.	51 (13.3%)	38 (9.3%)	38 (9.4%)	47 (12.4%)	4 (14.8%)
Surgical and medical procedures	No. of Aes	21	24	31	24	2
	No. of Pat.	16 (4.2%)	21 (5.1%)	23 (5.7%)	20 (5.3%)	2 (7.4%)
Vascular disorders	No. of Aes	135	119	122	143	1
	No. of Pat.	111 (28.9%)	92 (22.5%)	95 (23.6%)	111 (29.2%)	1 (3.7%)
Hypertension	No. of Aes	57	50	55	48	0
	No. of Pat.	55 (14.3%)	47 (11.5%)	52 (12.9%)	45 (11.8%)	0 (0%)
Lymphocele	No. of Aes	25	28	17	49	0
	No. of Pat.	24 (6.3%)	23 (5.6%)	16 (4.0%)	44 (11.6%)	0 (0%)
TOTAL	No. of Aes	2397	2319	2560	2340	41
	No. of Pat.	340 (88.5%)	352 (86.3%)	350 (86.8%)	344 (90.5%)	12 (44.4%)

(adapted from Roche CSR)

Reviewer Comment 1: Overall, tacrolimus/MMF (Group C) demonstrates a comparable safety profile to the cyclosporine/MMF regimens (Group A and Group B). While Group C exhibited higher rates of diarrhea and nervous system disorders, it also exhibited lower rates of hyperlipidemia and hypercholesterolemia than Groups A and B.

Adverse Events of Special Interest

In addition to a review of all adverse with an incidence greater than 5%, specific investigations were performed to analyze safety concerns of particular interest to the patient population (kidney transplant patients on immunosuppresion) and/or previously identified as potentially worse for

patients using a combination of tacrolimus and MMF. The serious adverse events of interest included infections (including opportunistic infections); gastrointestinal disorders; anemia and leucopenia; and diabetes.

Adverse Events due to Infections:

In addition to submitting adverse events captured under MedDRA SOC *Infections and infestations* (see **Table 7.2.4A** above), investigators reported details regarding opportunistic infections through electronic Case Report Forms (eCRFs). Details regarding the nature of the general infections and opportunistic infections, respectively, may be found in **Table 7.2.4C**and **Table 7.2.4D**.

Table 7.2.4B: Total Infections in Symphony-ELiTE

System Organ Class		Group A (N=384)	Group B (N=408)	Group C (N=403)	Group D (N=380)	Group O (N=27)
Infections and infestations	No. of Aes	434	398	443	388	8
	No. of Pat.	208 (54.2%)	206 (50.5%)	211 (52.4%)	200 (52.6%)	5 (18.5%)
Opportunistic infections	No. of Aes	147	119	104	91	0
	No. of Pat.	100 (26.0%)	93 (22.8%)	80 (19.9%)	77 (20.3%)	0 (0%)
TOTAL	No. of Aes	581	517	547	479	8
	No. of Pat.	241 (62.8%)	230 (56.4%)	229 (56.8%)	226 (59.5%)	5 (18.5%)

Table 7.2.4C: Infections According to Specific Categories

CATEGORY		A (N=384)	B (N=408)	C (N=403)	D (N=380)	O (N=27)	TOTAL (N=1602)
Abscess	No. of AEs	2	2	3	2	0	9
	No. of Pat.	2 (0.5%)	2 (0.5%)	3 (0.7%)	2 (0.5%)	0 (0%)	9 (0.6%)
Fungal	No. of AEs	5	6	2	4	0	17
	No. of Pat.	5 (1.3%)	6 (1.5%)	2 (0.5%)	4 (1.1%)	0 (0%)	17 (1.1%)
GI	No. of AEs	16	12	24	16	0	68
	No. of Pat.	16 (4.2%)	12 (2.9%)	23 (5.7%)	16 (4.2%)	0 (0%)	67 (4.2%)
Pneumonia	No. of AEs	25	14	16	32	0	87
	No. of Pat.	25 (6.5%)	12 (2.9%)	16 (4.0%)	26 (6.8%)	0 (0%)	79 (4.9%)
Sepsis	No. of AEs	32	15	28	24	1	100
	No. of Pat.	26 (6.8%)	14 (3.4%)	23 (5.7%)	22 (5.8%)	1 (3.7%)	86 (5.4%)
Skin	No. of AEs	16	15	7	7	0	45
	No. of Pat.	15 (3.9%)	12 (2.9%)	7 (1.7%)	7 (1.8%)	0 (0%)	41 (2.6%)
URTI	No. of AEs	73	76	96	66	1	312
	No. of Pat.	54 (14.1%)	63 (15.4%)	73 (18.1%)	50 (13.2%)	1 (3.7%)	241 (15.0%)
UTI	No. of AEs	219	196	206	164	3	788
	No. of Pat.	135 (35.2%)	123 (30.1%)	120 (29.8%)	114 (30.0%)	2 (7.4%)	494 (30.8%)
Viral	No. of AEs	13	11	10	10	0	44
	No. of Pat.	13 (3.4%)	10 (2.5%)	9 (2.2%)	10 (2.6%)	0 (0%)	42 (2.6%)
Wound	No. of AEs	16	23	24	37	2	102
	No. of Pat.	16 (4.2%)	21 (5.1%)	22 (5.5%)	31 (8.2%)	1 (3.7%)	91 (5.7%)
Other	No. of AEs	0	2	0	0	0	2
	No. of Pat.	(0%)	2 (0.5%)	(0%)	(0%)	0 (0%)	2 (0.1%)
TOTAL	No. of AEs	434	398	443	388	8	1671
	No. of Pat.	208 (54.2%)	206 (50.5%)	211 (52.4%)	200 (52.6%)	5 (18.5%)	830 (51.8%)

(adapted from Roche CSR)

Table 7.2.4D: All Opportunistic Infections According to Pathogen

PATHOGEN AS PER PROTOCOL		A (N=384)	B (N=408)	C (N=403)	D (N=380)	O (N=27)	TOTAL (N=1602)
Aspergillus	No. of AEs	2	2	3	1	0	8
	No. of Pat.	1 (0.3%)	2 (0.5%)	3 (0.7%)	1 (0.3%)	0 (0%)	7 (0.4%)
BK Polyoma virus	No. of AEs	3	4	7	3	0	17
	No. of Pat.	3 (0.8%)	4 (1.0%)	7 (1.7%)	3 (0.8%)	0 (0%)	17 (1.1%)
Candida	No. of AEs	30	22	13	21	0	86
	No. of Pat.	29 (7.6%)	19 (4.7%)	12 (3.0%)	19 (5.0%)	0 (0%)	79 (4.9%)
Cryptococcus	No. of AEs	0	0	3	0	0	3
	No. of Pat.	0 (0%)	0 (0%)	1 (0.2%)	0 (0%)	0 (0%)	1 (0.1%)
Cytomegalovirus (CMV)	No. of AEs	71	57	42	23	0	193
	No. of Pat.	55 (14.3%)	45 (11.0%)	39 (9.7%)	23 (6.1%)	0 (0%)	162 (10.1%)
Herpes simplex virus	No. of AEs	25	15	23	27	0	90
	No. of Pat.	21 (5.5%)	15 (3.7%)	18 (4.5%)	23 (6.1%)	0 (0%)	77 (4.8%)
Pneumocystis	No. of AEs	1	2	0	1	0	4
	No. of Pat.	1 (0.3%)	2 (0.5%)	0 (0%)	1 (0.3%)	0 (0%)	4 (0.2%)
Varicella-Zoster Virus (VZV)	No. of AEs	15	16	12	13	0	56
	No. of Pat.	13 (3.4%)	15 (3.7%)	12 (3.0%)	12 (3.2%)	0 (0%)	52 (3.2%)
Unspecified pathogen	No. of AEs	0	1	1	2	0	4
	No. of Pat.	0 (0%)	1 (0.2%)	1 (0.2%)	2 (0.5%)	0 (0%)	4 (0.2%)
TOTAL	No. of AEs	147	119	104	91	0	461
	No. of Pat.	100 (26.0%)	93 (22.8%)	80 (19.9%)	77 (20.3%)	0 (0%)	350 (21.8%)

(adapted from Roche CSR)

*Reviewer comment 1: The data from Symphony-ELiTE (as reported in **Tables 7.2.4B, 7.2.4C, and 7.2.4D)** do not convincingly support the hypothesis that the use of tacrolimus in conjunction with MMF leads to higher incidence of infection due to over-immunosuppresion.*

Reviewer comment 2: The Symphony-ELiTE study was notable for its low incidence of adverse events related to BK virus. Some literature exists to suggest that the incidence of BK nephropathy increased after the use of tacrolimus and MMF became commonplace. While the data in Symphony-ELiTE are insufficient to refute the possibility of an association between tacrolimus/MMF use and BK disease, they suggest that the current monitoring strategies (primarily routine urine cytology looking for decoy cells) have been successful at mitigating of BK nephropathy in renal transplant patients.

Reviewer comment 3: An appreciable trend towards increased incidence of CMV infections is notable among the groups treated with cyclosporine and MMF combinations. Risk factors for CMV disease (i.e., donor and recipient CMV serum antibody status) were equally distributed among the groups. The occurrence of acute rejection episodes prior to CMV reactivation has been noted as a risk factor for CMV disease.[45] A plausible explanation for the trend, then, relates to the greater incidence of rejection episodes among the cyclosporine/MMF groups.

*Reviewer comment 4: Tables **7.2.4B**, **7.2.4C**, and **7.2.4D** derive from the Roche Clinical Study Report. Some of the data were generated the eCRFs which were not submitted. Those data could not, therefore, be independently validated during the clinical review.*

Gastrointestinal Adverse Events

Side effects related to MPA exposure include diarrhea and other GI symptoms. Given that the use of MMF in combination with tacrolimus (or sirolimus) may result in greater MPA exposure than the use of MMF in combination with cyclosporine, particular attention was given to the 1,098 gastrointestinal adverse events reported during the Symphony-ELiTE trial. As expected, the incidence of diarrhea was significantly higher in patients randomized to tacrolimus (25.6%) than to either cyclosporine group (15.6% and 13.0%). In addition, more patients (n=39) from the tacrolimus group reported abdominal pain compared to the cyclosporine groups (n=27 and n=33).

Table 7.2.4E: All Gastrointestinal Events in Symphony-ELiTE

Preferred Term		Group A (N=384)	Group B (N=408)	Group C (N=403)	Group D (N=380)	Group O (N=27)	TOTAL (N=1602)
Not coded	No. of AEs No. of Pat.	0 0 (0%)	1 1 (0.2%)	0 0 (0%)	1 1 (0.3%)	0 0 (0%)	2 2 (0.1%)
Abdominal discomfort	No. of AEs No. of Pat.	7 4 (1.0%)	15 13 (3.2%)	10 10 (2.5%)	6 5 (1.3%)	0 0 (0%)	38 32 (2.0%)
Abdominal hematoma	No. of AEs No. of Pat.	4 3 (0.8%)	3 3 (0.7%)	4 4 (1.0%)	3 3 (0.8%)	0 0 (0%)	14 13 (0.8%)
Abdominal pain	No. of AEs No. of Pat.	38 27 (7.0%)	44 33 (8.1%)	45 39 (9.7%)	24 20 (5.3%)	1 1 (3.7%)	152 120 (7.5%)
Ascites	No. of AEs No. of Pat.	0 0 (0%)	0 0 (0%)	2 2 (0.5%)	2 2 (0.5%)	0 0 (0%)	4 4 (0.2%)
Colitis	No. of AEs No. of Pat.	1 1 (0.3%)	1 1 (0.2%)	2 2 (0.5%)	0 0 (0%)	0 0 (0%)	4 4 (0.2%)
Constipation	No. of AEs No. of Pat.	34 25 (6.5%)	22 22 (5.4%)	30 27 (6.7%)	26 23 (6.1%)	1 1 (3.7%)	113 98 (6.1%)
Diarrhea	No. of AEs No. of Pat.	73 60 (15.6%)	65 53 (13.0%)	137 103 (25.6%)	96 74 (19.5%)	0 0 (0%)	371 290 (18.1%)
GI bleeding	No. of AEs No. of Pat.	2 2 (0.5%)	3 3 (0.7%)	7 6 (1.5%)	4 4 (1.1%)	0 0 (0%)	16 15 (0.9%)
Hemorroides / fissure	No. of AEs No. of Pat.	5 5 (1.3%)	3 3 (0.7%)	2 2 (0.5%)	7 7 (1.8%)	0 0 (0%)	17 17 (1.1%)
Hernia	No. of AEs No. of Pat.	4 4 (1.0%)	4 3 (0.7%)	6 5 (1.2%)	6 6 (1.6%)	0 0 (0%)	20 18 (1.1%)
Ileus	No. of AEs No. of Pat.	4 3 (0.8%)	2 2 (0.5%)	3 3 (0.7%)	8 8 (2.1%)	0 0 (0%)	17 16 (1.0%)
Intestinal perforation	No. of AEs No. of Pat.	0 0 (0%)	1 1 (0.2%)	1 1 (0.2%)	1 1 (0.3%)	0 0 (0%)	3 3 (0.2%)
Nausea and vomiting	No. of AEs No. of Pat.	41 29 (7.6%)	34 28 (6.9%)	41 29 (7.2%)	27 18 (4.7%)	0 0 (0%)	143 104 (6.5%)
Non-ulcer	No. of AEs No. of Pat.	20 15 (3.9%)	16 15 (3.7%)	22 21 (5.2%)	15 14 (3.7%)	1 1 (3.7%)	74 66 (4.1%)
Oral	No. of AEs No. of Pat.	21 20 (5.2%)	27 24 (5.9%)	11 10 (2.5%)	23 18 (4.7%)	0 0 (0%)	82 72 (4.5%)
Other	No. of AEs No. of Pat.	0 0 (0%)	1 1 (0.2%)	2 2 (0.5%)	2 2 (0.5%)	0 0 (0%)	5 5 (0.3%)
Pancreatitis	No. of AEs No. of Pat.	1 1 (0.3%)	0 0 (0%)	1 1 (0.2%)	0 0 (0%)	0 0 (0%)	2 2 (0.1%)
Peritonitis	No. of AEs No. of Pat.	2 2 (0.5%)	1 1 (0.2%)	3 3 (0.7%)	3 3 (0.8%)	0 0 (0%)	9 9 (0.6%)
Ulcer	No. of AEs No. of Pat.	2 2 (0.5%)	5 4 (1.0%)	4 3 (0.7%)	1 1 (0.3%)	0 0 (0%)	12 10 (0.6%)
TOTAL	**No. of AEs No. of Pat.**	**259 128 (33.3%)**	**248 133 (32.6%)**	**333 167 (41.4%)**	**255 132 (34.7%)**	**3 2 (7.4%)**	**1098 562 (35.1%)**

(adapted from Roche CSR)

Reviewer comment 1: The use of tacrolimus in combination with MMF resulted in a higher incidence of diarrhea (25.6%) than the use of cyclosporine in combination with MMF

*(15.6% and 13.0%). Interestingly, the use of tacrolimus in combination with MMF also resulted in a higher incidence of diarrhea than the use of sirolimus in combination with MMF(19.5%) – suggesting that, while increased MPA exposure may account for some of the effect, tacrolimus itself may contribute to the incidence of diarrhea. While diarrhea was a common adverse event, especially among patients randomized to tacrolimus/MMF, most of the events did not result in significant morbidity (see section **7.2.2**).*

Reviewer comment 2: Except for diarrhea and abdominal pain, the incidence of all other gastroinstestinal adverse events appeared similar across study groups.

*Reviewer comment 3: In terms of deaths associated with gastrointestinal events, the original review of Study 02-0-158 noted four deaths were connected to GI complications. That review noted that none of the deaths occurred in patients taking cyclosporine, implying that the GI related deaths may have been due to the combined use of tacrolimus and MMF. However, two of the four deaths actually occurred among the patients randomized to cyclosporine: patient 10222007 (who never received any study drug of any type as the patient developed GI-based sepsis in immediate post-op setting) and patient 10212009 (who first developed persistent CMV viremia on cyclosporine prior to converting to tacrolimus). A third patient had been randomized to a third study arm (Advagraf in combination with MMF). The only one of those four patients who had been randomized to the tacrolimus arm of the study developed a bowel perforation in the immediate post-operative period (most likely as a result of a surgical complication) and required a colostomy. That patient died of a GI bleed and myocardial infarction shortly after an operation to reverse to colostomy. In my own opinion, those data do not collectively support a hypothesis that the combined use of tacrolimus and MMF resulted in increased mortality due to GI complications in Study 02-0-158. The data from Symphony-ELiTE also did not suggest an imbalance among study groups in terms of mortality from gastrointestinal events (see section **7.2.1**).*

Adverse Events due to Anemia and Leucopenia

MPA exposure may also result in anemia and leucopenia. Given that the use of MMF in combination with tacrolimus may result in greater MPA exposure than the use of MMF in combination with cyclosporine, particular attention was given adverse events with the Preferred Terms of anemia and leucopenia. As expected, more patients in the tacrolimus/MMF group had an adverse event of leucopenia reported relative to the cyclosporine/MMF groups. The difference, however, was small and was not observed when comparing serious adverse events related to leucopenia (see section **7.2.2**). The same trend, moreover, was not seen for the Preferred Term of anemia.

Table 7.2.4F: Adverse Events of Anemia and Leucopenia in Symphony-ELiTE

Preferred Term		Group A (N=384)	Group B (N=408)	Group C (N=403)	Group D (N=380)	Group O (N=27)
Anemia	No. of AEs	79	79	79	102	2
	No. of	71	71	69	95	2 (7.4%)

	Pat.	(18.5%)	(17.4%)	(17.1%)	(25.0%)	
Leucopenia	No. of AEs	48	47	59	42	0
	No. of Pat.	39 (10.2%)	41 (10.0%)	54 (13.4%)	39 (10.3%)	0 (0%)

Reviewer comment: It is slightly surprising that the data demonstrate a greater incidence of anemia among patients on tacrolimus/MMF regimens than cyclosporine/MMF regimens. Inspection of the patient level laboratory data for hemoglobins and hematocrits, however, supports the findings of the MedDRA data. Similarly, the patient level laboratory data suggested that the impact of immunosuppression on white blood cell count did not differ dramatically across treatment groups.

Diabetes

New onset diabetes after transplantation (NODAT) is an important adverse event that may confer increased risk of cardiac events, graft failure, and death. While both tacrolimus and cyclosporine have been associated with the development of NODAT, some evidence suggests that tacrolimus-based regimens may lead to a greater incidence of NODAT than cyclosporine-based regimens.[2] The criteria for diagnosing NODAT include fasting plasma glucose (FPG) ≥ 126 mg/dL or a 2 hour plasma glucose ≥ 200 mg/dL during an oral glucose tolerance test or a casual plasma glucose ≥ 200 mg/dL.[1] Inspection of the definition shows that, without careful design, trials will not reliably capture events of NODAT. Unfortunately, SYMPHONY-ELiTE lacked such a design: while the Roche Clinical Study Report refers to fasting glucose levels, the datasets do not clearly identify which blood draws were performed both under fasting conditions and also in the absence of anti-hyperglycemic treatments.

The study instead relied on the reporting of diabetes mellitus as an adverse event (tallying instances of the preferred terms of "Diabetes mellitus", "Diabetes mellitus (non-)insulin dependent", and "Diabetes mellitus inadequate control" while excluding patients with pre-transplant diabetes) to identify cases of NODAT. At the twelve month timepoint, that methodology led to the conclusion that the rate of NODAT was 6.4% in group A, 4.7% in group B, 10.6% in group C, and 7.8% in group D – surprisingly low rates relative to the findings of previous investigations into post-transplant diabetes.

Table 7.2.4G: Incidence of NODAT in Symphony-ELiTE

SAFETY POPULATION	Group A (N=272)	Group B (N=312)	Group C (N=292)	Group D (N=265)
Week 4	4.33%	2.02%	6.90%	1.22%
Week 8	5.69%	2.33%	8.39%	3.60%
Month 3	6.42%	2.64%	9.91%	4.71%
Month 6	6.42%	4.30%	10.55%	6.79%
Month 9	6.42%	4.66%	10.55%	7.75%
Month 12	6.42%	4.66%	10.55%	7.75%

* excluding patients with pre-Tx diabetes

(Taken from Roche CSR)

The study also examined the incidence of patients who required at least 3 months of treatment for diabetes (based on medications reported in the electronic case report forms). Based on that criteria, the Symphony-ELiTE study identified even fewer patients in any group with new onset diabetes.

Table 7.2.4H: Rates of NODAT Requiring Continued Treatment

SAFETY POPULATION	Group A (N=272)	Group B (N=312)	Group C (N=292)	Group D (N=265)
Week 4	0.93%	0.58%	1.42%	0.30%
Week 8	0.93%	0.88%	2.02%	0.63%
Month 3	1.30%	1.20%	2.34%	0.63%
Month 6	1.30%	1.53%	2.66%	1.04%
Month 9	1.30%	1.53%	2.66%	1.04%
Month 12	1.30%	1.53%	2.66%	1.04%

* patients with documented anti diabetic treatment for at least 3 months or up to study conclusion, excluding patients with pre-TX diabetes

(Taken from Roche CSR)

Reviewer comment 1: The data from Symphony-ELiTE suggest that the incidence of NODAT may be higher among patients using tacrolimus/MMF than cyclosporine/MMF but that the incidence of the condition is relatively rare. Due to its study population (essentially entirely Caucasian), however, Symphony-ELiTE may underestimate the incidence of NODAT in a US kidney transplant population following identical immunosuppressant regimens. The study design of Symphony-ELiTE, moreover, may have resulted in under-reporting of the true incidence of NODAT.

Reviewer comment 2: By comparison, the DIRECT study – which had been designed specifically to capture such events – reported an incidence of NODAT or impaired fasting glucose (IFG) of 26.0% in its cyclosporine arm and of 33.6% in its tacrolimus arm (p-value < 0.05 in that study). Of note, however, the study patients in DIRECT also received significantly higher exposures of tacrolimus than the Symphony-ELiTE patients: mean tacrolimus troughs in DIRECT oscillated between 9 and 14 ng/ml over the course of the trial, whereas mean tacrolimus troughs in Symphony-ELiTE approximated 7 ng/ml throughout the study. The higher levels of tacrolimus exposure, then, may also have contributed to the greater incidence of NODAT in DIRECT compared to Symphony-ELiTE.

*Reviewer comment 3: **Table 7.2.4H** derives from the Roche Clinical Study Report. The data were generated from the eCRFs which were not submitted. Those data could not, therefore, be independently validated during the clinical review.*

7.3 Other Safety Explorations

7.3.1 Dose Dependency for Adverse Events

The clinical pharmacology group detected a trend towards increased incidence of serious infection at higher exposures to tacrolimus and MMF (see **Table 7.3.1A**).

Table 7.3.1A: Incidence of Serious Infection as Function of Tacrolimus and MMF Exposure

Mean Tacrolimus Trough(ng/mL)	TA-MMF dose (g/Day)			
	<1	1-<2	2	Overall
≤6	14.3% (2/14)	10.3% (4/39)	13.2% (5/38)	12.1% (11/91)
6-≤9	11.1% (3/27)	14.5% (11/76)	18.2% (18/99)	15.8% (32/202)
>9	18.9% (3/16)	11.5% (3/26)	23.8% (5/21)	17.5% (11/63)
Overall	14.0% (8/57)	12.8% (18/141)	17.8% (28/158)	15.2% (54/356)

(adapted from Clinical Pharmacology Review)

*Reviewer comment: While the clinical pharmacology findings suggest that (see section **7.1.2**) efficacy outcomes might potentially improve with greater immunosuppression, their review also suggests that the increasing patient exposure to tacrolimus and MMF beyond the doses used in Symphony-ELiTE may result in increased morbidity and mortality due to serious infections. It is worth noting that patients who remained on MMF at 2g/day throughout the study exhibited the highest rate of serious infection in Symphony-ELiTE.*

7.3.2 Time Dependency for Adverse Events

The results of Symphony-ELiTE provide some data to support the hypothesis that induction agents may provide long-term benefits. While Group B exhibited more late rejection than Group A, a benefit of daclizumab (based on the incidence of BPAR between Group A and Group B) was still evident at 12 months after transplant (see Figure 7.3.2A).

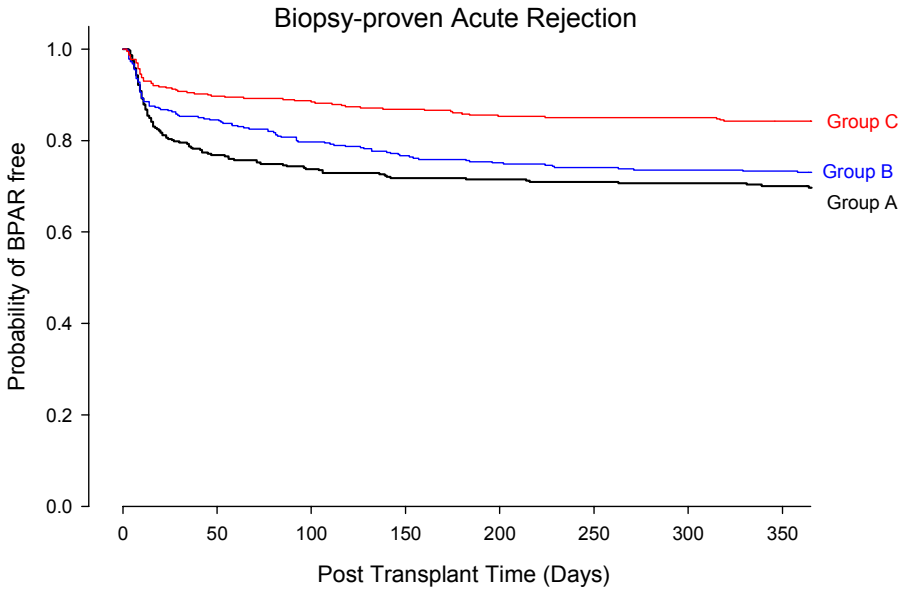


Figure 7.3.2A: BPAR as Function of Time
(adapted from Clinical Pharmacology Review)

Reviewer comment: The data from Symphony-ELiTE demonstrate that the contribution from daclizumab to the overall efficacy of Group B was significant. Subgroup analysis also demonstrated that, at similar exposures to CsA, the incidence of BPAR was substantially greater in Group A compared to Group B. Based on the findings of Symphony-ELiTE, changes to the daclizumab label may also be warranted.

7.3.3 Drug-Demographic Interactions

Symphony-ELiTE, due to its demographics and exclusion criteria, did not explore whether the regimens it studied would exhibit specific interactions with several populations of interest to the transplant community in the United States. Additional investigations to explore the use of those regimens in non-Caucasian and in hepatitis C positive populations would be valuable.

8 Appendices

8.1 Literature Review/References

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8.2 Labeling Recommendations

1) The following sentence should be modified in the **INDICATIONS AND USAGE** section of the Prograf labeling: "In heart transplant recipients, it is recommended that Prograf be used in conjunction with azathioprine or mycophenolate mofetil (MMF)" should be changed to "In heart and kidney transplant recipients…"

2) In the **CLINICAL STUDIES** section under the **Kidney Transplantation** header, the labeling should be modified to read:

Prograf/azathioprine
Prograf-based immunosuppression in conjunction with azathioprine and corticosteroids following kidney transplantation was assessed in a Phase 3 randomized, multicenter, non-blinded, prospective study. There were 412 kidney transplant patients enrolled at 19 clinical sites in the United States. Study therapy was initiated when renal function was stable as indicated by a serum creatinine ≤ 4 mg/dL (median of 4 days after transplantation, range 1 to 14 days). Patients less than 6 years of age were excluded.

There were 205 patients randomized to Prograf-based immunosuppression and 207 patients were randomized to cyclosporine-based immunosuppression. All patients received prophylactic induction therapy consisting of an antilymphocyte antibody preparation, corticosteroids and azathioprine. Overall 1 year patient and graft survival was 96.1% and 89.6%, respectively and was equivalent between treatment arms.

Because of the nature of the study design, comparisons of differences in secondary endpoints, such as incidence of acute rejection, refractory rejection or use of OKT3 for steroid-resistant rejection, could not be reliably made.

Prograf/mycophenolate mofetil (MMF)

Prograf-based immunosuppression in conjunction with MMF, corticosteroids, and induction has been studied. In a randomized, open-label, multi-center trial (Study 1), 1589 kidney transplant patients received Prograf (Group C, n=401), sirolimus (Group D, n=399), or one of two cyclosporine regimens (Group A, n=390 and Group B, n=399) in combination with MMF and corticosteroids; all patients, except those in one of the two cyclosporine groups, also received induction with daclizumab. The study was conducted outside the United States; the study population was 93% Caucasian. In this study, mortality at 12 months in patients receiving Prograf/MMF was similar (2.7%) compared to patients receiving cyclosporine/MMF (3.3% and 1.8%) or sirolimus/MMF (3.0%). Patients in the Prograf group exhibited higher estimated creatinine clearance rates (eCL_{cr}) using the Cockcroft-Gault formula (Table 1) and experienced fewer efficacy failures, defined as biopsy proven acute rejection, graft loss, death, and/or lost to follow-up (Table 2) in comparison to each of the other three groups. Patients randomized to Prograf/MMF were more likely to develop diarrhea and diabetes after the transplantation and experienced similar rates of infections compared to patients randomized to either cyclosporine/MMF regimen (see **ADVERSE REACTIONS**).

Table 1: Estimated Creatinine Clearance at 12 Months in Study 1

Group	eCLcr [ml/min] at Month 12**				
	N	MEAN	SD	MEDIAN	Difference with Group C , 99.2% CI*
CyA/MMF/CS (A)	390	56.5	25.8	56.9	(-13.7, -3.7)
CyA/MMF/CS/Daclizumab (B)	399	58.9	25.6	60.9	(-11.2, -1.2)
Tac/MMF/CS/Daclizumab (C)	401	65.1	27.4	66.2	-
Siro/MMF/CS/Daclizumab (D)	399	56.2	27.4	57.3	(-14.1, -3.9)
Total	1589	59.2	26.8	60.5	

*Adjusted for multiple (6) pairwise comparisons using Bonferroni corrections.

** All death/graft loss (n=41, 27, 23 and 42 in Groups A, B, C and D) and patients whose last recorded creatinine values were prior to month 3 visit (n=10, 9, 7 and 9 in groups A, B, C and D) were imputed with GFR of 10 ml/min; a subject's last observed creatinine value from month 3 on was used for the remainder of subjects with missing creatinine at month 12 (n=11, 12, 15 and 19 for groups A, B, C and D). Weight was also imputed in the calculation of estimated GFR, if missing.

Key: CyA=Cyclosporine, CS=Corticosteroids, Tac=Tacrolimus, Siro=Sirolimus

Table 2: Incidence of BPAR, Graft Loss, Death or Loss to Follow-up at 12 Months in Study 1

	A N=390	B N=399	C N=401	D N=399
Overall Failure	141 (36.2%)	126 (31.6%)	82 (20.4%)	185 (46.4%)
Components of efficacy failure				
BPAR	113 (29.0%)	106 (26.6%)	60 (15.0%)	152 (38.1%)
Graft loss excluding death	28 (7.2%)	20 (5.0%)	12 (3.0%)	30 (7.5%)
Mortality	13 (3.3%)	7 (1.8%)	11 (2.7%)	12 (3.0%)
Lost to follow-up	5 (1.3%)	7 (1.8%)	5 (1.3%)	6 (1.5%)
Difference of efficacy failure				

compared to Group C, 99.2% CI*	(7.1%, 24.3%)	(2.7%, 19.5%)	-	(17.2%, 34.7%)

See Table 1 for components of regimen A, B, C, and D

*Adjusted for multiple (6) pairwise comparisons using Bonferroni corrections.

The protocol-specified target tacrolimus trough concentrations (C_{trough},Tac) were 3-7 ng/mL; however, the observed median $C_{troughs}$,Tac approximated 7 ng/mL throughout the 12 month study (Table 3).

Table 3. Tacrolimus Whole Blood Trough Concentrations (Study 1)

Time	Median (P10-P90*) tacrolimus whole blood trough concentrations (ng/mL)
Day 30 (N=366)	6.9 (4.4 – 11.3)
Day 90 (N=351)	6.8 (4.1 – 10.7)
Day 180 (N=355)	6.5 (4.0 – 9.6)
Day 365 (N=346)	6.5 (3.8 – 10.0)

*: Range of Ctrough,Tac that includes 80% of patients

The protocol-specified target cyclosporine trough concentrations (C_{trough},CsA) for Group B were 50-100 ng/mL; however, the observed median $C_{troughs}$,CsA approximated 100 ng/mL throughout the 12 month study. The protocol-specified target $C_{troughs}$,CsA for Group A were 150-300 ng/mL for the first 3 months and 100-200 ng/mL from month 4 to month 12; the observed median $C_{troughs}$, CsA approximated 225 ng/ml for the first 3 months and 140 ng/ml from month 4 to month 12.

While patients in all groups started MMF at 1g BID, the MMF dose was reduced to <2 g/day in 63% of patients in tacrolimus arm by month 12 (Table 4); approximately half of these MMF dose reductions were because of adverse events. By comparison, the MMF dose was reduced to <2 g/day in 49% and 45% of patients in the two cyclosporine arms (Group A and Group B, respectively), by month 12 and approximately two-fifth (40%) of MMF dose reductions were because of adverse events.

Table 4. MMF dose over time in Group C (Study 1)

Time period (Days)	Time-averaged MMF dose (g/day)[a]		
	<2.0	2.0	>2.0
0-30 (N=364)	37%	60%	2.2%
0-90 (N=373)	47%	51%	2.1%
0-180 (N=377)	56%	42%	1.6%
0-365 (N=380)	63%	36%	1.3%

Time-averaged MMF dose = (total MMF dose)/(duration of treatment)

[a]: Percentage of patients for each time-averaged MMF dose range during various treatment periods. Two g/day of time-averaged MMF dose means that MMF dose was not reduced in those patients during the treatment periods.

In a second randomized, open-label, multi-center trial (Study 2), 424 kidney transplant patients received Prograf (n=212) or cyclosporine (n=212) in combination with MMF 1 gram BID,

basiliximab induction, and corticosteroids. In this study, the rate for the combined endpoint of biopsy-confirmed acute rejection, graft failure, death, and/or lost to follow-up at 12 months in the Prograf/MMF group was similar to the rate in the cyclosporine/MMF group. There was, however, an imbalance in mortality at 12 months in those patients receiving Prograf/MMF (4.2%) compared to those receiving cyclosporine/MMF (2.4%), including cases attributed to overimmunosuppression (Table 5).

Table 5: Incidence of BPAR, Graft Loss, Death or Loss to Follow-up at 12 Months in Study 2

	Prograf/MMF (n=212)	Cyclosporine/MMF (n=212)
Overall Failure	32 (15.1%)	36 (17.0%)
Components of efficacy failure		
BPAR	16 (7.5%)	29 (13.7%)
Graft loss excluding death	6 (2.8%)	4 (1.9%)
Mortality	9 (4.2%)	5 (2.4%)
Lost to follow-up	4 (1.9%)	3 (1.4%)
Difference of efficacy failure compared to Prograf/MMF group, 95% CI*	-	(-5.2%, 9.0%)

*95% confidence interval calculated using Fisher's Exact Test

The protocol-specified target tacrolimus whole blood trough concentrations (C_{trough},Tac) in Study 2 were 7-16 ng/mL for the first three months and 5-15 ng/mL thereafter. The observed median $C_{troughs}$,Tac approximated 10 ng/mL during the first three months and 8 ng/mL from month 4 to month 12 (Table 6).

Table 6. Tacrolimus Whole Blood Trough Concentrations (Study 2)

Time	Median (P10-P90*) tacrolimus whole blood trough concentrations (ng/mL)
Day 30 (N=183)	10.5 (6.3 – 16.8)
Day 60 (N=183)	9.2 (5.9 – 15.3)
Day 120 (N=178)	8.3 (4.6 – 13.3)
Day 180 (N=174)	7.9 (5.5 – 13.2)
Day 365 (N=180)	7.1 (4.2 – 12.4)

*: Range of Ctrough,Tac that includes 80% of patients

The protocol-specified target cyclosporine whole blood concentrations (C_{trough},CsA) were 125 to 400 ng/mL for the first three months, and 100 to 300 ng/mL thereafter. The observed median $C_{troughs}$ CsA approximated 275 ng/mL during the first three months and 190 ng/ml from month 4 to month 12.

Patients in both groups started MMF at 1g BID. The MMF dose was reduced to <2 g/day by month 12 in 62% of patients in the Prograf/MMF group (Table 7) and in 47% of patients in the cyclosporine/MMF group. Approximately three-fifth (63% and 55%) of these MMF dose reductions were because of adverse events in the Prograf/MMF group and the cyclosporine/MMF group, respectively.

Table 7. MMF dose over time in the Prograf/MMF group (Study 2)

Time period (Days)	Time-averaged MMF dose (g/day)[a]		
	<2.0	2.0	>2.0
0-30 (N=212)	25%	69%	5.6%
0-90 (N=212)	41%	53%	6.1%
0-180 (N=212)	52%	41%	6.6%
0-365 (N=212)	62%	34%	3.8%

Time-averaged MMF dose=(total MMF dose)/(duration of treatment)
[a]: Percentage of patients for each time-averaged MMF dose range during various treatment periods. Two g/day of time-averaged MMF dose means that MMF dose was not reduced in those patients during the treatment periods.

3) In the **ADVERSE REACTIONS** section, under the **Kidney Transplantation** heading, the labeling should be modified to read:

The most common adverse reactions reported were infection, tremor, hypertension, abnormal renal function, constipation, diarrhea, headache, abdominal pain and insomnia.

Adverse events that occurred in ≥15% of kidney transplant patients treated with Prograf in conjunction with azathioprine are presented below:

KIDNEY TRANSPLANTATION: ADVERSE EVENTS OCCURRING IN ≥ 15% OF PATIENTS TREATED WITH PROGRAF IN CONJUNCTION WITH AZATHIOPRINE

	Prograf (N=205)	CBIR (N=207)
Nervous System		
Tremor (see **WARNINGS**)	54%	34%
Headache (see **WARNINGS**)	44%	38%
Insomnia	32%	30%
Paresthesia	23%	16%
Dizziness	19%	16%
Gastrointestinal		
Diarrhea	44%	41%
Nausea	38%	36%
Constipation	35%	43%
Vomiting	29%	23%
Dyspepsia	28%	20%
Cardiovascular		
Hypertension (see **PRECAUTIONS**)	50%	52%
Chest pain	19%	13%
Urogenital		

Creatinine Increased (see **WARNINGS**)	45%	42%
Urinary Tract Infection	34%	35%
Metabolic and Nutritional		
Hypophosphatemia	49%	53%
Hypomagnesemia	34%	17%
Hyperlipemia	31%	38%
Hyperkalemia (see **WARNINGS**)	31%	32%
Diabetes Mellitus (see **WARNINGS**)	24%	9%
Hypokalemia	22%	25%
Hyperglycemia (see **WARNINGS**)	22%	16%
Edema	18%	19%
Hemic and Lymphatic		
Anemia	30%	24%
Leukopenia	15%	17%
Miscellaneous		
Infection	45%	49%
Peripheral Edema	36%	48%
Asthenia	34%	30%
Abdominal Pain	33%	31%
Pain	32%	30%
Fever	29%	29%
Back Pain	24%	20%
Respiratory System		
Dyspnea	22%	18%
Cough Increased	18%	15%
Musculoskeletal		
Arthralgia	25%	24%
Skin		
Rash	17%	12%
Pruritus	15%	7%

Adverse events that occurred in 10% of kidney transplant patients treated with Prograf in conjunction with MMF in Study 1 are presented below:

KIDNEY TRANSPLANTATION: ADVERSE EVENTS OCCURRING IN > 10% OF PROGRAF-TREATED PATIENTS			
	Prograf (Group C) (N=403)	**Cyclosporine (Group A) (N=384)**	**Cyclosporine (Group B) (N=408)**
Anemia	17%	19%	17%
Leucopenia	13%	10%	10%
Diarrhea	25%	16%	13%
Edema peripheral	11%	12%	13%
Urinary tract infection	24%	29%	24%
Hyperlipidemia	10%	15%	13%

Hypertension (see **PRECAUTIONS**)	13%	14%	12%

* Study 1 was conducted entirely outside of the United States. Such studies often report a lower incidence of adverse events in comparison to US studies.

Adverse events that occurred in 15% of kidney transplant patients treated with Prograf in conjunction with MMF in Study 2 are presented below:

KIDNEY TRANSPLANTATION: ADVERSE EVENTS OCCURRING IN > 15% OF PROGRAF-TREATED PATIENTS		
	Prograf (N=212)	**Cyclosporine (N=212)**
Gastrointestinal Disorders		
Diarrhea	44%	26%
Nausea	39%	47%
Constipation	36%	41%
Vomiting	26%	25%
Dyspepsia	18%	15%
Injury, Poisoning, and Procedural Complications		
Post Procedural Pain	29%	27%
Incision Site Complication	28%	23%
Graft Dysfunction	24%	18%
Metabolism and Nutrition Disorders		
Hypomagnesemia	28%	22%
Hypophosphatemia	28%	21%
Hyperkalemia (see **WARNINGS**)	26%	19%
Hyperglycemia (see **WARNINGS**)	21%	15%
Hyperlipidemia	18%	25%
Hypokalemia	16%	18%
Nervous System Disorders		
Tremor	34%	20%
Headache	24%	26%
Blood and Lymphatic System Disorders		
Anemia	30%	28%
Leukopenia	16%	12%
Miscellaneous		
Edema Peripheral	35%	46%
Hypertension (see **PRECAUTIONS**)	32%	35%
Insomnia	30%	21%
Urinary Tract Infection	26%	22%

Less frequently observed adverse reactions in both liver transplantation and kidney transplantation patients are described under the subsection **Less Frequently Reported Adverse Reactions** shown below.

4) In the **WARNINGS** section, "Prograf in Combination with MMF or Sirolimus" should be modified to "Prograf in Combination with Sirolimus". The paragraph descriptive of Study 02-0-158 should be removed; it has been incorporated into the changes to the **CLINICAL STUDIES** section.

5) In the **DOSAGE AND ADMINISTRATION** section, under the heading **Prograf capsules (tacrolimus capsules)**, the labeling should be modified as follows:

Summary of Initial Oral Dosage Recommendations and Observed Whole Blood Trough Concentrations

Patient Population	**Recommended Initial Oral Dose***	**Observed Whole Blood Trough Concentrations**
Adult kidney transplant patients In combination with azathioprine	0.2 mg/kg/day	month 1-3 : 7-20 ng/mL month 4-12 : 5-15 ng/mL
In combination with MMF/daclizumab	0.1 mg/kg/day	month 1-12: 4-11 ng/mL
In combination with MMF/basiliximab	0.15 -0.2 mg/kg/day	month 1-3: 6-16 ng/mL month 4-12: 5-12 ng/mL
Adult liver transplant patients	0.10-0.15 mg/kg/day	month 1-12 : 5-20 ng/mL
Pediatric liver transplant patients	0.15-0.20 mg/kg/day	month 1-12 : 5-20 ng/mL
Adult heart transplant patients	0.075 mg/kg/day	month 1-3: 10-20 ng/mL month ≥ 4: 5-15 ng/mL

*Note: two divided doses, q12h

6) In the **DOSAGE AND ADMINISTRATION** section, under the heading **Blood Concentration Monitoring**, the **Kidney Transplantation** section should be modified to read:

Data from a Phase 3 study of Prograf in conjunction with azathioprine indicate that trough concentrations of tacrolimus in whole blood, as measured by IMx® were most variable during the first week of dosing. During the first three months of that trial, 80% of the patients maintained trough concentrations between 7-20 ng/mL, and then between 5-15 ng/mL, through 1 year.

In a separate clinical trial of Prograf in conjunction with MMF and daclizumab, approximately 80% of patients maintained tacrolimus whole blood concentrations between 4-11 ng/mL through 1 year post-transplant.

In another clinical trial of Prograf in conjunction with MMF and basiliximab, approximately 80% of patients maintained tacrolimus whole trough blood concentrations between 6-16 ng/mL by month 3 and, then, between 5-12 ng/mL from month 4 through 1 year.

The relative risks of toxicity and efficacy failure are related to tacrolimus whole blood trough concentrations. Therefore, monitoring of whole blood trough concentrations is recommended to assist in the clinical evaluation of toxicity.

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/s/

Patrick Archdeacon
5/15/2009 03:50:56 PM
MEDICAL OFFICER

Renata Albrecht
5/17/2009 08:34:30 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	SE8
Submission Number	50-708 and 50-709
Submission Code	027 and 021
Letter Date	February 13, 2006
Stamp Date	February 14, 2006
PDUFA Goal Date	March 14, 2007
Reviewer Name	Hui-Hsing Wong, M.D., J.D.
Review Completion Date	March 14, 2007
Established Name	tacrolimus
(Proposed) Trade Name	Prograf
Therapeutic Class	Immunosuppressant Drug
Applicant	Astellas Pharma US, Inc.
Priority Designation	S
Formulation	Capsule
Dosing Regimen	Prograf+MMF 1 gram BID
Indication	Kidney Transplantation
Intended Population	Adult and Pediatric

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Kidney Transplantation:
The Applicant submitted a supplement to add the adjunct therapy of mycophenolate mofetil (MMF) to the Prograf Package Insert for the indication of prophylaxis of organ rejection in transplant patients. In the submission, the Applicant requested that Study 02-0-158 be included in the CLINICAL STUDIES section and the INDICATIONS AND USAGE section include the use of MMF with Prograf.

1) Given the results of Study 02-0-158, the safety and efficacy of Prograf in combination with CellCept (as recommended in the current CellCept Package Insert) was not established when compared with Neoral and CellCept.

2) An alternative dose of CellCept to be used in combination with Prograf was not established from the results of this study.

3) Since these two drugs are both lawfully marketed products and already being used in combination, the primary reason for incorporating the results of this clinical study in the label is for promotional purposes or to use as an active comparator in future clinical study for drug approval. Given the safety profile of the studied doses of CellCept in combination with Prograf, promotion of these results or use of this regimen for future clinical studies cannot be recommended.

4) However, the information from this study is clinically important for two reasons:

a) Because this unapproved regimen is viewed as the "standard of care" post-kidney transplantation, other drug companies developing drugs for the prophylaxis of rejection in kidney transplantation have requested this combination as the active comparator for clinical trials. The results from Study 158 (which was conducted mostly in the United States) suggest that MMF 2 grams/day is **NOT** the standard of care in the United States because subjects did not consistently use 2 grams/day in the Prograf arm. Furthermore, the manner in which these investigators were using MMF 2 grams/day led to an unacceptable increased risk of serious infections and deaths due to the immunosuppression.

b) This combination is currently being used in the majority of adult kidney transplant recipients in the United States. Although many transplant programs may be aware of the absence of interaction between Prograf and MMF, these patients are often managed by their referring nephrologist or primary care physician. The current Package Inserts for CellCept, Myfortic, and cyclosporine

do not contain any information regarding this critical drug interaction and the potential for overimmunosuppression and MMF toxicity when the MMF is used in combination with drugs other than cyclosporine. The overimmunosuppression and MMF toxicity can result in serious infections and death.

Action: Both Prograf and MMF are lawfully marketed products; therefore, physicians are able to use the two drugs in combination. However, the results of Study 158 do not support labeling of the combination as studied and raise concerns about the safe and effective use of this combination. Instead of changing the Package Insert in accordance with the Applicant's request, the following actions are recommended:

1) Given the safety concerns in the Prograf+MMF arm in Study 158, it would be reasonable and consistent with other Package Inserts to include information in the WARNING section about the higher mortality rates in Prograf+MMF arm compared with the Neoral+MMF arm and that the increase in mortality was due to infection related deaths. The current Zenapax Package Insert has similar language regarding the results of a clinical trial in heart transplantation and could be used as a model for language to include in the Prograf Package Insert.

2) In addition to the information in the Prograf Package Insert, changes should also be made to the cyclosporine, CellCept, and Myfortic Package Inserts to address the drug interaction between cyclosporine and mycophenolic acid (MPA). The current Neoral, CellCept, and Myfortic package inserts do not include information regarding the drug interaction and implies that there are no drug interactions between cyclosporine and MPA.

(b) (4)

Heart Transplantation: The Prograf Package Insert currently includes language stating that Prograf can be used in combination with MMF in heart transplantation. Re-evaluation of the data from this study showed that doses in the MMF arm dropped much more than doses in the cyclosporine arm, consistent with the results of Study 158. Further elaboration or discussion about the risk/benefit assessment of this combination in heart transplantation cannot be made because a full review of the original clinical study to support labeling was not re-reviewed as part of this submission.

Action: Recommend that the label include information to reflect that subjects using Prograf+MMF had to reduce their MMF doses more than subjects using cyclosporine+MMF. Recommend that more safety data be analyzed with this combination and that Astellas submit any follow-up data from this study that may not have been submitted when the study was first reviewed. Because the doses used in the

Prograf arm were different from the doses used in the approved comparator arm (and not consistent with the current CellCept Package Insert), recommend that this combination not be used for future clinical trials in heart transplantation until the dose of CellCept is more appropriately characterized and a complete comparative safety analysis has been conducted to assure that the appropriate risk-benefit analysis can be performed.

1.2 Recommendation on Postmarketing Actions

N/A

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Tacrolimus is a macrolide lactone, calcineurin phosphatase inhibitor produced by *Streptomyces tsukubaensis,* in the class of immunosuppressant drugs called calcineurin inhibitors. Tacrolimus immediate-release (or Prograf) is currently approved for use as prophylaxis against organ rejection in kidney transplantation, liver transplantation, and heart transplantation. In this submission, the Applicant is seeking approval for the use of tacrolimus with mycophenolate mofetil (MMF) in kidney (b) (4) transplantation. MMF is an inhibitor of inosine monophosphate dehydrogenase (IMPDH). Currently, MMF is approved for use with cyclosporine, another calcineurin inhibitor, at the fixed dosage of 1 gram twice a day in kidney transplantation.

The Applicant submitted a large three-arm Phase 3 study (Study 02-0-158) to support the use of tacrolimus with MMF 2 grams/day. In this Phase 3 study, kidney transplant recipients were randomized to receive Neoral+MMF at 2 grams/day (the approved active comparator), Prograf+MMF at 2 grams/day or MR4+MMF at 2 grams/day. MR4 is a modified-release formulation of tacrolimus and (b) (4) (b) (4) therefore, the focus of this review is the comparison of Prograf+MMF and Neoral+MMF using 2 grams of MMF.

There were 424 kidney transplant recipients from the United States, Canada, and South America randomized to the three arms discussed above. There were 212 subjects in the Prograf+MMF arm and 212 subjects in the Neoral+MMF arm. Subjects also received induction with basiliximab and concomitant adrenal corticosteroids in the study arms. The study was designed as 1-year efficacy and safety study with a clinical continuation phase of a minimum of 2 years.

1.3.2 Efficacy

The primary endpoint was the composite endpoint of biopsy-confirmed acute rejection (Banff Grade $\geq$ I), graft loss, patient death, and lost to follow-up. The study was designed as a non-inferiority study with a margin for the composite endpoint set at 10%. In addition to this

endpoint, the Division required an endpoint of the combination of graft and patient survival with a non-inferiority margin of 5-10%.

Study 158 was an open-label non-inferiority study comparing Prograf+MMF with Neoral+MMF. In addition to being open label, the study was designed to permit crossovers from Prograf to Neoral, Neoral to Prograf, MR4 to Prograf, or MR4 to Neoral. No subjects could cross over to MR4. Because of various "incentives" in the study design, biases in the clinical practice of investigators, and the relative ease for subjects to crossover within the study, there was an imbalance in the number of crossovers from Neoral to Prograf that confounded both the efficacy and safety analyses.

For the primary endpoint, the Applicant met the pre-specified non-inferiority margins of the composite endpoint. When the Prograf and the Neoral arms were compared, the Prograf arm appeared to have a lower acute rejection rate, but higher graft loss, patient deaths, and lost to follow-up rates.

Efficacy Failure	Prograf+MMF	Neoral+MMF
BCAR	16 (7.5%)	29 (13.7%)
Graft Failure*	6 (2.8%)	4 (1.9%)
Death	9 (4.2%)	5 (2.4%)
Lost to Follow-up	4 (1.9%)	1 (0.5%)

* Permanent return to dialysis (> 30 days) or retransplantation not resulting in death

The acute rejections rates were read by the local pathologists, but a blinded central assessment found much lower acute rejection rates of 3.8% and 6.6% in the Prograf and Neoral arms, respectively. According to the blinded central assessment, there were 6 subjects in the Prograf arm and 10 subjects in the Neoral arm with ≥Banff Grade II acute rejection.

The lower acute rejection rates in the Prograf+MMF arm appears to have been achieved at the expense of more deaths due to overimmunosuppression (discussed in the safety section). The reason for the overimmunosuppression was likely due to the role of MMF when used in combination with Prograf. During the development of MMF, the systemic exposures and the doses evaluated for approval were based on the concomitant use of MMF with cyclosporine. At the time of the approval of the recommended dose of CellCept 1 gram BID in renal transplant recipients, it was not known that cyclosporine interrupts the enterohepatic recirculation of mycophenolic acid (MPA) resulting in lower systemic exposures of MPA when used with cyclosporine compared with other drugs. Tacrolimus does not appear to affect the enterohepatic recirculation of MPA. In Study 02-0-158, subjects in the Prograf+MMF arm were unable to consistently achieve 1 gram BID and appeared to have difficulty tolerating the MMF 2 grams/day. Because of the study design, a safe and effective dose of MMF to be used with Prograf could not be established.

1.3.3 Safety

The safety profile of Prograf+MMF reflected more adverse events associated with overimmunosuppression and MMF toxicity -- greater diarrhea, loose stools, leukopenia, and infections. These findings were confirmed when the adverse events of the 39 subjects who

crossed over from Neoral to Prograf were evaluated. Although these subjects were more stable because they had passed the immediate post-operative period, they experienced higher rates of diarrhea, loose stools, leukopenia, and infections than the subjects who remained on Neoral. Based on the pattern of use of MMF, it is likely that the adverse events, and possibly deaths, would have been even greater had subjects actually used the MMF 2 grams consistently.

Ultimately, this unfavorable safety profile was not the only reason for concerns about the safety of the Prograf+MMF combination. In the Prograf+MMF arm, there were more deaths that appeared to be related to overimmunosuppression/infections. At one year (day 365), 5 of the 9 deaths in the Prograf arm were due to serious infections whereas only 1 out of 5 deaths in the Neoral arm was due to a serious infection. At year 2, 7 out of the 12 deaths in the Prograf arm appear to be related to the immunosuppression, whereas only 2 out of the 7 deaths in the Neoral arm were attributable to the immunosuppression. Not only was overimmunosuppression a potential preventable cause of death, but the GI toxicity of MMF may have been associated with some of the deaths. There were 3 subjects who died of GI associated events that occurred while on the MMF 2 grams without Neoral. Two subjects were on Prograf at the time of the GI associated death and one subject had been randomized to the Neoral arm, but received only 3 days of MMF when the event occurred. Based these findings, the higher systemic exposures of MPA cannot be ruled out as contributing to the excess deaths in the Prograf arm.

1.3.4 Dosing Regimen and Administration

Prograf+MMF (b) (4) cannot be recommended. A safe and effective dose of MMF to be used with Prograf cannot be established.

1.3.5 Drug-Drug Interactions

The absence of a drug interaction between Prograf and MMF is critical to the determining the safe and effective dose of MMF to be used with Prograf. Recommend that the maximum dose of MMF to be evaluated in future clinical studies using MMF would be the dose that achieves comparable MPA AUC as achieved with MMF 2 grams/day when used with cyclosporine.

1.3.6 Special Populations

Patients with renal failure should comply with the CellCept Package Insert regarding the exposures achieved when MMF is used in renal failure.

2. Introduction and Background

2.1 Product Information

Tacrolimus is a macrolide lactone, calcineurin phosphatase inhibitor produced by *Streptomyces tsukubaensis,* in the class of immunosuppressant drugs called calcineurin inhibitors. Tacrolimus inhibits T-lymphocyte activation, although the exact mechanism of action is not known. Experimental evidence suggests that tacrolimus binds to an intracellcular protein, FKBP-12, forming a complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin, and thus inhibiting the phosphatase activity of calcineurin. This effect is thought to prevent the dephosphorylation and translocation of nuclear factor of activated T-cell (NF-AT), a nuclear component thought to initiate gene transcription for the formation of lymphokines (such as interleukin-2, gamma interferon). The net result is the inhibition of T-lymphocyte activation, leading to immunosuppression. [Prograf Package Insert, Mechanism of Action].

Prograf is currently approved for use as prophylaxis against organ rejection in kidney transplantation, liver transplantation, and heart transplantation. Clinical trials to support the approval of Prograf in kidney transplantation included the use of Prograf with azathioprine, an immunosuppressive antimetabolite, and corticosteroids. With this submission, the Applicant is seeking approval of Prograf for use with CellCept (Mycophenolate Mofetil [MMF]) in kidney transplantation.

MMF is metabolized to the active metabolite, mycophenolic acid (MPA), a selective, uncompetitive, and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), thus inhibiting the *de novo* pathway of guanosine nucleotide synthesis without incorporation into DNA. MPA inhibits the proliferative responses of T- and B-lymphocytes to both mitogenic and allospecific stimulation. MPA also suppresses antibody formation by B-lymphocytes. MMF does not inhibit early events in the activation of human peripheral blood mononuclear cells, such as the production of interleukin-1 (IL-1) and interleukin-2 (IL-2), but does block the couple of these events to DNA synthesis and proliferation [Package Insert – Mechanism of Action]. Currently, MMF is approved for use with cyclosporine, another calcineurin inhibitor, at the fixed dosage of 1 gram twice a day (or 2 grams/day) in kidney transplantation. MMF is approved for the prophylaxis against organ rejection in kidney, liver, and heart transplantation. The dosing recommended for use in kidney transplantation is 1 gram BID, whereas the dose for liver and heart transplantation is 1.5 grams BID. The Applicant is requesting labeling to allow for the use of MMF with Prograf instead of cyclosporine because the mechanism of action for immunosuppression for Prograf and cyclosporine are similar – both are calcineurin inhibitors.

In the clinical studies used to support the approval of MMF in kidney transplantation, both 1 gram BID and 1.5 grams BID were studied in blinded, placebo/azathioprine controlled trials. Although the acute rejection rates were slightly lower when using the 3 g/day dose, the early termination without prior acute rejection and the incidence of combined graft loss or patient death at 12 months were greater in the 3 g/day. Tables 1 and 2 below are from the CellCept Package Insert and illustrate these findings. The advantage to using CellCept in the clinical

studies for approval was lower acute rejection rates. However, there was no advantage of CellCept with respect to graft loss or patient death. Based on these results and the risk/benefit assessment made by both the Applicant for CellCept (Syntex at the time, now Roche) and the FDA, the 2 g/day dose became the recommended approved dose of CellCept in kidney transplantation.

Table 1: Kidney Transplant Studies: Incidence of Treatment Failure (Biopsy-Proven Rejection or Early Termination for Any Reasons)

USA Study[a] (N=499 patients)	**CellCept 2 g/day (n=167 patients)**	**CellCept 3 g/day (n=166 patients)**	**Azathioprine 1 to 2 mg/kg/day (n=166 patients)**
All treatment failures	31.1%	31.3%	47.6%
Early termination without prior acute rejection[b]	9.6%	12.7%	6.0%
Biopsy-proven rejection episode on treatment	19.8%	17.5%	38.0%
Europe/Canada/ Australia Study[c] (N=503 patients)	**CellCept 2 g/day (n=173 patients)**	**CellCept 3 g/day (n=164 patients)**	**Azathioprine 100 to 150 mg/day (n=166 patients)**
All treatment failures	38.2%	34.8%	50.0%
Early termination without prior acute rejection[b]	13.9%	15.2%	10.2%
Biopsy-proven rejection episode on treatment	19.7%	15.9%	35.5%
Europe Study[d] (N=491 patients)	**CellCept 2 g/day (n=165 patients)**	**CellCept 3 g/day (n=160 patients)**	**Placebo (n=166 patients)**
All treatment failures	30.3%	38.8%	56.0%
Early termination without prior acute rejection[b]	11.5%	22.5%	7.2%
Biopsy-proven rejection episode on treatment	17.0%	13.8%	46.4%

[a]Antithymocyte globulin induction/MMF or azathioprine/cyclosporine/corticosteroids.
[b]Does not include death and graft loss as reason for early termination.
[c]MMF or azathioprine/cyclosporine/corticosteroids.
[d]MMF or placebo/cyclosporine/corticosteroids.
Source: Table 4 Package Insert

Table 2: Kidney Transplant Studies: Cumulative Incidence of Combined Graft Loss or Patient Death at 12 Months

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

Source: Table 5 from CellCept Package Insert

In the CellCept Package Insert, severe neutropenia [absolute neutrophil count < 0.5 x $10^3/\mu L$] developed in 2.0% of renal transplant patients receiving CellCept 3 grams daily (see **WARNINGS**) and gastrointestinal bleeding (requiring hospitalization) was seen in 3% of renal transplant patients using CellCept 3 grams daily (see **PRECAUTIONS**). Comparative rates of leukopenia were 23.2% vs. 34.5% and of diarrhea were 31.0% and 36.1%, for CellCept 2 g/day vs. 3 g/day, respectively.

(b) (4)

2.2 Currently Available Treatment for Indications

- Currently, in kidney transplantation,
  - Prograf is approved for use with corticosteroids and azathioprine.
  - MMF is approved for use with corticosteroids and cyclosporine.

Additionally, several immunosuppressants have been approved for the prophylaxis against rejection in organ transplantation (often in combination):

- tacrolimus (immediate release) with corticosteroids and azathioprine – kidney, liver, and heart transplantation
- cyclosporine and the microemulsion formulation – kidney, liver, and heart transplantation
- sirolimus (with cyclosporine and after withdrawing cyclosporine) – kidney transplantation
- mycophenolate mofetil (in combination with cyclosporine) – kidney, liver, and heart transplantation
- mycophenolic sodium (in combination with cyclosporine) – kidney transplantation
- azathioprine (only in combination with cyclosporine and tacrolimus) in kidney and heart transplantation
- corticosteroids (in combination with other drugs)

- daclizumab – induction in kidney transplantation
- basiliximab – induction in kidney transplantation
- thymoglobulin – treatment of acute rejection in kidney transplantation

These different types of immunosuppressants used in the prophylaxis against organ rejection can be classified as calcineurin-inhibitors, mTOR inhibitors, anti-proliferatives, adrenocorticosteroids, and IL-2 receptor antagonists.

2.3 Availability of Proposed Active Ingredient in the United States

Both Prograf and CellCept are lawfully marketed drugs in the United States.

2.4 Important Issues with Pharmacologically Related Products

Calcineurin-inhibitors are powerful immunosuppressants and the Package Insert contains a boxed WARNING about the increased susceptibility to infections and lymphoma. With the use of immunosuppressants for prophylaxis of rejection in organ transplantation, the clinician must balance the risks of under and over immunosuppression. Under-immunosuppression may lead to acute rejection, chronic rejection and ultimately, graft loss. Over-immunosuppression, on the other hand, will increase the risks of infections, malignancies, and pre-malignant conditions such as post-transplant lymphoproliferative disorders.

In addition to the risks of infection and malignancies, calcineurin inhibitors have toxicities associated with the blood concentrations, such as nephrotoxicity, neurotoxicity, glucose metabolism disturbances, gastrointestinal disturbances, hypertension and infections. For example, a statistically significant relationship between nephrotoxicity, as well as other toxicities, and tacrolimus whole blood trough concentration in liver transplant recipients has been reported.[1] There has also been data demonstrating a significant correlation between tacrolimus whole blood trough levels and the incidence of toxicity, with a positive relationship between the maximum posttransplant tacrolimus whole blood trough concentration levels and an increase in serum creatinine ≥0.5 mg/dL above the posttransplant nadir, as well as between the maximum tacrolimus whole blood trough levels and the initial incidence of any adverse event that required a reduction in tacrolimus dose for clinical management.[2] Other studies have shown a high correlation between tacrolimus trough concentrations and glucose metabolism disorders, insulin-dependent diabetes, and tremor in a cohort of renal transplant recipients.[3]

In addition to the adverse events associated with immunosuppression, CellCept is also associated gastrointestinal toxicities (such as diarrhea and gastrointestinal bleeding), anemia, and leukopenia.

2.5 Regulatory Activity

The Division was involved with the Applicant during the development of the protocol for the primary Study 02-0-158 (Study 158), a three arm study comparing Prograf+MMF, Neoral (cyclosporine)+MMF, and MR4+MMF. MR4 is the extended release formulation of tacrolimus (b) (4)

(b) (4)

In a **July 1, 2003** correspondence, the Division asked the Applicant about plans to determine the potential physicochemical drug-drug interactions following a coadministration of the modified-release tacrolimus formulation and drug products that are frequently used in transplant recipients (e.g. MMF and azathioprine). The Applicant responded that since Prograf does not interact with MMF or azathioprine, there is not basis for drug-drug interactions.

At the **July 28, 2003** End of Phase 2 meetings, the Applicant submitted its proposal for its Phase 3 study (Study 158).

The Division commented that an open label study design presented limitations, including the potential for bias in assessing and comparing rates of acute rejection. The Applicant responded that a blinded three-arm study would require triple-dummy dosing, which would result in patients taking an unacceptably high number of tablets and capsules.

Reviewer's Comments: The open-label design of the study created the potential of bias. Details of how the open-label design may have led to actual bias that affected the results of Study 158 are discussed throughout the review.

January 9, 2004 Division's Memorandum (comments from Statistician and Medial Officer): The Division agreed with the plans to make efficacy failure a primary endpoint, but noted that the Division would continue to expect adequate results near 5-10% non-inferiority margin for the endpoint of graft loss and death.

March 14, 2005 Type C teleconference
- Although the Division stated that the results of Study 02-0-158 (b) (4)
- The Division agreed that the proposed outline submitted by the applicant should be fileable but deferred final decision until the filing review.
- The division agreed to the applicants proposed approach to submitting the datasets.

(b) (4) Submission of NDA (b) (4)

February 13, 2006 Submission of SE8 to NDA 50-708 and 50-709

September 15, 2006 The Division received a major amendment which included extensive analyses regarding the use of mycophenolate mofetil and associated adverse events in the primary Phase 3 study 02-0-158. Included in the submission was a usable dataset for the Division to conduct its own analyses regarding the use of MMF.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINE

3.1 CMC (and Product Microbiology, if Applicable)

Please see the Package Inserts for Prograf and CellCept.

3.2 Animal Pharmacology/Toxicology

Please see the original Prograf and CellCept NDAs and Package Inserts for information regarding animal pharmacology/toxicology.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This NDA submission along with additional information at the request of reviewers was received electronically and can be found at the following locations.

Original submission &120-Day Safety Update: \\Cdsesub1\n50708\S_027\2006-02-13

Additional information requested during review:

\\Cdsesub1\n50708\S_027\2006-08-25\060825
\\Cdsesub1\n50708\S_027\2006-09-07
\\Cdsesub1\n50708\S_027\2006-09-07A
\\Cdsesub1\n50708\S_027\2006-09-15
\\Cdsesub1\n50708\S_027\2006-11-15

In addition to the clinical data from the submissions, clinical data from the following sources were reviewed:

- NDA 50-722 and 50-723, CellCept for the prophylaxis of organ rejection in kidney transplantation.
- BB-IND (b) (4)

4.2 Table of Clinical Study

Table 3: Clinical Study in Kidney Transplantation

Type of Study	Study No.	Objective	Design/ Control	Product/ Dose/Route	No. of Subjects E/C	Subject Type/ Diagnosis	Treatment Duration	Status
***De Novo* Kidney Transplantation**								
E & S	02-0-158 (Study 158)	1: Compare MR4/MMF to Neoral/MMF 2: Compare MR4/MMF to Prograf/MMF	Phase 3, multi-center, open-labeled, randomized non-inferiority study	Prograf/initial dose 0.075-0.10 mg/kg bid/oral + MMF/1 g bid + steroids MR4/initial dose 0.15 – 0.20 mg/kg qd AM/oral + MMF/1 g bid +steroids Neoral/initial dose 4 – 5 mg/kg bid/(25 and 100 mg capsules)/oral +MMF/1 g bid + steroids All 3 treatment groups received basiliximab induction. African-Americans were permitted MMF 1.5 g bid	668/513 *FAS* 638 212 Prograf/ MMF 214 MR4/MMF 212 Neoral/ MMF	De novo kidney transplant recipient ≥12 years	1 year report	1-year report provided; continua-tion ongoing

4.3 Review Strategy

Review of this submission involved a layered approach and is presented below:
- If the data showed that the regimen of tacrolimus+MMF was both safe and efficacious compared with the approved active comparator, Neoral+MMF, and that the results could be labeled so that results could be replicable, then the regimen could be approved.
- If tacrolimus+MMF had evidence of efficacy and safety, but could not be labeled for its safe and effective use, then the regimen would not be recommended for approval.
- If the regimen failed safety (especially safety), then recommend that the safety concerns be presented in the Package Insert.

This approached was used for both the review of (b) (4) Prograf+MMF. Because both Prograf and MMF are both lawfully marketed drugs and currently represent the most commonly used regimen in kidney transplantation, the primary purpose of approving this regimen would be to further promote the use of this combination as studied in Study 158 and to use this combination as an active comparator arm for future clinical studies.

4.4 Data Quality and Integrity

No DSI reviews occurred. At the time of the filing meeting, no single center stood out as having disproportionate contribution to the study. One site was placed as "Member Not in Good Standing" by the Organ Procurement and Transplantation Network (OPTN) for falsifying transplantation information in liver transplantation. The data from this center was not large enough on its own to impact the study results.

The applicant conducted its own internal "check" of the data quality by having a blinded central assessment of the slides from kidney biopsies. The findings from the central lab were not in concordance with the local pathology assessments, with the local pathologists diagnosing acute rejection at a rate of approximately 100% greater than the blinded central lab in all three arms.

Reviewer's Comments: The overdiagnosing of acute rejection by the local pathologists is an example of where the open-label aspect of the study may have biased the results (a concern raised by the Division in July 2003). The potential for bias could have been reduced by using the blinded pathology review as the basis for determining efficacy.

4.5 Compliance with Good Clinical Practices

There did not appear to be any violations of ethical standards for research. There were numerous protocol violations and they are described below.

Study 02-0-158 (Large Phase 3 *de novo* kidney transplant study)
A total of nine subjects included in the full analysis set were excluded from the per protocol set: three patients from each treatment group.

Table 4: Summary of Subjects Excluded from the Per Protocol Set but Included in the Full Analysis Set

Subject Number	Treatment Arm	Reason for Exclusion from Per Protocol Set
00081002	Prograf	Interruption of study drug > 2 weeks
00414001	MR4	Interruption of study drug > 2 weeks
07171005	MR4	Interruption of study drug > 2 weeks
00061004	Neoral	Interruption of study drug > 2 weeks
11232001	Neoral	Interruption of study drug > 2 weeks
00042001	Prograf	First dose of randomized study drug was > 96 hours post transplant procedure
10172004	MR4	First dose of randomized study drug was > 96 hours post transplant procedure.
10222001	Neoral	Administration of another investigational drug (calcium) within 30 days prior to transplant.
00442007	Prograf	Both dose interruption of randomized study drug > 2 weeks and receipt of first dose of study drug > 96 hours post transplant.

Source [Appendices 14.2.1, 14.4.1.1, 14.4.1.2.1, and 14.4.1.2.2].

A total of **42 subjects** were included in both the full analysis and per protocol sets, but failed to meet the study's entry criteria. They were granted waivers to participate in the study:

- 12 patients in the Prograf/MMF treatment group,

- 13 patients in the MR4/MMF treatment group,
- 17 patients in the Neoral/MMF treatment group.

Reasons provided in the appendices for subjects enrolling despite not meeting the protocol requirements include the following:

- The subject did not receive the first dose of study ≤ 48 hours,
- Subjects received the wrong study drug (all were in a tacrolimus arm),
- The maximum cold ischemia time was exceeded,
- A different type of induction (thymoglobulin) was chosen,
- Subject received a zero-antigen HLA mismatch organ from a living donor,
- Subject had a recent history of cancer that was outside of the protocol limitation.

Source: Appendices 14.2.1, 14.4.1.1, 14.4.1.2.1, 14.4.1.2.2, and 14.4.1.5, and 14.4.2.3.

Reviewer's Comments: Many of these permitted exceptions (such as the subject with a zero-antigen HLA mismatch living donor and the subjects with the more recent history of cancer) should not been included in the full analysis set because the clinical reasons for their failure to meet protocol requirements were likely to affect the outcome of the study. Therefore, their inclusion confounded the results of this study.

In addition to these 42 subjects, there were 30 subjects who had protocol deviations and never received a study drug [table submitted July 6, 2006 in response to Division facsimile from June 13, 2006]. In total, there appeared to be 72 subjects who had protocol deviations, 30 who never received the study drug and 42 who were permitted to enroll in the full analysis set. Review of the protocol deviations that occurred in these two groups revealed considerable overlap, making it impossible to determine the appropriateness of the decision to allow some subjects to enroll in the full analysis set and to remove other subjects from the study.

4.6 Financial Disclosures

The applicant submitted an attachment that listed only one investigator with a conflict, (b) (4) (b) (4)

5 Clinical Pharmacology

5.1 Pharmacokinetics

According to the CellCept Package Insert, mycophenolate mofetil undergoes complete metabolism to mycophenolic acid (MPA), the active metabolite. Metabolism to MPA occurs presystemically after oral dosing. MPA is metabolized principally by glucuronyl transferase to form the phenolic glucuronide of MPA (MPAG) which is not pharmacologically active. In vivo, MPAG is converted to MPA via enterohepatic recirculation.

Secondary peaks in the plasma MPA concentration-time profile are usually observed 6 to12 hours postdose. Cholestyramine (4 g tid) was found to decrease the MPA AUC by approximately 40% (largely as a consequence of lower concentrations in the terminal portion of the profile). These observations suggest that enterohepatic recirculation contributes to MPA plasma concentrations. Although the CellCept Package Insert does not address whether cyclosporine decreases the MPA AUC by interrupting the enterohepatic recirculation of MPA, the pharmacokinetic table from the CellCept label suggests that there may have been a similar effect with cyclosporine. Specifically, the Table 5 below demonstrates that the pharmacokinetic parameters for MPA in healthy individuals receiving 1 gram of MMF was comparable to kidney transplant recipients receiving 1.5 g/oral after > 3 months post-transplantation (who were also receiving cyclosporine). This data was confounded by the fact that the healthy volunteers received only a single dose and may not have reflected steady state.

More recently published literature[4, 5] as well as data from studies submitted by Roche under BB-IND (b) (4)[6] confirm that cyclosporine interrupts the enterohepatic recirculation of MPA and leading to a reduction in the systemic MPA exposure of approximately 40%.

Table 5: Pharmacokinetic Parameters for MPA [mean (±SD)] Following Administration of Mycophenolate Mofetil to Healthy Volunteers (Single Dose) and Kidney Transplant Patients

	Dose/Route	T_{max} (h)	C_{max} (µg/mL)	Total AUC (µg•h/mL)
Healthy Volunteers (single dose)	1 g/oral	0.80 (±0.36) (n=129)	24.5 (±9.5) (n=129)	63.9 (±16.2) (n=117)
Kidney Transplant Patients (bid dosing) Time After Transplantation	**Dose/Route**	**T_{max} (h)**	**C_{max} (µg/mL)**	**Interdosing Interval AUC(0-12h) (µg•h/mL)**
5 days	1 g/iv	1.58 (±0.46) (n=31)	12.0 (±3.82) (n=31)	40.8 (±11.4) (n=31)
6 days	1 g/oral	1.33 (±1.05) (n=31)	10.7 (±4.83) (n=31)	32.9 (±15.0) (n=31)

Early (<40 days)	1 g/oral	1.31 (±0.76) (n=25)	8.16 (±4.50) (n=25)	27.3 (±10.9) (n=25)
Early (<40 days)	1.5 g/oral	1.21 (±0.81) (n=27)	13.5 (±8.18) (n=27)	38.4 (±15.4) (n=27)
Late (>3 months)	1.5 g/oral	0.90 (±0.24) (n=23)	24.1 (±12.1) (n=23)	65.3 (±35.4) (n=23)

Source: Table 1 from CellCept Package Insert

5.2 Pharmacodynamics

See Package Inserts for Prograf and CellCept.

6. Integrated Review of Efficacy

6.1 Indication – kidney transplantation

The primary Phase 3 study submitted by the Applicant was Study 02-0-158, a large Phase 3 study in kidney transplantation comparing 3 arms: Prograf+MMF, MR4+MMF, and Neoral+MMF (active control). The primary indication sought by the Applicant in this submission is the use of Prograf in combination with MMF in the prophylaxis of organ rejection in kidney transplantation (b) (4) The Applicant proposes that if they are able to show efficacy and safety with kidney transplantation, (b) (4) (b) (4).

6.1.1 Methods

Data from Study 158 was the primary Phase 3 study submitted by the Applicant to show the safety and efficacy of Prograf and MMF compared with Neoral and MMF which are an approved combination.

6.1.2 General Discussion of Endpoints

The primary endpoints for this study were the failure rate of the following:

- Subject who died;
- Subject who experienced a graft failure (permanent return to dialysis [> 30 days] or retransplant);
- Subject had a biopsy-confirmed (Banff Grade ≥ I) acute rejection (BCAR),
- Subject was lost to follow-up

The following parameters were considered secondary endpoints for the initial treatment period:

- 1-year patient and graft survival rates;
- Incidence of BCAR (Banff Grade ≥ I) at 6 and 12 months;
- Time to first acute rejection episode;
- Incidence of anti-lymphocyte antibody therapy for treatment of rejection;
- Severity of acute rejection;
- Number of patients experiencing multiple rejection episodes;
- Number of clinically treated acute rejection episodes;
- Incidence of treatment failure (up to 12 months);
- Incidence of crossover for treatment failure; and,
- Evaluation of renal function

*Reviewer's Comments: The primary endpoint was designed as a composite endpoint of biopsy-confirmed acute rejection (BCAR), graft loss, patient death, and lost to follow-up. The Division told the Applicant that 1-year patient and graft survival rates would also be required as a co-primary endpoint and would be reviewed using a 5-10% non-inferiority margin [**see Section 2.5].***

The composite endpoint of BCAR, graft loss, and patient death has been used historically in drug approval for organ transplant rejection. The limitation of this composite endpoint is that it places the same value on each of the events, even if they have very different clinical meaning. For example, Banff Grade I acute rejection has the same "value" as Banff Grade III acute rejection or graft loss or patient death. Although the Division agreed to this composite endpoint, it poses a dilemma when assessing the risk-benefit of a treatment regimen. Because graft and patient survival are the gold standards of success in organ transplantation, the Division also required that the endpoint of graft and patient survival be included.

The endpoint of BCAR was based on an unblinded, local pathology assessment. In order for a subject to be treated for BCAR, the local pathologist had to find evidence of acute rejection. This protocol requirement led to potential biases in the local pathology assessment of acute rejection and over-diagnosing of acute rejections. Subsequently, a blinded central lab assessment found far less acute rejection in the same on pathology slides.

Many of the secondary endpoints were not considered important because of the potential biases of the study design – particularly the imbalance in crossovers. The secondary endpoints of patient and graft survival, severity of acute rejection and evaluation of renal function, however, were reviewed very carefully in developing the risk/benefit assessment of the proposed combination of tacrolimus+MMF.

6.1.3 Study Design

Study 158 was a Phase 3, randomized, open-label, comparative, multi-center, non-inferiority Study conducted in 60 to 70 centers throughout the United States, Canada, and Brazil. Approximately 660 subjects were enrolled and randomized in a 1:1:1 ratio into one of three treatment arms: Prograf+MMF, MR4+MMF or Neoral+MMF. The Neoral+MMF arm represented the active control of this non-inferiority study and is an approved combination. Subjects were stratified by donor type (living or deceased). All subjects received basiliximab induction therapy, corticosteroid treatment and MMF at a dose of 1 g bid (1.5 g bid was permitted in African American/black patients) throughout the study.

Subjects were allowed to cross over to another treatment regimen to address adverse events or severe refractory rejection which led to discontinuation of the study drug; however, crossover to the MR4+MMF arm was not permitted. Subjects who crossed over to another treatment regimen or discontinued primary study drug (but did not withdraw consent) were to be followed throughout the course of the study. MMF may have been withdrawn if the investigator believed it was in the best interest of the patient. Patients withdrawn from MMF therapy were to be followed throughout the course of the study.

Reviewer's Comments: Although the Applicant sought labeling that tacrolimus can be used with MMF, this protocol did not assess the use of MMF and there were no pre-specified evaluations of whether patients could tolerate the use of MMF with tacrolimus.

This study was designed as a 1-year efficacy and safety study with a clinical continuation phase of a minimum of 2 years or until commercial availability of MR4, unless the Data Safety Monitoring Board (DSMB) or sponsor specified otherwise. Safety data reviews were conducted by the DSMB periodically throughout the study.

6.1.3.1 Study 02-0-158 Protocol

Amendments

Amendment 1

Protocol amendment 1, dated May 8, 2003, is summarized below.

- Dosing amounts, schedules, and routes of administration were modified.
- Inclusion and exclusion criteria were modified.
- The study visit schedule for the initial treatment period was modified.
- Hepatic profile sample collection times were modified.
- Tests performed at central laboratories were clarified.
- Sponsor personnel contact information was updated.
- Typographical errors were corrected and minor clerical changes were incorporated.

Amendment 2

Protocol amendment 2, dated November 13, 2003, is summarized below.

- The primary and secondary efficacy assessments were modified.
- A section describing interim analyses was added.
- The inclusion criteria were clarified.
- Descriptions of statistical analyses were modified.
- The follow-up duration for adverse events was clarified.
- Typographical errors were corrected and minor clerical changes were incorporated.

Inclusion Criteria

Patients were eligible for the study if they met all of the following criteria:

1. Patient had been fully informed and had signed an IRB-/IEC-approved informed consent/authorization form and was willing and able to follow study procedures.
2. Patient was the recipient of a primary or retransplanted cadaveric or non-HLA-identical living kidney transplant.
3. Patient was ≥ 12 years of age.
4. Patient received first oral dose of randomized study drug within 48 hours of transplant procedure.
5. Female patient of child bearing potential had a negative urine or serum pregnancy test within 7 days prior to enrollment or upon hospitalization.

Exclusion Criteria

Fulfillment of any of the following criteria resulted in exclusion from the study:

1. Patient had previously received, or was receiving, an organ transplant other than a kidney.
2. Patient received a kidney from a non-heart-beating donor.
3. Patient received an ABO blood group incompatible donor kidney.
4. Recipient or donor was known to be seropositive for HIV.

5. Patient had a current malignancy or a history of malignancy (within the previous 5 years), except non-metastatic basal or squamous cell carcinoma of the skin that had been successfully treated.
6. Patient had significant liver disease, defined as continuously having serum glutamic oxaloacetic transaminase (SGOT/AST) or serum glutamic pyruvate transaminase (SGPT/ALT) levels > 3 times the upper limit of the normal range used at the investigational site, during the 28 days prior to transplant.
7. Patient had an uncontrolled concomitant infection or any other unstable medical condition that could potentially interfere with the study objectives.
8. Patient was taking, or had been taking, another investigational drug within 30 days prior to transplant.
9. Patient received everolimus or enteric-coated mycophenolic acid at any time during the study.
10. Patient had a known sensitivity to tacrolimus, cyclosporine, mycophenolate mofetil, or corticosteroids.
11. Patient was pregnant or lactating.
12. Patient was unlikely to comply with the visits scheduled in the protocol.
13. Patient had any form of substance abuse, psychiatric disorder, or a condition that, in the opinion of the investigator, could invalidate communication with the investigator.
14. Patient received a kidney with a cold ischemia time of ≥ 36 hours.
15. Patient received a kidney from a cadaveric (deceased) donor ≥ 60 years of age.
16. Patient received intravenous immunoglobulin (IVIG) therapy prior to randomization or within 48 hours after randomization.

Crossover Criteria
Patients were allowed to cross over to an alternative primary calcineurin inhibitor regimen (either the Prograf+MMF or Neoral+MMF treatment arms) to address an adverse event which led to randomized study drug discontinuation or in the case of severe or refractory rejection. Crossover to the MR4+MMF treatment arm was not permitted. All reasons for crossover were to be documented on the patient's CRF. Crossover treatments were permitted after discussion with and approval by the sponsor's medical monitor.

Reviewer's Comment: Details of the crossover are discussed in Section 6.1.3.2 which discusses the likelihood that there was actual bias in Study 158.

Study Withdrawal Criteria
Patients may have been removed from the study for any of the following reasons:
• Patient experienced graft failure (permanent return to dialysis [>30 days] or retransplant).
• Patient withdrew consent.
• Investigator believed it was no longer in the best interest of the patient to remain in the study due to safety or efficacy issues.
• Patient was lost to follow-up.
• Study was discontinued by the sponsor.

Adverse events and patient and graft survival were to be obtained for all patients throughout the study regardless of the reason for randomized study drug discontinuation, unless the patient withdrew consent.

Treatment Arms

MR4 + MMF
The first dose of MR4 was to be administered orally prior to or within 48 hours following transplantation with the initial dose between 0.15 and 0.20 mg/kg/day as a single oral dose in the morning. MR4 was to be given once daily (qd) in the morning with dose adjustments based on clinical evidence of efficacy, occurrence of adverse events, and whole blood tacrolimus trough concentrations. The target range for whole blood tacrolimus trough concentrations was 7 to 16 ng/mL for days 0 through 90, and 5 to 15 ng/mL thereafter.

Prograf + MMF
The first dose of Prograf was to be administered orally prior to or within 48 hours after transplantation with the initial dose between 0.075 and 0.10 mg/kg bid. Dose adjustments were to be based on clinical evidence of efficacy, occurrence of adverse events, and whole blood tacrolimus trough concentrations. The target range for whole blood tacrolimus trough concentrations was the recommended trough concentration range for Prograf: 7 to 16 ng/mL for days 0 through 90 and 5 to 15 ng/mL thereafter.

Neoral + MMF
The first dose of Neoral was to be administered orally prior to or within 48 hours following transplantation with the initial dose to be between 4 to 5 mg/kg bid. Dose adjustments were based on clinical evidence of efficacy, occurrence of adverse events, and whole blood cyclosporine trough concentrations. The target range for whole blood cyclosporine trough concentrations was 125 to 400 ng/mL for days 0 through 90, and 100 to 300 ng/mL thereafter.

Mycophenolate Mofetil (MMF)
All MMF doses were to be 1.0 g bid according to the MMF labeling. African-American/black subjects were allowed to receive 1.5 g MMF if necessary. The first dose of MMF was to be administered orally or intravenously prior to or within 48 hours of transplantation. The doses could be divided three times a day or four times a day if the subject had difficulty tolerating MMF. ***Dose changes for adverse events were permitted at the investigator's discretion if clinically indicated***. Patients who withdrew from MMF were to be followed throughout the study.

Reviewer's Comments: Although the same doses of MMF were used in all three arms, the mycophenolic acid (MPA) exposure was likely greater in the tacrolimus arms compared with the cyclosporine because of the pharmacokinetic interactions between cyclosporine and MMF. Although systemic exposures of MPA was not measured in this study, the MPA trough levels in this study was consistently higher in the tacrolimus arms compared with the Neoral arm, despite subjects using lower doses of MMF in the tacrolimus arm.

Another shortcoming of the study was that the protocol also permitted too much physician discretion in adjusting MMF dosing. Because the Applicant wanted to show that MMF could be used safely and effectively with tacrolimus, there should have been a more rigorous protocol design that permitted limited reductions of MMF doses. As mentioned earlier, "MMF use" was not included as an endpoint even though the primary intention for including a Prograf+MMF arm was to show the safety and efficacy of tacrolimus+MMF.

Corticosteroids
The initial dose of methylprednisolone was to be a 500 to 1000 mg (or equivalent dose) intravenous bolus administered on day 0; methylprednisolone 200 mg (or equivalent dose) orally on day 1. Prednisone was then tapered according to the followings schedule:

Time Relative to Transplant	Prednisone Equivalent
By Day 14	20 to 30 mg
By Month 1	10 to 20 mg
By Month 2	10 to 15 mg
By Month 3 to 12	5 to 10 mg

Antibody Induction Therapy
All patients were to receive 20 mg basiliximab intravenously on day 0 before skin closure. A second 20 mg basiliximab intravenous dose was administered between days 3 and 5.

Treatment of Rejection Episodes
All episodes of kidney dysfunction were to be evaluated for possible rejection after exclusion of other causes. All patients were to have biopsy confirmation of rejection episodes before treatment for rejection was begun, or within 48 hours of initiation of treatment for acute rejection.

The local pathologist at the clinical site was responsible for grading all biopsies using the 1997 Banff criteria. Blinded, central reviews of biopsies obtained for suspected new rejection were also performed; however, the decision to begin treatment for rejection was based on the results of the local review.

Initial rejection episodes were to be treated with oral or intravenous corticosteroids with the dose not to exceed 1 g/day for a maximum of 3 to 5 days. Subsequently,

corticosteroids were to be tapered according to institutional practice. If a patient had histologically-proven Banff Grade II or III rejection, the patient could be initiated on anti-lymphocyte antibodies (OKT®3, Thymoglobulin®, ATGAM®) as per institutional protocol.

The protocol did not permit routine surveillance biopsies during the study because the practice of routine surveillance biopsies was not common standard of care across most institutions and the results would have introduced bias related to the endpoints of acute rejections and time to acute rejection. Steroid-resistant rejection was to be treated with anti-lymphocyte antibody treatment according to institutional practice.

Reviewer's Comments: Although the Applicant was concerned about introducing bias from protocol surveillance biopsies, they failed to acknowledge the greater potential for bias from using an unblinded pathologist reading of a biopsy performed by an unblinded investigator as a primary endpoint. Protocol biopsies read by a blinded pathologist would have provided a more reliable assessment of clinical and subclinical acute and chronic rejection; and would have been a preferable endpoint.

Prophylaxis for Cytomegalovirus, Pneumocystic carinii, anti-fungal and anti-bacterial prophylaxis
Were all performed according to individual institutional protocol.

Endpoints and Asessments

Procedures Performed at Baseline

• Medical history prior to transplant was obtained, including diagnosis for transplant and any medications taken within the 14 days prior to transplant.
• Physical examination was performed.
• Subject height, weight, and vital signs.
• Transplant data - date of transplant, cold ischemia time, type of transplant, and length of surgery.
• Concomitant medications were recorded.
• Initial dose of intravenous corticosteroids was administered.
• Samples for anti-human leukocyte antigen (anti-HLA) antibody screening (class I and II) and transforming growth factor-beta (TGF-beta) levels were to be obtained prior to transplant. If this was not possible, samples were to be drawn within 24 hours of transplant completion. Sample collection for anti-HLA antibody screening and TGF-beta levels collected post transplant was considered a protocol deviation.
• Samples for hemoglobin A_{1C} (glycosylated hemoglobin, HbA_{1C}) and C-reactive protein (CRP) were obtained.
• Patient was randomized into one of the three treatment groups for the study.

Reviewer's Comments: This protocol did not specify the timeframe required for the baseline procedures to be performed, but the study subjects appeared to be randomized prior to transplantation because there were 30 study subjects who randomized but never received the study drug (some subjects never even received the kidney transplant). The Applicant could have randomized study subjects after transplantation because all the subjects were to receive the same initial induction. By randomizing after transplantation, the Applicant could assure that almost all subjects who randomized would receive the study drug and be enrolled in the full analysis set. As discussed in Section 6.1.3.2 and Section 4.5, in addition to the 30 subjects who were randomized but did not receive study drug, there were 42 subjects who did not meet inclusion/exclusion criteria, but were permitted to enroll in the study. Almost half of these subjects did not meet inclusion/exclusion criteria because they received the first dose of study drug after 48 hours. If the randomization occurred after transplantation, then subjects who were not able to take the study drug within 48 hours after transplantation would not have randomized. This issue became important during the conduct of the study.

Procedures Performed on Day 1

The following procedures were to be completed on day 1:

- Clinical assessments.
- Vital signs pre-dose, if possible.
- Adverse events were recorded.
- Postoperative dose of study drug was administered within 48 hours of completion of transplant procedure, per randomized drug treatment assignment.
- Corticosteroid doses were administered.
- Routine clinical laboratory assessments.
- Study drug dosing information recorded.
- All concomitant medication use recorded.

Procedures Performed on Day 2 Through Month 10

- Clinical assessment of patient and graft status was performed at all study visits.
- Vital signs.
- Adverse events were recorded at all study visits.
- Routine clinical laboratory assessments were obtained per the schedule provided in the protocol.
- Samples for whole blood tacrolimus or cyclosporine trough levels were obtained at all study visits.
- Samples for mycophenolic acid trough levels were obtained at months 1 and 6.
- Quality of Life Questionnaire was completed by patients at months 1 and 6.
- ECG was performed on day 14.
- Samples for anti-HLA antibodies (class I and II), TGF-beta, HbA_{1C}, and CRP levels were obtained at month 6.
- Study drug dosing information was recorded at all study visits.
- Concomitant medication information was recorded at all study visits.
- If warranted, and based on clinical assessments, additional samples for evaluation may have obtained at any study visit.

Procedures Performed at Month 12 or Last Day of Study Drug Dosing
• Clinical assessment of patient and graft status was performed.
• Physical examination was performed.
• All adverse events and concomitant medication information were recorded.
• ECG was performed.
• Vital signs, including oral body temperature, pulse rate, blood pressure, and weight were obtained.
• Samples for routine clinical laboratory testing were obtained.
• Sample for whole blood tacrolimus or cyclosporine trough level was obtained.
• Sample for mycophenolic acid trough level was obtained.
• Patient and graft survival information was documented for all patients at month 12.
• Quality of Life Questionnaire was completed by patient.
• Samples for anti-HLA antibodies (class I and II), TGF-beta, HbA_{1C}, and CRP levels were obtained.
• Drug accountability was completed.
• Patients randomized to receive Prograf or Neoral were converted to commercial drug supplies.
• Patients randomized to receive MR4 who were continuing into the clinical continuation phase of the study were provided with MR4 supplies.

Unscheduled Study Visits
Unscheduled visits may have occurred in addition to the scheduled visits outlined in the protocol. All unscheduled visits involving adverse events were to be documented on the patient's CRF. Samples for study drug trough levels were to be obtained at all unscheduled visits, prior to receiving the next dose of study drug.

6.1.3.2 Biases in the Protocol Design

There were several sources of potential bias in the study. All of these sources of potential bias could have been removed if the study had been blinded. Instead, the protocol design increased the potential for bias.

Open-Label:
The primary Phase 3 study was open-label.

Randomized But Never Received Study Drug:
There were 30 subjects who randomized but never received study drug. There was a slight imbalance in the study arms for reasons the subjects never received the study drug, with the MR4 arm having more subjects who received a more aggressive form of induction and more subjects in the Neoral arm who never even received a transplant.

Did Not Meet Protocol Inclusion/Exclusion Criteria but Still Included in the Study:
There were 42 subjects who did not meet the inclusion/exclusion but were allowed to enroll in the study and were included in the per protocol data set. The decision to include these subjects was made by the Applicant's medical director.

Imbalance in Crossover:
There was an imbalance in the crossover of Neoral subjects into the Prograf arm. After reviewing the adverse events and the acute rejection rates, there did not appear to be an imbalance of adverse events or acute rejections in the Neoral arm over the other two arms that would explain the difference among the three arms.

Reviewer's Comments: Review of the informed consent documents also raised the question of whether the imbalance in crossovers may have been exacerbated by the study design. During the first year post-transplantation, there was no penalty if study subjects crossed from their randomized arm into Prograf or Neoral – study subjects were entitled to free Prograf or Neoral, even if they crossed over from the originally randomized arm. In a clinical practice, 72% of all kidney transplant recipients are discharged on a Prograf-based regimen compared to 21% on a cyclosporine-based regimen.[7] In 2003, at 1-year post-transplantation, 51% of kidney patients were receiving tacrolimus/MMF compared with 17% receiving cyclosporine/MMF.[7] Since there is a clinical bias towards using tacrolimus instead of cyclosporine, there is a greater potential for bias towards crossing over from Neoral to Prograf.

There was also a bias in the study design that gave study subjects randomized into the MR4 incentive to ***not*** *cross-over. According to the informed consent documents submitted by the Applicant [submitted August 15, 2006], study subjects in the MR4 would receive free MR4 for 3 years post-transplantation.*

Assessment of Acute Rejection:
The assessment of acute rejection was based on the local, unblinded pathologist reading with a requirement that acute rejection be diagnosed before the investigator could initiate treatment. This requirement led to inappropriate overdiagnoses of acute rejection. The pathology slides were ultimately reviewed by a blinded, central pathologist who interpreted a number of the lower grade acute rejections to be calcineurin toxicity and found only about half of the acute rejection episodes as the local pathologists.

6.1.4 Efficacy Findings

Based on an agreement with the Division, the evidence for efficacy from Study 158 would be based on two parameters: a composite endpoint of biopsy confirmed acute rejection (BCAR), graft failure, and patient failure and the combined endpoint of graft and patient survival. The non-inferiority margin for the composite endpoint was to be set at 10%, whereas a more rigorous

non-inferiority margin of 5-10% was required for the combination of graft and patient survival. The study was powered to capture the composite endpoint of BCAR, graft failure and death with lost to follow-up counting as an event. [see Section 2.5 Presubmission Regulatory Activity]

6.1.4.1 Demographics and Baseline Characteristics of Subjects and Donors

Tables 6-9 summarize the demographics and characteristics of study subjects. Although none of the differences between the study subjects reached statistical significance, there were trends in the baseline characteristics that seem to favor the MR4 arm compared with the Prograf and Neoral arms: fewer study subjects with diabetes or hypertension at baseline; fewer recipients with a history of a previous transplant; younger recipients; more male recipients; younger donors; lower mean cold ischemia time; lower mean PRA; more white donors; more recipients with polycystic kidney disease; and more male donors (especially more male donors for female recipients). The MR4 arm did have fewer living donors, more recipients ≥ 65 years, and more recipients with hypertension as reason for renal failure.

Table 6: Subject Demographics for Study 158

	Treatment Group			
	Prograf (n = 212)	**MR4 (n = 214)**	**Neoral (n = 212)**	**Total (n = 638)**
Sex				
Male	136 (64.2%)	138 (64.5%)	130 (61.3%)	404 (63.3%)
Female	76 (35.8%)	76 (35.5%)	82 (38.7%)	234 (36.7%)
Race				
White	152 (71.7%)	160 (74.8%)	163 (76.9%)	475 (74.5%)
Black	51 (24.1%)	41 (19.2%)	36 (17.0%)	128 (20.1%)
Asian	5 (2.4%)	5 (2.3%)	8 (3.8%)	18 (2.8%)
Other†	4 (1.9%)	8 (3.7%)	5 (2.4%)	17 (2.7%)
Ethnicity				
Hispanic	29 (13.7%)	31 (14.5%)	31 (14.6%)	91 (14.3%)
Non-Hispanic	183 (86.3%)	183 (85.5%)	181 (85.4%)	547 (85.7%)
Age (years)				
Mean ± SD	48.62±12.855	47.84±12.995	47.63±12.953	48.03±12.921
Median	50.50	48.00	48.50	49.00
Range	19.0-74.0	17.0-77.0	17.0-77.0	17.0-77.0
Age Group (years)				
< 65	189 (89.2%)	190 (88.8%)	192 (90.6%)	571 (89.5%)
≥ 65	23 (10.8%)	24 (11.2%)	20 (9.4%)	67 (10.5%)

Patient base: Full analysis set; all randomized subjects who received at least one dose of study drug.
†Other: Brazilian Indian (4); Filipino (4); East Indian (2); Indian (2); Native Hawaiian – Other Pacific Islander (2); Phillipino (2); and Indian Subcontinent (1).
Source: Table 13.2.1 and Appendix 14.4.1.4.1.

Table 7: Study Subjects' Baseline Characteristics

Characteristic	Treatment Group			
	Prograf (n = 212)	MR4 (n = 214)	Neoral (n = 212)	Total (n = 638)
Primary Diagnosis				
Nephrosclerosis / Hyper-tensive Nephropathy	54 (25.5%)	56 (26.2%)	43 (20.3%)	153 (24.0%)
Diabetic Nephropathy	46 (21.7%)	38 (17.8%)	46 (21.7%)	130 (20.4%)
Glomerulonerphritis	44 (20.8%)	43 (20.1%)	43 (20.3%)	130 (20.4%)
Polycystic Kidney Disease	20 (9.4%)	26 (12.2%)	20 (9.4%)	66 (10.3%)
Tubular/Interstitial Disease	9 (4.2%)	5 (2.3%)	16 (7.5%)	30 (4.7%)
Systemic Vasculitis	9 (4.2%)	10 (4.7%)	7 (3.3%)	26 (4.1%)
Congenital / Hereditary Nephropathy	7 (3.3%)	7 (3.3%)	13 (6.1%)	27 (4.2%)
Reflux	1 (0.5%)	0	1 (0.5%)	2 (0.3%)
Unknown	17 (8.0%)	24 (11.2%)	17 (8.0%)	58 (9.1%)
Other†	5 (2.4%)	5 (2.3%)	6 (2.8%)	16 (2.5%)
Donor Type				
Living	106 (50.0%)	103 (48.1%)	111 (52.4%)	320 (50.2%)
Cadaveric (Deceased)	106 (50.0%)	111 (51.9%)	101 (47.6%)	318 (49.8%)
Previous Transplant				
No	205 (96.7%)	206 (96.3%)	203 (95.8%)	614 (96.2%)
Yes	7 (3.3%)	8 (3.7%)	9 (4.2%)	24 (3.8%)
HLA Mismatches				
0	6 (2.8%)	12 (5.6%)	15 (7.1%)	33 (5.2%)
1	7 (3.3%)	10 (4.7%)	12 (5.7%)	29 (4.5%)
2	27 (12.7%)	31 (14.5%)	27 (12.7%)	85 (13.3%)
≥ 3	172 (81.1%)	161 (75.2%)	158 (74.5%)	491 (77.0%)
Panel Reactive Antibody (%)				
Mean ± SD	2.72 ± 11.343	2.49 ± 10.668	4.09 ± 13.315	3.10 ± 11.819
Median	0.00	0.00	0.00	0.00
Range	0.0 – 78.0	0.0 – 87.0	0.0 – 95.0	0.0 – 95.0
Cold Ischemia Time (hr)				
Mean ± SD	19.41 ± 7.267	17.88 ± 7.732	18.44 ± 7.109	18.56 ± 7.388
Median	19.57	17.87	18.00	18.02
Range	0.5 – 37.3	0.8 – 34.8	2.3 – 38.0	0.5 – 38.0

Patient base: Full analysis set; all randomized subjects who received at least one dose of study drug.
†Other: (4 subjects) obstructive uropathy; (1 patient each) hypertension/diabetes, secondary to ruptured aortic aneurysm, severe arterionephrosclerosis with focal global and segmental glomerulosclerosis, chronic nephrolithiasis, chronic pyelonephritis, non-steroidal anti-inflammatory drugs, bilateral ureteral strictures and hydronephrosis, urinary vesical reflux and neurogenic bladder, membrano-proliferative glomerulonephritis – type I, cholesterol emboli and severe atherosclerotic disease, bladder outlet obstruction secondary to benign prostatic hypertrophy, and nephrocalcinosis.
Source: Tables 13.2.2, 13.2.4, and Appendix 14.4.1.6.

Table 8: Summary of the Presence of Hypertension, Diabetes, or Hyperlipidemia at Baseline

Parameter	Treatment Group			
	Prograf (n = 212)	MR4 (n = 214)	Neoral (n = 212)	Total (n = 638)
Hypertension				
No	20 (9.4%)	35 (16.4%)	22 (10.4%)	77 (12.1%)
Yes	192 (90.6%)	179 (83.6%)	190 (89.6%)	561 (87.9%)
Diabetes Type I or II (not PTDM)				
No	152 (71.7%)	164 (76.6%)	154 (72.6%)	470 (73.7%)
Yes	60 (28.3%)	50 (23.4%)	58 (27.4%)	168 (26.3%)
Hyperlipidemia				
No	149 (70.3%)	144 (67.3%)	137 (64.6%)	430 (67.4%)
Yes	63 (29.7%)	70 (32.7%)	75 (35.4%)	208 (32.6%)

Patient base: Full analysis set; all randomized patients who received at least one dose of study drug.
PTDM: Post-transplant diabetes mellitus.
Source: Table 13.2.5 and Appendix 14.4.1.5.

Table 9: Summary of Donor Demographics

	Treatment Group			
	Prograf (n = 212)	MR4 (n = 214)	Neoral (n = 212)	Total (n = 638)
Sex				
Male	86 (40.6%)	113 (52.8%)	96 (45.3%)	295 (46.2%)
Female	126 (59.4%)	101 (47.2%)	116 (54.7%)	343 (53.8%)
Race				
White	173 (81.6%)	174 (81.3%)	171 (80.7%)	518 (81.2%)
Black	25 (11.8%)	21 (9.8%)	20 (9.4%)	66 (10.3%)
Asian	4 (1.9%)	6 (2.8%)	8 (3.8%)	18 (2.8%)
Other†	5 (2.4%)	6 (2.8%)	7 (3.3%)	18 (2.8%)
Missing	5 (2.4%)	7 (3.3%)	6 (2.8%)	18 (2.8%)
Age (years)				
Mean ± SD	38.98 ± 13.378	38.22 ± 12.924	39.93 ± 11.175	39.04 ± 12.530
Median	41.00	39.00	40.50	40.00
Range	0.0 – 68.0	2.0 – 72.0	17.0 – 63.0	0.0 – 72.0
Age Group (years)				
< 45	122 (57.5%)	147 (68.7%)	135 (63.7%)	404 (63.3%)
≥ 45	90 (42.5%)	67 (31.3%)	77 (36.3%)	234 (36.7%)

Patient base: Full analysis set; all randomized patients who received at least one dose of study drug.
† Other was noted as: Unknown (3); Mixed (3); Hispanic (3); Native American/Other Pacific Islander (3); Brazilian Indian Des. (2), Indian (1), Mexican (1), Mulata (1), and, Native American/Alaskan Native (1).
Missing: Donor demographic characteristic was not provided.
Source: Table 13.2.4 and Appendix 14.4.1.4.2.

There was a significant difference across treatment arms for donor sex (p-value = 0.0381; chi-square test). There were no significant differences across treatment arms for any of the other donor demographic parameters (race, age, and age group). There were numerically more males

in the Prograf treatment group (85/136; 62.5%) who received a kidney from a female donor than males in the MR4 treatment group (68/138; 49.3%) or Neoral treatment group (73/130; 56.2%).

Reviewer's Comments: The tables of study subject characteristics and donor characteristics show a trend for lower risk "healthier" recipient and donors in the MR4 arm compared with the Prograf or Neoral arms. The differences were not statistically significant in any one variable, but these variables have all been shown to have some effect on outcomes (which is why they are variables in the survival models used by the Scientific Registry of Transplant Recipients for the Annual Report of the OPTN/SRTR).

6.1.4.2 Disposition of Study Subjects

Table 10 summarizes the disposition of the study subjects. What is notable is that the Neoral arm had a large number of crossovers for rejection and adverse events.

Table 10: Study Subject Population and Disposition

Data Set	Prograf (n = 219)	MR4 (n = 226)	Neoral (n = 223)	Total (n = 668)
All Randomized Patients	219 (100.0%)	226 (100.0%)	223 (100.0%)	668 (100.0%)
Full Analysis Set	212 (96.8%)	214 (94.7%)	212 (95.1%)	638 (95.5%)
Per Protocol Set	209 (95.4%)	211 (93.4%)	209 (93.7%)	629 (94.2%)
Crossover †	6 (2.7%)	10 (4.4%)	39 (17.5%)	55 (8.2%)
Final Disposition (Full Analysis Set)				
Disposition	**(n = 212)**	**(n = 214)**	**(n = 212)**	**(n = 638)**
Completed 1-year of Randomized Therapy	179 (84.4%)	183 (85.5%)	151 (71.2%)	513 (80.4%)
Discontinued Randomized Therapy	33 (15.6%)	31 (14.5%)	61 (28.8%)	125 (19.6%)
Adverse Event	23 (10.8%)	19 (8.9%)	37 (17.5%)	79 (12.4%)
Rejection	0	1 (0.5%)	16 (7.5%)	17 (2.7%)
Non-compliance	4 (1.9%)	2 (0.9%)	5 (2.4%)	11 (1.7%)
Graft Failure	3 (1.4%)	2 (0.9%)	1 (0.5%)	6 (0.9%)
Withdrawal of Consent	0	4 (1.9%)	1 (0.5%)	5 (0.8%)
Lost to Follow-up	1 (0.5%)	0	0	1 (0.2%)
Other §	2 (0.9%)	3 (1.4%)	1 (0.5%)	6 (0.9%)

Patient base: All randomized subjects. Full analysis set: All randomized subjects who received at least one dose of study drug. Per protocol set: All randomized subjects who had no major protocol violations or other events during the study that would make a patient's data invalid for one or more analyses.
† Crossover: All patients who crossed over from their randomized treatment arm to another treatment arm. Crossover to the MR4/MMF treatment arm was prohibited.
‡ Lost to follow-up for patient disposition reflects the investigator's assessment of patient status on the final assessment case report form.
§ Other: Investigator discretion/converted to rapamycin, acute tubular necrosis, incorrect study drug dispensed, investigator discretion/possible toxicity, improper absorption of study drug, and subsequent pancreas transplant.
Source: Tables 13.1.1, 13.1.2, and Appendix 14.4.1.3.

Reviewer's Comments: Although there were considerable differences in the crossover rates, there appeared to be biases associated with the crossovers. As discussed in Section 6.1.3.2, the protocol design "rewarded" subjects in the MR4 arm by assuring free immunosuppression (MR4) for 3 years if the subject remained on MR4, and there was no penalty for subjects who crossed from Prograf to Neoral and vice versa. Other evidence that the large number of crossovers was due to bias is the large number of subjects in the Neoral arm who crossed over for acute rejection. The incidence of acute rejections were similar between the Neoral arm and the MR4 arm, but only 1 subject in the MR4 armed crossed over for rejection, whereas 16 subjects from the Neoral arm crossed over because of rejection. There were also a large number of Neoral subjects who crossed over because of adverse events. However, review of dropouts for serious adverse events [Section 7.1.3.2] showed the incidence of crossovers for serious adverse events to be similar between the Prograf and Neoral arms, implying that the adverse events leading to the Neoral crossovers were not serious. Given that the safety profile of Neoral was comparable or better than the tacrolimus arms, the decision to discontinue the Neoral treatment appeared driven more by bias rather than the adverse events.

6.1.4.3 Composite Efficacy Endpoint

Table 11 was supplied by the Statistics Reviewer, LaRee Tracy and summarizes the composite endpoints of BCAR, graft failure, death and lost to follow-up. Both the Prograf and MR4 arms meet this endpoint based on the pre-specified 10% non-inferiority margin.

Table 11: Efficacy Failure at Day 365 in Study 158

Day 365	Prograf (n=212)	MR4 (n=214)	Neoral (n=212)	Difference, 95.2% CI, p-value		
				MR-Neoral	Prograf-Neoral	MR-Prograf
Efficacy failure[1]	32 (15.1)	30 (14.0)	36 (17.0)	-3.0, [10.0, 4.0], 0.4	-1.9, [-9.0, 5.2], 0.6	-1.1, [-7.9, 5.8], 0.8
Reason for failure: BCAR	16 (7.5)	22 (10.3)	29 (13.7)	-3.4, [-9.7, 2.8], 0.3	-6.1, [-12.2, -0.2], 0.04	2.7, [-2.8, 8.4], 0.4
Graft Failure[2]	6 (2.8)	4 (1.9)	4 (1.9)			
Death[3]	9	3	5	-0.9, [-4.2, 2.0], 0.5	1.9, [-1.7, 5.8], 0.3	-2.8, [-6.6, 0.3], 0.08
LTF[4]	4	3	1 (0.5)			

[1]Incidence of the first occurrence of graft failure, death, local confirmed acute rejection or loss to follow-up
[2] Permanent (>30 days) return to dialysis or re-transplant not resulting in death. Note that 1 subject in each arm had a BCAR prior to experiencing graft failure.
[3] Note that 2 Neoral/MMF subjects experienced BCAR prior to death, 2 patients in Neoral group died after crossing over to Prograf and one patient in the Prograf/MMF group died after crossing over to Neoral/MMF.
[4] One subject in the MR/MMF and 1 subject in the Prograf/MMF were LTF after experiencing an acute rejection. An additional patient on the Prograf/MMF arm was LTF after experiencing graft failure.
*95% CI and p-value calculated using Fisher's Exact Test

For the composite endpoint for BCAR, graft failure and death, there were no differences by age (16 to < 65 years and ≥ 65 years) or baseline of diabetes. Differences in efficacy were noted by sex, race, ethnicity, and donor type. See Table 12.

Table 12: Summary of 1-year Composite Endpoint Failure Rate by Recipient Sex, Race, Ethnicity, and Donor Type

	Efficacy Failure†		
Parameter	**Prograf**	**MR4**	**Neoral**
Sex			
Male	19/136 (14.0%)	14/138 (10.1%)	23/130 (17.7%)
Female	13/76 (17.1%)	16/76 (21.1%)	13/82 (15.9%)
Race			
Black	11/51 (21.6%)	8/41 (19.5%)	10/36 (27.8%)
White	21/152 (13.8%)	20/160 (12.5%)	23/163 (14.1%)
Ethnicity			
Hispanic	4/29 (13.8%)	7/31 (22.6%)	3/31 (9.7%)
Non-Hispanic	28/183 (15.3%)	23/183 (12.6%)	33/181 (18.2%)
Donor Type			
Living Donor	12/106 (11.3%)	14/103 (13.6%)	11/111 (9.9%)
Deceased Donor	20/106 (18.9%)	16/111 (14.4%)	25/101 (24.8%)

Patient base: Full analysis set; all randomized patients who received at least one dose of study drug.
† For efficacy failure, a patient was only counted once regardless of how many criteria were met. Only events up to day 365 are included in the analyses.
Graft failure: Permanent return to dialysis (> 30 days) or retransplant.
BCAR: Biopsy-confirmed acute rejection. Biopsy results were from local assessments.
Source: Tables 14.3.5.3.2, 14.3.5.3.3, 14.3.5.3.4, 14.3.5.3.6

Reviewer's Comments: Because acute rejection occurred at a much higher rate than death or graft loss, acute rejection was the primary contributor to differences in the efficacy results seen in Table 12. However, given the large number of misdiagnosed acute rejections, it is likely that the difference would be reduced if the blinded central assessment was used. Ultimately, there were very few clinically relevant acute rejection (≥ Grade IIA) episodes found in the blinded, central assessment, making it difficult to find real differences within the subgroup analyses for the composite endpoint [see Section 6.1.4.5].

6.1.4.4 Graft and Patient Survival

Tables 13-15, provided by the Statistical Reviewer, LaRee Tracy, summarize the patient and graft survival at 1-year, 1 ½ years, and 2 years. What is notable about the findings in the three tables are the following:

- The Prograf arm had a higher graft failure rate, a higher mortality rate, and a higher lost to follow-up rate.
- The higher rates for each of these three parameters persisted at 1 ½ years and 2 years post-transplantation.
- The graft failure rate of the MR4 arm "catches up" to the Prograf arm by year 2.
- The graft and patient survival in the MR4+MMF arm meets the pre-specified non-inferiority margin of 5-10%.
- The patient survival in the Prograf+MMF arm exceeds the 5% margin and is discussed further in the safety analysis.

Table 13: Patient and Graft Survival at 1-year Post-Transplantation (Intent-to-Treat)

Day 365 (1 yr follow-up)	Prograf (n=212)	MR4 (n=214)	Neoral (n=212)	Difference, 95.2% CI, p-value		
				MR4-Neoral	Prograf-Neoral	MR4-Prograf
Patient Survival	**199 (93.9)**	**208 (97.2)**	**206 (97.2)**	**0, [-3.6, 3.6], 0.99**	**-3.3, [-7.8, 0.7], 0.1**	**3.3, [-6.9, 7.8], 0.1**
Reason:						
Death	9 (4.2)	3 (1.4)	5 (2.3)	-0.9, [-4.2, 2.0], 0.5	1.9, [-1.7, 5.8], 0.3	-2.8, [-6.6, 0.4], 0.08
LTF	4 (1.9)	3 (1.4)	1 (0.5)			
Graft Survival	**194 (91.5)**	**204 (95.3)**	**202 (95.3)**	**0, [-4.3, 4.4], 0.99**	**-3.8, [-8.9, 1.0], 0.1**	**3.8, [-0.9, 8.9], 0.1**
Reason:						
Death	9 (4.2)	3 (1.4)	5 (2.3)			
Graft Failure[1]	9 (4.2)	5 (2.3)	4 (1.9)			
LTF[2]	4 (1.9)	3 (1.4)	1 (0.5)			

[1]Permanent (>30 days) return to dialysis or re-transplant not resulting in death.
Note: 1 patient in MR/MMF and 3 patients in Prograf/MMF died after experiencing graft failure
[2] Note that 1 subject in the Prograf/MMF was LTF after experiencing graft failure.
*95% CI and p-value calculated using Fisher's Exact Test

Table 14: Patient and Graft Survival at 1 ½ -years Post-Transplantation (Intent-to-Treat)

Day 547 (1.5 yr follow-up)	Prograf (n=212)	MR4 (n=214)	Neoral (n=212)	Difference, 95.2% CI, p-value		
				MR4-Neoral	Prograf-Neoral	MR4-Prograf
Patient Survival	**195 (92.0)**	**207 (96.7)**	**204 (96.2)**	**0.5, [-3.3, 4.4], 0.8**	**-4.2, [-9.2, 0.3], 0.06**	**4.7, [0.3, 9.6], 0.03**
Reason:						
Death	12 (5.7)	4 (1.9)	7 (3.3)	-1.4, [-5.0, 1.8], 0.5	2.4, [-1.7, 6.7], 0.2	-3.8, [-7.9, -0.2], 0.04
LTF	5 (2.3)	3 (1.4)	1 (0.5)			
Graft Survival	**190 (89.6)**	**202 (94.4)**	**198 (93.3)**	**1.0, [-3.8, 5.9], 0.7**	**-3.8, [-9.4, 1.6], 0.2**	**4.8, [-0.4, 10.3], 0.07**
Reason						
Death	12 (5.7)	4 (1.9)	7 (3.3)			
Graft Failure[1]	9 (4.2)	6 (2.8)	6 (2.8)			
LTF[2]	5 (2.3)	3 (1.4)	1 (0.5)			

[1]Permanent (>30 days) return to dialysis or re-transplant not resulting in death.
Note: 1 patient in MR/MMF and 3 patients in Prograf/MMF died after experiencing graft failure
[2] Note that 1 subject in the Prograf/MMF was LTF after experiencing graft failure.
*95% CI and p-value calculated using Fisher's Exact Test

Table 15: Patient and Graft Survival at 2-years Post-Transplantation (Intent-to-Treat)

Day 780 (2 yr follow-up)	Prograf (n=212)	MR4 (n=214)	Neoral (n=212)	Difference, 95.2% CI, p-value		
				MR4-Neoral	Prograf-Neoral	MR4-Prograf
Patient Survival	**195 (92.0)**	**206 (96.3)**	**204 (96.2)**	**0, [-39, 4.0], 0.99**	**-4.2, [-9.2, 0.3], 0.06**	**4.3, [-0.2, 9.2], 0.06**
Reason:						
Death	12 (5.7)	5 (2.3)	7 (3.3)	-1.0, [-4.6, 2.5], 0.6	2.4, [-1.7, 6.7], 0.2	-3.8, [-7.9, -0.2], 0.04
LTF	5 (2.3)	3 (1.4)	1 (0.5)			
Graft Survival	**190 (89.6)**	**198 (92.5)**	**196 (92.4)**	**0, [-5.2, 5.3], 0.99**	**-2.8, [-8.5, 2.7], 0.3**	**2.9, [-2.6, 8.6], 0.3**
Reason						
Death	12 (5.7)	5 (2.3)	7 (3.3)			
Graft Failure[1]	9 (4.2)	9 (4.2)	8 (3.8)			
LTF[2]	5 (2.3)	3 (1.4)	1 (0.5)			

[1]Permanent (>30 days) return to dialysis or re-transplant not resulting in death.
Note: 1 patient in MR4/MMF and 3 patients in Prograf/MMF died after experiencing graft failure
[2] Note that 1 subject in the Prograf/MMF was LTF after experiencing graft failure.
*95% CI and p-value calculated using Fisher's Exact Test

Reviewer's Comments: The difference in patient survival between the Prograf and the Neoral arm almost reached statistical significance at 1 ½ years (p-value 0.06). The higher mortality rate in the Prograf arm is extremely troubling because kidney transplantation would have been primarily life-enhancing, not life-saving, for these study subjects. In heart and liver transplantation, individuals are transplanted because they will die if they do not receive a transplant. In kidney transplantation, however, individuals are not transplanted because death is imminent without a transplant because of the option of dialysis.

To the extent that the inclusion/exclusion criteria would have the limited the number of high risk patients enrolled in the study, the Division would expect patient survival rates for this clinical trial to be better than the survival rates seen in the national database. However, the actual survival rate for the Prograf arm (95.75%) was comparable to the national survival rate (96.09%).[8] When the survival rate of the Prograf arm in Study 158 are compared with the survival rates in the clinical trials conducted by Astellas for heart transplantation, the comparative differences are even more dramatic. In heart transplantation, the 1-year survival rate for the clinical trials was 91.7% and 93.5% [Prograf Package Insert], whereas the national survival rate for heart transplantation is 87.96%.[9]

Table 16 (below) lists all the graft failures and subject deaths at 2 years post-transplantation. The case report forms and narratives of all graft failures and deaths were carefully reviewed. The excess deaths in the Prograf arm appear to be related to adverse events associated with over immunosuppression, such as infections and malignancy. The reason for the increased in graft failures in the Prograf arm could not be determined, but most of the graft losses appeared to have occurred earlier in the study. Meanwhile, the graft losses in the MR4 arm occurred later – most occurring after the 1 year study endpoint (5/9). In the MR4 arm, there were 4 subjects who lost their graft due to rejection (acute and vascular), compared with one in the Prograf arm, and none in the Neoral arm. Three of the MR4 study subjects (02082016, 10172004, 00522003) who experienced graft failure, also had evidence of treatment non-compliance that may have contributed to the graft loss.

Table 16: Summary of Graft Losses and Deaths in Study 158, 2-years Post-Transplantation

Subject Number	Graft Loss (Day)	Death (Day)	Reason for Graft Loss / Primary Cause of Death
Prograf + MMF			
00162005	4	No	Acute thrombosis of iliac artery
00162009‡	50	No	DGF
00352003	No	123	Sepsis related to vancomycin-resistant enterococci infection.
00432002	No	383	Cardiac arrest
00442004	No	141	Possible pulmonary embolism
00512003	No	178	Subdural bleed after fall
01092004	68	No	Acute tubular necrosis and non-compliance
01652002	65	69	Nephrectomy / Sepsis
01811002	No	1	Cardiac arrest

Prograf + MMF			*(continued)*
02032001	10	No	Acute rejection
02082013	No	311	Homicide
04062008	No	415	Septic shock
07172001	69	No	DGF
07502001	No	374	Metastatic renal carcinoma with hemothorax
10181003	197	218	Chronic allograft nephropathy / Sepsis
10192003	77	No	Recurrent disease
10202005	7	No	Renal vein thrombosis
10202007	No	57	Tissue invasive strongyloidosis
10211002	134	142	Recurrent disease / Miliar[y] tuberculosis
MR4 + MMF			
00232002	284	No	Acute rejection (Retransplant, day 598)
00292003	No	57	Cardiac and respiratory arrest
00502001	338	No	Acute tubular necrosis
00512005	No	53	Lymphocytic Choriomeningitis
00522003	567	No	Acute rejection
00711010	No	429	Probable myocardial infarction
00712002	No	663	Sepsis
00821003	333	No	Vascular rejection and collapsing FSGN
01092001	53	227	Chronic allograft nephropathy / Stroke
02061008	536	No	Polyoma virus infection
02082016	603	No	Acute rejection
10172004	621	No	Non-compliance
10222002	8	No	Renal vein thrombosis
Neoral + MMF			
00251003	566	No	Recurrent disease
00252003	No	472	Suicide
00292009	4	No	Primary non-functioning graft
00321006	No	324	Myocardial infarction
00411001	668	No	Chronic allograft nephropathy
00522012	367	No	Chronic allograft nephropathy
00711012	440	No	Unknown
00712001	No	55	Probable pulmonary embolus
01362001	83	No	Acute tubular necrosis
01812009	No	371	Encephalitis
02031002	3	No	Renal artery and vein thrombosis (Retransplant, day 70)
10212009	No	222	Diverticulitis
10222001	No	45	Pulmonary edema
10222007‡	§	19	Septic shock
10232003	9	No	Acute tubular necrosis
10931013	No	35	Myocardial infarction

DGF: Delayed Graft Function; FSGN: Focal Segmental Glomerulonephritis.
‡ Patient Numbers 00162009 (Prograf+MMF) and 10222007 (Neoral+MMF) never received study drug.

Reviewer's Comments: More detailed discussions about the deaths are presented in Section 7.1.1 of the Safety analysis. However, the higher mortality and graft loss in the Prograf arm is consistent with the lower acute rejection also seen in that arm. If subjects receive an excess of immunosuppressive drugs, they are more likely to die from infections and malignancies or lose the graft due to calcineurin toxicity or polyomavirus infection.

In the MR4 arm, subjects 02082016, 10172004, and 00522003 appeared to have lost their graft due to non-compliance:
02082016 – On Day 572, subject's dose of MR4 was listed as 0.0 mg because of "non-compliance." The subject developed acute rejection and graft loss on Day 603.
10172004 – Listed as having graft loss on day 621 due to non-compliance.
00522003 – Starting on Day 287, subject had "treatment non-compliance" listed as an adverse event that continued. The subject developed acute rejection on Day 425 and graft loss on Day 567.

The reasons for graft loss in both the Prograf and the Neoral arms appear to be very similar; the primary difference between the two arms is when the graft losses occurred. By year two, no additional graft losses occurred (9/9 graft losses occurred during the first year) in the Prograf arm, whereas there were 4 additional graft losses after year 1 for a total of 8 graft losses in the Neoral arm.

6.1.4.5 Acute Rejection

Tables 17 and 18 show the incidence of acute rejection in each of the 3 arms. Although the difference between the Prograf and Neoral reaches statistical significance in the intent-to-treat analyses, there is no difference in the on-therapy analyses.

Table 17: BCAR on Therapy at 1-year Post-Transplantation

	Prograf	MR4	Neoral	MR4 v. Neoral	Prograf v. Neoral
BCAR	15 (7.7%)	21 (10.4%)	23 (11.6%)	**p-value**	
[95% CI]	[3.9%, 11.4%]	[6.2%, 14.6%]	[7.1%, 16.1%]	0.700	0.184

Kaplan-Meier Estimates of BCAR (censored at the time of last randomized dose)
Source: Table 14.3.5.4.2

Table 18: BCAR Intent-to-Treat at 1-year Post-Transplantation

	Prograf	MR4	Neoral	MR4 v. Neoral	Prograf v. Neoral
BCAR	16 (7.8%)	22 (10.4%)	29 (11.6%)	**p-value**	
[95% CI]	[4.1%, 11.4%]	[6.3%, 14.5%]	[9.1%, 18.4%]	0.292	0.047

Kaplan-Meier Estimates of BCAR (censored at the time of last follow-up). P-value using Greenwood formula.
Source: Table 14.3.5.4.1

Reviewer's Comments: There was no difference in the BCAR rates when analyzed "On-Therapy," (Table 17), whereas there was a statistically significant difference in BCAR rates between the Prograf and Neoral arms when analyzed as "Intent-to-Treat." Given the large number of crossovers from Neoral to Prograf, it is difficult to determine if the additional acute rejections in the Neoral arm in the intent-to-treat analysis were a consequence of the subjects having been on Neoral, or a result of the crossover. Since the study design did not allow study subjects to cross into the MR4 arm, it would be difficult to evaluate the clinical impact of crossing from Prograf or Neoral into MR4.

Tables 19 and 20 compare the rate of acute rejections when read by the local pathologist compared with the blinded, central pathologist, as well as the grade of acute rejection. The blinded, central assessment found 50% fewer acute rejections than the local assessments. The blinded, central assessment found that the number of ≥ Banff Grade IIA rejections very similar across the three arms: MR4 = 9; Prograf = 6 and Neoral = 10. **Based on the results of the blinded, central assessment, the Prograf arm had a mortality rate greater than its acute rejection rate (4.2% v. 3.8%)**.

Table 19: Acute Rejections at 1-year Post-Transplantation

Acute Rejections	Prograf (%)	MR4 (%)	Neoral (%)	Prograf v. Neoral	MR4 v. Neoral
	n = 212	n = 214	n = 212	p-values*	
Local Assessment	16 (7.5)	22 (10.3)	29 (13.7)	0.047	0.292
Blinded, Central Assessment	8 (3.8)	10 (4.7)	14 (6.6)	0.192	0.353

Source: Table 14.3.5.5.1
* P-values obtained from Chi-square test.

Table 20: Maximum Grade of Acute Rejection at 1-year Post-Transplantation

Max Grade of Acute Rejection	Prograf		MR4		Neoral	
	Central	Local	Central	Local	Central	Local
Grade IA	1	8	0 (1)	11	3 (4)	14
Grade IB	1	4	1	3	1 (2)	6
Grade IIA	6	3	5	6	7	6
Grade IIB	0	1	3	1	2	1
Grade III	0	0	1	2	1	2
Total	8	16	11	23	16	29

( ) = value imputed when the central lab value was not available.
Source: Table 14.3.5.5.1

There appeared to be a higher acute rejection rate for women using tacrolimus compared to the men; the opposite was true for the Neoral arm. In females, a treatment by race interaction was observed with respect to the incidence of BCAR. A higher incidence of BCAR was observed in black women (35.7%, 5/14) compared to black men (3.7%, 1/27) in the MR4 arm, and in black men (31.8%, 7/22) compared to black women (7.1%,1/14) in the Neoral arm.
Source: Table 14.3.5.3.2 and Table 28 of Study 158 Report.

Reviewer's Comments: The difference in the acute rejection rates seen between the local and central assessments highlights the limitations of an open-label study and the problems when a protocol design places the burden of treatment (for acute rejection) on the interpretation of a pathologist, who does not treat patients. In reviewing the data, the central assessment did not find as many episodes of the lower grade acute rejection as the local pathologists.

The finding of higher acute rejection rates in women compared with men in the tacrolimus arms requires further exploration to determine if these findings were due to the overdiagnoses by the local pathologist or related to the dosing concerns with MR4.

6.1.4.6 Troughs of Prograf and Neoral

Table 21 displays the comparative troughs between Prograf and Neoral.

Table 21: Mean Dosing and Troughs of Study Subjects in Study 158

	Prograf (mean tacrolimus trough)	Neoral (mean CsA trough)
Day 7	10.71	286.74
Day 10	10.53	312.97
Day 14	11.72	320.41
Day 21	11.08	324.17
Month 1	11.18	311.31
Month 2	10.06	261.09
Month 4	8.80	218.13
Month 6	8.61	205.04
Month 8	8.06	192.69
Month 10	7.92	187.33
Month 12	7.75	176.93

Source: Tables 13.3.1.1 and 13.3.1.2 from Study 158 Report

The tables 13.3.1.3 from the Appendix of Study 158 (shown below) displays the percentage of subjects whose troughs were within target range, above the target range or below the target range. The MR4 had more subjects below the target range than the Prograf arm. Through most of the study, more subjects in the Neoral arm had troughs above the targeted range.

506E 02-0-158 -FINAL-

TABLE 13.3.1.3
PATIENTS BELOW/ABOVE TARGET STUDY DRUG TROUGH CONCENTRATIONS BY VISIT
(FULL ANALYSIS SET)

	TREATMENT GROUP							
	PROGRAF+MMF (N=212)				MR4+MMF (N=214)			
VISIT	N	WITHIN TARGET	BELOW TARGET	ABOVE TARGET	N	WITHIN TARGET	BELOW TARGET	ABOVE TARGET
DAY 3	172	77(44.8%)	48(27.9%)	47(27.3%)	189	95(50.3%)	58(30.7%)	36(19.0%)
DAY 7	153	104(68.0%)	31(20.3%)	18(11.8%)	173	102(59.0%)	50(28.9%)	21(12.1%)
DAY 10	146	103(70.5%)	29(19.9%)	14(9.6%)	167	114(68.3%)	39(23.4%)	14(8.4%)
DAY 14	153	105(68.6%)	23(15.0%)	25(16.3%)	167	118(70.7%)	29(17.4%)	20(12.0%)
DAY 21	162	118(72.8%)	25(15.4%)	19(11.7%)	183	128(69.9%)	37(20.2%)	18(9.8%)
MONTH 1	166	122(73.5%)	23(13.9%)	21(12.7%)	182	118(64.8%)	36(19.8%)	28(15.4%)
MONTH 2	165	125(75.8%)	29(17.6%)	11(6.7%)	181	138(76.2%)	33(18.2%)	10(5.5%)
MONTH 4	151	124(82.1%)	20(13.2%)	7(4.6%)	174	143(82.2%)	18(10.3%)	13(7.5%)
MONTH 6	148	135(91.2%)	8(5.4%)	5(3.4%)	169	134(79.3%)	29(17.2%)	6(3.6%)
MONTH 8	139	122(87.8%)	16(11.5%)	1(0.7%)	167	136(81.4%)	27(16.2%)	4(2.4%)
MONTH 10	139	120(86.3%)	15(10.8%)	4(2.9%)	159	127(79.9%)	28(17.6%)	4(2.5%)
MONTH 12	148	123(83.1%)	21(14.2%)	4(2.7%)	165	129(78.2%)	33(20.0%)	3(1.8%)

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TABLE 13.3.1.3
PATIENTS BELOW/ABOVE TARGET STUDY DRUG TROUGH CONCENTRATIONS BY VISIT
(FULL ANALYSIS SET)

	TREATMENT GROUP			
	NEORAL+MMF (N=212)			
VISIT	N	WITHIN TARGET	BELOW TARGET	ABOVE TARGET
DAY 3	172	123(71.5%)	23(13.4%)	26(15.1%)
DAY 7	158	118(74.7%)	15(9.5%)	25(15.8%)
DAY 10	147	102(69.4%)	11(7.5%)	34(23.1%)
DAY 14	154	111(72.1%)	8(5.2%)	35(22.7%)
DAY 21	159	122(76.7%)	3(1.9%)	34(21.4%)
MONTH 1	165	129(78.2%)	4(2.4%)	32(19.4%)
MONTH 2	159	133(83.6%)	12(7.5%)	14(8.8%)
MONTH 4	147	118(80.3%)	8(5.4%)	21(14.3%)
MONTH 6	139	114(82.0%)	8(5.8%)	17(12.2%)
MONTH 8	139	121(87.1%)	7(5.0%)	11(7.9%)
MONTH 10	129	117(90.7%)	7(5.4%)	5(3.9%)
MONTH 12	127	109(85.8%)	13(10.2%)	5(3.9%)

Reviewer's Comments: The higher troughs in the Neoral arm may explain the slightly worse renal function seen in the Neoral arm. When comparing the mean troughs at month 1, 6 and 12, the mean Neoral troughs were consistently higher within the target range compared with Prograf and MR4. There was also evidence of more CNI toxicity in the Neoral arm as seen in the types of adverse events described as well as the results of the central assessment of the kidney biopsies. The greater exposure to CNI's in the Neoral arm may explain differences in the renal function between the Neoral and MR4 arms. It is possible that subjects in the Neoral arm could have achieve the same efficacy without as much toxicity if the mean trough concentrations were lower.

Source Submission on February 16, 2006, File 020158, BIOP.xpt.

6.1.4.7 Dosing of MMF

The dosing of MMF for this study was 2 grams per day in accordance with the usage information from the Package Insert for MMF. The current recommended dosing for MMF in kidney transplantation is based on blinded studies comparing MMF 3 grams and 2 grams when used with cyclosporine. Data from the original CellCept NDA, approved in 1995, showed that although there is slightly better acute rejection rates with the MMF 3 gram dose, the subjects in that arm also had greater adverse events and discontinuations that did not justify the higher dose in normal risk kidney transplantation.[10] Because cyclosporine interferes with the enterohepatic recirculation of mycophenolic acid, but tacrolimus does not, the Prograf and MR4 arms used doses of MMF that would result in exposures of MPA that may have been comparable to the 3 gram dose.[5,6, 11]

Pharmacokinetic data from the CellCept Package Insert also suggests that the pharmacokinetic parameters for MPA in health individuals receiving 1 gram of MMF was comparable to the renal transplant recipients receiving 1.5 g/oral after > 3 months post-transplantation; but this data is confounded by the fact that the healthy volunteers received only a single dose (see Table 5 below).

Table 5: Pharmacokinetic Parameters for MPA [mean (±SD)] Following Administration of Mycophenolate Mofetil to Healthy Volunteers (Single Dose) and Kidney Transplant Patients

	Dose/Route	T_{max} (h)	C_{max} (µg/mL)	Total AUC (µg•h/mL)
Healthy Volunteers (single dose)	1 g/oral	0.80 (±0.36) (n=129)	24.5 (±9.5) (n=129)	63.9 (±16.2) (n=117)
Kidney Transplant Patients (bid dosing) Time After Transplantation	**Dose/Route**	**T_{max} (h)**	**C_{max} (µg/mL)**	**Interdosing Interval AUC(0-12h) (µg•h/mL)**
5 days	1 g/iv	1.58 (±0.46) (n=31)	12.0 (±3.82) (n=31)	40.8 (±11.4) (n=31)
6 days	1 g/oral	1.33 (±1.05) (n=31)	10.7 (±4.83) (n=31)	32.9 (±15.0) (n=31)
Early (<40 days)	1 g/oral	1.31 (±0.76) (n=25)	8.16 (±4.50) (n=25)	27.3 (±10.9) (n=25)
Early (<40 days)	1.5 g/oral	1.21 (±0.81) (n=27)	13.5 (±8.18) (n=27)	38.4 (±15.4) (n=27)
Late (>3 months)	1.5 g/oral	0.90 (±0.24) (n=23)	24.1 (±12.1) (n=23)	65.3 (±35.4) (n=23)

Source: Table 1 from CellCept Package Insert

Therefore, for purposes of determining dosing and efficacy, the pattern of MMF use in the Prograf and MR4 arms was examined to determine whether the subjects in these arms were in fact using the 2 grams/day. The Clinical Pharmacology Reviewer, Seong Jang, Ph.D., supplied Table 22 below which showed that the pattern of MMF use in the MR4 and Prograf arm were very similar to each other but different from the Neoral arm. From 6 months to the 12 months the mean dose of MMF in the tacrolimus arms was approximately 85% of the dose used in the Neoral arm. The differences reflect the difficulty in tolerating the higher exposures of mycophenolic acid – a finding consistent with the data from the original CellCept NDA that showed higher doses were more difficult to tolerate (the higher dose of 3 g/day when used with cyclosporine may have resulted in systemic exposures of MPA comparable to 2 g/day when used with Prograf).

Table 22: Average daily dose (mg/day) of MMF for the MR4+MMF, Prograf+MMF, and Neoral+MMF treatment arms during different treatment periods

Time period (Days)		Treatment Group		
		MR4+MMF	Prograf+MMF	Neoral+MMF
1-30	Mean±SD N Median [Range]	1871±344 214 1967 [633-3000][a]	1851±396 212 1967 [250-2950]	1962±410 210 1967 [166.7-5500]
31-90	Mean±SD N Median [Range]	1748±477 208 2000 [0-3000]	1737±538 206 2000 [0-3000]	1881±439 200 2000 [0-3000]
91-183	Mean±SD N Median [Range]	1635±552 203 1973 [0-3000]	1571±639 201 1978 [0-3000]	1765±526 185 2000 [0-3000]
183-365	Mean±SD N Median [Range]	1489±646 186 1671 [0-3000]	1405±669 187 1500 [0-3000]	1708±560 170 2000 [0-3000]

The average daily dose was calculated by dividing total dose of MMF for a given treatment period by total treatment days. For example, if Patient A received MMF 2g until Day 45 and 1.5g thereafter until Day 210 and died (or crossover: i.e., stopped dosing of Neoral, Prograf, or MR4 because of any reason) on Day 210, the average daily dose of MMF for different treatment periods was calculated as follows:
Average daily dose for Days 1-30 = (2g * 30 day)/30 = 2g
Average daily dose for Days 31-90 = (2g * (45 -30) + (1.5g * (90-45)) /(90-30)=1.625 g
Average daily dose for Days 91-183 = (1.5g*(183-91))/(183-91)=1.5g
Average daily dose for Days 183-365 = (1.5g * (210-183))/(210-183)=1.5g
If MMF dose was stopped while Prograf, MR4 or Neoral was given, then MMF dose was considered 0.

Reviewer's Comments: The protocol design for Study 158 would not be considered scientifically sound because it allowed investigators to reduce the MMF dose based on the investigator's judgment. While this approach may not have been scientifically sound, it may have been clinically necessary in order to avoid pressuring investigators into using unsafe doses of MMF. The Applicant, however, should have been aware about the difference in MPA exposure when the same dose of MMF was used in tacrolimus versus cyclosporine. This information has been in the literature since 1999.[4] Therefore, the higher dose (2 grams/day) would be more difficult to tolerate when used with tacrolimus.[12]

In using higher MPA exposure in the tacrolimus arms, the Applicant was able to use lower tacrolimus doses and maintain the trough levels at the lower end of the trough range. A lower

blood concentration of tacrolimus has the advantage of reducing the nephrotoxicities of tacrolimus -- resulting in better renal function. However, the Applicant did not adequately anticipate the toxicities associated with the higher MPA exposures such as anemia, leukopenia, and diarrhea [see reviewer's comments in Section 7.1.5.4].

When MMF was approved in 1995, two doses were studied in kidney transplant subjects, 3 grams and 2 grams. The comparative results of 2 blinded studies with cyclosporine and MMF showed that although the 3 gram/day dose improved acute rejection, there were more adverse events and premature withdrawals from the studies in the 3 gram arm. Therefore, the risk-benefit analysis led to the decision to recommend using 2 grams of MMF with cyclosporine. [Cellcept Package Insert]. Although MPA AUC_{0-12} was not studied in Study 158, MMF 2 grams, when used with tacrolimus, can be estimated to be similar to the AUC_{0-24} of MMF 3 grams when used with cyclosporine. (b) (4) *Other studies have suggested that when used with Prograf, 1 gram of MMF provided equivalent efficacy as 2 grams of MMF, but fewer adverse events.*[12, 14]

The Applicant's approach to addressing the toxicities of MMF (recommending that physicians reduce the dose according to their clinical judgment in response to adverse events) cannot be recommended because of the uncertainty and unpredictability regarding the efficacy of that approach.[13] *In a 2003 article by Knoll, et al, the clinical efficacy of dropping MMF doses was evaluated, retrospectively. In the article, the reasons for dose reduction included leukopenia (55.1%), gastrointestinal symptoms (22.2%), infection (7.4%) malignancy (1.1%) and unknown reasons (14.2%). The authors found that the relative risk of rejection increased by 4% for every week that the MMF dose was reduced below full dose.*[13] *Furthermore, by dosing MMF to the point of toxicity and then reducing the dose in response to the toxicity, patients would be subjected to unnecessary and preventable morbidities as their clinicians try to "guess" the correct dose of MMF to use.*

In kidney transplantation, the regimen of cyclosporine+MMF appears to have a very narrow therapeutic window where the risk/benefit of MMF justifies its use compared with azathioprine. That "therapeutic window" was determined to be 2 grams/day when used with cyclosporine. MMF 2 grams/day cannot be recommended for use with tacrolimus based on the pattern of MMF use in the tacrolimus arms, the greater adverse events typically associated with MMF, the higher mortality and graft failure seen in the Prograf+MMF arm, and the higher MPA AUC_{0-12} associated with MMF when they drug is ***not*** *used with cyclosporine. Review of the pattern of MMF use in the tacrolimus arm did not show a systematic dropping of the MMF doses. Instead, doses were decreased (or held) when subjects developed adverse events, and then returned to the original 2 gram dose until the next time the subject developed adverse events. This approach to dosing MMF is not consistent with how MMF is dosed with cyclosporine and has the potential of exposing patients to adverse events, unnecessarily. Exploratory efforts were conducted by the Reviewers to evaluate whether the data from Study 158 was adequate to provide a safe and effective dose to use in combination with tacrolimus; however, the data did not provide adequate*

information to establish the appropriate dose of MMF to use in combination with Prograf.

6.1.4.7.1 Dosing of MMF after Crossover from Neoral to Prograf

Because of the larger number of subjects who crossed over from Neoral to Prograf in Study 158, the effect on the MMF dose could be evaluated. In the Neoral+MMF arm, more patients had MMF dose decreases compared to increases after crossover to Prograf. Table 23 summarizes the mean doses of MMF after crossover. Because the number of subjects in the Prograf and MR4 are relatively small, the significance of the results is less relevant. However, subjects in both tacrolimus steadily increased their MMF doses after crossing over whereas subjects in the Neoral arm decreased their doses.

Table 23: Mean Dose of MMF after Crossover

Time after Crossover	Prograf+MMF (n=4)	MR4+MMF (n=4)	Neoral+MMF (n=39)
	Mean (mg/day) (n)	Mean (mg/day) (n)	Mean (mg/day) (n)
Day 3	1312 (n= 4)	1750 (n=4)	1869 (n=39)
Day 7	1437.5 (n=4)	2000.0 (n=3)	1854.2 (n=39)
Day 10	1468.8 (n=4)	2000.0 (n=3)	1810.9 (n=39)
Day 14	1537.5 (n=4)	2000.0 (n=3)	1791.0 (n=39)
Day 21	1453.1 (n=4)	2000.0 (n=3)	1771.4 (n=38)
Month 1	1437.5 (n=4)	2000.0 (n=3)	1745.6 (n=38)
Month 2	1435.5 (n=3)	2000.0 (n=3)	1592.0 (n=34)
Month 4	1322.2 (n=3)	2000.0 (n=3)	1618.3 (n=32)
Month 6	1500.0 (n=2)	2000.0 (n=3)	1616.2 (n=24)
Month 8	1500.0 (n=2)	2000.0 (n=3)	1515.9 (n=17)
Month 10	2000.0 (n=1)	2000.0 (n=2)	1468.6 (n=15)
Month 12			1450.0 (n=5)

Source: Table 4.2, Folder B.2, submitted September 15, 2006 to NDA 50-708 and 50-709.

Reviewer's Comments: The mean dose of MMF steadily decline in subjects who crossed over from Neoral to Prograf. The decreasing "n" in each of the three arms may be a reflection of those subjects who died after crossover, lost their grafts after crossover, stopped taking MMF after crossover, or crossed over relatively late in the study.

The effect of the decreasing dose of MMF highlights two important aspects of this study: 1) the MPA exposure was not balanced between the Neoral arm versus the tacrolimus arms, with the Neoral subjects likely receiving less MPA relative to the subjects in the tacrolimus arms; 2) the intolerability of the higher system exposures of MPA at MMF 2 grams with Prograf forced subjects who crossed over from Neoral to Prograf to reduce their doses of MMF. This "natural" experiment confirms that use of MMF 2 grams with Prograf cannot be tolerated by most kidney transplant recipients and cannot be recommended.

6.1.5 Clinical Microbiology

Not applicable because this drug, though an antibiotic, is not used to target microorganisms.

6.1.6 Efficacy Conclusions

The large Phase 3 study (Study 158) showed that the combination of Prograf+MMF met non-inferiority margins of the efficacy endpoints: composite of BCAR, graft survival, patient survival and the combined patient and graft survival. However, the use of (b) (4) Prograf cannot be recommended for the following reason:

- Subjects in neither the Prograf arm nor the MR4 arm consistently used 2 grams/day of MMF.
- The correct dose of MMF needed to achieve safety and efficacy could not be determined from the data submitted from the study.
- The Prograf+MMF arm had an excess of patient deaths which appear to be due to overimmunosuppression (infections and malignancy).
- The results of the Prograf+MMF arm calls into question the (b) (4)

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The primary source for the safety assessment was the primary Phase 3 study, Study 158. Because tacrolimus is a drug that has been on the market for 12 years, certain safety events were targeted for special consideration during the conduct of the study such as diabetes, hyperglycemia, hypertension, hyperlipidemia, renal function, gastrointestinal disorders, and infections.

7.1.1 Deaths

The list of all the deaths up to 2 years can be found in Section 6.1.4.4. Table 24 presents the deaths prior to submission of the 120 day safety update with comments next to the deaths that appeared to be due to overimmunosuppression.

Table 24: Summary of Patient Deaths Before Submission of 120 Safety-update

Patient Number	Last Dose Day†	Randomized Treatment	Day of Death	Primary Cause of Death (investigator description)	*Reviewer's Comments*
00352003	65	Prograf	123	Sepsis – related to VRE infection	*Overimmunosuppression.*
00442004	140	Prograf	141	Possible pulmonary embolism	
00512003	177	Prograf	178	Subdural bleed after fall	
01652002	64	Prograf	69	Sepsis	*Overimmunosuppression.*
01811002	0	Prograf	1	Cardiac arrest	
02082013	310	Prograf	311	Homicide	
07502001	344	Prograf	374	Metastatic renal carcinoma with hemothorax	*Subject had a history of renal ca that recurred. Not only did he develop metastatic renal carcinoma, but he had repeated episodes of infection and sepsis before his death.*
10181003	196	Prograf	218	Sepsis	*Overimmunosuppression.*
10202007	56	Prograf	57	Tissue invasive strongyloidosis	*Overimmunosuppression. Only the Prograf arm had subjects with strongyloidosis.*
10211002	42	Prograf	142	Miliary tuberculosis	*This subject had crossed over to Neoral, so the death is likely due to immunosuppression on Neoral.*
00292003	54	MR4	57	Cardiac and respiratory arrest	*This subject actually died of such severe gastroenteritis that he went into cardiorespiratory arrest.*
00512005	32	MR4	53	Lymphocytic choriomeningitis	*This subject had a donor transmitted infection.*
01092001	23	MR4	227	Stroke	
01812009	362	Neoral	371	Encephalitis	*No organism was ever identified as the cause of the encephalitis.*
10212009	128	Neoral	222	Diverticulitis	*This subject had crossed over to Prograf, so the cause of death was likely due to treatment with Prograf.*
10222001	11	Neoral	45	Pulmonary edema	
10931013	34	Neoral	35	Myocardial infarction	
00321006	324	Neoral	324	Myocardial infarction	
00712001	55	Neoral	55	Probable pulmonary embolus	

Patient base: Full analysis set; all randomized patients who received at least one dose of study drug.
Patient Number 10222007 (Neoral/MMF) died on day 19 but was never administered study drug. This patient is not included in the full analysis set and, therefore, is not included in this table. After day 365, two patients died (Patient Numbers 01812009 [Neoral/MMF] and 07502001 [Prograf/MMF]) and are included in this table but were not included in any efficacy analyses.
† Last dose of randomized study drug.
Source: Appendices 14.4.4.1 and 14.4.4.2.

At the one-year endpoint (day 365), there were 9 deaths in the Prograf+MMF arm, of which 5/9 deaths were attributable to infections. One of the infection deaths was a subject (10211002) who

had crossed over to Neoral and developed miliary TB. In the Neoral arm, there were a total of 5 deaths, of which only 1 was attributable to an infection. The one infection related death was in subject 10212009 who crossed over to Prograf and developed diverticulitis, perforation and sepsis-like death. Because there was a balance in the number of the infection related cross-over deaths, differences in the infection related deaths between Prograf versus Neoral did not change when the crossover issue was considered. At year 1, there were 5 infection/overimmunosuppression related deaths in the Prograf arm compared with the 1 death in the Neoral arm.

At the 2 year endpoint, there were a total of 12 deaths in the Prograf+MMF arm, of which 7/12 deaths were attributable to infections/overimmunosuppression including one death in the Prograf arm due to unexpected, aggressive metastatic malignancy. In the Neoral+MMF arm, there were a total of 7 deaths, of which 2/7 deaths were attributable to infections/overimmunosuppression (see Section 6.1.4.4).

Reviewer's Comments: Based on detail review of the case report forms and narratives of subjects who died, it appears that the combination of Prograf+MMF 2 grams may have been too toxic for study subjects and resulted in overimmunosuppression. At year 2, there were 7 deaths in the subjects using Prograf+MMF that were due to overimmunosuppresion (Subjects 00352003, 01652002, 04062008, 07502001, 10181003, 10202007, and 10212009). One death (subject 10212009) occurred in a subject randomized to the Neoral arm, but this subject had crossed over to Prograf+MMF on day 128, so was off Neoral for 3 months before developing the life-threatening diverticulitis. Subject 10202007's death from strongyloidosis was unusual because only the Prograf arm had subjects (4) develop strongyloidosis, an intestinal parasite.

In the MR4 arm, there were 3 deaths due to overimmunosuppression (00292003, 00712002, 00512005). Study subject 00292003's death was listed as cardiac and respiratory death. However, review of the case report form and death narrative suggests that subject died from an infection: on day 41, the subject developed sepsis which resolved on day 44. By day 48, however, the subject developed diarrhea and was diagnosed with gastroenteritis on day 51 until day 57. The subject developed hypotension on day 48 and died of cardio-respiratory arrest on day 57. The sequence of events found in the case report form and narrative are consistent with the clinical picture of sepsis leading to cardio-respiratory arrest.

In the Neoral arm, there were two deaths attributable to overimmunosuppression (01812009, 10211002). Subject 01812009 died of encephalitis, but no infectious cause for the encephalitis was ever determined. Study subject 10211002 died of miliary TB. Although the subject was initially randomized to the Prograf arm, the subject crossed over to Neoral on day 42; therefore, she was on Neoral for about 3 months before dying from miliary TB. There was a third subject (10222007 who randomized to the Neoral arm) but never received a dose of Neoral. This subject, however, received 4 days of MMF (at doses ranging from 1gram to 2 grams/days) before developing an intestinal perforation, sepsis, and death.

Evaluation of the differences in the deaths may not have appeared clinically significant at first

glance. If the deaths had been primarily due to heart attacks, strokes, pulmonary emboli, etc, a difference of 9 deaths versus 5 deaths could be explained by slight differences in the baseline characteristics of the study subjects. However, the difference in mortality between Prograf and Neoral was driven exclusively by events due to overimmunosuppression (infections and malignancy). Although the Applicant acknowledges the number of infection-driven deaths (see p. 74 of the Summary of Clinical Safety Report), the Applicant believed that "[t]here were no obvious, clinically relevant differences with respect to cause of death among the three treatment groups." (see page 36 of the Summary of Clinical Safety Report).

7.1.1.1 No Role of BCAR Treatment on Infection Related Deaths

One possible justification given for overimmunosuppressing patients is that the treatment for BCAR places the patient at greater risk of infection and infection-related deaths. In order to explore whether the treatment of BCAR was related to the immunosuppression-related deaths, the acute rejection rates of those subjects who died from events related to overimmunosuppression at 2 years post-transplantation was evaluated. Table 25, provided by the Statistical Reviewer, LaRee Tracy, summarizes the acute rejection rates seen in these study subjects.

Table 25: Acute Rejection Prior to Deaths in Subjects Identified as due to Overimmunosuppression

PT ID	Acute Rejections Prior to Death**	Day of Last BCAR	Day of Death
Prograf+MMF			
00352003	0	NA	123
01652002	0	NA	69
04062008	1 (Grade 1-not treated)	231	415
07502001	0	NA	374
10181003	0	NA	218
10202007	0	NA	57
10212009	3 (1^{st} on day 17, 2^{nd} considered ongoing on day 26, 3^{rd} considered ongoing on 118. Local assessment read as Grade 1A & B, but central assessment read as no acute rejection. Subject crossed over from Neoral to Prograf on day 129.)	118 (last treatment for BCAR was day 30 - steroids)	222
MR4+MMF			
00292003	0	NA	57
00512005	0	NA	53
00712002	0	NA	663
Neoral+MMF			
01812009	0	NA	371
10211002	0	NA	142

** confirmed BCAR via local assessment (obtained from rej.xpt dataset in 120 update submission).

Only 2 subjects had BCAR prior to dying from immunosuppression related events, subjects 04062008 and 10212009. However, treatment for BCAR did not appear to be associated with the events that led to the subjects' deaths.

Subject 04062008 experienced BCAR on day 231, but never received therapy for his Grade 1 BCAR; therefore, the treatment for BCAR could not have contributed to his death from septic shock. This subject did stop Prograf on day 310 and MMF on day 321, but the subject developed a wound infection and wound dehiscience on day 316. According to the case report, the wound infection began on day 316 and continued until death from septic shock on day 415. The close proximity of the development of the wound infection with the use of Prograf and MMF suggests that these immunosuppressants cannot be ruled out as contributing to the development of the wound infection that persisted until death and may have contributed to the death from septic shock.

Subject 10212009 was originally randomized to the Neoral arm. The case report suggests that renal function was never very good after transplantation and the subject had numerous biopsies while on Neoral. The local pathologist read the biopsies as Grade 1A and B acute rejection although a blinded, central assessment never found acute rejection. The last day that the subject received therapy for acute rejection was day 30, and he received steroids. On day 129, the subject switched to the Prograf+MMF. The case report did not show any evidence of further treatment for acute rejection after switching to Prograf+MMF. The patient's death on day 222 was over 6 months after the last treatment for BCAR.

Reviewer's Comments: Subjects in the Neoral+MMF arm and the MR4+MMF arms had the most episodes of acute rejection, but treatment for the BCAR did not result in any deaths due to infection or overimmunosuppression.

The overall low acute rejection rates in this study suggest that patients are being overimmunosuppressed. In assessing the risks of infections/overimmunosuppression from BCAR therapy versus chronic overimmunosuppression, the results from Study 158 suggest that chronic overimmunosuppression increases the risk of mortality compared with BCAR therapy. In clinical practice, if a patient has to be treated for acute rejection, the patient is likely to have more careful monitoring of infections and other possible adverse events associated with the treatment. If the patient is overimmunosuppressed and sent home (to the local nephrologist/primary care physician), the patient is less likely to be appropriately monitored for infections, resulting catastrophic and life-threatening infections.

7.1.1.2 Deaths Associated with GI Events

In addition to the infection/immunosuppression drive deaths, four deaths (00432002, 00292003, 10212009, and 10222007) in the 3 arms appear to be related to gastrointestinal complications, suggesting a relationship between some of the deaths and the known toxicity of MMF. Three of the subjects (00432002, 00292003, and 10212009) were on tacrolimus and MMF 2 grams (or greater)/day when they developed the gastrointestinal hemorrhage/disorder/perforation that led to death. Subect 10222007 had randomized to the Neoral+MMF arm, but was receiving only MMF 2 grams when she developed intestinal ischemia, septic shock, and death. In this patient, the absence of Neoral likely resulted in higher systemic exposures of MPA.

Reviewer's Comments: In addition to the greater risk of death from overimmunosuppression, higher systemic exposures of MPA may have contributed to 4 deaths in the study. All four of the subjects described as having GI precipitated deaths (see above) were on MMF 2 grams or greater without cyclosporine when the GI events occurred, leading to the deaths. Therefore, it would be reasonable to conclude that the GI toxicities seen with MMF are not benign and efforts should be made to prevent these adverse events rather than respond to the GI adverse events after they begin.

7.1.2 Other Serious Adverse Events

Table 26: Summary of Treatment-Emergent Serious Adverse Events Not Resulting in Death Occurring ≥ 1% in Any Treatment Group

MedDRA (v. 6.1) System Organ Class Preferred Term	Treatment Group		
	Prograf (n = 212)	MR4 (n = 214)	Neoral (n = 212)
All Systems			
Any Adverse Event	109 (51.4%)	97 (45.3%)	110 (51.9%)
Infections and Infestations			
Cytomegalovirus Infection	12 (5.7%)	10 (4.7%)	11 (5.2%)
Urinary Tract Infection	7 (3.3%)	8 (3.7%)	11 (5.2%)
Human Polyomavirus Infection	4 (1.9%)	1 (0.5%)	1 (0.5%)
Urosepsis	4 (1.9%)	2 (0.9%)	2 (0.9%)
Pyelonephritis	3 (1.4%)	2 (0.9%)	2 (0.9%)
Sepsis	2 (0.9%)	3 (1.4%)	1 (0.5%)
Pneumonia	1 (0.5%)	1 (0.5%)	3 (1.4%)
Gastroenteritis	0	9 (4.2%)	1 (0.5%)
Gastrointestinal Disorders			
Diarrhea	9 (4.2%)	8 (3.7%)	3 (1.4%)
Nausea	4 (1.9%)	4 (1.9%)	2 (0.9%)
Vomiting	4 (1.9%)	5 (2.3%)	4 (1.9%)
Abdominal Pain	3 (1.4%)	1 (0.5%)	4 (1.9%)
Abdominal Strangulated Hernia	0	0	3 (1.4%)
Metabolism and Nutrition Disorders			
Dehydration	7 (3.3%)	7 (3.3%)	5 (2.4%)
Hyperglycemia	4 (1.9%)	5 (2.3%)	0
Diabetes Mellitus Inadequate Control	3 (1.4%)	1 (0.5%)	1 (0.5%)
Diabetes Mellitus	2 (0.9%)	5 (2.3%)	4 (1.9%)
Hyperkalemia	2 (0.9%)	5 (2.3%)	1 (0.5%)
Injury, Poisoning, and Procedural Complications			
Graft Dysfunction	4 (1.9%)	2 (0.9%)	2 (0.9%)
Therapeutic Agent Toxicity	4 (1.9%)	2 (0.9%)	1 (0.5%)
Investigations			
Blood Creatinine Increased	11 (5.2%)	8 (3.7%)	13 (6.1%)
Renal and Urinary Disorders			
Hydronephrosis	2 (0.9%)	1 (0.5%)	4 (1.9%)
Renal Failure Acute	2 (0.9%)	3 (1.4%)	3 (1.4%)
Hematuria	0	3 (1.4%)	4 (1.9%)
Vascular Disorders			
Deep Vein Thrombosis	5 (2.4%)	4 (1.9%)	2 (0.9%)
Hypotension	2 (0.9%)	4 (1.9%)	1 (0.5%)
Lymphocele	2 (0.9%)	1 (0.5%)	4 (1.9%)
Blood and Lymphatic System Disorders			
Anemia	3 (1.4%)	4 (1.9%)	1 (0.5%)
General Disorders and			

Administration Site Condition			
Pyrexia	3 (1.4%)	2 (0.9%)	7 (3.3%)
Chest Pain	2 (0.9%)	3 (1.4%)	0
Nervous System Disorders			
Convulsion	3 (1.4%)	1 (0.5%)	1 (0.5%)
Endocrine Disorders			
Hyperparathyroidism Tertiary	3 (1.4%)	0	0

Patient base: Full analysis set; all randomized patients who received at least one dose of study drug. Within a MedDRA system organ class, patients may have experienced more than one adverse event. The sum of the terms may exceed 100%.
All systems: Shows the number of patients with any adverse event.
Source: Table 13.5.1.5 and Appendix 14.4.4.1.

7.1.2.1 Comparisons of Serious Adverse Events

Tables 27 and 28 compare the serious adverse events among MR4, Prograf, and Neoral. As expected, the tacrolimus arms had more serious adverse events associated with diabetes. However, the higher number of serious adverse events related to GI disorders and infections was not expected.

Table 27: Serious Adverse Events in Study 02-0-158: Higher in MR4 than Neoral

MedDRA (v. 6.1) System Organ Class Preferred Term	MR4 (n=214)	Neoral (n=212)
Blood and Lymphatic System Disorders		
Anemia	4 (1.9%)	1 (0.5%)
Gastrointestinal Disorders		
Diarrhea	8 (3.7%)	3 (1.4%)
Vomiting	5 (2.3%)	4 (1.9%)
Nausea	4 (1.9%)	2 (0.9%)
General Disorders and Administration Site Conditions		
Chest Pain	3 (1.4%)	0
Infections and Infestations		
Gastroenteritis	9 (4.2%)	1 (0.5%)
Sepsis	3 (1.4%)	1 (0.5%)
Metabolism and Nutrition Disorders		
Dehydration	7 (3.3%)	5 (2.4%)
Diabetes Mellitus	5 (2.3%)	4 (1.9%)
Hyperkalaemia	5 (2.3%)	1 (0.5%)
Hyperglycemia	5 (2.3%)	0
Vascular Disorders		
Deep Vein Thrombosis	4 (1.9%)	2 (0.9%)
Hypotension	4 (1.9%)	1 (0.5%)

Full analysis set: all patients who received at least one dose of study drug.
Within a MedDRA class, patients may have reported more than one adverse event. The sum of the terms by organ class may exceed 100%. Serious adverse events in this table occurred in ≥ 1% of patients in the MR4 arm and had an incidence greater than that in the Neoral arm.
Source: Study 02-0-158, Table 13.5.1.5, Table 7 Summary of Clinical Safety

Table 28: Serious Adverse Events in Study 02-0-158: Higher in Prograf than Neoral

MedDRA (v. 6.1) System Organ Class Preferred Term	Prograf (n=212)	Neoral (n=212)
Blood and Lymphatic System Disorders		
Anemia	3 (1.4%)	1 (0.5%)
Endocrine Disorders		
Hyperparathyroidism tertiary	3 (1.4%)	0
Gastrointestinal Disorders		
Diarrhea	9 (4.2%)	3 (1.4%)
Nausea	4 (1.9%)	2 (0.9%)
Infections and Infestations		
Cytomegalovirus Infection	12 (5.7%)	11 (5.2%)
Human Polyomavirus Infection	4 (1.9%)	1 (0.5%)
Sepsis	4 (1.9%)	1 (0.5%)
Urosepsis	4 (1.9%)	2 (0.9%)
Pyelonephritis	3 (1.4%)	2 (0.9%)
Strongyloidiasis	3 (1.4%)	0
Injury, Poisoning and Procedural Complications		
Graft Dysfunction	4 (1.9%)	2 (0.9%)
Therapeutic Agent Toxicity	4 (1.9%)†	1 (0.5%)‡
Metabolism and Nutrition Disorders		
Dehydration	7 (3.3%)	5 (2.4%)
Hyperglycemia	4 (1.9%)	0
Diabetes Mellitus Inadequate Control	3 (1.4%)	1 (0.5%)
Nervous System Disorders		
Convulsion	3 (1.4%)	1 (0.5%)
Respiratory, Thoracic and Mediastinal Disorders		
Pulmonary Embolism	3 (1.4%)	2 (0.9%)
Vascular Disorders		
Deep Vein Thrombosis	5 (2.4%)	2 (0.9%)

Full analysis set: all patients who received at least one dose of study drug. Within a MedDRA class, patients may have reported more than one adverse event. The sum of the terms by organ class may exceed 100%. Serious adverse events in this table occurred in ≥ 1% of patients in the Prograf arm and had an incidence greater than that in the Neoral arm.
† Includes the following Investigator descriptions: Prograf toxicity (2), tacrolimus toxicity (1), FK toxicity (1). ‡ Includes the following Investigator descriptions: cyclosporine neurotoxicity (1).
Source: Study 02-0-158, Table 13.5.1.5, Table 8 Summary of Clinical Safety

7.1.2.2 Severe or Life-Threatening Treatment-Emergent Adverse Events

Table 29: Summary of Severe or Life-Threatening Treatment-Emergent Adverse Events with an Incidence ≥ 1% in Any Treatment Group

MedDRA (v. 6.1) System Organ Class Preferred Term	Treatment Group		
	Prograf (n = 212)	MR4 (n = 214)	Neoral (n = 212)
All Systems			
Any Adverse Event	67 (31.6%)	71 (33.2%)	68 (32.1%)
Gastrointestinal Disorders			
Diarrhea	5 (2.4%)	3 (1.4%)	3 (1.4%)
Nausea	3 (1.4%)	1 (0.5%)	1 (0.5%)
Abdominal pain	1 (0.5%)	3 (1.4%)	2 (0.9%)
Infections and Infestations			
Sepsis	4 (1.9%)	1 (0.5%)	0
Cytomegalovirus Infection	2 (0.9%)	3 (1.4%)	0
Urinary Tract Infection	1 (0.5%)	1 (0.5%)	3 (1.4%)
Gastroenteritis	0	5 (2.3%)	0
Injury, Poisoning, and Procedural Complications			
Graft Dysfunction	4 (1.9%)	3 (1.4%)	3 (1.4%)
Post Procedural Pain	1 (0.5%)	2 (0.9%)	3 (1.4%)
Metabolism and Nutrition Disorders			
Hyperglycemia	2 (0.9%)	4 (1.9%)	1 (0.5%)
Blood and Lymphatic System Disorders			
Anemia	5 (2.4%)	3 (1.4%)	3 (1.4%)
Vascular Disorders			
Hypertension	3 (1.4%)	2 (0.9%)	3 (1.4%)
Investigations			
Blood Creatinine Increased	0	2 (0.9%)	3 (1.4%)
Nervous System Disorders			
Headache	0	5 (2.3%)	4 (1.9%)
General Disorders and Administration Site Condition			
Edema Peripheral	0	3 (1.4%)	2 (0.9%)

Patient base: Full analysis set; all randomized patients who received at least one dose of study drug.
Within a MedDRA system organ class, patients may have experienced more than one adverse event. The sum of the terms may exceed 100%.
All systems: Shows the number of patients with any adverse event.
Source: Table 13.5.1.4.

Although "severe and life-threatening" have not been defined in regulations or guidance, Table 29 provided a different way of examining the intensity of the adverse events seen. When using the Applicant's definition of "severe and life-threatening," there were few differences between Prograf and MR4, except for the adverse events of gastroenteritis and headache.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Table 10 in Section 6.1.4.2 summarizes the disposition of all the study subjects, including those that left the study or crossed over to another study arm. Table 30 is a subset of Table 26.

Table 30: Summary of Subject Dispositions

Final Disposition (Full Analysis Set)				
Disposition	**Prograf (n = 212)**	**MR4 (n = 214)**	**Neoral (n = 212)**	**(n = 638)**
Completed 1-year of Randomized Therapy	179 (84.4%)	183 (85.5%)	151 (71.2%)	513 (80.4%)
Discontinued Randomized Therapy	33 (15.6%)	31 (14.5%)	61 (28.8%)	125 (19.6%)
Adverse Event	23 (10.8%)	19 (8.9%)	37 (17.5%)	79 (12.4%)
Rejection	0	1 (0.5%)	16 (7.5%)	17 (2.7%)
Non-compliance	4 (1.9%)	2 (0.9%)	5 (2.4%)	11 (1.7%)
Graft Failure	3 (1.4%)	2 (0.9%)	1 (0.5%)	6 (0.9%)
Withdrawal of Consent	0	4 (1.9%)	1 (0.5%)	5 (0.8%)
Lost to Follow-up	1 (0.5%)	0	0	1 (0.2%)
Other §	2 (0.9%)	3 (1.4%)	1 (0.5%)	6 (0.9%)

Reviewer's Comments: As discussed in Section 6.1.3.2, the biases of this open-label study specifically designed to permit subjects to easily leave one treatment arm for another and also gave subjects incentive to stay in the MR4 arm, made it extremely difficult to assess the true importance of the higher cross-over of subjects in the Neoral arm compared with subjects in the Prograf and MR4 arms. When comparing crossovers due to adverse events and rejection, the Neoral arm appeared to have more subjects leave randomized therapy for those reasons compared with the Prograf and the MR4 arms despite not having more adverse events compared with Prograf or more acute rejection episodes compared with MR4.

7.1.3.2 Adverse events associated with dropouts

Evaluation of treatment emergent serious adverse events that led to discontinuation suggests very little difference between the three study arms. MR4 arm had fewer of these events, but there was strong incentive for subjects in the MR4 arm to not discontinue even when they experienced serious adverse events because they would receive free MR4 for up to 3 years after transplantation [see Section 6.1.3.2]. The Prograf and Neoral arms had the same incidence of serious adverse events leading to discontinuation even though the Neoral arm many more subjects discontinue randomized therapy (61 vs. 33). As discussed in the efficacy section, the dropout rate was likely influenced by biases in the clinical practice of kidney transplantation in the United States favoring the use of tacrolimus+MMF as the preferred regimen. Table 31 lists the treatment emergent serious adverse events that led to discontinuation.

Table 31: Incidence of Treatment Emergent Serious Adverse Events that Led to Discontinuation

MedDRA (v. 6.1) System Organ Class Preferred Term	Prograf	MR4	Neoral
All Systems			
Any AE	17 (8.0%)	9 (4.2%)	16 (7.5%)
Blood and Lymphatic System Disorders			
Any AE	3 (1.4%)	0	0
Anemia	1 (0.5%)	0	0
Thrombocytopenia	1 (0.5%)	0	0
Thrombotic Microangiopathy	1 (0.5%)	0	0
Infections and Infestations			
Any AE	2 (0.9%)	3 (1.4%)	1 (0.5%)
Human Polyomavirus Infection	1 (0.5%)	0	0
Strongyloidiasis	1 (0.5)	0	0
Choriomeningitis Lymphocytic	0	1(0.5%)	0
E. Coli Urinary Tract Infection	0	1 (0.5%)	0
Gastroenteritis	0	1 (0.5%)	0
Streptococcal Bacteremia	0	0	1 (0.5%)
Renal and Urinary Disorders			
Any AE	2 (0.9%)	2 (0.9%)	4 (1.9%)
Renal Impairment	1 (0.5%)	0	1 (0.5%)
Renal Vein Thrombosis	1 (0.5%)	1 (0.5%)	1 (0.5%)
Azotemia	0	1 (0.5%)	0
Dysuria	0	0	1 (0.5%)
Nephropathy Toxic	0	0	1 (0.5%)
Renal Artery Thrombosis	0	0	1 (0.5%)
Respiratory, Thoracic and Mediastinal Disorders			
Any AE	2 (0.9%)	0	1 (0.5%)
Lung Disorder	1 (0.5%)	0	0
Pulmonary Embolism	1 (0.5%)	0	1 (0.5%)
Cardiac Disorders			
Any AE	1 (0.5%)	1 (0.5%)	3 (1.4%)
Cardiac Arrest	1 (0.5%)	0	1 (0.5%)
Cardio-Respiratory Arrest	0	1 (0.5%)	0
Myocardial Infarction	0	0	2 (0.9%)
Gastrointestinal Disorders	0	0	0
Any AE	1 (0.5%)	2 (0.9%)	0
Small Intestinal Obstruction	1 (0.5%)	0	0
Acute Abdomen	0	1 (0.5%)	0
Nausea	0	1 (0.5%)	0
Injury, Poisoning and Procedural Complications			
Any AE	1 (0.5%)	2 (0.9%)	3 (1.4%)
Subdural Hematoma	1 (0.5%)	0	0
Drug Toxicity	0	0	2 (0.9%)
Graft Dysfunction	0	0	1 (0.5%)
Incision Site Complication	0	1 (0.5%)	0
Therapeutic Agent Toxicity	0	1 (0.5%)	0
Investigations			
Any AE	1 (0.5%)	0	2 (0.9%)

MedDRA (v. 6.1) System Organ Class Preferred Term	Prograf	MR4	Neoral
Blood Creatinine Increased	1 (0.5%)	0	0
Urine Output Decreased	0	0	2 (0.9%)
Metabolism and Nutrition Disorders			
Any AE	1 (0.5%)	1 (0.5%)	0
Diabetes Mellitus	1 (0.5%)	0	0
Diabetes Mellitus Inadequate Control	0	1 (0.5%)	0
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polys)			
Any AE	1 (0.5%)	0	1 (0.5%)
Metastatic Renal Cell Carcinoma	1 (0.5%)	0	0
Lymphoproliferative Disorder	0	0	1 (0.5%)
Social Circumstances			
Any AE	1 (0.5%)	0	0
Murder	1 (0.5%)	0	0
Surgical and Medical Procedures			
Any AE	1 (0.5%)	0	0
Nephrectomy	1 (0.5%)	0	0
Musculoskeletal and Connective Tissue Disorders			
Any AE	0	1 (0.5%)	0
Arthralgia	0	1 (0.5%)	0
Nervous System Disorders			
Any AE	0	0	1 (0.5%)
Encephalitis	0	0	1 (0.5%)
Vascular Disorders			
Any AE	0	0	1 (0.5%)
Hypotension	0	0	1 (0.5)

Full Analysis Set: All Randomized subjects who received at least one dose of study medication.
Within a MedDRA system organ class, a patient may experience more than one adverse event. The sum of the terms may exceed 100%.
All Systems: shows the number of patients with any adverse event.
Source: Table 13.5.1.6, Study 158 Report

7.1.3.3 Other significant adverse events

Organ transplant recipients experience many adverse events that would be considered significant adverse events according to ICH definition because of the nature of the surgical procedure and the level of immunosuppression. Therefore, the tables of serious adverse events that did not lead to death (see table above) adequately characterizes the types of risks that would be seen with the use of tacrolimus and MR4.

7.1.4 Other Search Strategies

Please see Section 7.1.5.6 which includes additional analyses performed.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

An adverse event was defined as any reaction, side effect, or other untoward medical occurrence, regardless of relationship to study drug, that occurred during the conduct of the clinical study.

- Clinically significant adverse changes in clinical status, ECGs, x-rays, routine laboratory studies, or physical examinations were considered adverse events.
- A treatment-emergent adverse event was defined as any adverse event that occurred after the completion of the transplant procedure. Any infectious adverse events that occurred up to 28 days following the last study drug dose were to be captured on the patient's CRF.
- Adverse events resulting in death were to be captured on the patient's CRF up to 28 days after the last dose of study drug.
- All other events were to be captured up to 10 days following the last dose of study drug.
- A serious adverse event was defined as any experience that resulted in death, was life threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, congenital anomaly or birth defect, or was considered an important medical event.
- Hospitalization, or prolongation of hospitalization, for routine surgical procedures such as protocol biopsies was not considered a serious adverse event. The term "severe" was used to grade intensity and was not synonymous with the term "serious".
- Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 6.1. The causal relationships for all adverse events were categorized as definite, probable, possible, unlikely, or not related to study drug. The causal relationship of adverse events to primary immunosuppressive (Prograf, MR4, or Neoral) or MMF was to be assessed by the investigator. Adverse event data are presented as related to study drug overall (considered by the investigator to have a possible, probable, or definite relationship to primary study drug and/or MMF), related to primary study drug only, and related to both primary study drug and MMF.

Adverse Events of Special Interest were collected to better identify and categorize the adverse events

Infections

To be considered an adverse event of special interest, an infection was defined as:

- Positive culture results obtained from specimens of sterile sites; and,
- Pathologic identification of microbial agents; or,
- Clinically significant serologic changes related to clinical symptoms; or,
- Typical clinical presentation of disease or infection documented by the investigator or appropriate consultant that requires treatment with an antimicrobial agent other than prophylaxis.
- In the event a patient experienced a bacterial, viral, or fungal disease, administration of an appropriate antimicrobial agent was to be initiated. Whether or not the patient was to continue taking prescribed study drug was left to the discretion of the investigator.

Glucose Intolerance

Glucose intolerance was monitored throughout the study. The following assessments were to be made:

- Fasting plasma glucose;
- HbA1C;
- Insulin use ≥ 30 days; and,
- Oral hypoglycemic use.
- All medications used to treat glucose intolerance were to be recorded.

Gastrointestinal Disturbances

- Gastrointestinal disturbances were to be captured on the CRF according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC).
- Gastrointestinal events which qualified under the NCI-CTC as Grade 1, 2, or 3 were to be considered mild, moderate, or severe, respectively.
- The accompanying intensity of each qualifying event was to be captured on the CRF.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The Applicant used MedDRA 6.1 to categorize adverse events and most of the events appeared to be appropriate. There are a few categories where the higher level associated may not have been appropriate. The adverse event of "hirsutism" is categorized as an Endocrine Disorder and the majority of subjects who developed hirsutism were in the Neoral arm. Neoral is known to cause hirsutism, but the pathophysiological basis for the hirsutism does not appear to be endocrine driven. Therefore, categorizing it as an Endocrine Disorder would not be appropriate.

7.1.5.3 Incidence of common adverse events

7.1.5.4 Common adverse event tables

A 5% cutoff was chosen to display commonly occurring adverse events, resulting in approximately 10 subjects (out of 212 subjects per arm) experiencing the adverse event. This higher rate was chosen because the sample size was only 212 per arm and transplant patients generally experience numerous adverse events post-transplantation because of the surgical procedure and the long duration of the clinical study. Table 32 summarizes the common adverse events >5%.

Table 32: Summary of Common Adverse Events > 5%

MedDRA (v. 6.1) System OrganClass Preferred Term	Prograf N=212 (%)	MR4 N=214 (%)	Neoral N=212 (%)	Prograf vs. Neoral p-value
All Systems				
Any AE	212	214	210	0.4988
Gastrointestinal Disorders				
Any AE	190 (89.6)	188 (87.9)	185 (87.3)	0.5438
Diarrhea	94 (44.3)	97 (45.3)	54 (25.5)	<0.0001
Nausea	82 (38.7)	90 (42.1)	99 (46.7)	0.1160
Constipation	76 (35.8)	89 (41.6)	87 (41)	0.3181
Vomiting	54 (25.5)	56 (26.2)	52 (24.5)	0.9107
Dyspepsia	38 (17.9)	32 (15.0)	32 (15.1)	0.5132
Abdominal Pain	27 (12.7)	29 (13.6)	38 (17.9)	0.1773
Flatulence	22 (10.4)	15 (7.0)	16 (7.5)	0.3955
Abd Pain Upper	21 (9.9)	16 (7.5)	18 (8.5)	0.7372
Abdominal Distention	16 (7.5)	11 (5.1)	18 (8.5)	0.8583
Loose Stools	15 (7.1)	11 (5.1)	4 (1.9)	0.0166
GERD	5 (2.4)	10 (4.7)	13 (6.1)	0.0892
Hemorrhoids	5 (2.4)	12 (5.6)	6 (2.8)	1.0000
Injury, Poisoning and Procedural Complications				
Any AE	163 (76.9)	148 (69.2)	156 (73.6)	0.4997
Post Procedural Pain	61 (28.8)	63 (29.4)	58 (27.4)	0.8289
Incision Site Complication	60 (27.8)	44 (20.6)	49 (23.1)	0.2664
Graft Dysfunction	50 (23.6)	39 (18.2)	37 (17.5)	0.1487
Complications of Transplant Surgery	15 (7.1)	7 (3.3)	13 (6.1)	0.8453
Therapeutic Agent Toxicity	12 (5.7)	7 (3.3)	10 (4.7)	0.8272
Post Procedural Discharge	7 (3.3)	11 (5.1)	13 (6.1)	0.2516
Metabolism and Nutrition Disorders				
Any AE	162 (76.4)	170 (79.4)	170 (80.2)	0.4096
Hypomagnesemia	60 (28.3)	55 (25.7)	47 (22.2)	0.1795
Hypophosphatemia	59 (27.8)	51 (23.8)	45 (21.2)	0.1420
Hyperkalemia	54 (25.5)	47 (22.0)	41 (19.3)	0.1619
Hyperglycemia	45 (21.2)	41 (19.2)	32 (15.1)	0.1302
Hyperlipidemia	37 (17.5)	35 (16.4)	52 (24.5)	0.0946
Hypokalemia	34 (16.0)	34 (15.9)	37 (17.5)	0.7949
Diabetes Mellitus	24 (11.3)	30 (14.0)	14 (6.6)	0.1250
Dehydration	20 (9.4)	16 (7.5)	9 (4.2)	0.0527
Hypocalcemia	18 (8.5)	18 (8.4)	28 (13.2)	0.1593
Fluid Overload	17 (8.0)	10 (4.7)	12 (5.7)	0.4420
Metabolic Acidosis	14 (6.6)	17 (7.9)	13 (6.1)	1.0000
Hypercholesterolemia	10 (4.7)	8 (3.7)	16 (7.5)	0.3115
Dyslipidemia	4 (1.9%)	12 (5.6)	6 (2.8)	0.7509
Infections and Infestations				
Any AE	146 (68.9)	148 (69.3)	123 (58.0)	0.0263
Urinary Tract Infection	54 (25.5)	34 (15.9)	47 (22.2)	0.4940

MedDRA (v. 6.1) System OrganClass Preferred Term (continued)	Prograf N=212 (%)	MR4 N=214 (%)	Neoral N=212 (%)	Prograf v Neoral p-value
Upper Respiratory Tract Infection	24 (11.3)	27 (12.6)	29 (13.7)	0.5572
Cytomegalovirus Infection	17 (8.0)	15 (7.0)	16 (7.5)	1.0000
Oral Candidiasis	9 (4.2)	15 (7.0)	13 (6.1)	0.5121
Sinusitis	7 (3.3)	15 (7.0)	5 (2.4)	0.7711
Gastroenteritis	1 (0.5)	14 (6.5)	4 (1.9)	0.3720
General Disorders & Administration Site Conditions				
Any AE	139 (65.6)	139 (65.0)	145 (68.4)	0.6057
Edema Peripheral	74 (34.9)	76 (35.5)	97 (45.8)	0.0292
Edema	28 (13.2)	19 (8.9)	25 (11.8)	0.7692
Pyrexia	25 (11.8)	24 (11.2)	35 (16.5)	0.2095
Asthenia	23 (10.8)	17 (7.9)	23 (10.8)	1.0000
Fatigue	23 (10.8)	34 (15.9)	26 (12.3)	0.7615
Chest Pain	17 (8.0)	22 (10.3)	12 (5.7)	0.4420
Pain	11 (5.2)	14 (6.5)	15 (7.1)	0.5444
Anasarca	8 (3.8)	12 (5.6)	5 (2.4)	0.5750
Nervous System Disorders				
Any AE	134 (63.2)	135 (63.1)	117 (55.2)	0.1137
Tremor	73 (34.4)	75 (35)	42 (19.8)	0.0010
Headache	51 (24.1)	46 (21)	52 (24.5)	1.0000
Dizziness	27 (12.7)	21 (9.8)	24 (11.3)	0.7655
Hypoesthesia	5 (2.4)	10 (4.7)	11 (5.2)	0.2013
Paresthesia	3 (1.4)	12 (5.6)	13 (6.1)	0.0189
Blood and Lymphatic System Disorder				
Any AE	105 (49.5)	109 (50.9)	97 (45.3)	0.4365
Anemia	64 (30.2)	72 (33.6)	59 (27.8)	0.6687
Leukopenia	33 (15.6)	35 (16.4)	25 (11.8)	0.3225
Polycythemia	13 (6.1)	12 (5.6)	9 (4.2)	0.5121
Leukocytosis	4 (1.9)	12 (5.6)	9 (4.2)	0.2593
Vascular Disorders				
Any AE	105 (49.5)	109 (50.9)	111 (52.4)	0.6272
Hypertension	68 (32.1)	64 (29.9)	74 (34.9)	0.6069
Hypotension	18 (8.5)	23 (10.7)	20 (9.4)	0.8652
Orthostatic Hypotension	10 (4.7)	15 (7.0)	5 (2.4)	0.2929
Musculoskeletal and Connective Tissue Disorders				
Any AE	103 (48.6)	110 (51.4)	115 (54.2)	0.2851
Back Pain	27 (12.7)	32 (15.0)	30 (14.2)	0.7760
Pain in Extremity	27 (12.7)	27 (12.6)	26 (12.3)	1.0000
Arthralgia	26 (12.3)	27 (12.6)	28 (13.2)	0.8843
Muscle Cramp	17 (8.0)	20 (9.3)	23 (10.8)	0.4064
Osteopenia	12 (5.7)	13 (6.1)	13 (6.1)	1.0000
Respiratory, Thoracic and Mediastinal Disorders				
Any AE	93 (43.9)	91 (42.5)	86 (40.6)	0.5552
Cough	27 (12.7)	16 (7.5)	21 (9.9)	0.4437

MedDRA (v. 6.1) System OrganClass Preferred Term (continued)	Prograf N=212 (%)	MR4 N=214 (%)	Neoral N=212 (%)	Prograf vs. Neoral p-value
Dyspnea	24 (11.3)	29 (13.6)	28 (13.2)	0.6572
Pharyngolaryngeal Pain	15 (7.1)	17 (7.9)	11 (5.2)	0.5444
Dyspnea Exertional	12 (5.7)	10 (4.7)	8 (3.8)	0.4929
Skin and Subcutaneous Tissue Disorders				
Any AE	92 (43.4)	98 (45.8)	78 (36.8)	0.1976
Pruritus	22 (10.4)	28 (13.1)	16 (7.5)	0.3955
Alopecia	15 (7.1)	14 (6.5)	4 (1.9)	0.0166
Acne	13 (6.1)	18 (8.4)	22 (10.4)	0.1572
Rash	11 (5.2)	11 (5.1)	5 (5.2)	0.2013
Psychiatric Disorders				
Any AE	89 (42.0)	87 (40.7)	77 (36.3)	0.2737
Insomnia	64 (30.2)	55 (25.7)	45 (21.2)	0.0451
Anxiety	24 (11.3)	27 (12.6)	22 (10.4)	0.8760
Depression	13 (6.1)	12 (5.6)	11 (5.2)	0.8340
Renal and Urinary Disorders				
Any AE	81 (38.2)	79 (36.9)	106 (50.0)	0.0187
Dysuria	23 (10.8)	15 (7.0)	20 (9.4)	0.7480
Hematuria	18 (8.5)	19 (8.9)	23 (23)	0.5114
Proteinuria	5 (2.4)	14 (6.5)	11 (5.2)	0.2013
Cardiac Disorders				
Any AE	39 (18.4)	37 (17.3)	38 (17.9)	1.0000
Tachycardia	12 (5.7)	11 (5.1)	10 (4.7)	0.8272
Reproductive System and Breast Disorders				
Any AE	34 (16.0)	33 (15.4)	37 (17.5)	0.7949
Eye Disorders				
Any AE	25 (11.8)	30 (14.0)	24 (11.3)	1.0000
Endocrine Disorders				
Any AE	15 (7.1)	30 (4.2)	26 (12.3)	0.0993
Hirsutism	0 (0.0)	0 (0.0)	18 (8.5)	<0.0001
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)				
Any AE	13 (6.1)	9 (4.2)	12 (5.7)	1.0000

Full Analysis Set: All randomized patients who received at least one dose of the study medication. Within a MedDRA system organ class, a patient may experience more than one adverse event. The sum of the terms may exceed 100%.
All Systems: Shows the number of patients with any adverse events
(1) P-value is from a Fisher's Exact Test (2-tailed).
Source: Table 14.2.2.1 Study 158 Report

Reviewer's Comments: Most of the adverse events over the course of the one-year clinical study were expected. However, the higher rates of adverse events associated with MMF toxicity in the tacrolimus arms was not expected. Although subjects in the Prograf and MR4 arms decreased their doses of MMF to a mean dose of approximately 1500 mg/day, these subjects still experienced more adverse events associated with MMF than subjects in the Neoral arm such as diarrhea, loose stools, leukopenia, anemia, and infections. Not surprising, subjects in the tacrolimus arms also had a higher incidence of "orthostatic hypotension" and "dehydration" which may have been a consequence of the severity of the diarrhea, loose stools, and gastroenteritis. The difference in these adverse events are likely due to the higher exposures (despite lower doses of MMF) of MPA experienced by subjects in the tacrolimus arms compared with the cyclosporine arm.

The subjects in the MR4 arm had significantly more gastroenteritis compared with the subjects in Prograf. Although the Applicant proposes that the higher gastroenteritis is due to the MMF, both arms had comparable exposures of MMF. The difference may have been due to a higher diagnosis rate in the MR4 arm compared with the Prograf arm. In order to be categorized as having gastroenteritis, the subject required a positive culture or laboratory test documenting an infectious agent; therefore, differences could exist if there are biases in the investigation for an infectious etiology.

MR4 versus Neoral

There were no significant differences between the MR4 and the Neoral arms in study subjects ≥ 65 years. Study subjects 16 to 64 years of age in the MR4 arm compared with those in the Neoral arm had a significantly ($p \leq 0.05$, Fisher's exact test) higher incidence of

- diarrhea (46.3% versus 24.5%)
- tremor (34.7% versus 19.8%)
- diabetes mellitus (13.2% versus 6.3%)
- chest pain (11.6% versus 5.2%)
- sinusitis (7.4% versus 2.6%)
- gastroenteritis (7.4% versus 1.6%)
- alopecia (6.8% versus 2.1%)
- blood phosphorous decreased (5.8% versus 1.6%)
- pruritus generalized (2.6% versus 0)
- dysphagia (2.6% versus 0)

and a lower incidence of

- hirsutism (0 versus 8.3%)
- gingival hyperplasia (0.5% versus 4.2%)
- hydronephrosis (0.5% versus 4.2%)
- white blood cell count decreased (0 versus 3.1%).

Reviewer's Comments: Based on the trends seen in the list of incidence of common adverse events, the lower incidence of "white blood cell count decreased" may be a result of an anomaly in categorization because the MR4 arm actually had a higher incidence of leukopenia.

Prograf versus Neoral

Study subjects ≥ 65 years in the Prograf arm had a significantly ($p \leq 0.05$, Fisher's exact test) higher incidence of hyperglycemia compared with those in the Neoral/MMF group (34.8% versus 5.0%).

Study subjects 16 to 64 years of age in the Prograf arm compared with those in the Neoral arm had a significantly ($p \leq 0.05$, Fisher's exact test) higher incidence of

- diarrhea (45.0% versus 24.5%)
- tremor (33.3% versus 19.8%)
- insomnia (31.2% versus 20.8%)
- alopecia (7.4% versus 2.1%)
- loose stools (7.4% versus 1.6%)

and a lower incidence of

- hirsutism (0 versus 8.3%)
- paresthesia (1.6% versus 6.3%)
- hyponatremia (0.5% versus 4.7%)
- gingival hyperplasia (0 versus 4.2%)

7.1.5.5 Identifying common and drug-related adverse events

7.1.5.5.1 Calcineurin Inhibitor Associated Adverse Events

There are number of adverse events commonly associated with CNI exposure and toxicities. Table 33 summarizes these adverse events, comparing the rates in tacrolimus versus cyclosporine.

Table 33: Summary of CNI Adverse Events

MedDRA (v. 6.1) System Organ Class Preferred Term	Prograf (n=212)	MR4 (n=214)	Neoral (n=212)
Hypertension	68 (32.1)	64 (29.9)	74 (34.9)
Hypomagnesemia	60 (28.3)	55 (25.7)	47 (22.2)
Hypophosphatemia	59 (27.8)	51 (23.8)	45 (21.2)
Hyperkalemia	54 (25.5)	47 (22.0)	41 (19.3)
Graft Dysfunction	50 (23.6)	39 (18.2)	37 (6.1)
Hyperlipidemia	37 (17.5)	35 (16.4)	52 (24.5)
Hypercholesterolemia	10 (4.7)	8 (3.7)	16 (7.5)
Dyslipidemia	4 (1.9%)	12 (5.6)	6 (2.8)
Acne	13 (6.1)	18 (8.4)	22 (10.4)
Nervous System Disorders			
Any AE	134 (63.2)	135 (63.1)	117 (55.2)
Tremor	73 (34.4)	75 (35)	42 (19.8)
Headache	51 (24.1)	46 (21)	52 (24.5)
Dizziness	27 (12.7)	21 (9.8)	24 (11.3)
Hypoesthesia	5 (2.4)	10 (4.7)	11 (5.2)
Paresthesia	3 (1.4)	12 (5.6)	13 (6.1)

Reviewer's Comments: Although the Applicant had hoped that the MR4 arm would have fewer adverse events, the subjects in the MR4 arm did not have fewer adverse events associated with the use of CNI's. It is possible that the MR4 arm appears to have the same number of adverse events as the Prograf arm because subjects in the MR4 arm had more days of exposure to MR4 than in the Prograf arm (due to the fewer crossovers, the fewer graft losses, and the fewer deaths).

7.1.5.6 Additional analyses and explorations

Adverse events of particular interest include: diabetes and glucose intolerance, hyperlipidemia, hypertension, renal function, diarrhea and loose stools, and infections.

7.1.5.6.1 Diabetes and Glucose Intolerance

Subjects in both the Prograf and MR4 arms continue to have more complications with diabetes and glucose intolerance compared with the Neoral arm despite the lower dosing and trough concentrations in the two tacrolimus arms. There were very few differences between the Prograf and the MR4 except in the reporting of glucose abnormalities in black versus non-black subjects. The black subjects had fewer total incidences (29.3% vs. 41.2%) in the MR4 arm compared with the Prograf arm. Tables 34-57 compare the parameters and adverse events associated with glucose intolerance and diabetes.

Table 34: Summary of Glucose Intolerance

Parameter	Treatment Group		
	Prograf (n = 212)	MR4 (n = 214)	Neoral (n = 212)
Days 0 through 30			
Glucose Intolerance – Composite†	89/150 (59.3%)	82/163 (50.3%)	78/152 (51.3%)
Fasting Plasma Glucose ≥ 126 mg/dL	88/150 (58.7%)	81/163 (49.7%)	78/152 (51.3%)
HbA1C ≥ 6%	0/150	0/163	0/152
Insulin Use ≥ 30 days	3/150 (2.0%)	1/163 (0.6%)	1/152 (0.7%)
Oral hypoglycemic Use	7/150 (4.7%)*	4/163 (2.5%)	1/152 (0.7%)
Any Time During Study			
Glucose Intolerance – Composite†	112/150 (74.7%)*	113/163 (69.3%)	93/152 (61.2%)
Fasting Plasma Glucose ≥ 126 mg/dL	96/150 (64.0%)*	92/163 (56.4%)	80/152 (52.6%)
HbA1C ≥ 6%	59/150 (39.3%)***	66/163 (40.5%)***	28/152 (18.4%)
Insulin Use ≥ 30 days	9/150 (6.0%)	9/163 (5.5%)	4/152 (2.6%)
Oral hypoglycemic Use	15/150 (10.0%)*	23/163 (14.1%)***	5/152 (3.3%)

Patient base: Full analysis set; all randomized patients who received at least one dose of study drug. Only patients in the at-risk population (patients with no history of diabetes at baseline) were considered in the analyses.
†Patient counted once regardless of how many glucose intolerance criteria were met. The sum of the terms may exceed 100%.
Statistical significance determined using Fisher's exact test (2-tailed) versus Neoral/MMF.
* Statistical significance at 0.05. *** Statistical significance at 0.001.
Source: Study 158 Report, Table 13.5.2.2; Table 20 Summary Clinical Safety

Table 35: Incidence of Glucose Abnormality in Blacks

MedDRA (v. 6.1) System Organ Class Preferred Term	Prograf (n = 51)	MR4 (n=41)	Neoral (n=36)	Prograf v. Neoral	MR4 v. Neoral
Glucose abnormality					
Any AE	21 (41.2%)	12 (29.3%)	10 (27.8%)	0.257	1.000
Blood Glucose Increased	0 (0.0%)	1 (2.4%)	0		1.000
Diabetes Mellitus	5 (9.8%)	7 (17.1%)	4 (11.1%)	1.000	0.528
Diabetes Mellitus Inadequate Control	1 (2.0%)	2 (4.9%)	1 (2.8%)	1.000	1.000
Diabetes Mellitus Non-Insulin Dependant	1 (2.0%)	0	0	1.000	
Diabetes with Hyperosmolarity	0	0	1 (2.8%)	0.414	0.468
Glucose Tolerance Impaired	1 (2.0%)	0	0	1.000	
Hyperglycemia	14 (27.5%)	4 (9.8%)	5 (13.9%)	0.188	0.726

Source: Table 11.4 MR4 Integrated Summary of Safety

Table 36: Incidence of Glucose Abnormality in Non-Blacks

MedDRA (v. 6.1) System Organ Class Preferred Term	Prograf (n = 161)	MR4 (n=173)	Neoral (n=176)	Prograf v. Neoral	MR4 v. Neoral
Glucose abnormality					
Any AE	56 (34.9%)	62 (35.8%)	43 (24.4%)	0.042	0.026
Blood Glucose Abnormal	0	0	1 (0.6%)	1.000	1.000
Blood Glucose Increased	5 (3.1%)	4 (2.3%)	3 (1.7%)	0.486	0.722
Diabetes Mellitus	19 (11.8%)	23 (13.3%)	10 (5.7%)	0.053	0.017
Diabetes Mellitus Inadequate Control	6 (3.7%)	3 (1.7%)	3 (1.7%)	0.319	1.000
Diabetes Mellitus Insulin Dependant	0	1 (0.6%)	1 (0.6%)	1.000	1.000
Diabetes Mellitus Non-Insulin-Dependent	0	1 (0.6%)	1 (0.6%)	1.000	1.000
Glucose Tolerance Impaired	2 (1.2%)	1 (0.6%)	0	0.227	0.496
Hyperglycemia	31 (19.3%)	37 (21.4%)	27 (15.3%)	0.387	0.167

Source: Table 11.4 MR4 Integrated Summary of Safety

Table 37: Incidence of Treatment Emergent Glucose Abnormalities in Hispanics

MedDRA (v. 6.1) Preferred Term	Prograf (n = 29)	MR4 (n=31)	Neoral (n=31)	Prograf v. Neoral	MR4 v. Neoral
Glucose abnormality					
Any AE	13 (44.8%)	10 (32.3%)	7 (22.6%)	0.100	0.570
Blood Glucose Increased	1 (3.4%)	0	0	0.483	
Diabetes Mellitus	5 (17.2%)	4 (12.9%)	3 (9.7%)	0.465	1.000
Diabetes Mellitus Inadequate Control	2 (6.9%)	1 (3.2%)	0	0.229	1.000
Diabetes Mellitus Insulin Dependant	0	0	1 (3.2%)	1.000	1.000
Hyperglycemia	7 (24.1%)	7 (22.6%)	3 (9.7%)	0.175	0.301

Source: Table 11.4 MR4 Integrated Summary of Safety

Table 38: Incidence of Treatment Emergent Adverse Events – Glucose Abnormalities in Non-Hispanics Study 158

MedDRA (v. 6.1) System Organ Class Preferred Term	Prograf (n = 183)	MR4 (n=183)	Neoral (n=181)	Prograf v. Neoral	MR4 v. Neoral
Glucose abnormality					
Any AE	64 (35%)	64 (35.0%)	46 (25.4%)	0.053	0.053
Blood Glucose Abnormal	0	0	1 (0.6%)	0.497	0.497
Blood Glucose Increased	4 (2.2%)	5	3 (1.7%)	1.000	0.724
Diabetes Mellitus	19 (10.4%)	26 (14.2%)	11 (6.1%)	0.182	0.014
Diabetes Mellitus Inadequate Control	5 (2.7%)	4 (2.2%)	4 (2.2%)	1.000	1.000
Diabetes Mellitus Insulin Dependant	0	1 (0.5%)	0	1.000	1.000
Diabetes Mellitus Non-Insulin-Dependent	1 (0.5%)	1 (0.5%)	1 (0.6%)	0.497	0.497
Diabetes with Hyperosmolarity	0	1 (0.5%)	1 (0.6%)	0.248	1.000
Glucose Tolerance Impaired	3 (1.6%)	1 (0.5%)	0	0.280	0.580
Hyperglycemia	38 (20.8%)	34 (18.6%)	29 (16.0%)	0.280	0.580

Source: Table 11.4 MR4 Integrated Summary of Safety

7.1.5.6.2 Hyperlipidemia

There was a higher incidence of hyperlipidemia in the Neoral arm compared with the Prograf and MR4 arm and more adverse events associated with lipid abnormalities.

Table 39: Summary of Select Lipid-Related Treatment-Emergent Adverse Events of Interest

MedDRA (v. 6.1) Preferred Term	Treatment Group		
	Prograf (n = 212)	MR4 (n = 214)	Neoral (n = 212)
Any Select Lipid-Related Adverse Event	54 (25.5%)*	60 (28.0%)	75 (35.4%)
Hyperlipidemia	37 (17.5%)	35 (16.4%)*	52 (24.5%)
Hypercholesterolemia	10 (4.7%)	8 (3.7%)	16 (7.5%)
Dyslipidemia	4 (1.9%)	12 (5.6%)	6 (2.8%)
Blood Cholesterol Increased	2 (0.9%)	2 (0.9%)	2 (0.9%)
Hypertriglyceridemia	2 (0.9%)	2 (0.9%)	0 (0.0%)
Lipids Increased	1 (0.5%)	1 (0.5%)	1 (0.5%)
Low Density Lipoprotein Increased	1 (0.5%)	1 (0.5%)	0 (0.0%)
Blood Triglycerides Increased	0 (0.0%)	1 (0.5%)	0 (0.0%)

Patient base: Full analysis set; all randomized patients who received at least one dose of study drug.
Patients may have experienced more than one lipid-related adverse event of interest. The sum of the terms may exceed 100%.
Statistical significance determined using Fisher's exact test (2-tailed) versus Neoral/MMF.
* Statistical significance at 0.05.
Source: Table 14.2.2.4.

Although the Neoral arm had a worse lipid profile, there only 59 more subjects who used a medication for hyperlipidemia compared with the baseline use. This increase was comparable to the increases in Prograf (50 subjects) and MR4 (58 subjects). The Neoral arm had more subjects taking 2 drugs, but it also had more subjects using medication at baseline, so the use of 2 drugs could reflect the worse baseline.

Table 40: Hyperlipidemia Drug Use

	Prograf (n = 212)	MR4 (n = 214)	Neoral (n = 212)
Baseline Use	45/212 (21.2%)	51/214 (23.8%)	70/212 (33.0%)
During course of Study	95/212 (44.8%)	109/214 (50.9%)	129/212 (60.8%)
Taking 1 drug	76/212	82/214	93/212
Taking 2 drugs	16/212	19/214	31/212
Taking > 2 drugs	3/212	8/214	5/212

Source: Table 13.3.4.3

Reviewer's Comments: The data regarding subjects who were on lipid medications differed considerably from the subjects who were considered to have hyperlipidemia from their demographic profile. In the demographic section, subjects in the Prograf arm reported 63 subjects with hyperlipidemia, but only 45 (71.4%) required treatment. In the MR4 arm, 70 subjects reported hyperlipidemia, but only 51 (72.9%) required treatment. In the Neoral arm, however, 75 subjects reported hyperlipidemia and 70 (93.3%) subjects required treatment at baseline. These differences suggest a difference in the randomization of subjects with hyperlipidemia with subjects in the Neoral arm having worse hyperlipidemia at baseline.

7.1.5.6.3 Hypertension

There were no differences in select treatment-emergent adverse events associated with hypertension.

Table 41: Summary of Select Hypertension-Related Treatment-Emergent Adverse Events of Interest

MedDRA (v. 6.1) Preferred Term	Treatment Group		
	Prograf (n = 212)	MR4 (n = 214)	Neoral (n = 212)
Any Select Hypertension-Related Adverse Event	69 (32.5%)	70 (32.7%)	76 (35.8%)
Hypertension	68 (32.1%)	64 (29.9%)	74 (34.9%)
Blood Pressure Increased	1 (0.5%)	4 (1.9%)	1 (0.5%)
Blood Pressure Systolic Increased	1 (0.5%)	0	0
Hypertensive Crisis	0	2 (0.9%)	1 (0.5%)
Blood Pressure Fluctuation	0	1 (0.5%)	0

Patient base: Full analysis set; all randomized patients who received at least one dose of study drug.
Patients may have experienced more than one hypertension-related adverse event of interest. The sum of the terms may exceed 100%.
Source: Table 14.2.2.4.

Table 42: Hypertension Drug Use

	Prograf (n = 212)	MR4 (n = 214)	Neoral (n = 212)
Baseline Use	169/212 (79.7)	165/214 (77.1%)	167/212 (78.8%)
During course of Study	202/212 (95.3%)	218/214 (97.2%)	203/212 (95.8%)
Taking 1 drug	21/212	25/214	20/212
Taking 2 drugs	42/212	44/214	60/212
Taking > 2 drugs	139/212	139/214	123/212

Source: Table 13.3.4.3

The baseline demographics show differences (though not statistically significant) in the baseline hypertension. In the Prograf arm, 192 subjects were listed as having hypertension, but only 169 (88.0%) subjects were on medication at baseline. In the MR4 arm, 179 subjects were listed as having hypertension, but only 165 (92.2%) subjects were on medications. In the Neoral arm, 190 subjects were considered to have hypertension, but only 167 (87.9%) were on medications. The Prograf arm and Neoral arm appear to have very similar baselines, but the Prograf arm had

more subjects taking > 2 drugs for hypertension during the course of the study than the Neoral arm, 139 (65.6%) versus 123 (58.0%). The MR4 arm had a larger increase in the number of subjects who did not require medications at baseline to requiring medication during the course of the study, 53 (24.8%) subjects, compared with Prograf, 33 (15.6%) subjects and Neoral, 36 (17.0%). Similar to the Prograf arm, the MR4 arm had more subjects taking > 2 drugs for hypertension than the Neoral arm, 139 (65.0%) v. 123 (58.0%).

Reviewer's Comments: Although differences in the report of hypertension as a treatment emergent adverse event did not reach statistical significance, there were more reports of these events in the Neoral arm compared with the tacrolimus arm. The difference is similar to the difference seen in the reporting of lipid events (does not reconcile with use of medications to affect or manage these subjects). Conclusions about these differences cannot be made, but highlight the concerns about open-label studies and the potential biases in reporting and categorizing adverse events.

7.1.5.6.4 Renal Function

Table 43: Summary of Select Renal Treatment-Emergent Adverse Events of Interest

MedDRA (v. 6.1) Preferred Term	Treatment Group		
	Prograf (n = 212)	MR4 (n = 214)	Neoral (n = 212)
Any Select Renal Adverse Event	58 (27.4%)	50 (23.4%)	59 (27.8%)
Blood Creatinine Increased	49 (23.1%)	40 (18.7%)	48 (22.6%)
Renal Failure Acute	5 (2.4%)	3 (1.4%)	3 (1.4%)
Renal Impairment	4 (1.9%)	4 (1.9%)	3 (1.4%)
Nephropathy Toxic	1 (0.5%)*	3 (1.4%)	8 (3.8%)
Blood Creatinine Abnormal	1 (0.5%)	2 (0.9%)	0
Nephropathy	1 (0.5%)	0	1 (0.5%)
Renal Insufficiency	0	2 (0.9%)	1 (0.5%)
Blood Urea Increased	0	0	1 (0.5%)

Patient base: Full analysis set; all randomized patients who received at least one dose of study drug.
Patients may have experienced more than one renal adverse event of interest. The sum of the terms may exceed 100%.
Statistical significance determined using Fisher's exact test (2-tailed) versus Neoral/MMF.
* Statistical significance at 0.05.
Source: Table 14.2.2.4.

The overall incidence of select renal adverse events was comparable across the three treatment arms. The Neoral arm had a significantly higher incidence of nephropathy toxic (p-value = 0.037; Fisher's exact test) than the Prograf arm, and also a numerically higher incidence than the MR4 arm. No other significant differences in the incidence of select renal adverse events were observed. Although not examined as a select renal adverse event, the incidence of hydronephrosis was significantly higher (p-value = 0.0105; Fisher's exact test) in the Neoral (9/212; 4.2%) arm compared with the MR4 (1/214; 0.5%) arm and numerically higher than the Prograf (2/212, 0.9%) arm [Tables 14.2.2.2 and 14.2.2.4]. There were no notable differences in the incidence of renal adverse events by age group, sex, race, ethnicity, or baseline diabetes status [Table 14.3.6.1.1, 14.3.6.1.2, 14.3.6.1.3, 14.3.6.1.4, and 14.3.6.1.5].

The Prograf arm had numerically more subjects who experienced delayed graft function based on the protocol definition of delayed graft function.

Table 44: Summary of Delayed Graft Function

	Treatment Group			p-Values†	
	Prograf (n = 212)	MR4 (n = 214)	Neoral (n = 212)	Prograf v. Neoral	MR4 v. Neoral
Delayed Graft Function					
Incidence	46 (21.7%)	38 (17.8%)	38 (17.9%)	0.330	0.964

Patient base: Full analysis set; all randomized patients who received at least one dose of study drug.
Only events up to day 365 are included in the analyses. Delayed graft function was defined as at least one dialysis episode within the first 7 days after completion of the transplant procedure. Acute tubular necrosis requiring dialysis within the first week following transplant met the definition of delayed graft function.
† p-values obtained using chi-square test.
Source: Table 13.4.5.

Reviewer's Comments: There are several possible reasons for the increased delayed graft function in the Prograf arm:

- *The subtle differences in the baseline characteristics of the subjects and donor may have led to higher incidence of delayed graft function;*
- *The initial higher AUC_{0-24} of Prograf compared with MR4 may have had a nephrotoxic effect on the kidneys resulting in more delayed graft function.*

Table 45: Summary of Mean ± SD Serum Creatinine Values (mg/dl) at Month 1, Month 6, and Month 12

	Treatment Group		
Time Point Statistic	Prograf (n = 212)	MR4 (n = 214)	Neoral (n = 212)
Month 1			
n	202	199	195
Mean ± SD	1.62 ± 1.17	1.63 ± 1.14	1.68 ± 0.99
Month 6			
n	186	188	173
Mean ± SD	1.42* ± 0.43	1.46 ± 0.55	1.51 ± 0.50
Month 12			
n	175	185	150
Mean ± SD	1.42 ± 0.56	1.39* ± 0.44	1.48 ± 0.51

Patient base: Full analysis set; all randomized patients who received at least one dose of study drug.
* Statistical significance of $p < 0.05$ versus Neoral using two-way analysis of variance (ANOVA) with treatment and center as factors.
SD: Standard deviation.
Source: Table 13.4.7.1.

There was very little difference between the 3 arms in terms of creatinine values. Using change from baseline (with baseline being at month 1), the changes in creatinine in the Prograf, MR4

and Neoral arms were decreases of 0.2, 0.2, and 0.24 respectively. Tests of statistical significance between the "changes in creatinine" were not performed, but the clinical value of a 0.04 difference in creatinine over 1 year is difficult to measure.

The Division asked Astellas to analyze the GFR of subjects using both the Modification of Renal Disease Study Group (MDRD) and the Cockcroft-Gault formula. Tables 46 and 47 summarize the results.

Table 46: Change in Creatinine Clearance Using the Full MDRD Formula

Time	Prograf (n=212) Mean (std)	MR4 (n=214) Mean (std)	Neoral (n=212) Mean (std)	Prograf v. Neoral	MR4 v. Neoral	Prograf v. MR4
				p-values		
True Intent to Treat						
Month 12	-0.1 (22.81)	3.0 (18.46)	-0.4 (21.60)	0.5190	0.0622	0.2227
Modified Intent to Treat						
Month 12	1.1 (20.97)	2.7 (17.41)	-0.8 (18.05)	0.1201	0.0412	0.6308
On-therapy Analysis	1.4 (20.29)	2.9 (16.25)	-0.9 (18.40)	0.0547	0.0204	0.6973

(1) 170 X [SERUM CREATININE (mg/dL)]^(-0.999) X [AGE]^(-0.176) X [0.762 IF PATIENT IS FEMALE] X [1.180 IF PATIENT IS BLACK] X [BUN (mg/dL)]^(-0.170) X [ALBUMIN (g/dL)]^(0.318). (Note: The unit for this estimate is mL/min per 1.73 m^2.)
(2) from contrasts in a two-way ANOVA, with treatment and center as factors.
Source: Submission July 17, 2006 Submission in Response to FDA request for Information

Table 47: Change in Baseline GFR using Cockcroft-Gault Method for estimating Renal Function

Time		Prograf (n=212) Mean (std)		MR4 (n=214) Mean (std)		Neoral (n=212) Mean (std)	Prograf v. Neoral	MR4 v. Neoral
	n				n			
Month 12	173	1.5 (16.07)	182	2.62 (14.32)	145	-0.25 (14.54)	0.154	0.051
Minimum (2)	199	-7.96 (14.48)	193	-6.52 (12.79)	185	-8.74 (14.13)	0.420	0.119

Creatinine clearance calculated using Cockcroft-Gault formula, using ideal body weight
(1) P-values obtained from two-way ANOVA, with treatment and center as factors.
(2) Minimum value more than 30 days after skin closure date
Source: Table 13.4.7.2 Study 158 report

Reviewer's Comments: Although differences in the change in GFR between the 3 arms appeared significant in the MR4 arm with a difference of ~ 3 mL/min with the modified intent-to-treat analysis and the on-therapy analysis, the clinical significance of this difference would have to be weighed against the safety risks associated with MR4. Because there was little difference in the incidence of acute rejection between MR4 and Neoral, this difference is likely due to the lower amount of CNI required when a higher dose of MMF is used. The subjects in the Neoral arm had troughs in the higher range and more subjects who had troughs above the target range. The higher troughs may have results in more adverse events associated with toxic nephropathy. Another possible reason for the better renal function could be because the MR4 had a greater number of female subjects who received kidneys from male donors and a slightly healthier

baseline for kidney recipients and donors. None of the analyses showed a significant difference in the GFR between Neoral and Prograf compared with baseline.

7.1.5.6.5 Diarrhea and Loose Stools

As discussed in other sections, there was a higher incidence of diarrhea and loose stools in the tacrolimus arms. Not only was the incidence higher, but the duration of these events were also greater. Tables 48-51 summarize the differences between the three arms. The Prograf and MR4 arms were very similar to each other, but different from Neoral.

Table 48: Summary of Diarrhea and Duration in Study 158

Diarrhea	Prograf N=212	MR4 N=214	Neoral N=212
Patients	94	97	54
Events	134	134	72
Duration of diarrhea Mean no. of days	31.25	31.08	21.5

Source: ADV.xpt Dataset
Mean duration was calculated using the ADUR listed.
For events listed as "continuing" the duration was calculating the following:
If the subject completed the study, duration was calculated as (365 – first day of adverse event).
If the subject crossed over to another arm, duration was calculated as (last day in the randomized arm – first day of adverse event + 10 days).

Table 49: Summary of Severity of Diarrhea

Severity of Diarrhea	Prograf N=212	MR4 N=214	Neoral N=212
Mild	90	90	44
Moderate	39	41	25
Severe	5	3	3

Source: ADV.xpt dataset

Table 50: Summary of Loose Stools and Duration

Loose Stools	Prograf N=212	MR4 N=214	Neoral N=212
Patients	15	11	3
Events	15	12	3
Duration of loose stools Mean no. of days	31.2	47.75	8.3

Source: ADV. Dataset
Mean duration was calculated using the ADUR listed.
For events listed as "continuing" the duration was calculating the following:
If the subject completed the study, duration was calculated as (365 – first day of adverse event).
If the subject crossed over to another arm, duration was calculated as (last day in the randomized arm – first day of adverse event + 10 days).

Table 51: Summary of Severity of Loose Stools

Severity of Loose Stools	Prograf N=212	MR4 N=214	Neoral N=212
Mild	13	10	3
Moderate	2	2	0
Severe	0	0	0

Source: ADV.xpt Dataset

Because the diarrhea and loose stool events were believed to be related to MMF, the dataset was explored to determine whether the diarrhea was associated with a particular dose. If a dose – adverse event relationship were determined, then recommendations would be made about a safer dose of MMF to use. The Clinical Pharmacology Reviewer analyzed the data presented in the table below:

Table 52: Incidence of GI-related Adverse Events (i.e., Diarrhea and Loose Stool) as a Function of MMF dose in the Prograf+MMF arm

Severity of GI-Related Adverse Events	High MMF Dose Group (N=52)[e]	Low MMF Dose Group (N=160)[f]
S[a]	1.9% (1/52)	2.5% (4/160)
S_M[b]	11.5 (6/52)	20% (32/160)
S_M_M[c]	33% (17/52)	51% (81/160)

[a]: Severity is "Life-threatening" or "Severe"
[b]: Severity is "Life-threatening" or "Severe" or "Moderate"
[c]: "Life-threatening" or "severe" or "Moderate" or "Mild"
[e]: Average daily dose of MMF during all treatment periods >= 1950 mg
[f]: Average daily dose of MMF during any treatment period < 1950 mg

Based on this analysis, the incidence of GI-related adverse events was greater in the low MMF Dose group compared with the high MMF Dose group. This finding was most likely to due subjects being placed on the higher dose of MMF until they developed diarrhea and then having the dose dropped to a lower level during the diarrheal episode. Once the adverse event resolved, the subjects were placed back on the higher dose of MMF.

Reviewer's Comments: Because a "safer" dose of MMF could not be determined from the data in Study 158, the Applicant would need to conduct another study to determine the correct dose of MMF to use with Prograj (b) (4) in order to receive approval for the use of tacrolimus with MMF. It would be recommended that the Applicant not exceed the dose that would provide the equivalent systemic exposure of MPA, when used with tacrolimus, as 2 grams of MMF when used with cyclosporine.

The clinical consequences of excessive diarrhea should not be minimized. Excessive diarrhea can result in poor absorption of other medications taken by the transplant patients such as the medicines for infection prophylaxis, the medications for lipid disorders, hypertension, and diabetes. In addition to poor medication absorption from excessive diarrhea, the erosive nature of the MMF induced diarrhea places patients at greater risk for other medical complications.

7.1.5.6.6 Hematologic Adverse Events

Both the Prograf and MR4 arms had more hematologic adverse events associated with MMF use. Anemia in the MR4 (33.6%) and the Prograf (30.2%) arms were greater than the Neoral (27.8%) arm; leukopenia was also greater in with MR4 (16.4%) and Prograf (15.6%) arms compared with the Neoral (11.8%) arm. Duration of leukopenia was explored further because of the increased risk of infection with prolonged leukopenia. The mean duration of leukopenia was similar between the Prograf and MR4 arms and greater than the Neoral arm.

Table 53: Adverse Event of Leukopenia

Leukopenia	Prograf N=212	MR4 N=214	Neoral N=212
Patients	33	35	25
Events	41	40	30
Duration of Leukopenia Mean no. of Days	99.93	85.2	50.37

Source: ADV.xpt Dataset
Mean duration was calculated using the ADUR listed.
For events listed as "continuing" the duration was calculating the following:
If the subject completed the study, duration was calculated as (365 – first day of adverse event).
If the subject crossed over to another arm, duration was calculated as (last day in the randomized arm – first day of adverse event + 10 days).

Table 54: Severity of Leukopenia

Severity of Leukopenia	Prograf N=212	MR4 N=214	Neoral N=212
Mild	19	21	12
Moderate	22	19	17
Severe	0	0	1

Source: ADV.xpt Dataset

7.1.5.6.7 Infections

There was a significantly higher incidence of infections in the Prograf (68.9%) and MR4 (69.3%) arms compared with Neoral (58.0%, p-value 0.0252). The MR4 had a significantly higher incidence of gastroenteritis compared with both Prograf and Neoral (p-value 0.0007).

Table 55 below summarizes the serious adverse events classified as infections and infestations. Although the total number of subjects with serious adverse events due to infections and infestations was similar between the Prograf and Neoral arms, there were differences in the number of events reported.

Table 55: Serious Adverse Events – Infections and Infestations: Comparing Prograf v. Neoral*

MedDRA (v. 6.1) System Organ Class **Infections and Infestations**	**Prograf+MMF**	**Neoral+MMF**
Any AE	49 (23.1)	47 (22.2)
CMV Related		
**CMV	12 (5.7)	11 (5.2)
**CMV Viremia	2 (0.9)	0
**CMV Colitis	1 (0.5)	0
**CMV Gastritis	0	2 (0.9)
Genitourinary		
UTI	7 (3.3)	11 (5.2)
**Urosepsis	4 (1.9)	2 (0.9)
Pyelonephritis	3 (1.4)	2 (0.9)
Pyelonephritis Acute	0	2 (0.9)
Bacterial Pyelonephritis	1 (0.5)	0
Perinephric Abscess	0	1 (0.5)
E Coli UTI	0	3 (1.4)
Urinary Tract Infection Enterococcal	1 (0.5)	0
**Urinary Tract Infection Pseudomonal	1 (0.5)	0
UTI bacterial	0	1 (0.5)
Orchitis	1 (0.5)	0
Pulmonary/Oropharyngeal		
Pneumonia	1 (0.5)	3 (1.4)
**Bronchopulmonary Aspergillosis	1 (0.5)	0
**Pneumonia Fungal	1 (0.5)	0
**Lung Infection Pseudomonal	1 (0.5)	0
Pneumonia Staphylococcal	1 (0.5)	0
Lobar Pneumonia	0	1 (0.5)
Mycobacterium Avium Complex Infection	1 (0.5)	0
Bronchitis	1 (0.5)	1 (0.5)
Bronchitis Acute	1 (0.5)	0
Tracheobronchitis	1 (0.5)	0
**Tuberculosis	1 (0.5)	1 (0.5)
Tonsillitis	0	1 (0.5)
Generalized Bacterial Infection		
**Sepsis	4 (1.9)	1 (0.5)
Catheter Sepsis	1 (0.5)	0
**Streptococcal Sepsis	1 (0.5)	0
**Streptococcal Bacteremia	0	1 (0.5)
E coli Bacteremia	1 (0.5)	1 (0.5)
Bacteremia	1 (0.5)	0
**Endocarditis	2 (0.9)	0
**Endocarditis Bacterial	0	1 (0.5)
Catheter Related Infection	1 (0.5)	0
Staphylococcal Infection	1 (0.5)	0
**VRE Infection	1 (0.5)	0
**Osteomyelitis	0	1 (0.5)
Gastrointestinal Infections		

Gastroenteritis Viral	2 (0.9)	1 (0.5)
Gastroenteritis	0	1 (0.5)
Diarrhea Infectious	1 (0.5)	0
**Strongyloidiasis	3 (1.4)	0
**Clostridium Colitis	1 (0.5)	1 (0.5)
**Clostridial Infection	1 (0.5)	0
Viral Infections (not CMV)		
Viral Infection	1 (0.5)	1 (0.5)
**Herpes Virus Infection	0	1 (0.5)
**Herpes Zoster	2 (0.9)	0
**Human Polyomavirus Virus	4 (1.9)	1 (0.5)
Influenza	0	1 (0.5)
Parvovirus	0	1 (0.5)
Localized Type Infections		
Localized Infection	1 (0.5)	1 (0.5)
Abscess	1 (0.5)	0
Furuncle	1 (0.5)	1 (0.5)
Infected cyst	1 (0.5)	0
Wound Infection	1 (0.5)	1 (0.5)
Postoperative Infection	0	2 (0.9)
Cellulitis	0	2 (0.9)

* MedDRA 6.1 Preferred Term used. Reviewer reorganized and grouped terms according to types of infections.
** Reviewer identified serious infectious related adverse events that are particularly unusual or difficult to manage.
Source: Table 13.5.1.5 from Study Report 158.

*Reviewer's Comments: In order to better understand the clinical significance of the serious adverse events, the events were reorganized so that similar types of events were grouped together. Infections that were considered particularly unusual or difficult to managed were then annotated with ** and these events were counted. Kassa Ayalew, MD, a Board Certified Pediatric Infectious Disease specialist reviewed the initial list of events marked ** (by the primary reviewer) and expanded the number of particularly unusual or difficult to manage to include urosepsis and VRE infection. When the events were counted, the Prograf+MMF arm had 43 serious adverse events determined to be unusual or more difficult to manage compared with the Neoral+MMF arm which had 23 serious adverse events.*

Since all transplant recipients experience some type of adverse events during the first year post-transplantation and numerous recipients experience serious adverse events, the difference in the number of serious adverse events between the two arms (when the number of subjects was similar) suggest there were clinically relevant differences in the level of immunosuppression between the two study arms.

7.1.5.6.8 Adverse Events after Crossing Over

Evaluation of adverse events that occurred after crossing over to the other treatment arm was limited to subjects who crossed over from Neoral to Prograf. The findings from those subjects (n=39) suggest that the Prograf+MMF arm was associated with more adverse events. See Table 56 below.

Table 56: Incidence of Treatment Emergent Adverse Events After Crossover (>5%) and Before Crossover

MedDRA (v. 6.1) System Organ Class Preferred Term	Neoral+MMF (after crossover) (n=39)	*Neoral +MMF (before crossover) (n=212)	*Prograf+MMF (before crossover) (n=212)
All Systems			
Any AE	36 (92.3%)		
Investigations			
Any AE	11 (28.2%)		
Blood Creatinine	5 (12.8%)		
Metabolism and Nutrition Disorders			
Any AE	17 (43.6%)	170 (80.2%)	162 (76.4%)
Hypokalemia	6 (15.4%)	37 (17.5%)	34 (16.0%)
Hyperkalemia	5 (12.8%)	41 (19.3%)	54 (25.5%)
Metabolic Acidosis	5 (12.8%)	13 (6.1%)	14 (6.6%)
Hypomagnesemia	4 (10.3%)	47 (22.2%)	60 (28.3%)
Hypercholesterolemia	3 (7.7%)	16 (7.5%)	10 (4.7%)
Diabetes Mellitus	3 (7.7%)	14 (6.6%)	24 (11.3%)
Hyperglycemia	3 (7.7%)	32 (15.1%)	45 (21.2%)
Hypophosphatemia	3 (7.7%)	45 (21.2%)	59 (27.8%)
Dehydration	2 (5.1%)	9 (4.2%)	20 (9.4%)
Diabetes Mellitus Non-Insulin Dependent	1 (2.6%)		
Diabetic Ketoacidosis	1 (2.6%)		
Musculoskeletal and Connective Tissue Disorders			
Any AE	14 (35.9%)	115 (54.2%)	103 (49.5%0
Back Pain	3 (7.7%)	30 (14.2%)	27 (12.7%)
Pain in Extremity	3 (7.7%)	26 (12.3%)	27 (12.7%)
Arthralgia	5 (12.8%)	28 (13.2%)	26 (12.3%)
Blood and Lymphatic System Disorders			
Any AE	20 (51.3%)	97 (45.3%)	105 (49.5%)
Anemia	13 (33.3%)	59 (27.8%)	64 (30.2%)
Leukopenia	9 (23.1%)	25 (11.8%)	33 (15.6%)
Neutropenia	2 (5.1%)		
Gastrointestinal Disorders			
Any AE	27 (69.2%)	185 (87.3%)	190 (89.6%)
Diarrhea	16 (41.0%)	54 (25.5%)	94 (44.3%)
Nausea	12 (30.8%)	99 (46.7%)	82 (38.7%)
Abdominal Pain	4 (10.3%)	38 (17.9%)	27 (12.7%)
Vomiting	4 (10.3%)	52 (24.5%)	54 (25.5%)
Loose Stool	4 (10.3%)	4 (1.9%)	15 (7.1%)
Abdominal Distention	3 (7.7%)		

Abdominal Pain Upper	3 (7.7%)		
Constipation	2 (5.1%)		
Hemorrhoids	2 (5.1%)		
Ascites	2 (5.1%)		
Dyspepsia	2 (5.1%)		
Melena	2 (5.1%)		
Stomatitis	2 (5.1%)		
General Disorders and Administration Site Conditions			
Any AE	18 (46.2%)	145 (68.4%)	139 (65.6%)
Fatigue	7 (17.9%)	26 (12.3%)	23 (10.8%)
Edema Peripheral	6 (15.4%)	97 (45.8%)	74 (34.9%)
Chest Pain	2 (5.1%)		
Asthenia	2 (5.1%)		
Edema	2 (5.1%)		
Pain	2 (5.1%)		
Infections and Infestations			
Any AE	26 (66.7%)	123 (58%)	146 (68.9%)
CMV Infection	6 (15.4%)	16 (7.5%)	17 (8.0%)
Upper Respiratory Tract Infection	6 (15.4%)	29 (13.7%)	24 (11.3%)
Urinary Tract Infections	6 (15.4%)	47 (22.2%)	54 (25.5%)
Cellulitis	3 (7.7%)	6 (2.8%)	4 (1.9%)
Human Polyoma Virus	3 (7.7%)	5 (2.4%)	9 (4.2%)
Sinusitis	3 (7.7%)	5 (2.4%)	7 (3.3%)
Renal and Urinary Disorders			
Any AE	15 (38.5%)	106 (50.0%)	81 (38.2%)
Dysuria	3 (7.7%)	20 (9.4%)	23 (10.8%)
Proteinuria	3 (7.7%)	11 (5.2%)	5 (2.45)
Hydronephrosis	2 (5.1%)		
Renal Failure Acute	2 (5.1%)		
Renal Impairment	2 (5.1%)		
Cardiac Disorders			
Any AE	5 (12.8%)	38 (17.9%)	39 (18.4%)
Tachycardia	2 (5.1%)		
Injury Poisoning and Procedural Complications			
Any AE	9 (23.1%)	156 (73.6%)	163 (76.9%)
Complications of Transplant Surgery	2 (5.1%)		
Graft Dysfunction	2 (5.1%)		
Therapeutic Agent Toxicity	2 (5.1%)		
Thermal Burn	2 (5.1%)		
Nervous System Disorders			
Any AE	15 (38.5%)	117 (55.2%)	134 (63.2%)
Tremor	8 (20.5%)	42 (19.8%)	73 (34.4%)
Headache	5 (12.8%)	52 (24.5%)	51 (24.1%)
Dizziness	3 (7.7%)	24 (11.3%)	27 (12.7%)
Psychiatric Disorders			
Any AE	7 (17.9%)	77 (36.3%)	89 (42.0%)
Depression	4 (10.3%)	11 (5.2%)	13 (6.1%)
Insomnia	3 (7.7%)	45 (21.2%)	64 (30.2%)
Anxiety	2 (5.1%)		
Respiratory, Thoracic and Mediastinal			

Any AE	19 (48.7%)	86 (40.6%)	93 (43.9%)
Cough	7 (17.9%)	21 (9.9%)	27 (12.7%)
Dypsnea	5 (12.85)	28 (13.2%)	24 (11.3%)
Dypsnea Exertional	4 (10.3%)	8 (3.8%)	12 (5.7%)
Pharyngeal Pain	2 (5.1%)		
Rhinorrhea	2 (5.1%)		
Skin and Subcutaneous Tissue Disorders			
Any AE	12 (30.8%)	78 (36.8%)	92 (43.4%)
Acne	3 (7.7%)	22 (10.4%)	13 (6.1%)
Hyperhidrosis	2 (5.1%)		
Night Sweats	2 (5.1%)		
Skin Lesion	2 (5.1%)		
Vascular Disorders			
Any AE	10 (25.6%)	111 (52.4%)	105 (49.5%)
Hematoma	2 (5.1%)		
Hypertension	2 (5.1%)	74 (34.9%)	68 (32.1%)
Orthostatic Hypotension	2 (5.1%)	5 (2.4%)	10 (4.7%)
Ear and Labyrinth Disorder			
Any AE	3 (7.7%)		
Ear Pain	2 (5.1%)		

* Select comparative adverse events from subjects on randomized therapy were included. These
Source: Table 11.1.1, Folder B.3, Submission September 15, 2006 to NDA 50-708 and 50-709.

Reviewer's Comments: One would expect that the incidence of adverse events in the Neoral subjects who crossed over to Prograf would be lower than either of the two arms (Neoral or Prograf) because subjects had already passed the high-risk, immediate post-operative period. And, in many of the categories, these results were observed. However, the Neoral subjects that crossed over to Prograf also appeared to experience more adverse events associated with MMF toxicity and overimmunosuppression compared to the baseline Neoral incidences (see highlighted rows). Specifically, the incidence of treatment emergent diarrhea, loose stools, orthostatic hypotension, anemia, leukopenia, CMV infections, and Human Polyomavirus infection were higher in the crossover subjects compared to the Neoral subjects before crossover. Since the number of subjects who crossed over from Prograf to Neoral was only 4, comparison of the incidence of these adverse events would not be reliable.

7.1.6 Less Common Adverse Events

Since Study 158 lasted an entire year, there were numerous adverse events reported that would be that may not have been associated with the study drug.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Please see Section 7.1.1.4 for further details. Laboratory testing was conducted at the local transplant center during the one-year follow-up period. The laboratory testing was quite comprehensive because of the complex clinical course for kidney transplant recipients. All subjects participating in the study had baseline labwork and subsequent follow-up labwork. Although there may have been intermittent missing data, subjects were followed for an entire year – therefore, subjects who did not return for follow-up labwork as part of their evaluation were listed as lost to follow-up.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Not applicable. This study included an active control arm that provided comparative data for analyses.

7.1.7.3 Standard analyses and explorations of laboratory data

Table 57: Summary of Select Laboratory Parameters of Interest

		Prograf	MR4	Neoral
Glucose	**≥ 200 mg/dl**	38/144 (26.4%)	33/157 (21.0%)	42/159 (26.4%)
LDL	**≥ 200 mg/dl**	2/169 (1.2%)	6/162 (3.7%)	9/155 (5.8%)
Platelets	**< 100**	21/204 (10.3%)	15/198 (7.6%)	11/198 (5.6%)
SGOT/AST	**≥ 100 U/L**	8/178 (4.5%)	6/179 (3.4%)	10/181 (5.5%)
SGPT/ALT	**≥ 100 U/L**	21/181 (11.6%)	28/182 (15.4%)	31/185 (16.8%)
Total Cholesterol	**≥ 300 mg/dl**	6/176 (3.4%)	8/168 (4.8%)	18/166 (10.8%)
Triglycerides	**≥ 500 mg/dl**	7/174 (4.0%)	7/170 (4.1%)	6/165 (3.6%)
WBC's	**< 2.0**	13/209 (6.2%)	10/209 (4.8%)	10/209 (4.8%)

Source: Table 13.6.5 Study 158 Report

7.1.7.4 Additional analyses and explorations

Not applicable. These additional analyses are discussed throughout the review in other section.

7.1.7.5 Special assessments

See Section 7.1.1.9 for details about special assessments regarding renal function and hyperglycemia.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Monitoring of vital signs was described in the efficacy section on protocols.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Study 158 was the primary study used for analysis.

7.1.8.3 Standard analyses and explorations of vital signs data

There no clinically significant differences in the mean values for pulse rate, temperature, blood pressure, and weight among the three treatment arms.

Table 58: Summary of Mean Systolic and Diastolic Blood Pressures

Mean Blood Pressure	Prograf (std) N* = 212/211	MR4 (std) N* = 214/214	Neoral (std) N* = 212/211
Systolic			
Baseline	145.4 (23.12)	143.9 (23.30)	144.5 (23.3)
End of Treatment	133.1 (20.08)	132.1 (16.81)	133 (18.89)
Diastolic			
Baseline	80.8 (14.49)	80.9 (14.99)	79.6 (14.87)
End	76.4 (11.61)	77.0 (10.67)	76.5 (13.17)

*N = subjects at baseline/subjects at end of treatment.
Source: Table 13.7.1 from Study 158 Report.

Reviewer's Comments: Review of the blood pressure data did not show any clinically significant differences between the mean blood pressures of the three treatment arms.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECG's were performed as part of the routine baseline and follow-up. No unusual trends were noted on the results of the ECG of study subjects. Because these subjects have a complicated medical history, there were abnormalities noted in a number of the ECGs, but no trends suggestive of an ECG abnormality associated with the any of the study arms. Tacrolimus is not known to be cardiotoxic or cause ECG abnormalities.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable.

7.1.9.3 Standard analyses and explorations of ECG data

ECG data was reviewed.

7.1.9.4 Additional analyses and explorations

Not applicable.

7.1.10 Immunogenicity

Not applicable.

7.1.11 Human Carcinogenicity

Please see class labeling in the boxed WARNING in the Prograf and CellCept Package Inserts.

7.1.12 Special Safety Studies

Not applicable.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Not applicable.

7.1.14 Human Reproduction and Pregnancy Data

Please see Prograf and CellCept Package Inserts.

7.1.15 Assessment of Effect on Growth

No assessment of effect on growth was conducted because Study 158 involved only adults.

7.1.16 Overdose Experience

Please see Prograf and CellCept Package Inserts.

7.1.17 Postmarketing Experience

Both Prograf and CellCept are lawfully marketed products. The use of these two drugs in combination currently represents the primary immunosuppression regimen for the majority of kidney transplant recipients in the United States.

7.2 Adequacy of Patient Exposure and Safety Assessments

Over 100 subjects in each of the two arms (study and comparator) were evaluated for one year post-transplantation.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Study 158 was adequate to evaluate safety.

7.2.1.1 Study type and design/patient enumeration

Section 4 and 7 include the relevant tables of study and subjects. Section 6 describes the demographic information for Study 158.

7.2.1.2 Extent of exposure (dose/duration)

The exposure of this drug was appropriate, with some subjects receiving the drug 2-3 years after transplantation.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Literature were reviewed to understand the toxicities of MMF. These secondary clinical data sources are discussed throughout the review. The original NDA and Package Insert for CellCept were also reviewed to evaluate safety of the combination of Prograf+MMF.

7.2.2.1 Literature

Literature references were made throughout the review and are included after Appendix 10. The Applicant literature review was adequate.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The Applicant proposes that (b) (4) can be used safely and effectively with Prograf.

8.2 Drug-Drug Interactions

There does not appear to be any drug-drug interaction between Prograf and CellCept. It is the ***absence*** of a drug-drug interaction that is more relevant because this absence of interaction resulted in higher systemic exposures of MPA in the tacrolimus arms (Prograf and MR4) compared with the Neoral arm. The higher systemic exposures resulted in greater

immunosuppression and more adverse events associated with CellCept in the Prograf arm. Since CellCept was developed in combination with cyclosporine, the doses and the systemic exposures evaluated to determine the safety and efficacy of CellCept for kidney transplantation reflect the interruption in the enterohepatic recirculation of MPA.

8.3 Special Populations

Not Applicable.

8.4 Pediatrics

Not applicable.

8.5 Advisory Committee Meeting

Not applicable.

8.6 Literature Review

Already discussed in several other Sections.

8.7 Postmarketing Risk Management Plan

Not applicable.

8.8 Other Relevant Materials

Not applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

Prograf + MMF

CellCept was approved for use in combination with cyclosporine and corticosteroids. Combining Prograf with mycophenolate mofetil in an immunosuppressive regimen is not as simple as substituting one calcineurin inhibitor (cyclosporine) with another calcineurin inhibitor because the safe and effective dose of CellCept to be used in kidney transplantation was developed in combination with a drug (cyclosporine) that inhibits the enterohepatic recirculation of mycophenolic acid (MPA). Therefore, if the same dose of CellCept is used in combination with any other drug that does not inhibit this enterohepatic recirculation, the combination will result in systemic exposures of MPA greater than the exposures achieved in the approved dose of CellCept (2 grams/day). Since tacrolimus does not interfere with the enterohepatic recirculation of CellCept, the combination of Prograf+MMF 2 grams/day resulted in systemic exposures of MPA greater than the Neoral+MMF 2 grams/day arm.

Efficacy:

Although the purpose of the study was to evaluate the safety and efficacy of Prograf+MMF 2 grams/day, the study design permitted investigators to vary the dose of MMF according to adverse events. As a result, the dose of MMF used in combination with Prograf was significantly lower than the dose of MMF when used in combination with cyclosporine, the approved combination regimen. Based on the pattern of MMF use (decreasing the dose when an adverse event developed and then returning the subject to the higher dose until another adverse event developed), the data from the study could not be used to determine a safe and effective dose of MMF to use in combination with Prograf.

The combination of Prograf+MMF met the primary combined efficacy endpoint of biopsy-confirmed acute rejection, graft loss, and patient death with an efficacy failure of 15.1% compared with 17% in the Neoral+MMF arm. However, evaluation of the 95% confidence interval around the difference of the composite endpoint of graft survival and patient survival found that the Prograf+MMF arm exceeded the 5% margin. Because the margin exceeded 5% for graft and patient survival, greater scrutiny was placed on the evaluation of the graft and patient survival.

Although the Prograf arm had fewer acute rejection episodes according to the local pathology assessment [16 (7.5%)] compared with Neoral [29 (13.7%)], the decrease in the acute rejection rate did not benefit subjects in the Prograf arm because they had more graft losses [6 (2.8%) v. 4 (1.9%)] and more deaths [9(4.2%) v. 5 (2.4%)]. Furthermore, the local assessments of acute rejection were erroneous approximately 50% of the time when compared with the blinded central

assessment. According to the blinded central assessments, the acute rejection rate in the Prograf arm was 3.8% (8 subjects) compared with Neoral's 6.6% (14 subjects). For ≥Banff Grade IIA rejection, subjects in the Prograf arm had a rate of 2.8% (6 subjects) and subjects in the Neoral arm had a rate of 4.2% (9 subjects). No differences were found in renal function of subjects in the Prograf arm compared with the Neoral arm when evaluating the mean creatinine level at month 12 or changes from the baseline GFR.

In conclusion, the Prograf+MMF immunosuppressive regimen studied in Study 158 involved a dose of MMF that could not be determined and resulted in only a slight improvement in the acute rejection rate that ***did not*** translate to actual clinical benefit such as improved renal function, improved graft survival or improved patient survival. Using the blinded, central assessment of the rate of biopsy-confirmed acute rejection, subjects in the Prograf+MMF arm had a higher mortality rate than an acute rejection rate.

Safety:

In evaluating the risk-benefit of Prograf+MMF compared with Neoral+MMF, the relative inconsequential benefit had to be weighed against the safety profile of Prograf+MMF compared with Neoral+MMF.

The most clinically significant safety difference between Prograf+MMF and Neoral+MMF was the higher mortality rate in the Prograf+MMF arm. The difference was noted at the one-year endpoint and continued upon follow-up 2 years post-transplantation. The difference in the mortality rate in the Prograf+MMF arm was due to the larger number infection/overimmunosuppression related deaths [5 out of 9 at year 1 (day 365) and 7 out of 12 in year 2) compared to the Neoral arm [1 out of 5 at year 1 (day 365) and 2 out of 7 at year 2). Detailed evaluation of these deaths revealed that none of the infection/immunosuppression deaths were precipitated by treatment for acute rejection. Of all the subjects who died because of infection/overimmunosuppression, only 1 subject received treatment for acute rejection; this subject last received steroids on day 30 for Grade I rejection that was subsequently read as "no rejection), but did not die until day 222, approximately 3 months after crossing over to Prograf+MMF.

In addition to the higher mortality, subjects in the Prograf+MMF arm experienced more adverse events associated with MMF toxicity such as diarrhea, loose stools, anemia, and leukopenia and more adverse events related to overimmunosuppression such as total infections, including more subjects with Human Polyoma Virus infections (9 vs. 5). The total incidence of infections was also greater in the Prograf arm compared with the Neoral arm. When **serious** adverse events due to infections and infestations were evaluated, there were differences noted in the number of events even though the number of subjects affected were comparable between the two arms. In a comparison of serious infections that were determined to be clinically difficult to manage or were unusual (determination made by the Division's internal ID specialist), the Prograf arm had almost twice the number of these serious infections compared with the Neoral arm (43 v. 23 events). Approximately 39 subjects in the Neoral arm crossed over to Prograf during the course of the study. Evaluation of adverse events in those 39 subjects also reflected more adverse

events consistent with overimmunosuppression and MMF toxicity. These subjects had a higher incidence of diarrhea, loose stools, leukopenia, CMV infections, and Human Polyoma Virus infections (3 subjects developed Human Polyoma Virus after crossing over to Prograf+MMF) compared to the Neoral subjects while on randomized therapy.

Since subjects in the Prograf+MMF arm did not consistently achieve 2 grams/day of MMF in the study, the difference in adverse events relating to MMF toxicity and overimmunosuppression would have been even greater had subjects actually used MMF according to the CellCept label.

In conclusion, the safety profile of Prograf+MMF was worse than the safety profile of Neoral+MMF. The difference in the safety profile and the higher mortality was likely associated with the higher systemic exposures of MPA in the Prograf arm compared with the Neoral arm since Neoral reduces the systemic exposures of MPA. However, since MPA AUC's were not measured during the study, actual differences in the MPA exposures could not be confirmed. Based on data from Study 158, the overall risk-benefit analysis cannot support the use of Prograf and MMF 2 grams/day. Furthermore, the data from the study does not support a lower dose of MMF to be used in combination with Prograf, although it would be reasonable to expect a safety profile comparable to Neoral+MMF if a lower dose of MMF had been studied in combination with Prograf.

Remarkably (or as expected), the clinical profile of Prograf+MMF in Study 158 was similar to the clinical profile of CellCept 3 grams/day when used with cyclosporine from the original studies used to support the initial CellCept NDA for kidney transplantation. In original CellCept studies, subjects in the arm with the higher dose of CellCept (3 grams/day) had a lower acute rejection rate, but more difficulty tolerating the higher dose of CellCept and a higher combined graft and patient loss compared with the CellCept (2 grams/day). In 1995, when the CellCept NDA was reviewed, it was noted that there may be some patients who benefit from the higher dose of CellCept, but the risk-benefit analysis supported recommending the lower dose of 2 grams/day. A similar conclusion can be made about Prograf+MMF 2 grams/day – there may be some patients who benefit from the CellCept 2 grams/day when used with Prograf, however, the risk-benefit analysis does not support the use of this dose of MMF with Prograf. Unlike the original CellCept NDA, no alternative dose of CellCept was studied and no data was provided to consider the use of an alternative dose of CellCept in combination with Prograf.

9.2 Recommendation on Regulatory Action

Kidney Transplantation:
The combination of Prograf+MMF was submitted as labeling change supported by clinical data. In that labeling request, the Applicant requested that Study 158 be included in the Clinical Studies Section and the dosage and use section include the use of MMF with Prograf.

1) Given the results of Study 02-0-158, the safety and efficacy of Prograf in combination with CellCept (as recommended in the current CellCept Package Insert) was not established when compared with Neoral and CellCept.
2) An alternative dose of CellCept to be used in combination with Prograf was not established from the results of this study.
3) Since these two drugs are both lawfully marketed products and already being used in combination, the primary reason for incorporating the results of this clinical study in the label is for promotional purposes or to use as an active comparator in future clinical study for drug approval. Given the safety profile of the studied doses of CellCept in combination with Prograf, promotion of these results or use of this regimen for future clinical studies cannot be recommended.
4) However, the information from this study is clinically important for two reasons:
    a) Because this commonly used, unapproved regimen is viewed as the "standard of care" for prophylaxis against rejection in kidney transplantation, other drug companies developing drugs for use in kidney transplantation have requested this combination as the active comparator for clinical trials. The results from Study 158 (which was conducted mostly in the United States) suggest that MMF 2 grams/day clearly is **NOT** the standard of care in the United States because subjects did not consistently use 2 grams/day in the Prograf arm. Furthermore, the manner in which these investigators were using MMF 2 grams/day led to an unacceptable increased risk of serious infections and deaths due to the immunosuppression.

    b) This combination is currently being used in the majority of adult kidney transplant recipients in the United States. Although many transplant programs may be aware of the absence of interaction between Prograf and MMF, these patients are often managed by their referring nephrologist or primary care physician. The current Package Inserts for CellCept, Myfortic, and cyclosporine did not contain any information regarding this critical drug interaction and the potential for overimmunosuppression and MMF toxicity when the MMF is used in combination with drugs other than cyclosporine. The overimmunosuppression and MMF toxicity can result in serious infections and death.

Action: Both Prograf and MMF are lawfully marketed products; therefore, physicians are able to use the two drugs in combination. However, the results of Study 158 (b) (4) raise concerns about the safe and effective use of this combination. Instead of changing the Package Insert in accordance with the Applicant's request, the following actions are recommended:

1) Given the safety concerns in the Prograf+MMF arm in Study 158, it would be reasonable and consistent with other Package Inserts to include information in the WARNING section about the higher mortality rates in Prograf+MMF arm compared with the Neoral+MMF arm and that the increase in mortality was due to infection related deaths. The current Zenapax Package Insert has similar language regarding the results of a clinical trial in heart transplantation and could be used as a model for language to include in the Prograf Package Insert.

2) In addition to the information in the Prograf Package Insert, changes should also be made to the cyclosporine, CellCept, and Myfortic Package Inserts to address the drug interaction between cyclosporine and mycophenolic acid (MPA). The current Neoral, CellCept, and Myfortic package inserts do not include information regarding the drug interaction and implies that there are no drug interactions between cyclosporine and MPA.

(b) (4)

(b) (4)

(b) (4)

Heart Transplantation: The Prograf Package Insert currently includes language stating that Prograf can be used in combination with MMF in heart transplantation. Re-evaluation of the data from this study showed that doses in the MMF arm dropped much more than doses in the cyclosporine arm, consistent with the results of Study 158. Further elaboration or discussion about the risk/benefit assessment of this combination in heart transplantation cannot be made because a full review of the original clinical study to support labeling was not re-reviewed as part of this submission.

Action: Recommend that the label include information to reflect that subjects using Prograf+MMF had to reduce their MMF doses more than subjects using cyclosporine+MMF. Recommend that more safety data be analyzed with this combination and that Astellas submit any follow-up data from this study that may not have been submitted when the study was first reviewed. Because the doses used in the Prograf arm were different from the doses used in the approved comparator arm (and not consistent with the current CellCept Package Insert), recommend that this combination not be used for future clinical trials in heart transplantation until the dose of CellCept is more appropriately characterized and a complete comparative safety analysis be conducted so that the results will be replicable.

9.3 Recommendation on Postmarketing Actions

Not Applicable.

9.3.1 Risk Management Activity

Not applicable.

9.3.2 Required Phase 4 Commitments

Not applicable.

9.3.3 Other Phase 4 Requests

Not applicable.

9.4 Labeling Review

1) The Applicant is proposing (b) (4)

Reviewer's Comments: No information regarding (b) (4)

2) The Applicant (b) (4)

Reviewer's Comments: No information from (b) (4)

3) The Applicant proposes to include information in the PRECAUTIONS section regarding the drug interaction between cyclosporine and MMF.

Reviewer's Comments: Agree with the Applicant's proposed change in the PRECAUTIONS section, but recommend creating a subsection entitled "Interactions with Other Immunosuppressantsthe following language:

> Due to the differences in the interruption of the enterohepatic recirculation of mycophenolic acid (MPA) between Prograf and cyclosporine, clinicians should be aware of the potential increase in MPA exposure after crossover from cyclosporine to tacrolimus in patients concomitantly receiving MMF or MPA.

4) ***Reviewer's Comments: Because of the worse safety profile of the Prograf+MMF arm compared with the Neoral+MMF arm and the increase in infection/overimmunosuppression deaths, recommend that the following language be inserted in the WARNINGS section of the Package Insert:***

> **Prograf in Combination with other Immunosuppressants**
> The use of Prograf and mycophenolate mofetil (MMF) 1 gram BID (2 grams/day) with basiliximab induction as an immunosuppressive regimen for kidney transplantation may be associated with an increase in mortality. In a randomized, open-label, multi-center trial, 424 patients received Prograf (n=212) or cyclosporine (n=212) in combination with MMF 1 gram BID with basiliximab induction. Mortality at 12 months was increased in those patients receiving Prograf/MMF (4.2%) compared to those receiving cyclosporine/MMF (2.4%) despite using lower mean doses of MMF in the patients on Prograf. The increase in mortality appeared related to a higher incidence of severe infections. At the 1-year endpoint, 5 out of the 9 deaths in the Prograf/MMF arm were due to infections whereas only 1 out of the 5 deaths was due to infections in the cyclosporine/MMF arm. The use of Prograf and MMF 1 gram BID (2 grams/day) is not recommended in kidney transplantation. A safe and effective dosing regimen of MMF in combination with Prograf has not been established in kidney transplantation.

The use of full-dose Prograf with sirolimus (2 mg per day) in heart transplant recipients was associated with increased risk of wound healing complications, renal function impairment, and insulin dependent post transplant diabetes mellitus, and is not recommended (see **CLINICAL STUDIES**).

5) ***Reviewer's Comments: More detailed information regarding the dose of MMF used in the clinical study describing Prograf+MMF for heart transplantation should be included:***

In the US study, at week 1 the dose of MMF (mean ± SD) was similar in both treatment arms (Prograf 2733 ± 661 mg/day vs. cyclosporine 2748 ± 647 mg/day); however, by month 12, the dose in the tacrolimus arm was lower than the dose in the cyclosporine modified arm (Prograf 1859 ± 877 mg/day vs. cyclosporine modified 2351 ± 1027 mg/day). (see **PRECAUTIONS**, **Interaction with Other Immunosuppressants**).

6) ***Reviewer's Comments: In the INDICATIONS AND USAGE section, the Applicant has information that concomitant use of azathioprine or MMF is recommended for use in combination with Prograf in heart transplantation. Parallel information regarding Prograf and azathioprine for kidney transplantation should be included in the Package Insert since that was the combination used in the original clinical studies in kidney transplantation. Alternatively, the Applicant can remove all references (except adrenal corticosteroids) to concomitant immunosuppressants from the INDICATIONS AND USAGE section.***

7) ***Reviewer's Comments: Insert the following subheadings in the WARNING section and reorganize the information under the appropriate categories:***

Post-Transplant Diabetes Mellitus
Nephrotoxicity
Hyperkalemia
Neurotoxicity
Malignancy and Lymphoproliferative Disorders
Prograf in Combination with other Immunosuppressants

9.5 Comments to Applicant

1) If the Applicant wishes to conduct another study of Prograf+MMF compared with cyclosporine with MMF, the maximum dose of MMF used in the study should be the dose of MMF that will achieve the same systemic exposure of MPA achieved when MMF 2 grams/day is used in combination with cyclosporine.

2) Any future studies to evaluate the safety and efficacy of a drug to be used in combination with Prograf should also include endpoints regarding the use and tolerability of that drug (not just of Prograf). Also, adverse events known to be caused by the other drug should be specifically and systematically defined and collected.

3) Future clinical trials in drug development should be not rely so greatly on physician discretion, especially regarding the dose used. Dose changes should be systematically prescribed and carefully characterized so that the data can be used to support alternative doses if the originally proposed dose was determined to be unacceptable.

10 Appendices

10.1 Review of Individual Study Reports

Not applicable. Primary study is incorporated throughout this review.

10.2 Line-by-Line Labeling Review

See 9.4 Labeling Review.

10.3 Abbreviations

ANOVA	Analysis of variance
ATGAM®	Anti-thymocyte globulin (equine) sterile solution (Pharmacia & Upjohn Company)
ATN	Acute tubular necrosis
BCAR	Biopsy-confirmed acute rejection
bid	Twice daily
BUN	Blood urea nitrogen
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CMV	Cytomegalovirus
CRF	Case report form
CRP	C-reactive protein
CYA	Cyclosporine (Neoral® - Novartis Pharmaceuticals Corporation)
DGF	Delayed graft function
DSMB	Data Safety Monitoring Board
EBV	Epstein-Barr virus
ECG	Electrocardiogram
HbA_{1C}	Hemoglobin A_{1C} (glycosylated hemoglobin, glycohemoglobin)
HBeAg	Hepatitis B envelope antigen
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus antibody
HCV-RNA	Hepatitis C virus ribonucleic acid (quantitative test for HCV)
HDL	High density lipoprotein (also referred to as HDL cholesterol)
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
IEC	Independent Ethics Committee
IRB I	Institutional Review Board
IVIG	Intravenous immunoglobulin
LDL	Low density lipoprotein (also referred to as LDL cholesterol)
MDRD	Modified Diet in Renal Disease Study Group
MedDRA	Medical Dictionary for Regulatory Activities
MMF	Mycophenolate mofetil (CellCept® - Roche Laboratories Inc.)
MPA	Mycophenolic acid
MR4	Tacrolimus modified-release formulation (FK506E)
NCI-CTC	National Cancer Institute Common Toxicity Criteria
OKT®3	Orthoclone OKT®3 (muromonab-CD3 – Ortho Biotech)
OPTN	Organ Procurement and Transplantation Network
PRA	Panel reactive antibody
PTDM	Post-transplant diabetes mellitus
qd	Once daily
qid	Four times daily
RBC	Red blood cells
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase (also aspartate aminotransferase [AST])
SGPT	Serum glutamic pyruvate transaminase (also alanine aminotransferase [ALT])
SRTR	Scientific Registry of Transplant Recipients
TGF-beta	Transforming growth factor-beta
tid	Three times daily
WBC	White blood cells

10.4 List of Investigators Participating in Study 02-0-158

In Brazil:

Deise R. De Boni Monteiro de Carvalho, M.D.
Hospital Geral de Bonsucesso
Av. Londres, 616 – 2o. andar
Rio de Janeiro – RJ
21041-003 - Brazil

Gentil Alves Filho, M.D.
Hospital das Clinicas – UNICAMP
Rua Tessalia Vieira de Camargo, 126 –
Disciplina de Nefrologia DCM FCM
Distrito Barão Geraldo – Cidade Universitária "Zeferino Vaz"
Campinas – SP – 13083-971 – Brazil

Valter Duro Garcia, M.D.
Irmandade da Santa Casa de Misericórdia de Porto Alegre
Rua Professor Annes Dias, 285 – Nefrologia
Porto Alegre – RS – 90020-090 – Brazil

Maria Cristina Ribeiro de Castro, M.D.
Hospital das Clinicas da Faculdade de Medicina
da USP Av. Dr. Enéas de Carvalho Aguiar, 255 –
Urologia – sala 7036
São Paulo – SP – 05422-970 - Brazil

Helio Tedesco Silva Junior, M.D.
Hospital do Rim E Hipertensã- Fundação Oswaldo Ramos
Rua Borges Lagoa, 960 – 11o. andar
Vila Clementino
São Paulo – SP – 04038-002

In Canada:

Dr. Anne Boucher, Néphrologue
Hôpital Maisonneuve-Rosemont
5415 Boulevard de l' Assomption
Montréal, Québec H1T2M4
Canada

Patricia Campbell, M.D.
University of Alberta Hospitals
11-107 Clinical Sciences Building
8440-112 Street
Edmonton, Alberta, Canada T6G 2B7

Michel R. Pâquet, M.D., Ph.D.
CHUM Hôpital Notre Dame
1560 Sherbrooke Est
Montréal, Québec H2L 4M1
Canada

Jean Shapiro, M.D.
BC Transplant Society
West Tower 3rd Floor
555 West 12th Avenue
Vancouver, BC V5Z3X7
Canada

Dr. Jeffrey Zaltzman
St. Michael's Hospital
61 Queen Street East 9th floor
Toronto, Ontario, Canada
M5C 2T2

In United States:

Marwan Abouljoud, M.D.
Henry Ford Hospital
Transplant Surgery (K-7)
2799 West Grand Blvd.
Detroit, MI 48202

Rita Alloway, Pharm.D.
University of Cincinnati
231 Albert Sabin Way
Medical Science Bldg #3465
Cincinnati, OH 45267

Scott Ames, M.D.
Mount Sinai School of Medicine
One Gustave L. Levy Place Box 1104
New York, NY 10029

Kenneth Andreoni, M.D.
2112 Bioinformatic Bldg.,
CB#7211
Chapel Hill, NC 27599-7211

William M. Bennett, M.D.
Legacy Transplant Services
Legacy Good Samaritan Hospital
1040 NW 22nd Avenue, Suite 480
Portland, OR 97210

Roy D. Bloom, M.D.
University of Pennsylvania Medical Center
Renal Division
415 Curie Boulevard/700 CRB
Philadelphia, PA 19104

Barbara Bresnahan
Medical College of Wisconsin
9200 West Wisconsin Avenue FMCLB 216
Milwaukee, WI 53226

Stéphan Busque, M.D.
750 Welch Road, Suite 319
Palo Alto, CA 94304

Khalid M. H. Butt, M.D., FACS
Director of Transplantation and Vascular Surgery
Medical Arts Atrium
19 Bradhurst Avenue, Suite 3150
Hawthorne, NY 10532

Jose Castillo-Lugo, M.D.
Dallas Nephrology Associates
1420 Viceroy Drive
Dallas, TX 75235

Laurence Chan. M.D.
University of Colorado Health & Sciences Center
4200 E. Ninth Ave., Box C281
Denver, CO 80262

Diane Cibrik, M.D.
University of Michigan
1500 E. Medical Center Dr.
3914 Taubman Center
Ann Arbor, MI 48109-0364

David J. Conti, M.D.
Albany Medical College
Department of Surgery
47 New Scotland Avenue
Mail Code: A-61
Albany, NY 12208-3479

A. Benedict Cosimi, M.D.
Department of Surgery
Massachusetts General Hospital
55 Fruit Street
Boston, MA 02114

James D. Eason, M.D., FACS
Ochsner Clinic Foundation
Multi-Organ Transplant Center
1514 Jefferson Highway
New Orleans, LA 70121

George C. Francos, M.D.
Thomas Jefferson University 111 South 11th Street, Suite 4290
Philadelphia, PA 19107

In the United States (cont'd):

Dr. Mahendra Govani
Indiana University Medical Center
550 N. University Blvd., Room 4601
Indianapolis, IN 46202

Robert Harland, M.D.
5841 S. Maryland Ave. (MC 5026)
Chicago, IL 60637

Marquis E. Hart, M.D.
UCSD Medical Center
402 Kickenson Street, Suite #280
San Diego, CA 92103-8401

Stephen Jensik
University Transplant
1725 West Harrison, #161 PB3
Chicago, IL 60612-3824

Johann Jonsson, M.D.
Inova Transplant Center
8503 Arlington Blvd., Suite 200
Fairfax, VA 22042

Bruce Kaplan, M.D.
University of Florida
1600 SW Archer Road
Box 100224
Gainesville, FL 32610

Clifton E. Kew, II, M.D.
University of Alabama at Birmingham
Division of Nephrology
Building THT 643
Birmingham, AL 35294

Paul C. Kuo, M.D., M.B.A.
Professor of Surgery
Section of Transplant Surgery
Bell Research Building, Room 110
Duke University Medical Center, Erwin Road
Durham, NC 27710

David Laskow, M.D.
125 Paterson Street
Clinical Academic Building, Suite 2160
New Brunswick, NJ 08901

Jimmy A. Light, M.D., F.A.C.S.
Director, Transplantation Services
Washington Hospital Center
110 Irving Street NW, Suite 3D31
Washington, DC 20010-2975

Martin L. Mai, M.D.
4205 Belfort Road, Suite 1100
Jacksonville, FL 32216

Rodrigo Mateo, M.D.
USC Keck School of Medicine
Healthcare Consultation Center
1510 San Pablo Street, 2nd Floor
Los Angeles, CA 90033

Joseph Keith Melancom, M.D.
Johns Hopkins Hospital
600 North Wolfe Street
Harvey 611
Baltimore, MD 21287

Larry B. Melton, M.D., Ph.D.
3500 Gaston Avenue
Dallas, TX 75246

Rafael Mendez, M.D.
National Institute of Transplantation
2200 West 3rd Street
Suite #100
Los Angeles, CA 90057

Shamkant Mulgaonkar, M.D.
Saint Barnabas Medical Center
94 Old Short Hills Road
Livingston, NJ 07039

In the United States (cont'd):

Laura Lyngby Mulloy, D.O.

Charles R. Nolan, III, M.D.

Professor of Medicine
Chief, Section of Nephrology, Hypertension and Transplantation Medicine
Medical College of Georgia
1120 15th Street
Augusta, GA 30912

Organ Transplantation MC 7858
The University of Texas Health Science Center at San Antonio
7703 Floyd Curl Drive
San Antonio, TX 78229-3900

Douglas J. Norman, M.D.
Oregon Health & Science University, PP-262
3314 SW US Veterans Hospital Road
Portland, OR 97239-2940

William A. Nylander, M.D.
Vanderbilt University Medical Center
912 Oxford House
Nashville, TN 37232-4750

Okechukwu Ojogho, M.D.
Loma Linda Univeristy Medical Center
Transplantation Institute
11234 Anderson St., Room 1405
Loma Linda, CA 92354

Oleh G. Pankewycz, M.D.
Kaleida Health – Buffalo General Hospital
Renal/Pancreas Transplant Department
100 High Street, A416
Buffalo, NY 14203

V. Ram Peddi, M.D.
California Pacific Medical Center
2340 Clay Street, 4th Floor
San Francisco, CA 94115

Alice Peng, M.D.
Cedars-Sinai Medical Center
8635 West Third Street, Suite 590-W
Los Angeles, CA 90048

Phuong-Thu Pham, M.D.
UCLA School of Medicine
Division of Nephrology
924 Westwood Blvd., Suite 860
Los Angeles, CA 90095-7309

John D. Pirsch, M.D.
University of Wisconsin
H4/772 Clinical Science Center
600 Highland Avenue
Madison, WI 53792-7375

Velma P. Scantlebury, M.D.
2451 Fillingin Street, Suite 10F
Mobile, AL 36617

Fuad Shihab, M.D.
University of Utah, 4R312 SOM
30 North 1900 East
Salt Lake City, UT 48132

Douglas Slakey, M.D.
Tulane Center for Abdominal Transplant
1415 Tulane Avenue, TW-35
New Orleans, LA 70112

Steven Marc Steinberg, M.D.
California Institute of Renal Research
7920 Frost Street
Suite 301
San Diego, CA 92123

Stephen J. Tomlanovich, M.D.
University of California, San Francisco
Kidney Transplant Service
505 Parnassus Avenue, Room 884M
San Francisco, CA 94143-0780

Charles T. Van Buren, M.D.
St. Luke's Episcopal Hospital
6720 Bertner Ave., MC 2-114B
Houston, TX 77030

In the United States (cont'd):

Thomas Wald, M.D.
University of Kentucky Medical Center

Harold C. Yang, M.D., Ph.D.
205 South Front Street

800 Rose Street, Rm C437
Lexington, KY 40536

Brady 8
Harrisburg, PA 17105-8700

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Efficacy

Study MRE 022

Events Rates through Month 6	**MMF2 N=165**	**MMF3 N=160**
Clinical event (death, graft loss or BPAR)	31 (19%)	26 (16%)
Other failure (premature withdrawal)	19 (12%)	36 (23%)
BPAR	28 (17%)	22 (14%)
Graft loss/death (no prior acute rejection)	3 (2%)	4 (3%)

Study ICM 1866 Efficacy

Events Rates through Month 6	**MMF2 N=167**	**MMF3 N=166**
Clinical event (death, graft loss or BPAR)	36 (22%)	31 (19%)
Other failure (premature withdrawal)	16 (10%)	21 (13%)
BPAR	33 (20%)	29 (18%)
Graft loss/death (no prior acute rejection)	3 (2%)	2 (1%)

Adverse Events in the original MMF NDA for Kidney Transplantation

Selected Adverse Events	**MMF2 (n=501)**	**MMF3 (n=490)**
Sepsis	19.0%	19.0%
Severe	6.6%	7.1%
Infection	16.4%	19.2%
Diarrhea	26.1%	30.4%
Severe	2.6%	2.9%
Leukopenia	19.4%	29%
Severe	2.4%	5.3%
Anemia	19%	20%
Severe	10.4%	12.4%
Thrombocytopenia	8.6%	6.9%

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Hui-Hsing Wong
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Marc Cavaille Coll
3/14/2007 04:59:50 PM
MEDICAL OFFICER
Concur with recommendation. See MOTL Review.