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APPLICATION NUMBER:

204096Orig1s000

STATISTICAL REVIEW(S)

Addendum to the Statistical Review of NDA 204096

NDA/BLA Serial #:	204096/Original 1
Drug Name:	Tacrolimus extended release capsules (Astagraf XL)
Indication(s):	Prophylaxis of organ rejection in adult patients receiving kidney transplants.
Applicant:	Astellas
Date(s):	Received 9/21/12 PDUFA due date 7/21/13
Biometrics Division:	Division of Biometrics IV
Statistical Reviewer:	Joy Mele, M.S.
Concurring Reviewers:	Karen Higgins, Sc.D. Team Leader
Medical Division:	Division of Transplant and Ophthalmology Products
Clinical Team:	Marc Cavaille Coll, M.D. Clinical Reviewer Joette Meyer, Pharm. D. Clinical Team Leader
Project Manager:	Jacquelyn Smith
Addendum Subject:	Number of patients whose treatment assignment remained blinded for 12 months for Study FG-506E-12-03

The full application including all study reports and datasets may be accessed via Global Submit at \\CDSESUB1\EVSPROD\NDA204096\204096.enx.

The clinical division director (Dr. Renata Albrecht) requested that the statistical reviewer compute the percentage of patients whose treatment assignment remained blinded for 12 months of Study FG-506E-12-03 (abbreviated as 1203). This information was not available in the study report for Study 1203. Please see the statistical review in DARRTS dated 6/4/2013 for details regarding Study 1203. The focus here is on all patients that were counted as part of the intent-to-treat population (99% of randomized patients, see Table 1 on the following page).

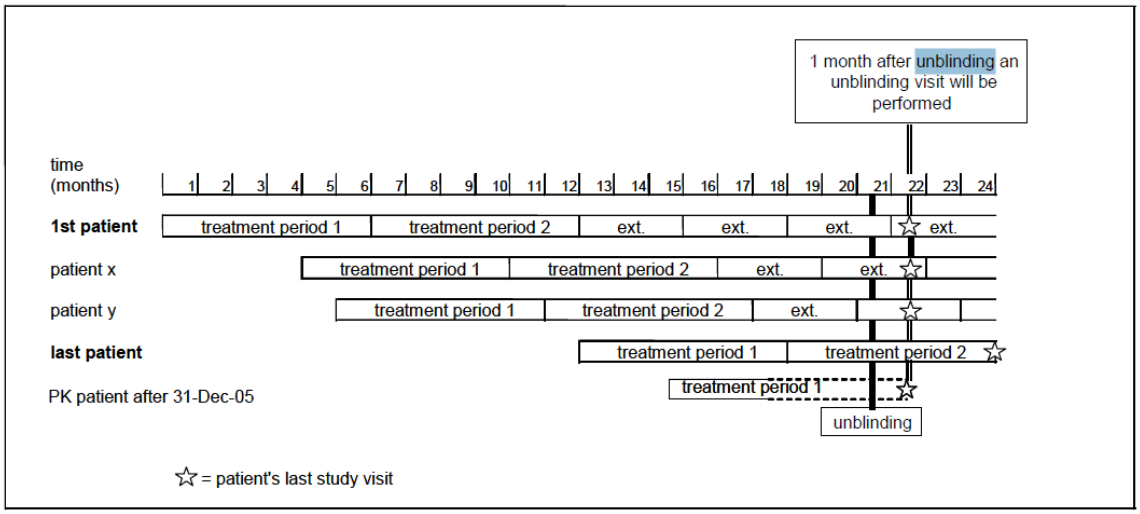
Study 1203 was conducted as a double-blind double-dummy trial until the last patient enrolled had completed 24 weeks on study. At that point the trial was unblinded and patients continued to be followed for 12 months on study. After completing 12 months on study, patients had the option to continue into an extension study. Table 1 contains information on how many patients reached the 12 month mark prior to study unblinding. Also reported are the number of patients who remained on study for 12 months of blinded treatment. Figure 1 is the applicant's schematic illustrating patient exposure based on time of randomization

Table 1 Study 1203 Patient Disposition[1]

	Tac-XL	Prograf	Total
Randomized for primary analysis population[2]	336 (100%)	340 (100%)	676 (100%)
Reason not included in ITT population			
No transplantation	2	3	5
No study treatment	1	0	1
Withdrew consent *(3 days after 1st dose)*	1	0	1
ADE *(on first day of dosing)*	1	1	2
Full Analysis Population (ITT)[3]	331 (99%)	336 (99%)	667 (99%)
ITT patients enrolled at least one year prior to trial unblinding	316 (95%)	325 (97%)	641 (96%)
ITT patients with >351 days on study at time of unblinding the study	300 (91%)	311 (93%)	611 (92%)

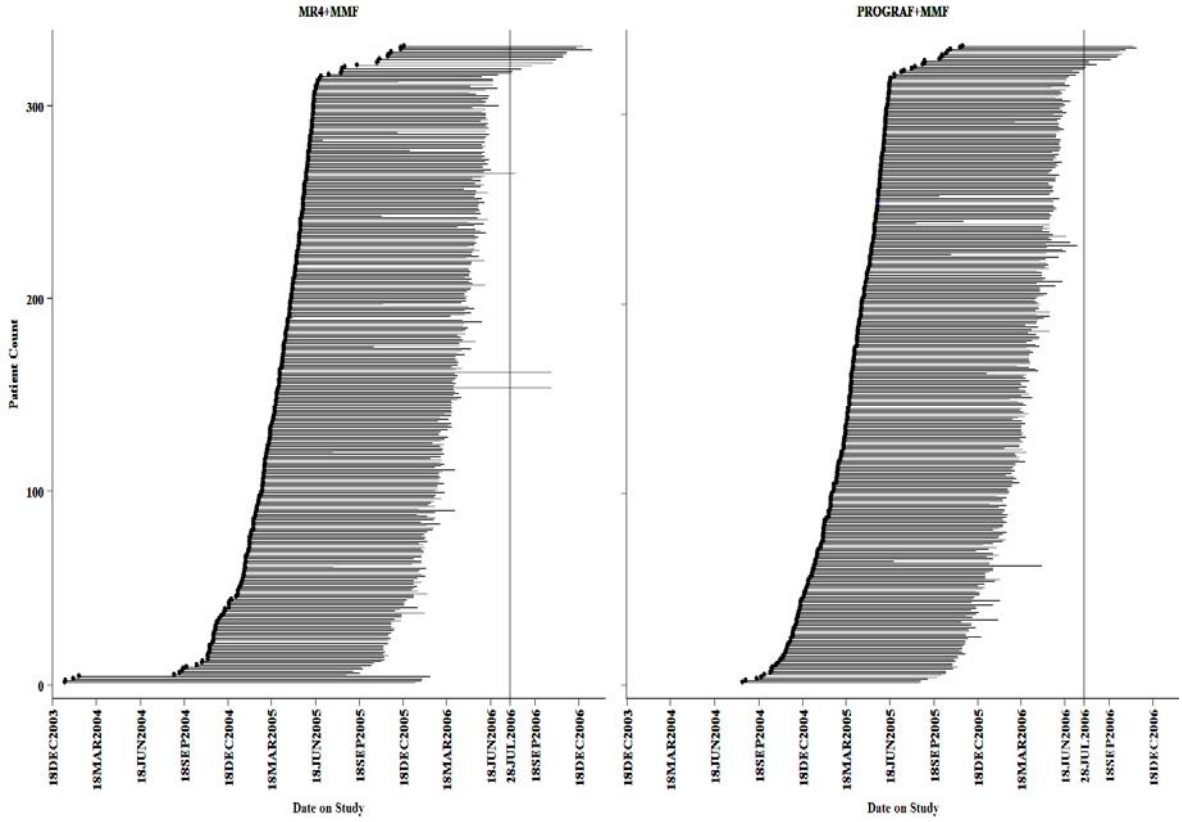
[1] The numbers for this table were computed by this reviewer based on the analysis dataset ACCT provided by the applicant.
[2]This population contains all patients that were enrolled and randomized to be followed for clinical endpoints. Twenty patients included in the PK sub-study and then followed for clinical endpoints are included in this population.
[3] This reviewer considers the full analysis population to be the intent-to-treat (ITT) population for efficacy analysis. All results for this review are based on this population.

Figure 1: Schematic Overview of Study Design



Based on dataset ACCT submitted by the applicant, patients were randomized from January 14, 2004 to November 21, 2005. Unblinding of the trial occurred on July 28, 2006. The last patient to enroll completed the study on December 28, 2006. The majority of patients (96%) were randomized at least 12 months before the trial was unblinded (Table 1). The treatment assignments for these patients remained blinded for 12 months regardless of their follow-up. Also the majority of patients had a full 12 months of blinded follow-up (92%); this number would exclude those patients who discontinued from the study due to death, lost-to-follow-up or other reasons without completing 12 months of blinded follow-up. The exposure for each patient is illustrated in Figure 2 below. It is clear that the majority of patients had completed their last visit for the 12 month study period by the time of the unblinding of the study.

Figure 2. Plot of time on study by patient. For each patient, the symbol represents the randomization date and the line represents the length on time to the last visit on the 12-month study. A line at July 28, 2006 represents the date the study was unblinded. The dates are based on data from dataset ACCT provided in the NDA submission.



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/s/

JOY D MELE
07/17/2013

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

Clinical Studies

NDA/BLA Serial #:	204,096/Original 1
Drug Name:	Tacrolimus extended release capsules (Astagraf XL)
Indication(s):	Prophylaxis of organ rejection in adult patients receiving kidney transplants.
Applicant:	Astellas
Date(s):	Received 9/21/12
	PDUFA due date 7/21/13
Review Priority:	Standard
Biometrics Division:	Division of Biometrics IV
Statistical Reviewer:	Joy Mele, M.S.
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	Joette Meyer, Pharm. D. Clinical Team Leader
Project Manager:	Jacquelyn Smith

Keywords: active control/non-inferiority

Link to keywords:
http://intranetapps.fda.gov/scripts/ob_apps/ob/eWork/uploads/eWork/2009/Keywords-in-DFS.htm

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1 EXECUTIVE SUMMARY

Tacrolimus, a calcinerin inhibitor marketed as Prograf given twice daily, was first approved in 1994 in the United States for the prophylaxis of organ rejection in patients receiving liver transplants and was approved 3 years later for use in patients receiving kidney transplants. With this present application, the applicant is seeking approval for the use of a once daily extended release formulation of tacrolimus (referred to here as Tac-XL). The trade name for this product is Astagraf XL. The results of three randomized, phase 3 clinical trials, 02-0-158, FG-506E-12-03 and PMR-EC-1210 were submitted to demonstrate the efficacy and safety of Tac-XL. Studies 158 and 1203 are both 12 month studies while Study 1210 is a 24 week study. The applicant considers Study 158 to be their pivotal trial; FDA considers both Study 158 and Study 1203 to be important for considering the approval of Tac-XL for use in kidney transplantations.

The designs for the three clinical trials are summarized in Tables 2.1.1 and 2.1.2. All trials contained treatment arms for Prograf and Tac-XL at an initial daily dose of 0.2 mg/kg then dosed based on target ranges. The Prograf initial dose is twice the dose recommended in labeling for Prograf; however the median trough levels observed in these studies were within the targeted trough levels suggested in the labeling. Studies 158 and 1210 were open label trials while Study 1203 contained an initial 24-week double-blind period followed by a 28-week open label period. Study 158 included induction with basiliximab while Studies 1203 and 1210 included a pre-dose of tacrolimus (0.1 mg/kg). The primary endpoints for the three trials were different but all three trials collected the data to assess efficacy failure by recording locally biopsied confirmed acute rejection, deaths, graft losses and losses to follow-up. The results for efficacy failure are the primary focus of this review.

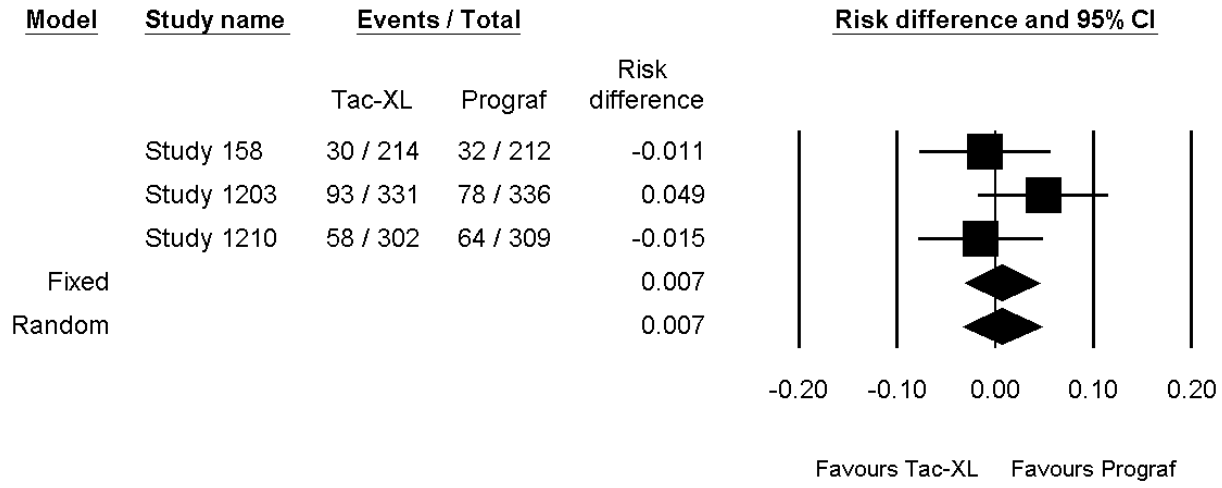
To demonstrate the efficacy of Tac-XL, it was necessary to show the non-inferiority of Tac-XL to Prograf. This reviewer computed an M1 of about 30% based on data from the literature. Showing that a confidence interval on the treatment difference excluded 30% would provide evidence that Tac-XL is better than placebo; however, this generally is not sufficient for demonstrating non-inferiority in that one would prefer to demonstrate that the new drug has retained a large proportion (usually 50% or more) of the effect of the active control (M2). In transplantation, a 10% margin is commonly used. However, the choice of the final margin as long as it is less than or equal to M1 is a clinical decision.

The efficacy results from all three clinical trials, Studies 158, 1203 and 1210, demonstrated the non-inferiority of Tac-XL, a once a day dosing regimen, to Prograf, a twice a day dosing regimen based on efficacy failure (locally biopsied confirmed acute rejection, death, graft loss or lost-to-follow-up) with a final margin choice no larger than 11.6%. In all three trials, most of the efficacy failures were due to LBCARs that occurred early in the trial (about half during the first 10 days). Although the event rates differed among the trials (Table 1.1), the treatment differences were comparable (Figure 1.1).

Table 1.1 Efficacy failure results for Studies 158, 1203 and 1210

	Study 158 12 mos		Study 1203 12 mos		Study 1210 24 wks	
	Tac-XL (n=214)	Prograf (n=212)	Tac-XL (n=331)	Prograf (n=336)	Tac-XL (n=302)	Prograf (n=309)
Efficacy Failure	30 (14%)	32 (15%)	93 (28%)	78 (23%)	64 (21%)	58 (19%)
Death	3 (1%)	9 (4%)	10 (3%)	8 (2%)	6 (1.9%)	8 (2.7%)
Graft Loss	5 (2%)	9 (4%)	28 (9%)	24 (7%)	18 (6%)	29 (10%)
BCAR	22 (10%)	16 (8%)	68 (21%)	54 (16%)	42 (14%)	31 (10%)
Lost-to-FU	3 (1%)	4 (2%)	4 (1%)	7 (2%)	8 (2.6%)	7 (2.3%)
Tac-XL-Prograf (CI)	-1% (-8%, +6%)		+4.9% (-2%, +11.5%)		-2% (-8%, +5%)	

Figure 1.1 Meta-analysis of efficacy failure



Treatment differences were also comparable across many subgroups for Studies 158 and 1203 with no significant treatment by subgroup differences observed. Subgroups defined by the initial dose of tacrolimus post-transplantation and by the first recorded C_{min} showed no significant differences in treatment effects.

Because of the FDA concern regarding a significant interaction for sex by treatment seen for deaths in a study for liver transplant patients, this reviewer looked at the deaths by sex for Studies 158 and 1203. There was no significant interaction seen in kidney transplant patients. For females, fewer deaths were seen on Tac-XL than Prograf in each of the two studies. See the statistical review of Study 1103 for the liver indication for details regarding the significant treatment by sex interaction seen for mortality.

Higher doses of Tac-XL were required to achieve trough levels within target ranges and also to achieve levels comparable to Prograf. This difference in daily doses did not seem to impact safety outcomes with comparable rates seen for adverse events commonly associated with tacrolimus (see Table 4.1.1). Also comparable rates of NODAT were seen for the two treatment groups with no evidence of a treatment difference by sex, as suggested in liver transplant Study 1103.

For kidney transplantation, from a statistical perspective, Tac-XL has been shown to have a comparable benefit-risk profile to Prograf, an approved product.

2 INTRODUCTION

2.1 Overview

With the submission of NDA 204-096, the applicant is seeking approval for the use of a once daily extended release formulation of tacrolimus[1] in patients receiving kidney transplantation or liver transplantation (these two indications were administratively separated as Original 1 and 2, respectively). This document is a review of the indication for kidney transplantation; the liver transplantation indication is reviewed in a separate document. Tacrolimus, a calcinerin inhibitor marketed as Prograf given twice daily, was first approved in 1994 in the United States for the prophylaxis of organ rejection in patients receiving liver transplants and was approved 3 years later for use in patients receiving kidney transplants. This present application was originally submitted under NDA 50-811 and an approvable letter was sent March 13, 2008 based on the results of one Phase 3 study (02-0-158). Because of safety concerns arising in liver transplantation trials (more mortality for women than men due to once a day dosing versus twice a day dosing) , FDA asked for additional data to establish that the same effect was not seen in kidney transplantation. In addition, the FDA required additional safety data to ascertain whether the 20% higher AUC for Tac-XL compared to Prograf on Day 7 and 14 seen in the PK sub-study of Study 1203 resulted in a higher incidence of tacrolimus-related adverse events due to Tac-XL compared to Prograf. FDA agreed that two studies (02-0-158 and FG-506E-12-03) would sufficiently support a new filing of an NDA submission.

The applicant's rationale for development of the once a day formulation is that this formulation would improve compliance with the dosing regimen and thereby improve immunosuppression and reduce late graft loss. The applicant cites several references to support this assumption.

The applicant summarized their development of a once a day dosing tacrolimus as follows (from page 11 of the applicant's Clinical Overview):

> *The target biopharmaceutic goals for the development of Advagraf were to achieve AUC relative to Prograf[2] within bioequivalence criteria and an equal or reduced Cmax as compared with that of Prograf. In addition, clinical development of a once-a-day formulation required a good correlation of trough concentration to AUC (similar to that obtained for Prograf), and the same trough target range as Prograf, so that patient care strategies and therapeutic monitoring techniques currently used with Prograf could be employed for Advagraf.*

The applicant states that a high correlation between steady state trough levels (C_{min}) and total exposure over a dosing interval (AUC) has been shown and that either measure is related to risk of acute rejection with lower levels associated with an increased incidence of acute rejections. However, the applicant also notes that high trough levels have been shown to be related to toxicity. Furthermore the applicant claims that that the pharmacokinetics of once a day are similar to the twice a day formulation.

From discussions with the FDA medical reviewer, Dr. Marc Cavaille Coll, primary issues in this application are whether the once a day dosing pharmacokinetics are acceptable and comparable to twice a day dosing and whether the safety profiles are the same for the two formulations. The PK issue will be addressed by the FDA clinical pharmacologist and the medical reviewer. For this statistical review, the

[1] Several names have been used for the extended release product including FK506E, MR4, Prograf XL and Advagraf. The applicant wishes to use the name Advagraf for marketing but the FDA has not agreed to that name.
[2] Prograf is the registered name for twice a day tacrolimus.

emphasis will be on clinical endpoints, more specifically on an efficacy failure endpoint (BPAR, death, graft loss or lost to follow-up), measured at Month 12 and an assessment of the comparability of the two formulations of tacrolimus (once daily and twice daily) for both safety and efficacy. The names for these products are abbreviated here as Tac-XL for the once a day formulation under review here and Prograf for the approved twice a day formulation.

The designs for the three trials reviewed here are summarized below in Table 2.1.1. All three studies listed in Table 2.1.1 are Phase 3 randomized trials that include treatment arms for Prograf and Tac-XL. Studies 02-0-158 (Study 158) and FG-506E-12-03 (Study 1203) are 12 month studies while PMR-EC-1210 (Study 1210) is a 24 week supportive study. Although different primary endpoints were used in these trials, data for efficacy failures was collected and analyzed by the reviewer for all three studies.

Study 158 was previously reviewed by FDA and results from that statistical review are included in this review (details are provided in section 3.1 of this review). The data of 34 evaluable patients from a PK substudy of Study 1203 were summarized but no statistical comparisons were performed because of the limited data. The full results of Study 1203 are reviewed here. Study 1210 was not previously submitted and is reviewed here to provide supportive evidence for the results of Studies 158 and 1203.

Table 2.1.1 Summary of Phase 3 trials using Tac-XL in patients undergoing kidney transplantations

Study	Design	Trt Duration & Primary Endpoint	Tac-XL[1]	Prograf[1]	Comments
02-0-158	Phase 3 multicenter, randomized, third arm of cyclosporine, plus MMF and corticosteroids, with basiliximab induction	Open-label (OL) 1 year Month 12 efficacy failure defined as death, graft failure, biopsy-confirmed acute rejection, or lost to follow-up	N=226 Initial dose of 0.15 to 0.2 mg/kg once daily (OD)	N=219 Initial dose of 0.075 to 0.1 mg/kg twice daily (BID)	FDA reviewed in full in 2007. Stat reviewer concluded that Tac-XL was effective compared to cyclosporine but more data was needed to assess dosing & safety.
FG-506E-12-03	Phase 3 multicenter, randomized 1:1 to once a day or twice a day tacrolimus plus MMF and corticosteroids, no induction therapy	Double Blind 24 wks OL 28 wks Week 24 biopsy-proven acute rejection Month 12 efficacy failure was a 2nd ep	N=346 Initial dose of 0.2 mg/kg OD	N=353 Initial dose of 0.1 mg/kg BID	Statistical review of PK substudy in 2008
PMR-EC-1210	Phase 3 multicenter Randomized to one of 4 arms plus MMF and corticosteroids	OL 24 wks Wk 24 graft loss, biopsy confirmed acute rejection, or graft dysfunction GFR < 40mL/min/1.73m2	Three OD mg/kg initial doses 0.2 (N=316) 0.3 (N=317) 0.2 + induction (N=298)	N=320 Initial dose of 0.1 mg/kg BID	Not previously reviewed by FDA

[1] Details regarding dosing, target trough levels and the full regimen of drugs used are provided on the following page in Table 2.1.2.

The immunosuppressant treatment regimens and dosing for these trials are summarized in Table 2.1.2 below. There are some notable differences among the three trials. Study 158 includes induction with basiliximab while Study 1203 includes no induction but does include dosing prior to transplantation. The Prograf and Tac-xl arms in Study 1210, like 1203, include no induction but do include dosing prior to transplantation

Table 2.1.2 Protocol-defined dosing in Phase 3 trials using Tac-XL in patients with kidney transplantations

	Induction	Pre-dose	Initial Dose	Target Trough level	MMF	CCS
Study 158						
Tac-XL	basiliximab Day 0: 20 mg Day 3, 4 or 5: 20 mg	NONE	0.15-0.2 mg/kg Per day	Days 0-90: 7-16 ng/ml Days >90: 5–15 ng/ml	Post-op 1 g BID [Blacks could get 1.5 g BID]	Methylprednisolone Day 0: iv bolus 500-1000 mg Day 1: oral 200 mg iPrednisone mg/d Days 2-14: 20-30 Days 15-30: 10-20 Days 31-60: 10-15 Mos 3-12: 5-10
Prograf		NONE	0.075-0.1 mg/kg BID			
CYC		NONE	4-5 mg/kg BID	Days 0-90: 125-400 ng/ml Days >90: 100-300 ng/ml		
Study 1203						
Tac-XL	NONE	0.1 mg/kg	0.2 mg/kg Per day	Days 0-28: 10–15 ng/ml Days 29-168 5–15 ng/ml Days >168: 5–10 ng/ml	Pre-op 1g BID Post-op Days 1-14 1g BID Days>14 0.5 g BID	Methylprednisolone iv bolus: Day 0: ≤ 1000 mg Day 1: 125 mg iPrednisone mg/d Days 2-14: 20 Days 15-28: 15 Days 29-42: 10 Days 43-84: 5 Days >84: ≤ 5 withdrawal for selected subjects
Prograf	NONE	0.1 mg/kg	0.1 mg/kg BID			
Study 1210						
Prograf	NONE	0.1 mg/kg	0.1 mg/kg BID	Days 0-14: 10–15 ng/ml Days 15- 42: 5–12 ng/ml Days 43-168: 5–10 ng/ml	Pre-op 1g Post-op 1g BID	Methylprednisolone iv bolus: Day 0: ≤ 500 mg Day 1: 125 mg iPrednisone mg/d Days 2-14: 20 Days 15-28: 15 Days 29-42: 10 Days 43-84: 5 Days 85-168: ≤ 5 withdrawal for selected subjects
Tac-XL 0.2	NONE	0.1 mg/kg	0.2 mg/kg Per day			
Tac-XL 0.3	NONE	0.15 mg/kg	0.3 mg/kg Per day			
Tac-XL 0.2+BAS	basiliximab Day 0: 20 mg Day 4: 20 mg	0.1 mg/kg	0.2 mg/kg Per day			Day 0: ≤ 500 mg i.v. bolus Days 1-168: 0 mg

All three studies have initial dosing after transplantation of Prograf at 0.1 mg BID; this dosing is higher than what is recommended in the labeling for Prograf where an initial dose, given with MMF and IL-2 induction, of 0.05 mg BID is recommended. The recommended trough levels for 12 months of treatment according to the labeling is 4 to 11 ng/mL which overlaps with the proposed long-term levels of 5-15 ng/mL in Study 158 and 5-10 ng/mL in Studies 1203 and 1210. The observed median long-term trough levels for the three studies were within the recommended range of 4-11 ng/mL; so although the initial dosing of Prograf differs from what is proposed in the label, the trough levels observed in these studies are consistent with the range recommended in the Prograf labeling.

Three conversion trials (Studies 02-0-131, 1202 and KT01) where Prograf is converted to Tac-XL in 165 kidney transplantation patients at least 6 months past transplantation are not reviewed here because these trial designs do not allow randomized treatment comparisons of clinical endpoints and are Phase 2 PK studies with follow-up. An additional Phase 2 PK study not reviewed here is FG-506E-12-01; this study is a 6-week open-label study comparing Prograf 0.1 mg BID to Tac-XL 0.2 mg once daily.

2.2 Data Sources and Quality

The data provided by the applicant was barely adequate for performing analyses. The data was not presented in a standardized format (such as CDISC ADaM). In addition, the define files provided with the datasets were not well done and clearly not designed for an FDA reviewer unfamiliar with the data. Each define file contained information for multiple studies; the applicant was advised at a pre-NDA meeting that this particular format would not be acceptable. Definitions for variables on the datasets were not sufficiently explicit and thereby presented many challenges for the reviewer.

The OUTCOME dataset was the primary dataset for analysis of the efficacy failure endpoint but the data in that dataset did not always agree with the EFF dataset or with results shown in the study reports necessitating an information request to the applicant. This reviewer found that the applicant's outcome events reported in the submission did not match the data provided for Study 1203. The applicant reported 68 BCARs in Table 21 of their study report, however, dataset EFF recorded 67 BCARs. The applicant responded by stating that one additional patient was identified as having a BCAR but not included as such in the submitted data. This reviewer requested a dataset be submitted with the corrected data to support the 1203 results.

The full application including all study reports and datasets may be accessed via Global Submit at \\CDSESUB1\EVSPROD\NDA204096\204096.enx.

All datasets may be linked to at \\Cdsesub1\EVSPROD\NDA204096\0000\m5\datasets.

Some of the application was difficult to navigate electronically particularly when using links within a document. The link would remove the reader from the document being viewed and not allow one to readily return to the original document.

Note that all tables and graphs in this review were created by the reviewer unless otherwise noted in the text. Also all text copied from the applicant's study reports are notated with the source.

3 Evaluation of Efficacy

3.1 Study 20-0-158

Protocol title: ñ*A phase III randomized, open-label, comparative, multi-center study to assess the safety and efficacy of Prograf® (tacrolimus)/MMF, modified release (MR4) tacrolimus/MMF, and Neoral® (cyclosporine)/MMF in de novo kidney transplant recipients"*

Design

Study 20-0-158 (henceforth referred to as Study 158) was reviewed by statistical reviewer, Dr. LaRee Tracy and her review with full details of the study is available in DARRTS (dated 1/12/2007 under NDA 50-811). An approvable letter requesting additional data to support safety in particular was issued 1/19/2007. This summary of Study 158 is based both on the study report available in the submission under review here and also based on Dr. Tracy's review.

This trial was designed to compare each tacrolimus arm (Prograf and Tac-XL) to cyclosporine (CYC) with concomitant treatment with mycophenolate mofetil (MMF) for all arms. Dr. Tracy concluded in her review that each tacrolimus arm was as effective as cyclosporine based on a 10% non-inferiority margin. For this review, the focus is on the efficacy of the Tac-XL arm compared to the Prograf arm; although both the comparison of Tac-XL to Prograf and the comparison of Tac-XL to CYC are included.

Study 158 was a Phase 3, open label, non-inferiority study. De novo kidney transplant patients were randomized to Prograf (twice daily tacrolimus), Tac-XL (once daily tacrolimus) or cyclosporine (Neoral) stratified by donor type (living or deceased) and transplant history (primary or retransplant). All patients received mycophenolate mofetil (MMF, dose of 1 g bid), corticosteroid treatment and induction with basiliximab. The actual MMF dosing differed for the arms with higher doses of MMF used for the tacrolimus arms than the cyclosporine arm; this was considered a deficiency in the approvable letter. Patients in any arm could be crossed over to Prograf or to cyclosporine (CYC) due to adverse events or severe refractory rejection leading to study drug discontinuation. Crossover rates were low in the tacrolimus arms (Tac-XL 5%, Prograf 3%) compared to the cyclosporine arm (18%); this difference was noted in the approvable letter as a deficiency in the application. The statistical review noted that several analyses were done to measure the impact of crossovers and the results did not differ from the primary analysis results for the comparison of Tac-XL to CYC. Note that differential crossover is not an issue for the comparison of Tac-XL to Prograf.

The primary endpoint was efficacy failure at one year where a failure is defined as death, graft loss, or biopsy confirmed acute rejection (BCAR). Patients missing endpoint data, i.e. lost to follow-up, were counted as failures in the primary analysis. Serum creatinine and creatinine clearance were named as secondary efficacy endpoints; the results for these endpoints are shown in Section 4.3 of this review. Only primary endpoint results are presented in this section of the review.

One interim analysis was conducted with 45% of the information and a priori an O'Brien-Fleming stopping rule was planned. The applicant states that an alpha of 0.2% (2-sided) was spent at the interim look and that the final look would be at 4.8% based on 5%-0.2%. The applicant has not computed the final alpha correctly. It is not based on subtracting the alpha spent from 5% but instead is based on numerical integration or on simulation. In addition, non-inferiority should be tested using an overall 2.5% 1-sided test. For a study with one interim look using an O'Brien-Fleming boundary, the alpha at the interim look could be 0.08% 1-sided and the final alpha to control overall alpha at 2.5% would be 2.4%. So non-inferiority would be based on a 1-sided 97.6% confidence interval. This would be equivalent to a 2-sided confidence interval of 95.2%. Although this is equivalent to the size of the CI used by the applicant, this interval is based on an interim alpha of 0.08% not the 0.1% planned by the applicant. This reviewer is assuming the applicant and the FDA statistical reviewer are correct in the alpha level used at

the final look but rounded the interim alpha up to 0.1% in the description of the interim plan. Nevertheless this reviewer does not see this as an important issue and thinks it is acceptable to report the 95.2% 2-sided confidence intervals used by both the applicant and the FDA statistical reviewer. The applicant's protocol stated that the confidence interval for the difference in rates would be computed using a normal approximation.

A non-inferiority margin of 10% was pre-specified for the comparison of each tacrolimus arm to cyclosporine and was accepted by the FDA statistical reviewer, Dr. Tracy. The FDA statistical reviewer cited a study (Asberg at al, 2006[1]) that she concluded supports a 10% margin when using cyclosporine as a comparator. The Asberg study reported a very large treatment effect of cyclosporine head to head against daclizumab of about -40% (95% CI -64%, -13%) for BPAR; daclizumab is approved and been shown to be more effective than placebo so therefore the effect of cyclosporine against placebo would most likely be larger than 40%. M1 based on this one small study against an active control is about 13% (smallest effect based on the 95% CI).

A non-inferiority margin for the comparison of Tac-Xl to Prograf would be based on an estimate of the effect of Prograf versus placebo. Results of published studies suggest a rejection rate for Prograf 0.1 mg BID + Induction+MMF+CCS of 14% (95% CI of 12%, 17%) and a rejection rate for the putative placebo, Induction+MMF+CCS, of 55% (95% CI 47%, 63%) (See Appendix 7.1 of this review for meta-analysis results). A conservative estimate of the treatment effect of Prograf over placebo would be 47% minus 17% which equals 30%. So an estimate of M1 for this comparison would be about 30%. A 50% retention of effect would suggest a non-inferiority margin (M2) of about 15%. It is a clinical decision as to the acceptable percent of retention of M1 to determine the non-inferiority margin for this study.

Results

A total of 668 patients were randomized to treatment (Table 3.1.1) with the majority of patients (81%) treated at US sites. The primary reason for not being included in the ITT population for all three groups was never received drug (Tac-XL:12 patients; Prograf:6 patients; CYC:11 patients, Appendix 14.4.1.3 of the applicant's study report). Discontinuation rates were similar for the two tacrolimus arms with about 2/3 due to adverse events; a higher discontinuation rate was seen for CYC.

Table 3.1.1 Study 158 Patient Disposition

	Tac-XL	Prograf	CYC
Randomized	226	219	223
Completed 1 yr	183 (86%)	179 (84%)	151 (71%)
ITT	214 (95%)	212 (97%)	212 (95%)
Discontinued Rand. Treatment	31 (15%)	33 (16%)	61 (29%)
ADE	9%	11%	18%
Rejection	0.5%	0%	8%
Graft Loss	0.9%	1.4%	0.5%
Lost to FU	0%	0.5%	0%
Non-compliance	0.9%	2%%	2%
Other	4%	1%	0.5%

Source Table 3.1 of Dr. Tracy's review

[1] Asberg A, Midtvedt K, Line PD, Narverud J, Holdaas H, Jenssen T, et al. Calcineurin inhibitor avoidance with daclizumab, mycophenolate mofetil, and prednisolone in DR-matched de novo kidney transplant recipients. Transplantation 2006; 82(1):62-8 In this trial, daclizumab+MMF +prednisolone is compared to cyclosporine A+MMF+prednisolone. The respective biopsy proven acute rejection rates in these two groups were 70% (19/27) and 30% (8/27). There was no difference between the groups regarding deaths or graft losses.

Treatment groups were balanced with respect to baseline demographics (Table 3.1.2). Most transplant recipients were white (about 75%) and male (about 64%). Almost all patients had no previous transplantation.

Table 3.1.2 Study 158 Patient Demographics [1]

	Tac-XL (n=214)	Prograf (n=212)	CYC (n=212)
Age			
Mean (SD)	48 (13)	49 (13)	48 (13)
Range	17-77	19-74	17-77
% ≥65years	11%	11%	9%
Donor Age			
Mean	38	39	40
Range	2-72	0-68	17-63
Gender			
% female	36%	36%	39%
Donor Gender			
% female	47%	59%	55%
Race			
% white	75%	72%	77%
% black	19%	24%	17%
No previous transplant	96%	97%	96%
Donor Type			
Living	48%	50%	52%
Deceased	52%	50%	48%
Cold ischemia time (hr) Mean (SD)	18 (7)	19 (7)	19 (7)
Donor recipient HLA-DR mismatch			
0	24%	17%	24%
1	44%	52%	51%
2	31%	35%	25%

[1]Results extracted from several tables in applicant's study report except for HLA-DR mismatches which this reviewer computed from the data

A summary of the observed dosing and trough levels are provided on the following page in table 3.1.3.

Mean days of exposure were essentially the same for the two tacrolimus groups with means of 328 days (SD=100) for Tac-XL and 327 days (SD=124) for Prograf. Also similar days of exposure were seen for MMF and corticosteroids.

The median daily doses for Tac-XL were higher than the dose observed for Prograf throughout the trial; however median trough levels were either lower or comparable for Tac-XL compared to Prograf.

Trough levels of tacrolimus were assessed about every two months with a goal of 7 to 16 ng/mL for days 0 to 90 and 5 to 15 ng/mL until study end. The applicant reports that after 1 week on treatment about 68% of Prograf and 59% of Tac-XL had trough levels within the predefined range; about 80% of the patients still on study in each tacrolimus group had trough levels in the target range from about Month 2 onwards.

Table 3.1.3 Study 158 Study drug exposures[1]

	Tac-XL (n=214)	Prograf (n=212)	CYC (n=212)
Randomized Treatment Days of Exposure Median	363	363	297
Daily dose of randomized treatment (mg/kg) Median			
Day 7	0.14	0.10	6.9
Month 1	0.13	0.10	5.2
Month 6	0.09	0.08	3.5
Month 12	0.08	0.07	3.0
Trough conc. rand. trt. Median			
Day 7 (target tac 7-16 ng/ml)	8.9	9.7	250
Month 1 (target tac 7-16 ng/ml)	10.5	10.5	302
Month 6 (target tac 5-15 ng/ml)	7.7	8.0	194
Month 12 (target tac 5-15 ng/ml)	7.2	7.2	169
Trough conc. MPA ug/ml Median			
Month 1	2.8	2.8	1.5
Month 6	2.9	2.7	1.9
Month 12	2.5	2.5	1.7

[1]Results extracted from applicant's study report

MPA trough levels were comparable for the two tacrolimus arms but notably higher than the levels seen for the cyclosporine arm. Note that MMF was supposed to be dosed the same in all groups according to the protocol. An approvable letter for NDA 50-811 noted that MMF exposures was higher in the tacrolimus arms and most likely explained the difference in the safety profile of Tac-XL and cyclosporine.

The Month 12 results for efficacy failure (Table 3.1.4) show that Tac-XL is comparable to both Prograf and cyclosporine with upper bounds of the confidence intervals of 6% or less; well within a non-inferiority boundary of 10%. Looking at the event rates by type of failure, most of the events are rejections, as would be expected and there are no notable differences between Tac-XL and Prograf. Note that the applicant and the FDA reviewer of Study 158 reported graft loss number as deaths, graft failures and lost-to-follow-ups (LTFU).

Table 3.1.4 Study 158 Month 12 Efficacy Results for the primary endpoint efficacy failure defined as death, graft loss, BCAR or lost-to-follow-up [1]

	Tac-XL (n=214)	Prograf (n=212)	CYC (n=212)	Tac-XL minus Prograf[2] 95.2% 2-sided CI	Tac-XL minus CYC[2] 95.2% 2-sided CI
Efficacy Failure	30 (14%)	32 (15%)	36 (17%)	-1% (-8%, +6%)	-3% (-10%, +4%)
Death	3 (1%)	9 (4%)	5 (2%)		
Graft Loss[3]	5 (2%)	9 (4%)	4 (2%)		
BCAR	22 (10%)	16 (8%)	29 (14%)		
LTFU	3 (1%)	4 (2%)	1 (<1%)		
Graft Loss[4]	10 (5%)	18 (9%)	10 (5%)		

1 Results based on applicant's study report and FDA statistical review dated 1/12/2007
2 Negative values favor Tac-XL
3 Graft loss includes all patients with a graft loss; 1 Tac-XL patient and 3 Prograf patients died after a recorded graft loss.
4 According to the study report, graft loss includes deaths, graft failures (permanent dialysis or retransplant) and LTFU

Analyzing time to efficacy failure yields a hazard ratio (HR) of 0.93 with a confidence interval of about 0.6 to 1.5 according to a Cox proportional model analysis by this reviewer. Both a log rank test and

Wilcoxon test produced essentially the same p-values of about 0.8. No non-inferiority margin based on the HR was named a priori so interpretation of these results is not straight-forward.

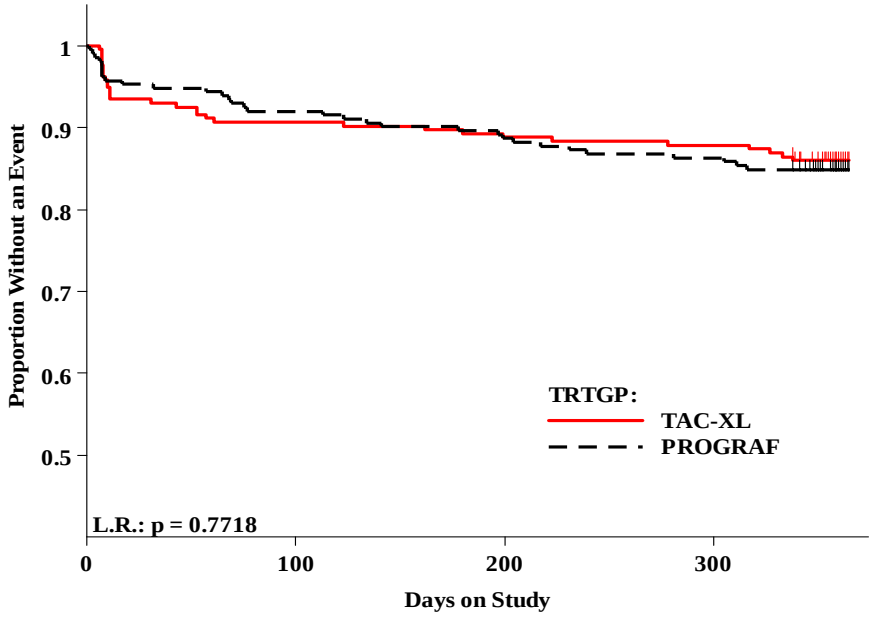
Table 3.1.5 Study 158 Reviewer's results for efficacy failure defined as death, graft loss, BCAR or lost-to-follow-up (ITT population) based on a Cox proportional hazards model analysis

	Tac-XL (n=214)	Prograf (n=212)	HR Tac-XL/Prograf[1] 95% 2-sided CI
Month 12 events Efficacy Failures	30 (14%)	32 (15%)	0.93 (0.57, 1.53)

[1]Values under 1 favor Tac-XL

The Kaplan-Meier plot illustrates the similarity between the treatment group responses for the duration of the trial.

Figure 3.1.1 Study 158 Kaplan–Meier plot of time to efficacy failure



In conclusion, the efficacy failure results from Study 158 show that Tac-XL is non-inferior to Prograf based on an estimate of M1 of about 30% and a non-inferiority margin of 10%.

3.2 Study FG-506E-12-03

Protocol title: ñ*A Multicenter, 1:1 Randomized, Double Blind, Two Arm Parallel Group Study to Evaluate and Compare the Efficacy and Safety of Modified Release Tacrolimus FK506E (MR4) Versus Tacrolimus FK506 in Combination with MMF (Cellcept®) and Steroids in Patients Undergoing Kidney Transplantation"*

Design

Study FG-506E-12-03 (henceforth referred to as 1203) was a multicenter Phase 3 trial with the first 24 weeks of the trial double-blind, double-dummy followed by an open label extension to one year. Unblinding occurred after all patients had completed at least 24 weeks on study, therefore some were treated in a blinded manner beyond 24 weeks. *De novo* kidney transplant patients were randomized to either Prograf (referred to as FK506 by the applicant) or Tac-XL (referred to as MR4 by the applicant) and all patients were given MMF plus steroid. The initial dose of tacrolimus was to be given within 12 hours prior to reperfusion (the day of reperfusion, also considered as the day of transplantation, was named as Day 0 of the trial). The target trough levels in Study 1203 were as follows: Days 0-28:10-15 ng/ml ; Days 29-168:15-15 ng/ml ; Days>168:5-10 ng/ml.

The primary endpoint for this study is described by the applicant as the event rate of biopsy-proven acute rejection (BPAR) by local assessment at Week 24. The incidence at Month 12, was a secondary endpoint. A test of non-inferiority based on a 95% 2-sided CI was planned to rule out a clinically important treatment difference of 10% or more. The protocol specified that this confidence interval would be computed using a normal approximation using Greenwood's formula to compute the standard error for the difference in estimates computed using the Kaplan-Meier method for time to event data censoring on subjects who died, had a graft loss or were lost to follow-up. The applicant also stated that the treatment groups were compared using the Wilcoxon-Gehan test with no explanation as to why this test was chosen. This test is a comparison of time to event data and weighs early events more and will be a more powerful test than the log rank test when censoring is low and the difference in survival curves varies over time but with an assumption that the curves do not cross.

Patient and graft survival were also assessed using Kaplan-Meier analyses of time to event data. Efficacy failure results were provided in the applicant's study report although efficacy failure was not named as an endpoint in the protocol. Efficacy failure is defined as one of the following: BPAR, graft loss, death or outcome unknown. This endpoint is consistent with how the endpoint of BPAR is analyzed by FDA statistical reviewers and is commonly the primary endpoint of first choice since it accounts for missing data for the endpoint of BPAR. This reviewer will report the results for this endpoint and its components.

Serum creatinine and creatinine clearance were named as secondary efficacy endpoints; the results for these endpoints are shown in Section 4.3 of this review. Only primary endpoint results are presented in this section of the review.

Documentation from the applicant to support the non-inferiority margin of 10% for Study 1203 is provided in Attachment 3 of the Summary of Clinical Efficacy. The study's original SAP named a 10% margin based on the margin being "clinically meaningful". This margin, then, was not based on an estimate of the effect of the control Prograf compared to placebo (M1) using a regimen of MMF and steroids (no induction).

The applicant stated in Attachment 3 of the Summary of Clinical Efficacy that "there are no known large randomized trials comparing Prograf to placebo in combination to MMF in de novo kidney transplant patients." The applicant cites a study, unpublished, named Study 93-0006 that showed Prograf (AR rate

of 31%, Table 3.2.1) to be significantly better than cyclosporine (AR rate of 46%) with a treatment difference of -16% (95% CI of -25% to -6%). The Symphony study also showed a lower rejection rate for Prograf (15%) compared to cyclosporine (27%) with about a -12% treatment difference (95% CI -17%, -5%; from FDA statistical review of Symphony). In addition, cyclosporine has been shown to be an effective treatment; in a study by Asberg, et al (2006) where a significant treatment difference in favor of cyclosporine compared to daclizumab (treatment difference of -41% with 95% CI of -65% to -16%) was seen. The applicant also cited three studies included in the Summary Basis of Approval for cyclosporine that showed reduced rejection rates for cyclosporine compared to azathioprine with reductions ranging from 45% to 62%. One might anticipate that the effect of cyclosporine against placebo would be larger than what has been seen against active controls. So taking the most conservative estimate of -16% (upper bound of the confidence interval), the cyclosporine effect is likely to be more than about 20% against placebo. Therefore one could estimate that the Prograf effect compared to placebo could be about 25% (20%+5% from the estimate for CYC versus placebo) or more. The applicant deduces that the effect of Prograf over placebo would be greater than the effect of cyclosporine and concludes that the effect must be greater than 20%.

However the studies cited by the applicant do not provide estimates of effects for Prograf without induction (the immunosuppressant regimen for Study 93-0006 was not provided). The question then is whether the effect of Prograf given with only MMF and steroids would be as large as estimated from the provided trials. A meta-analysis (see Appendix 7.2) done by this reviewer of two studies (Ahsan, 2002 and Meulen, 2004) with an arm of Prograf+MMF+steroids (the active control in 1203) yielded an estimate for acute rejections of 14% (95% CI of 10%, **19%**). However, there are no trials with an arm for the putative placebo of MMF+CCS. A conservative estimate of MMF+CCS would be the estimate computed for the putative placebo for Study 158; induction+MMF+CCS, of 55% (95% CI **47%**, 63%). The estimate of the Prograf effect over placebo would be **47%-19%=28%**. This is an estimate of **M1**. The non-inferiority margin would be equal to or less than M1. The choice of a margin is dependent on clinical input. A 50% retention of the Prograf effect over placebo would result in a margin of 14%.

Table 3.2.1 Completed studies considered in assessment of the non-inferiority margin

Study	Background Regimen	CYC arm AR rate	Prograf arm AR rate	Control arm AR rate	Prograf Trt Difference
93-0006 unpublished	NA	46% (96/2007)	31% (63/205)		-16% (-25%, -6%)
Symphony (FDA rev)	D+MMF+CS	27% (106/399)	15% (60/401)		-11% (-20%, -3%)
Asberg 2006	MMF+CS	30% (8/27)		Daclizumab 70% (19/27)	
CYC Approval studies Study 5 Study 7 Study 15	CS	 6% (3/47) 7% 1/14) 19% (4/21)		AZA 51% (26/51) 69% (9/13) 80% (16/20)	
Ahsan 2002	MMF+CS		16% (8/50)		
Meulen 2004	MMF+CS		13% (24/178)		

CCS=corticosteroids CYC=cyclosporine AZA=azathioprine

The original protocol specified a sample size of 600 patients based on a non-inferiority margin of 10% and a control BPAR rate of 20% for 80% power. With Amendment 3 (instituted about 15 months after trial initiation), the sample size was increased to 680 in order to have sufficient numbers of patients for the PK sub-study. Patients enrolled in the PK sub-study prior to 12/31/2005 were followed for clinical

endpoints while patients enrolled after that date were only analyzed as part of the PK study. This cut-off date was chosen to stop enrollment in the clinical endpoint part of the trial but continue enrollment in the PK study. The clinical data from the PK sub-study (34 evaluable patients) was reviewed by LaRee Tracy (statistical review dated 3/10/2008). This review contains the results from the entire population of 1203.

Results

A total of 699 patients were enrolled at 74 sites in 22 countries (the largest site with 22 patients was in Sweden) in Europe, North and South America (no US sites), Africa and Australia with 676 patients intended to be followed for the clinical endpoints (see Table 3.2.2). About 99% of these 676 patients composed the full analysis population (ITT) for this study where this population is defined as patients randomized, transplanted and treated with at least one dose. Reasons for not being included in the ITT population are summarized below with more than half removed due to not having a transplant. About 76% of Tac-XL patients and 81% of Prograf patients completed one year on treatment. The primary reason in both treatment groups for discontinuing treatment before one year was an adverse event with no preponderance in any particular system organ class. The only notable difference between the groups for ADEs associated with treatment discontinuation was more infections for Tac-XL with 10 (3%) infections compared to 3 (1%) infections for Prograf.

Table 3.2.2 Study 1203 Patient Disposition[1]

	Tac-XL	Prograf
All Randomized	346	353
Safety Analysis Population	345	352
Enrolled after 12/31/2005 for PK sub-study and not included in analysis population	10	13
Randomized for primary analysis population[2]	336 (100%)	340 (100%)
Reason not included in ITT population		
No transplantation	2	3
No study treatment	1	0
Withdrew consent *(3 days after 1st dose)*	1	0
ADE *(on first day of dosing)*	1	1
Full Analysis Population (ITT)[3]	331 (99%)	336 (99%)
Completed 24 weeks	269 (80%)	292 (86%)
Completed 1 year	257 (76%)	275 (81%)
Discontinuation of rand. treatment prior to 12 mos	74 (22%)	61 (18%)
Reasons for Discontinuing		
ADE	43 (13%)	39 (11%)
Death	4 (~1%)	2 (~1%)
Withdrawal of consent	5 (~1%)	5 (~1%)
Non-compliant	4 (~1%)	5 (~1%)
Excl/incl violation	6 (2%)	3 (~1%)
Other	12 (4%)	7 (2%)
Per Protocol Population	280 (83%)	291 (86%)

[1] The numbers for this table were computed by this reviewer based on the analysis dataset ACCT provided by the applicant.
[2]This population contains all patients that were enrolled and randomized to be followed for clinical endpoints. Twenty patients included in the PK sub-study and then followed for clinical endpoints are included in this population. This reviewer considers this population of patients as the all randomized population so all further percentages in this table are computed as a fraction of this population.
[3] This reviewer considers the full analysis population to be the intent-to-treat (ITT) population for efficacy analysis. All results for this review are based on this population.

The applicant named the per-protocol population (full analysis population excluding patients with major protocol violations) as the primary analysis population and the full analysis population as the population for sensitivity analyses. About 85% of the randomized population are included in the per protocol population. This reviewer considers the full analysis (ITT) population to be the primary population for analysis because this is the intent-to-treat (ITT) population and thereby does not exclude patients who are defined as protocol violators who may be so-defined for reasons related to treatment, potentially biasing the results.

The treatment groups for the full analysis population (ITT population) were comparable for baseline characteristics (Table 3.2.3) with the exception of baseline donor-recipient HLA-DR mismatches where the distribution of mismatches was different for the two treatment groups (chi square test, $p<0.02$). The majority of patients were male (about 63%) and Caucasian (about 82%). This patient population is similar to the one in Study 158 with the exception of donor type where 73% of donors were deceased in Study 1203 compared to about 50% in Study 158.

Table 3.2.3 Study 1203 Patient Demographics for ITT population[1]

	Tac-XL (n=331)	Prograf (n=336)
Age		
Mean (SD)	45 (12)	46 (12)
Range	18-69	18-65
% ≥ 65years	1.5%	2.4%
Donor Age		
Mean	45	45
Range	6-77	8-72
Gender		
% female	38%	36%
Donor Gender		
% female	42%	42%
Race		
% white	84%	81%
% black	4%	6%
No previous transplant	96%	94%
Donor Type		
Living	27%	27%
Deceased	73%	73%
Cold ischemia time (hr) Mean (SD)	17 (7)	16 (6)
Donor recipient HLA-DR mismatch[2]		
0	28%	35%
1	52%	54%
2	19%	12%

[1]Extracted from several tables in applicant's study report
[2]HLA-DR = human leukocyte antigen D-related

The median drug exposures are shown in Table 3.2.4. The median daily dosing (mg/kg) of Tac-XL is higher than the doses used for Prograf, however, the trough concentrations for the two groups look comparable. The tacrolimus exposures in Study 1203 are higher than what was observed in Study 158 with Month 12 trough concentrations of 8.1 in 1203 and 7.2 in 158. The applicant did not report MPA trough concentrations for Study 1203.

Table 3.2.4 Study 1203 Study drug exposures

	Tac-XL (n=331)	Prograf (n=336)
Randomized Treatment Days of Exposure Median	365.5	366
Daily dose of randomized treatment (mg/kg) Median		
Day 7	0.18	0.15
Month 1	0.18	0.14
Month 6	0.11	0.08
Month 12	0.09	0.07
Trough conc. rand. trt. Median		
Day 7 (target 10-15 ng/ml)	10.2	12.0
Month 1 (target 5-15 ng/ml)	12.0	12.6
Month 6 (target 5-10 ng/ml)	9.3	8.6
Month 12 (target 5-10 ng/ml)	8.1	8.1

Extracted from applicant's study report

The primary endpoint of BCAR (acute rejections biopsy confirmed by local assessment) was measured at Week 24. The results at Month 12 are an important secondary endpoint; for this review, the emphasis for both Studies 158 and 1203 is on the Month 12 results for efficacy failure. The applicant considered Study 158 as providing the pivotal results and proposed including only those results in the labeling; thereby the applicant considered Study 1203 as supportive results.

The applicant's primary variable results for locally assessed BCAR at Week 24 yielded a treatment effect of +3.8% with a 95% CI of -2.1% to +9.6% for the ITT population and for the per-protocol population +4.5% with a 95% CI of -1.8% to +10.9%. So the results for the protocol defined primary endpoint met the pre-defined non-inferiority margin of 10% (see discussion on pages 14-15 regarding this margin) using the full analysis population but not using the per-protocol population. However, it is clear that the results for both populations are nearly the same.

Table 3.2.5 Study 1203 Applicant's Week 24 primary endpoint (BCAR) results

	Tac-XL	Prograf	Tac-XL minus Prograf[1] 95% 2-sided CI
BCAR Week 24 rates			
Per-protocol population	59/280 (21%)	49/291 (17%)	
Full analysis ITT population	59/331 (18%)	50/336 (15%)	
Kaplan-Meier Analysis			
Per-protocol population	20%	16%	+4.5% (-1.8%, +10.9%)
Full analysis ITT population	19%	15%	+3.8% (-2.1%, +9.6%)

[1]Negative values favor Tac-XL

The efficacy failure results (Table 3.2.6) at both Week 24 and Month 12 showed about a 5% higher rate of failures for Tac-XL than Prograf. The upper bound for the confidence interval on the treatment difference was about 11%; this is one percent higher than the 10% margin proposed by the applicant. However, the confidence interval clearly indicates that Tac-Xl would be better than placebo based on a computed M1 of about 28%.

Table 3.2.6 Study 1203 Results for efficacy failure defined as death, graft loss, BCAR or lost-to-follow-up (ITT population)

	Tac-XL (n=331)	Prograf (n=336)	Tac-XL minus Prograf[1] 95% 2-sided CI
Efficacy Failure Applicant's K-M results[2]			
Week 24	24.2%	19.6%	+4.6% (-1.7%, +10.8%)
Month 12	28.1%	23.5%	+4.6% (-2.0%, +11.3%)
Month 12 events			
Efficacy Failures	93 (28%)	78 (23%)	+4.9% (-1.7%, +11.5%)[3]
Death	10 (3%)	8 (2%)	
Graft Loss	28 (9%)	24 (7%)	
BCAR (local)	68 (21%)[4]	54 (16%)	
Lost-to-FU	4 (1%)	7 (2%)	
Death or graft loss	28 (8.5%)	24 (7.1%)	+1.3% (-3%, +5%)

[1]Negative values favor Tac-XL
[2]Results based on applicant's Kaplan-Meier analyses which produced KM estimates and difference in estimates
[3]Computed by this reviewer.
[4]The applicant reported 68 BCARs in Table 21 of their study report, however, dataset EFF recorded 67 BCARs. Additional data was requested from the applicant to explain the discrepancy. One additional patient was identified (H8204) as having a BCAR but not included as such in the submitted data; however, the patient was recorded as an efficacy failure.

The reasons for being counted as a failure show that the treatment difference of about 5% is primarily driven by the difference in BCAR rates (Tac-XL 20% and Prograf 16%) and explains the consistency of findings between the BCAR and efficacy failure.

The results for efficacy failure agree with the results that were presented by the applicant in their Table 21 on page 84 of the applicant's study report. The reviewer used the dataset OUTCOME and the parameter for efficacy failure to compute the number of efficacy failures. The applicant also provided a dataset called EFF. From EFF, this reviewer computed 93 failures for Tac-XL and 74 failures for Prograf. The four additional events for Prograf recorded in OUTCOME but not in EFF were all due to lost-to-follow-up occurring between study days 342 and 350. According to the SAP, patients, who had a visit on Day 351 or later, were counted as completing 12 months on study. Exclusion of these events results in a wider confidence interval more favorable to Prograf [Tac-XL 93/331 (28%); Prograf 74/336 (22%); treatment difference of 6% with 95% CI of -0.5% to +12.6%]. Nevertheless an upper bound of 12.6% may be acceptable given that a conservative estimate of M1 is about 30%. This reviewer confirmed the counts in Table 3.2.6 and requested that the applicant submit an updated dataset to support the data shown in the table above.

A time to event analysis using a Cox proportional model yielded an hazard ratio of about 1.25 (Table 3.2.7) with an upper limit to the 95% confidence interval of about 1.7 (for Study 158, the upper limit was 1.5). So when considering time in the evaluation of the comparison of the two groups, the results still suggest no notable differences between the treatment groups (log rank test results p=0.15), although there is no pre-defined margin based on a hazard ratio from which to establish non-inferiority.

Table 3.2.7 Study 1203 Results for efficacy failure defined as death, graft loss, BCAR or lost-to-follow-up (ITT population)

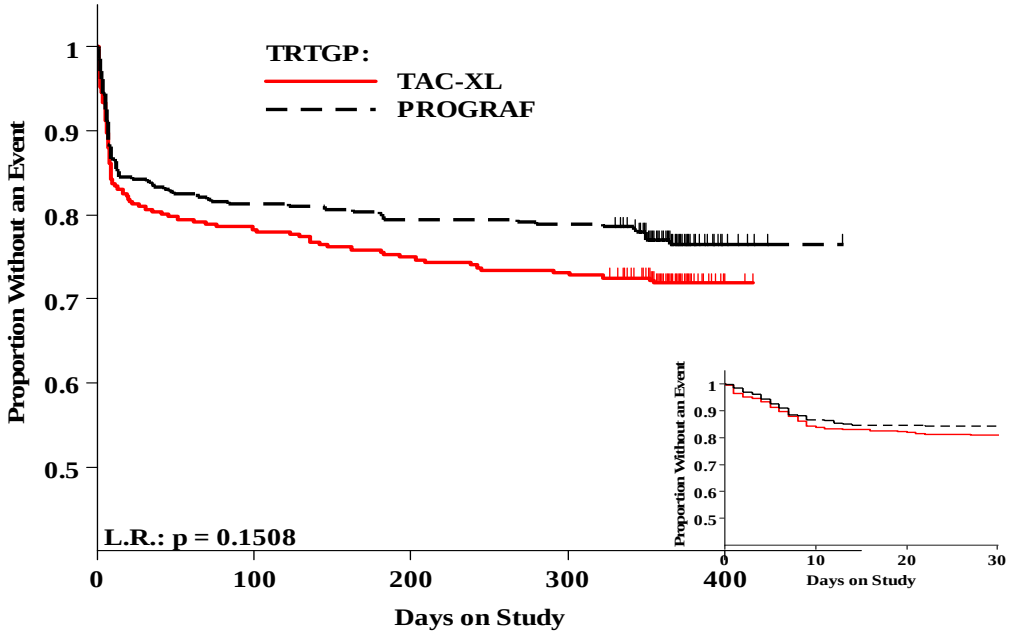
	Tac-XL (n=331)	Prograf (n=336)	Risk Difference Tac-XL minus Prograf[1] 95% 2-sided CI	Hazard ratio Tac-XL/Prograf[1] 95% 2-sided CI
Month 12 events Efficacy Failures	93 (28%)	78 (23%)		1.25 (0.9, 1.7)[3]

[1]Values under 1 favor Tac-XL

Note that the incidences at Month 12 are essentially the same as the Kaplan-Meier estimates (Table 3.2.6) computed using time to first event data and therefore the treatment differences and confidence intervals are essentially the same as well. The similarity between the analyses is due to the lack of censoring with all discontinuations counted as failures. Patients not having events are censored at the end of the study. So all the censoring is at the end of the study period as illustrated by the censor marks on the graph on the following page (Figure 3.2.1).

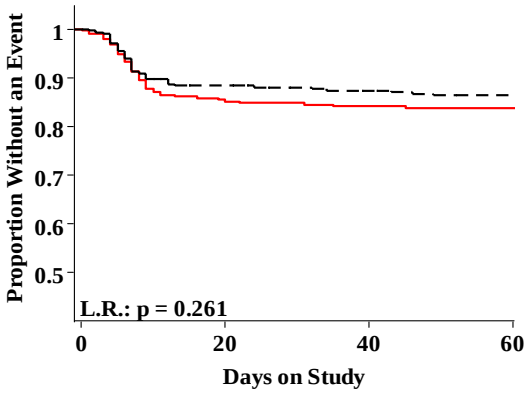
From Table 2.3.6 it can be seen that most of the events in both group occur with the first 6 months of the study. (See Appendix 7.3 for an illustration of the timing of events by type of event.) Figure 3.2.1 further illustrates that the majority of events occur within the first month; about half occurring within 10 days of transplantation. Almost all these events are locally biopsy confirmed acute rejections (LBCAR).

Figure 3.2.1 Study 1203 Kaplan–Meier plot of time to efficacy failure; inset shows events up to Day 30

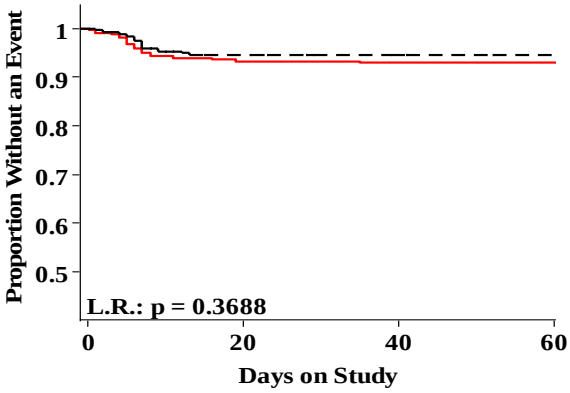


About 37% of the LBCARs in each group (25/331 for Tac-XL and 20/336 for Prograf) were corticosteroid resistant LBCARs. The graphs below illustrate the timing of all LBCARs on the left and the timing of corticosteroid resistant LBCARs on the right within the first 60 days of the trial. Most rejections occur early regardless of whether they are corticosteroid resistant or not.

Figure 3.2.2 LBCAR in first 60 days



Corticosteroid resistant LBCAR in first 60 days



In conclusion, from a statistical perspective, this reviewer thinks both the Week 24 and Month 12 efficacy results showed, statistically, the non-inferiority of Tac-Xl to Prograf based both on the primary endpoint of locally assessed BPAR and on the efficacy failures and based on demonstrating efficacy over the putative placebo. The upper boundary for the 95% confidence interval was about 9.6% for BPAR and about 11.5% for efficacy failure. Both estimates are below an M1 estimate of 30% and a non-inferiority margin of 15% based on conserving 50% of the treatment effect over placebo. The applicant's SAP named a non-inferiority margin of 10% for the primary endpoint based on clinical judgment. Based on our data driven estimate of M1, we believe that the applicant's proposed 10% margin is justified; however, whether the final results should be interpreted based on a 10% margin or a larger non-inferiority margin is a clinical decision.

3.3 Study PMR-EC-1210

Protocol title "*A Multicenter, Four Arm, Randomized, Open Label Clinical Study Investigating Optimized Dosing in a PrografR-/AdvagrafR-Based Immunosuppressive Regimen in Kidney Transplant Subjects (OSAKA Study)"*

Design

Study PMR-EC-1210 OSAKA (hereto referred to as 1210) was a Phase 3b, open-label, multicenter, randomized, parallel-group, non-inferiority trial designed to compare 4 treatment regimens:

Arm 1: Prograf (0.2mg/kg) + MMF + corticosteroids for 24 weeks
Arm 2: Tac-XL (0.2mg/kg) + MMF + corticosteroids for 24 weeks
Arm 3: Tac-XL (0.3mg/kg) + MMF + corticosteroids for 24 weeks
Arm 4: Tac-XL (0.2mg/kg) + MMF + basiliximab + corticosteroids 1 peri-operative bolus only

For this review, the emphasis is on the comparison of Arms 1 and 2 because these arms allow for a direct comparison of Tac-XL to Prograf and, thereby, are similar to the arms in Study 1203.

Patients undergoing kidney allograft transplantation were randomized stratifying by center and age (under 60 vs. 60 or older) to treatment and followed for 24 weeks. Patients who discontinued the study were followed for serious adverse events (AEs) and acute rejection for 28 days.

The primary efficacy variable was defined as the incidence or time to first event of graft loss, biopsy confirmed acute rejection (BCAR), or graft dysfunction glomerular filtration rate [eGFR] < 40 mL/min/1.73m2 estimated by the Modification of Diet in Renal Disease Study Equation. Secondary endpoints included assessment of graft function, BCAR and all acute rejections. Graft loss and death was considered a safety outcome. The protocol specified that each Tac-XL group would be compared to Prograf using Kaplan-Meier methods. A non-inferiority margin of 12.5% was named in the protocol for the primary endpoint. Secondary analyses of pairwise comparisons of the Tac-xl arms were planned. Adjustments for multiple comparisons were planned.

Two design factors distinguish this trial from Studies 158 and 1203; 1) there is no follow-up past 24 weeks and 2) the primary endpoint includes graft dysfunction as one of the components. The medical reviewer, Dr. Marc Cavaille Coll, considers the trial results from this study to be supportive primarily for safety. This reviewer thinks that the 24 week efficacy results can lend support to interpretation of the comparison of Prograf to Tac-XL given that two of the arms in 1210 have dosing similar to the dosing in 1203[1]. In order to understand if the 1210 results are consistent with the other two trials, this reviewer defined an efficacy failure outcome like the one used for studies 158 and 1203 with failure defined as incidence or time to first event of graft loss, biopsy confirmed acute rejection (BCAR) death or lost to follow-up (note that the applicant did not present results for this endpoint in their study report). To assess non-inferiority for this newly defined endpoint for the comparison of Prograf 0.2 to Tac-XL 0.2, this reviewer thinks that a margin named for Study 1203 would be appropriate. Since most events occur early in the trial, the difference in treatment effect of the control arm between a 6 month endpoint and a 12 month endpoint is likely small. For 1203, this reviewer estimated an M1 of 30%; the non-inferiority

[1] The target trough levels in Study 1203 were as follows: Days 0-28:10-15 ng/ml ; Days 29-168:15-15 ng/ml ; Days>168:5-10 ng/ml and in Study 1210 were as follows: Days 0-14:10-15 ng/ml ; Days 15-42:5-12 ng/ml ; Days 43-168:5-10 ng/ml

margin than would be less than 30%. It is a clinical decision as to how much of M1 to retain. If 50% is retained then the margin would be 15%.

The applicant named the per-protocol population as the primary analysis population but also included results for the full analysis population. The full analysis population includes all patients who received one dose of treatment and received a transplant. This reviewer considers the full analysis population as the ITT population and is the primary population for this reviewer's analyses.

Results

A total of 1252 patients were randomized at 110 sites in Europe, South America and South Africa (none in the US) with the most patients enrolled in France (24%), Germany (19%) and Spain (16%). The largest sites were two sites in France, each with 47 patients; most of the sites enrolled less than 20 patients. About 300 patients were randomized to each of the 4 treatment arms. Note that the numbers in Table 3.3.1 for number randomized do not match the numbers presented in the applicant's study report where a total of 1251 randomized patients were mentioned (see applicant's Table 4 on page 43 of the study report); however, the numbers of patients in the ITT (referred to as FAS by the applicant) population reported below do match the numbers in the applicant's report. Since the primary population for the FDA's analysis is the ITT population, this reviewer did not attempt to determine why there was a discrepancy regarding the number randomized. This reviewer used the applicant's dataset ACCT to compute all the numbers in Table 3.3.1 below.

About 4% of randomized patients were not included in the ITT population primarily due to not receiving kidney transplantation. The majority of patients (>80%) in the ITT population remained on treatment for the duration of the trial. The primary reasons for discontinuing treatment were adverse events or protocol violations. About half of the adverse events led to graft loss or death. More adverse events were seen in the Tac-XL arms (about 12%) compared to the Prograf arm (about 7%). Renal or urinary disorders were the most common ADE leading to study drug withdrawal.

Table 3.3.1 Study 1210 Patient Disposition

	Prograf	Tac-XL 0.2	Tac-XL 0.3	Tac-XL 0.2+Ind
Randomized	322	313	318	299
Reason not included in ITT pop.				
No transplantation	8	9	8	11
No study treatment	3	2	5	4
Protocol violation	1	0	0	1
ADE *(on first day of dosing)*	1	0	1	0
Full analysis pop. (ITT)	309 (96%)	302 (96%)	304 (96%)	283 (95%)
Per protocol pop.	237 (74%)	263 (84%)	246 (77%)	230 (77%)
Completed treatment	261 (85%)	240 (79.5%)	247 (81%)	211 (75%)
Reasons Discontinued				
Rand. Treatment (ITT pop)				
ADE	22 (7%)	38 (12%)	34 (11%)	37 (12%)
Rejection	5 (2%)	5 (2%)	2 (1%)	11 (4%)
Lost to FU	0	1 (<1%)	0	1 (<1%)
Non-compliance	0	1 (<1%)	0	1 (<1%)
Withdrawal of consent	5 (2%)	1 (<1%)	2 (1%)	3 (1%)
Protocol violation	15 (5%)	14 (4%)	17 (5%)	16 (5%)
Other	1 (<1%)	2 (1%)	2 (1%)	3 (1%)

The treatment groups were well-balanced on baseline demographics for patients and for donors (Table 3.3.2). The majority of patients were male and white. The mean age of the patients was about 50 years with about 16% 65 or older. About 95% of the patients had no history of a previous transplantation.

Table 3.3.2 Study 1210 Patient baseline demographics

	Prograf n=309	Tac-XL 0.2 N=302	Tac-XL 0.3 N=304	Tac-XL 0.2+Ind N=283
Age				
Mean (SD)	52 (13)	51 (13)	50 (14)	49 (13)
Range	19-79	18-76	18-77	18-78
% ≥ 65years	16%	16%	15%	14%
Donor Age				
Mean	51 (15)	52 (15)	50 (15)	52 (14)
Range	9-81	9-85	5-85	9-81
Gender				
% male	68%	68%	67%	65%
Donor Gender				
% male	57%	53%	54%	56%
Race				
% white	96%	94%	96%	94%
% black	2%	5%	2%	4%
No previous transplant	96%	95%	94%	94%
Donor Type				
Living	13%	11%	11%	13%
Deceased	87%	89%	89%	87%

Cold ischemia time was not reported. Source: Applicant's study report

The three treatment groups with initial dosing of tacrolimus 0.2 mg/kg/day had comparable median daily doses throughout the trial while the median dose for the 0.3 mg/kg/day treatment group was higher by about 20-30%. Median trough levels were within the targeted trough levels for all groups. About 70% of the patients in all groups were within the targeted range at the end of the trial.

Table 3.3.2 Study 1210 Study drug exposures

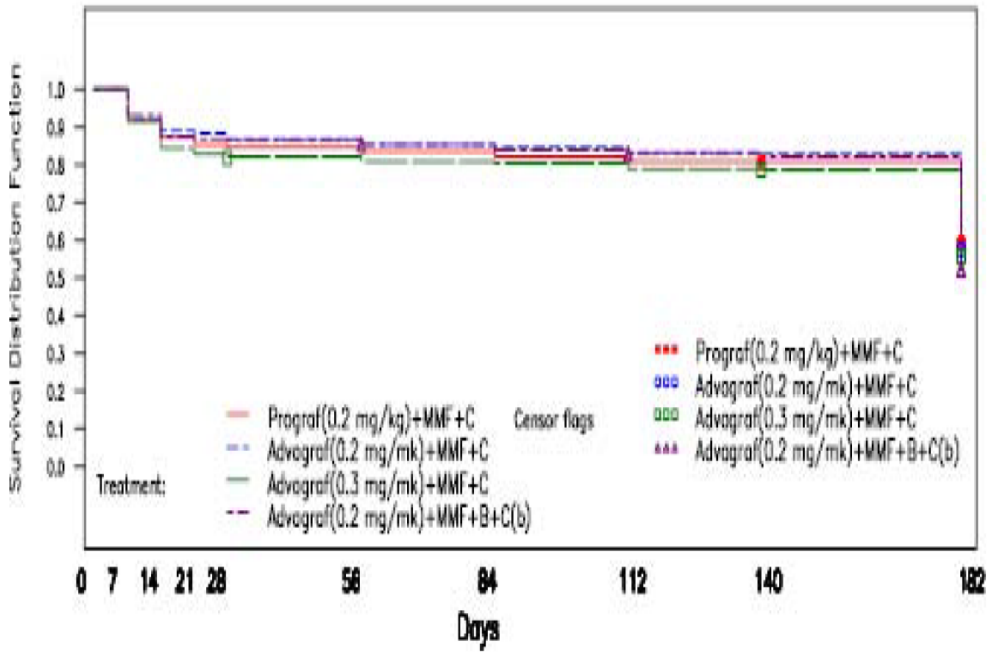
	Prograf n=309	Tac-XL 0.2 N=302	Tac-XL 0.3 N=304	Tac-XL 0.2+Ind N=283
Randomized Treatment Days of Exposure Median	169	169	169	169
Daily dose of randomized treatment (mg/kg) Median				
Day 7	0.16	0.17	0.23	0.18
Month 1	0.13	0.15	0.18	0.15
Month 6	0.07	0.08	0.09	0.08
Trough conc. rand. trt. Median				
Day 7 (target 10-15 ng/ml)	11.2	11.1	12.0	11.6
Month 1 (target 5-12 ng/ml)	10.9	10.9	11.6	11.4
Month 6 (target 5-10 ng/ml)	8.1	8.3	8.2	7.7

Source: Applicant's study report

The primary endpoint was a composite of graft loss, BCAR, death or graft dysfunction. The applicant defined this endpoint as "the incidence of and time to first incidence of one of the following events: graft loss, BCAR, or graft dysfunction at week 24" (page 38 of applicant's study report) and stated that Kaplan-Meier methods would be used to analyzed the endpoint. However, three of the components, graft loss, death and BCAR, were measured at the time of occurrence while graft dysfunction was assessed as GFR < 40 mL/min/1.73m2 (MDRD formula) only at Week 24. For patients who discontinued early, GFR was computed based on the last available serum creatinine. This reviewer does not agree with the applicant's survival analysis because graft dysfunction is based only on the last assessment of GFR not on a time to first occurrence of dysfunction. Thereby time does not have the same implication for all components of the composite endpoint. All patients who do not have a graft loss or rejection are considered in the final risk set for evaluating graft dysfunction whether they are available for assessment or not. The applicant's Figure 1 from the study report and the data in Table 3.3.3 show that most of the events for the primary endpoint are due to graft dysfunction and these events all occur at the end of the study (illustrated by the drop in the lines at about Day 168 in Figure 3.3.1). So time does not play a role in the interpretation of the outcome; in other words, days without an event do not imply a benefit to patients. Also it is worth noting that all patients without events are followed to the end of the study so all censoring occurs at the end of the study and therefore, censoring does not change the risk group over time and does not impact the outcome estimates. The time of exposure is relatively the same for both groups so there is no need for an analysis method that adjusts for different lengths of exposure. Also estimates of survival time (e.g. median survival time) are not important or relevant for this 24-week trial. These estimates would be relevant, for example, if one was looking at time to death over a long time period and one could illustrate an improvement in length of time alive.

Figure 3.3.1 Applicant's figure on page 53 of study report

Figure 1: Time to First Incidence of Efficacy Failure Rate (Kaplan-Meier Method)



The comparison of Tac-XL versus Prograf for the primary composite endpoint of death, graft loss, BCAR and graft dysfunction (Table 3.3.3) shows that the groups are comparable based on the non-inferiority margin of 12.5 % named in the protocol with an upper limit for the 95% confidence interval on the difference in incidences of 8.5%. This finding is primarily driven by the component of graft dysfunction.

Table 3.3.3 Study 1210 Week 24 Primary endpoint ITT population

	Prograf (n=309)	Tac-XL 0.2 (n=302)	Tac-XL 0.3 (n=304)	Tac-XL 0.2+Ind (n==283)	Tac-XL 0.2 minus Prograf 95% 2-sided CI
Primary EP	133 (43%)	132 (44%)	135 (44%)	139 (49%)	+1% (-7%, +8.5%)
Death	6 (1.9%)	8 (2.7%)	7 (2.3%)	3 (1.1%)	
Graft Loss	18 (6%)	29 (10%)	20 (7%)	23 (8%)	
BCAR	42 (14%)	31 (10%)	49 (16%)	36 (13%)	
Graft dysfunc.	111 (36%)	108 (36%)	113 (37%)	123 (44%)	

The results for the endpoint of death, graft loss, BCAR or lost-to-follow-up computed by this reviewer are shown in Table 3.3.4. Without graft dysfunction in the endpoint, the event rate is about half with rates around 20%. The results are favorable to Tac-XL 0.2 with a treatment difference compared to Prograf of -2% and 95% CI of -8% to +5%. The death and graft loss results go in the opposite direction but with an upper bound of 8% do not suggest a notable difference between Tac-XL and Prograf. Note that the results for all the regimens of Tac-XL are similar and suggest no regimen carries advantage over another based on these efficacy results.

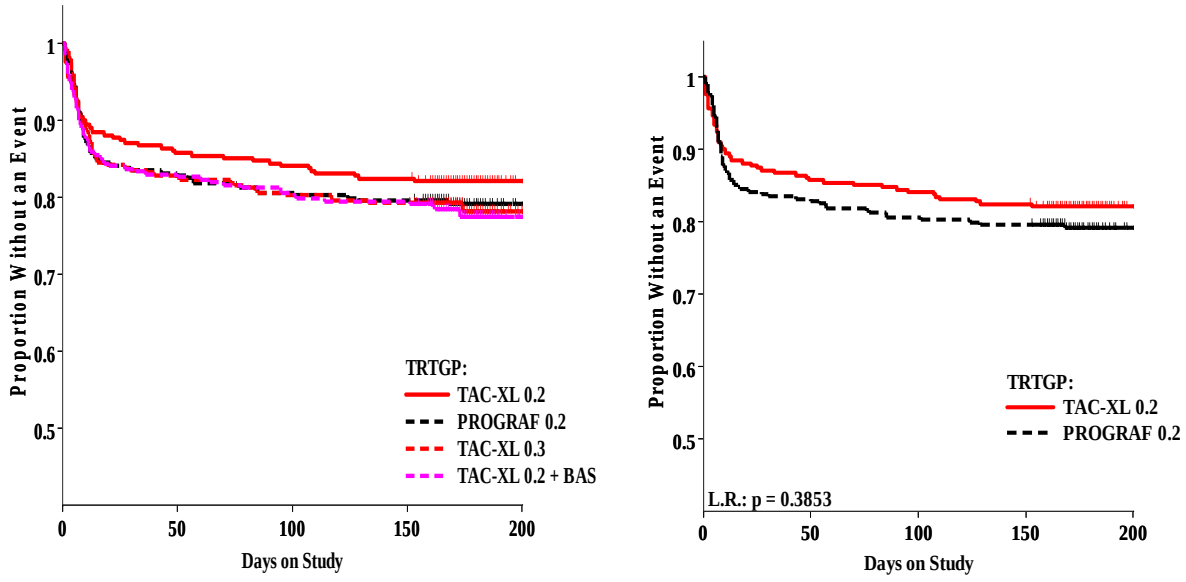
Table 3.3.4 Study 1210 Week 24 Efficacy Results for efficacy failure defined as death, graft loss, BCAR or lost-to-follow-up [1]

	Prograf (n=309)	Tac-XL 0.2 (n=302)	Tac-XL 0.3 (n=304)	Tac-XL 0.2+Ind (n==283)	Tac-XL 0.2 minus Prograf 95% 2-sided CI[2]
Efficacy Failure	64 (21%)	58 (19%)	67 (22%)	63 (22%)	-2% (-8%, +5%)
Death	6 (1.9%)	8 (2.7%)	7 (2.3%)	3 (1.1%)	
Graft Loss	18 (6%)	29 (10%)	20 (7%)	23 (8%)	
BCAR	42 (14%)	31 (10%)	49 (16%)	36 (13%)	
Lost-to-FU	8 (2.6%)	7 (2.3%)	5 (1.6%)	17 (6%)	
Death or Graft loss	18 (6%)	29 (10%)	20 (7%)	23 (8%)	+4% (-0.5%, +8%)

[1]Results based on applicant's dataset OUTCOME, includes deaths and graft losses occurring both on and off treatment; all lost-to-follow-ups are reported regardless of whether an event occurred prior to loss
[2]Negative values favor Tac-XL

A survival analysis comparing Tac-XL and Prograf yielded a hazard ratio of 0.93 with a 95% confidence interval of 0.7 to 1.3 unlike the results seen for Studies 158 and 1203 where hazard ratios were larger than 1. Two Kaplan-Meier curves illustrate the time to event by treatment group showing essentially no difference among the regimens.

Figure 3.3.2 Study 1210 Kaplan–Meier plots of time to efficacy failure (graft loss, death, BCAR or lost-to-follow-up) Graph on left shows results for all 4 treatment arms while graph on the right shows results for Tac-XL 0.2 and Prograf.



The efficacy results at Week 24 for Study 1210 are supportive of the results seen in Studies 158 and 1203 by showing Tac-XL to be non-inferior to Prograf based on a treatment difference of -2% and confidence interval of -8%, +5%. Assuming a non-inferiority margin of 10-15%, the upper limit is well within the bounds of non-inferiority.

4 Evaluation of Safety

4.1 Overall Safety

For the approval of the Prograf with MMF regimen the comparison of tacrolimus to cyclosporine for safety was reviewed and is not included here. The focus in this review is the comparison of Tac-XL to Prograf. This reviewer has summarized adverse events by Medra preferred terms (Table 4.1.1); these terms were chosen based on known side effects of tacrolimus and based on advice from the medical reviewer, Dr. Marc Cavaille Coll. Treatment group differences of 5% or more are highlighted in yellow. Notable differences between Study 158 and Study 1203 are highlighted in blue. The Week 24 results for Study 1210 are included to show that the results from this shorter study are not inconsistent with the studies of 12 month duration.

Table 4.1.1 Selected safety data for kidney transplantation Studies 158, 1203 and 1210

	Study 158 12 mos		Study 1203 12 mos		Study 1210 24 wks	
	Tac-XL (n=214)	Prograf (n=212)	Tac-XL (n=331)	Prograf (n=336)	Tac-XL 0.2 (n=302)	Prograf 0.2 (n=309)
Cardiac disorders	57%	69%	35%	40%	27%	26%
Renal disorders	13%	16%	47%	43%	49%	49%
Tubular necrosis	NA	NA	11%	12%	8%	8%
GI disorders	91%	91%	65%	71%	52%	51%
Gastroenteritis	7%	1%	3.3%	1%	1%	1.3%
Ascites	0.9%	1.4%	0%	0.6%	0.3%	0%
Diarrhea	47%	44%	28%	32%	23%	23%
Loose stools	6%	7%	0%	0.9%	0%	0%
All Infections	73%	70%	71%	68%	54%	57%
CMV infections	9%	11%	11%	6%	9%	8%
Glucose intolerance	NA	NA	1.5%	1.2%	2%	1%
Nervous sys. disorders	71.5%	73%	42%	39%	30%	29%
Tremors	36%	34%	18%	18%	13%	12%
Headache	22%	25%	12%	10%	4%	6%
Insomnia	27%	31%	9%	10%	10%	10%
Seizures	0.9%	1.4%	0.3%	0.6%	0.3%	0%
Vascular disorders	61%	61%	54%	51%	47%	42%
DVT	2.3%	2.8%	0.6%	0.6%	1%	1.3%
Arterial	0.5%	0%	0.3%	0%	0%	0.3%
Deaths	1%	5%	3.3%	2.4%	1.1%	0.8%
Any SAE	45%	51%	49%	55%	59%	55%
New onset diabetes (NODAT) in at-risk pts[1]	58/162 36%	53/151 35%	50/179 18%	54/179 18%	75/258 29%	83/268 31%
Kidney function[2] CrCl Mth12 Mean(SD)	58 (21)	56 (23)	52 (20)	55 (19)	Median 53	Median 56

Based on MEDRA preferred terms

[1]New onset diabetes for patients without pre-existing diabetes as shown in Table 34 of 1203 report; more details regarding NODAT are provided in Section 4.2.

[2]More details regarding kidney function in Studies 158 and 1203 are provided in Section 4.3. Studies 158 and 1203 CrCl computed using MDRD formula.

Both the applicant and the FDA statistical reviewer who originally reviewed Study 158 noted a statistically higher incidence of gastroenteritis for Tac-XL (7%) over Prograf (1%). Higher incidence was seen in 1203 as well with about 3% for Tac-XL compared to about 1% for Prograf but not in Study 1210.

There is no event in Table 4.1.1 where a higher incidence is seen in one group over the other group across all three studies.

4.2 NODAT

The onset of diabetes post transplant is a safety issue of concern after kidney transplantation. The results for new onset diabetes (NODAT) in Studies 158 and 1203 are examined in more detail in this section. NODAT is defined by the presence of any of 4 components: 2 or more Fasting Plasma Glucose (FPG) ≥ 126 mg/dL 30 or more days apart; insulin use for 30 or more consecutive days; oral hypoglycemic use for 30 or more consecutive days; other anti-diabetic use for 30 or more consecutive days and/or HbA_{1C} ≥ 6.5% anytime on study. Results for NODAT and the components for Studies 158 and 1203 were requested by FDA clinical staff and were received from the applicant on 3/25/2013. Note that NODAT is a measure of new onset diabetes so patients without evidence of diabetes prior to transplantation (i.e. no history of diabetes at baseline, no pre-transplant glucose > 200 mg/dL, no pre-transplant HbA1C > 6.5% and no extended anti-diabetic medication use just before transplantation) are assessed. The results for NODAT and components for Studies 158 and 1203 show similar results for both treatment groups (Table 4.2.1).

Table 4.2.1 NODAT results for Studies 158 and 1203 in patients without evidence of diabetes at baseline

	Study 158 12 mos		Study 1203 12 mos	
	Tac-XL (n=162)	Prograf (n=151)	Tac-XL (n=288)	Prograf (n=299)
Composite NODAT	58 (36%)	53 (35%)	105 (37%)	90 (30%)
≥ 2 FPG ≥ 126 mg/dL ≥ 30 days apart	**42 (26%)**	**35 (23%)**	**51 (18%)**	**47 (16%)**
Insulin use ≥ 30 consecutive days	10 (6%)	12 (8%)	29 (10%)	29 (10%)
Oral hypoglycemic use ≥ 30 consecutive days	22 (14%)	13 (9%)	20 (7%)	23 (8%)
HbA_{1C} ≥ 6.5%	**31 (19%)**	**33 (22%)**	**48 (17%)**	**39 (13%)**
HbA1c Mean (SD)	n=185[1]	n=189	n=237	n=252
Baseline	5.6 (1.2)	5.6 (1.1)	5.4 (1.0)	5.5 (1.2)
Change at endpoint	+0.8 (1.2)	+0.9 (1.5)	Approx. +0.5[2]	Approx. +0.3

Source: Applicant's Tables 2 and 1.2 in submission dated March 25, 2013 and Table 14.3.8 in the applicant's study report for Study 158 and Table 13.6.3.1 in the applicant's study report for Study 1203

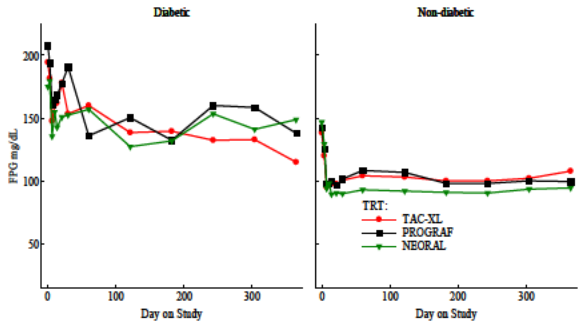
[1] The applicant reported endpoint HbA1c results for the ITT population.

[2] The applicant did not report change at endpoint so these numbers are approximated from the endpoint HbA1c.

The component results show that NODAT is largely driven by the FPG and HbA_{1c} results. Numerically higher incidences are seen for Tac-XL than Prograf for FPG in both studies although the differences are not statistically significant in either study. These results for FPG and HbA1c may be dependent on only 2 results for FPG and on only one result for HbA1c. To obtain an understanding of the impact on FPG and HbA1c over the course of the trial, this reviewer summarized the mean results by group overtime for both studies on the following pages. FPG results are summarized in Figures 4.2.1 and 4.2.2. On Day 0 or Day 1 more than half the patients in all groups have FPG values above 126 mg/dL. On average, FPG decreases by about 50 mg/dL for all groups for both baseline diabetics and non-diabetics. HbA1c increases on average for non-diabetics in all treatment groups in both studies (Table 4.2.1 and Figures 4.2.3 and 4.2.4). The boxplots illustrate the shift in the distribution of HbA1c with some patients having values greater than 6.5. Overall, there were no differences between Tac-XL and Prograf for NODAT with similar changes in NODAT, FPG and HbA1c occurring in both treatment groups.

Figure 4.2.1 Mean FPG by time and treatment and by diabetic status at baseline

Study 158



Study 1203

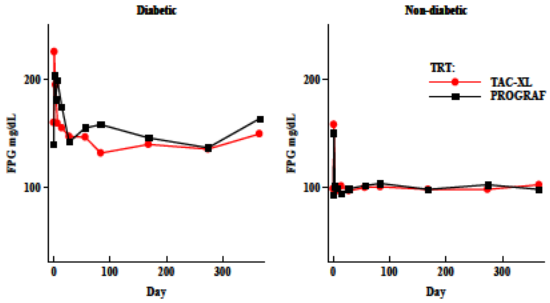
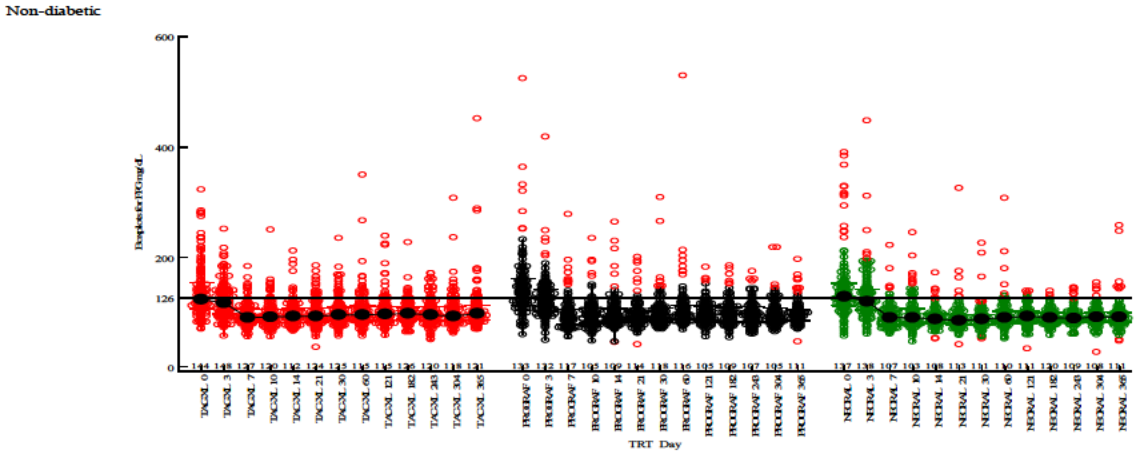


Figure 4.2.2 Boxplots of FPG by time and treatment for non-diabetics
Study 158



Study 1203

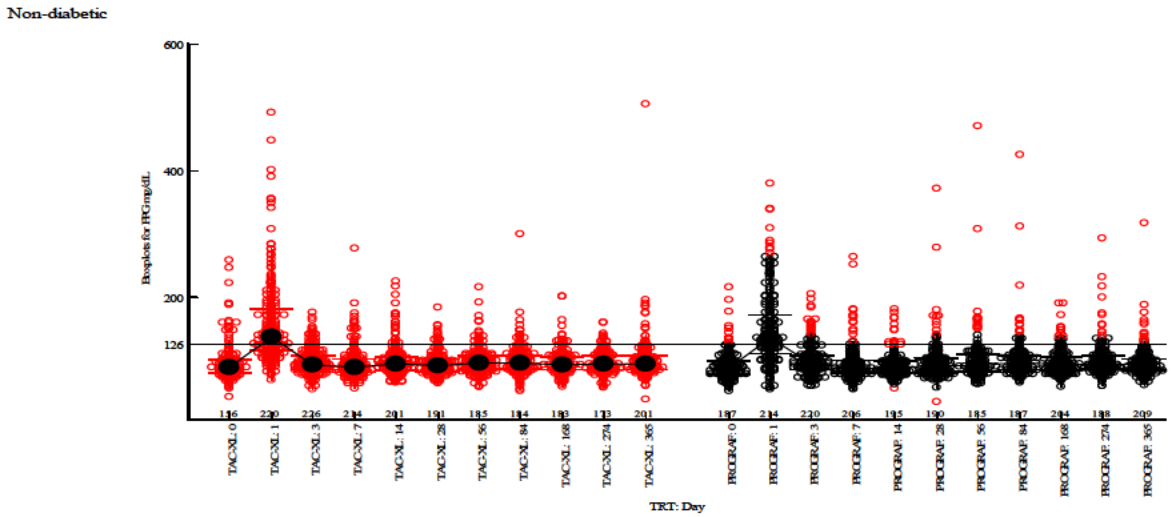


Figure 4.2.3 Mean HbA1c by time and treatment and by diabetic status at baseline

Study 158 Study 1203

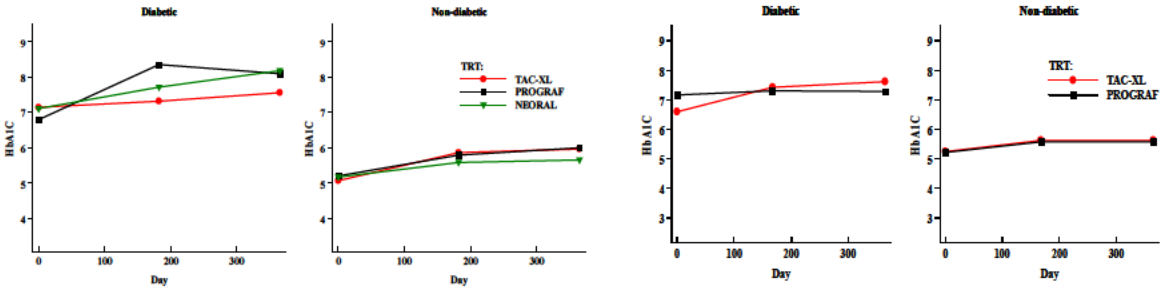
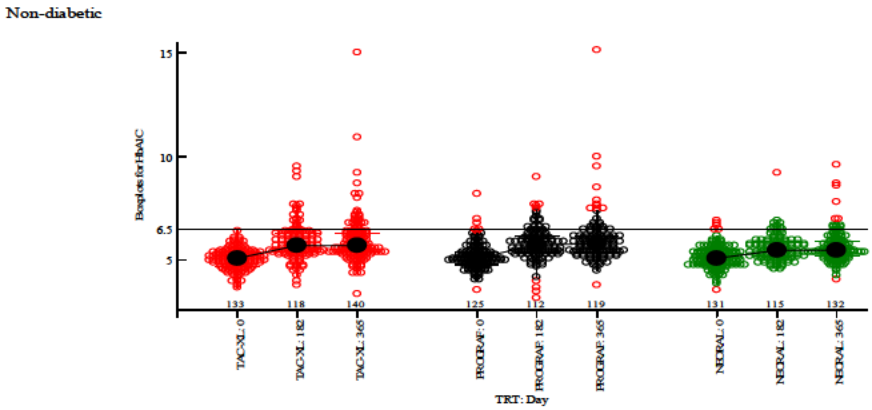
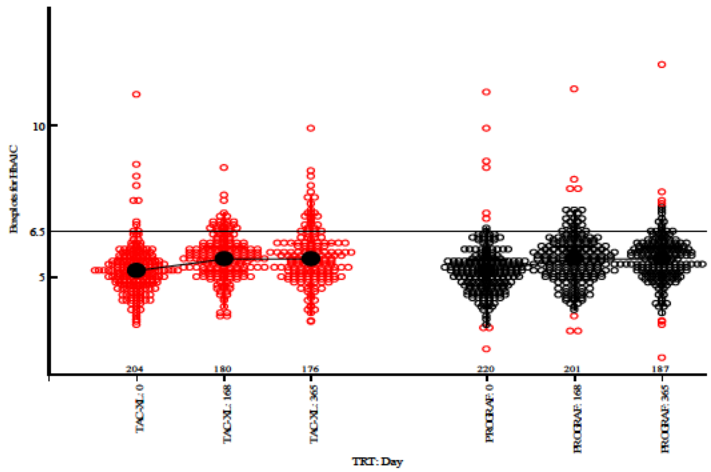


Figure 4.2.4 Boxplots of HbA1c by time and treatment for non-diabetics

Study 158



Study 1203



4.3 Kidney Function

In Study 158 and 1203, renal function was defined as a secondary efficacy endpoint along with more than 10 other endpoints; however, there were no predefined criteria for showing efficacy (namely non-inferiority) with renal function endpoints. Also renal function is characterized by the measurement of serum creatinine and creatinine clearance (CrCl) in both studies; laboratory results which are often considered as safety data. Protocols for both studies said that the Cockcroft-Gault formula would be used to compute CrCl; however, the LAB dataset contained CrCL computed using both the Cockcroft-Gault formula and the modification of Diet in Renal Disease (MDRD) formula while the GFREF dataset contained only values computed using the MDRD formula. According to the statistical plan for Study 158, means by timepoints from Week 1 to Month 12 would be compared with an ANOVA model. The define file accompanying the Study 158 data stated the Month 1 would be defined as baseline and that eGFR would be estimated by creatinine clearance and by imputing zeroes for patients who die or lose their kidney graft or are lost-to-follow-up. According to the statistical plan for Study 1203, means by pre-specified time periods from Week 1 to Month 10-12 would be computed but no statistical comparisons were planned and a baseline was not defined. As for 158, the define file accompanying Study 1203 eGFR data stated that GFR would be estimated by creatinine clearance and by imputing zeroes for patients who die or lose their kidney graft or are lost-to-follow-up. Note that the eGFR datasets were created for an integrated analysis of eGFR and so the data definitions are purportedly in accordance with the plans for an integrated analysis not reviewed here.

This reviewer focused only on Month 1 (baseline) and Month 12 (last observed value, LOCF); for plots of values overtime, see the applicant's study report or the clinical review.

Table 4.3.1 Kidney function at Month 1 (baseline) and Month 12 (last observed value)
Mean (SD) for serum creatinine (mg/dL) and creatinine clearance (mL/min per 1.73 m^2)

	Study 158		Study 1203	
	Tac-XL (n=214)	Prograf (n=212)	Tac-XL (n=331)	Prograf (n=336)
Serum Creatinine	n=199	n=202	n=279	n=292
Month 1 (baseline) [1]	1.57 (0.90)	1.66 (1.29)	1.81 (1.22)	1.72 (0.98)
Month 12				
LOCF	1.46 (0.68)	1.61 (1.24)	1.73 (1.40)	1.55 (0.89)
Mean Change	-0.10 (0.82)	-0.06 (0.82)	-0.08 (1.29)	-0.17 (1.10)
Median Change	-0.06	0	-0.09	-0.09
LSM Diff XL-Prograf[2]	**-0.08 (-0.22, +0.06)**		**+0.14 (-0.03, +0.31)**	
Creatinine Clearance[3]	n=201	n=202	n=287	n=300
Month 1 (baseline)	56 (20)	56 (21)	51 (19)	52 (20)
Month 12				
LOCF	58 (21)	56 (23)	52 (20)	55 (19)
Mean Change	+1.9 (18)	-0.66 (23)	+1.4 (20)	+2.8 (18)
Median Change	0	0	+3.8	+3.4
LSM Diff XL-Prograf[2]	**+2.3 (-1.3, +6.0)**		**-1.8 (-4.6, +0.8)**	

[1] Baseline for serum creatinine was defined in the Study 158 protocol as Month 1 while baseline was not defined for 1203. This reviewer applied the same window for Study 158 Month 1 (lab day 26 to 45) to Study 1203.
[2] Results of ANCOVA model with Month 1 as a covariate and change from baseline as response. LSM=least squares mean. Results are for patients with both a baseline value and a LOCF value post-baseline. Some patients were missing baseline values.
[3] Clearance computed using MDRD formula; patients who died, lost the graft or were lost to follow-up are imputed as zeroes.

There are no statistically significant differences between the treatment groups for serum creatinine at Month 1 and at the end of the trial with both groups showing a decrease in serum creatinine. There was also no statistically significant difference between Tac-XL and Prograf for creatinine clearance (Table 4.3.1). For both measures of renal function, the results from Study 158 are slightly more favorable to Tac-XL while the results for Study 1203 show results slightly more favorable to Prograf.

The applicant's proposed labeling for Study 158 reports both creatinine and creatinine clearance. The creatinine clearance results are labeled as computed by the Cockcroft-Gault formula; however the numbers in the table match MDRD computed results shown in the applicant's Table 20 in the Summary of Clinical Efficacy in the application and also match MDRD results computed by this reviewer and shown in the table above.

5 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

For all the subgroup analyses, this reviewer focused on the comparison of Tac-XL to Prograf in Studies 158 and 1203 for the efficacy failure endpoint of BCAR, graft loss, death or lost-to-follow-up. Both of these studies were 12-month studies and generally provide sufficient numbers of events to allow subgroup analyses.

The subgroup results are summarized by this reviewer with plots of the risk difference by study and subgroup; negative values for the risk difference favor Tac-XL. Note that the size of the symbols in the plots is proportional to the sample size. This reviewer performed Breslow-Day tests of homogeneity to test consistency of results across subgroups within studies. All tests yielded p-values > 0.2 so no statistical evidence of subgroup interactions among subgroups within studies was observed.

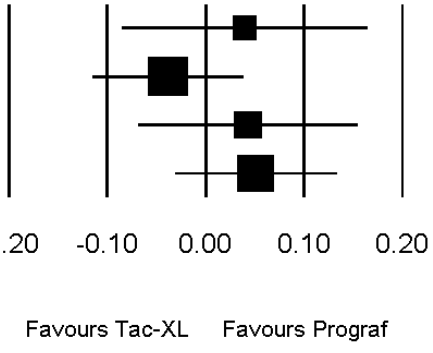
The overall analysis yielded slightly more favorable results for Tac-XL than Prograf in Study 158 (treatment difference of -1% with CI of -8% to +6%) while the results in Study 1203 the results were slightly more favorable to Prograf (treatment difference of +5% with CI of -2% to +11.5%); both studies demonstrated the non-inferiority based an M1 of about 30% and an M2 of about 15% assuming 50% retention of the Prograf effect over placebo. Subgroup results were generally consistent with these overall results.

5.1 Sex, Age, Race, and Geographic Region

5.1.1 Sex

In Study 158, the efficacy failure results for females look more favorable to Prograf while the results for males look more favorable to Tac-XL; however, this difference in treatment effects is not significant with a treatment by sex interaction p-value of 0.27.

Study	Sex	n / Total		Risk difference
		Tac-XL	Prograf	
Study 158	Female	16 / 76	13 / 76	0.039
Study 158	Male	14 / 138	19 / 136	-0.038
Study 1203	Female	38 / 127	31 / 121	0.043
Study 1203	Male	55 / 204	47 / 215	0.051



This reviewer also looked at deaths by sex (Table 5.1.1.1) and NODAT by sex (Table 5.1.1.2). Differential treatment effects for females and males were seen in the liver study 1103 for both mortality and NODAT so these interactions were tested for the kidney studies. More details regarding sex effects can be found in the statistical review of the liver study. No significant interaction for sex by treatment for each study was seen for deaths (p>0.3) and for NODAT (p>0.4) in the kidney studies.

Table 5.1.1.1 Deaths by sex and treatment for Studies 158 and 1203

	Tac-XL	Prograf	Trt Diff (CI)
Study 158			
Female	0/152 (0%)	3/152 (2%)	-2% (-4%, +0.2%)
Male	3/276 (1%)	7/272 (3%)	-1.5% (-4%, +0.7%)
Study 1203			
Female	3/127 (2.4%)	3/121 (2.5%)	-0.1% (-4%, +4%)
Male	7/204 (3.4%)	5/215 (2.3%)	+1% (-2%, +4%)

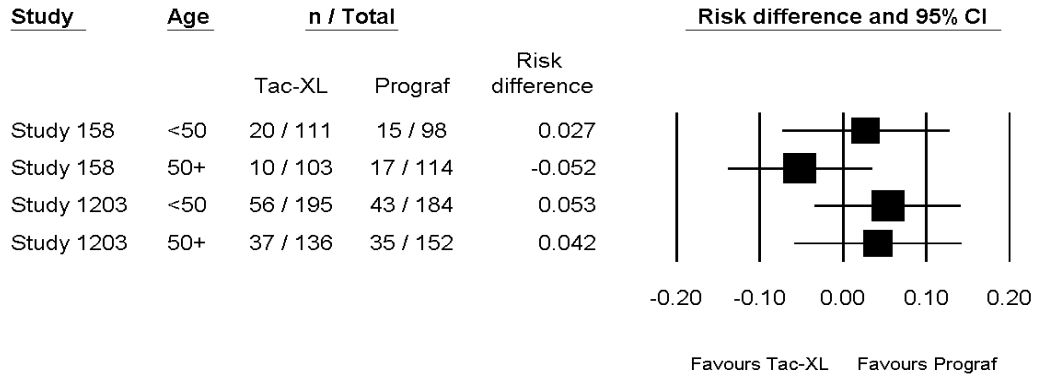
Table 5.1.1.2 NODAT by sex and treatment for non-diabetic patients at baseline in Studies 158 and 1203

	Tac-XL	Prograf	Trt Diff (CI)
Study 158[1]			
Female	25/62 (40%)	20/58 (35%)	+5.8% (-11%, +23%)
Male	33/100 (33%)	33/93 (35%)	-2.5% (-16%, +11%)
Study 1203[2]			
Female	47/120 (39%)	37/117 (32%)	+7.5% (-4.6%, +20%)
Male	58/168 (35%)	53/182 (29%)	+5.4% (-4.3%, +15%)

[1]Computed by reviewer from dataset NODAT [2]Computed by reviewer using data from Table 29 of Module 5.3.5.3 and Table 1.2 submitted in response to IR of 3/8/13; no data for NODAT was provided in the 1203 database

5.1.2 Age

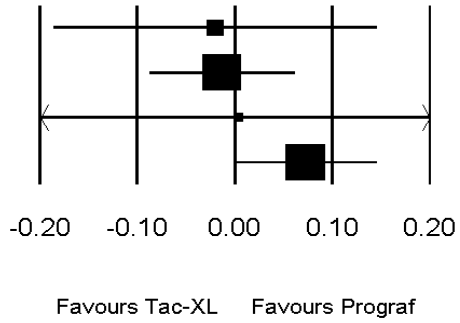
There were too few patients 65 years or older in either study so the median age was used to see if age had an impact on outcome. In Study 158, the results for older patients is more favorable to Tac-XL while the opposite is true for younger patients, however the interaction is not significant for treatment by age.



5.1.3 Race

The majority of the patients in these trials were Caucasian. There is no suggestion of a difference in treatment effects by race but the number of black patients is limited.

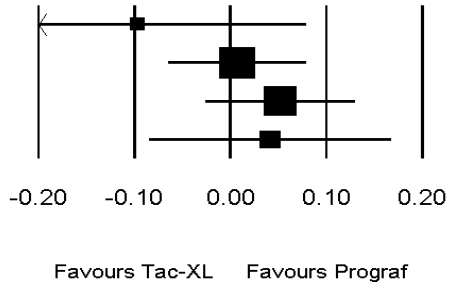
Study	Race	n / Total		Risk difference
		Tac-XL	Prograf	
Study 158	Black	8 / 41	11 / 51	-0.021
Study 158	White	20 / 160	21 / 152	-0.013
Study 1203	Black	3 / 14	4 / 19	0.004
Study 1203	White	84 / 277	63 / 273	0.072



5.1.4 Geographic Region

Study 158 was primarily conducted in the US while Study 1203 was primarily conducted in Europe. The US results in Study 158 yield a treatment difference of +0.7% with a confidence interval that excludes 10%.

Study	Region	n / Total		Risk difference
		Tac-XL	Prograf	
Study 158	Non-US	6 / 41	9 / 37	-0.097
Study 158	US	24 / 173	23 / 175	0.007
Study 1203	Europe	71 / 244	60 / 251	0.052
Study 1203	Non-Europe	22 / 87	18 / 85	0.041



5.2 Other Special/Subgroup Populations

5.2.1 Initial Dose and Initial Cmin

The results from Studies 158, 1203 and 1210 all showed that higher doses of Tac-XL were used to achieve comparable trough levels of tacrolimus. In this section, the relationship between dose, trough levels and clinical failure is examined for Studies 158 and 1203. The focus is on the first dose of tacrolimus and on the first trough level (C_{min}). This examination is relevant to understanding whether the proposed labeling for Tac-XL is supported by the data. The present labeling for Prograf recommends an initial dose with MMF of 0.10 twice a day and trough levels of 4-11 ng/ml. The proposed labeling for Tac-XL recommends an initial dose of (b) (4) and trough levels of 5-17 ng/ml. Also this examination is relevant to understanding whether the initial dose impacts the incidence of early events. Note that the latter is difficult given that a wide range of doses were not used and patients were not randomized to a range of doses; this examination of the impact of early events is purely exploratory.

Doses (and subsequently observed trough levels) given after the first dose are based on patient response so dose response cannot be measured in these trials where outcome impacts subsequent doses. The initial dose however is seemingly not based on how the patient is responding in the trial. Subgroup analyses were done by this reviewer based on subgroups defined by initial dose and by initial observed Cmin.

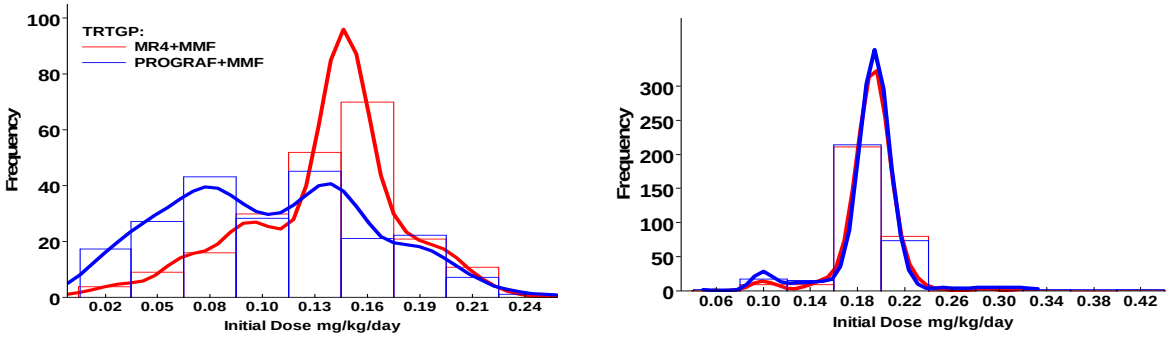
Comparable first doses were used for both treatment groups in Study 1203 while the doses in Study 158 were different (Table 5.2.1.1 and Figure 5.2.1.1). Recall that Study 1203 was blinded while Study 158 was open-label. Also for Study 1203 one starting dose was planned (0.2 daily) while for Study 158, a range was proposed (0.15-0.2 daily). The lack of blinding in Study 158 coupled with the allowance of a range of initial doses may have impacted the choice of initial dose. Overall higher initial doses were used in Study 1203 than in Study 158.

Table 5.2.1.1 First tacrolimus dose and first Cmin results by treatment and study

	Study 158		Study 1203	
	Tac-XL	Prograf	Tac-XL	Prograf
N	213	211	322	329
Median first dose mg/kg/day	0.14	0.11	0.19	0.19
% w/first dose ≥ 0.1	172 (81%)	111 (53%)	316 (98%)	321 (98%)
% w/first dose ≥ 0.14	126 (59%)	61 (29%)	319 (96%)	305 (93%)
N	212	211	322	327
Median first Cmin ng/ml	8.0	9.4	9.9	13.9
Mean (SD) first Cmin ng/ml	9.9 (6)	11.6 (8)	11.1 (7)	15.3 (9)
% w/first Cmin in target range[1]	41%	44%	26%	23%

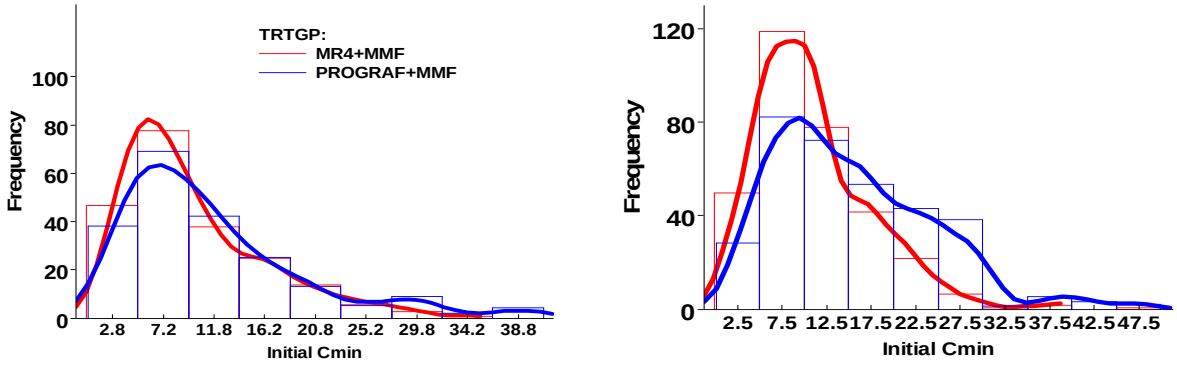
[1]Study 158 target=7-16 and Study 1203 target=10-15

Figure 5.2.1.1 Distribution of first doses by treatment and study (histograms and kernel density curves)
Study 158 Study 1203



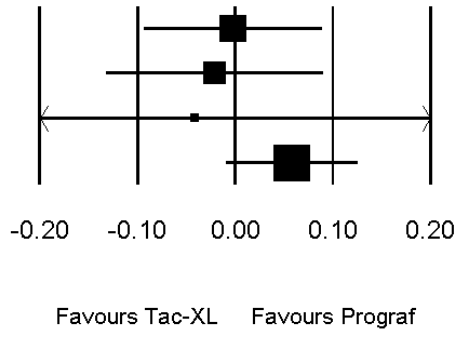
From Table 5.2.1.1 and Figure 5.2.1.2, higher first trough levels are seen for Prograf (blue line) than Tac-XL (red line) in each study.

Figure 5.2.1.2 Distribution of first trough levels by treatment and study (histograms and kernel density curves)
Study 158 Study 1203

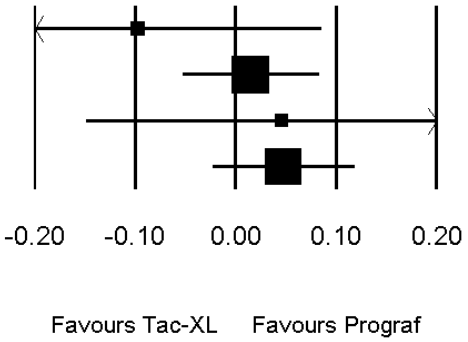


To see if there is a relationship between either first dose (0.14 as cutoff) or first trough level (5 as cutoff), this reviewer did subgroup analyses. The figures below do not suggest that there is a treatment by subgroup interaction. This data does not suggest that the effect of Tac-Xl compared to Prograf is impacted by first dose (note that other cutpoints for dose did not change this conclusion).

Study	Initial Dose	n / Total		Risk difference and 95% CI
		Tac-XL	Prograf	Risk difference
Study 158	< 0.14	12 / 87	21 / 150	-0.002
Study 158	0.14+	18 / 126	10 / 61	-0.021
Study 1203	< 0.14	3 / 12	7 / 24	-0.042
Study 1203	0.14+	84 / 310	65 / 305	0.058



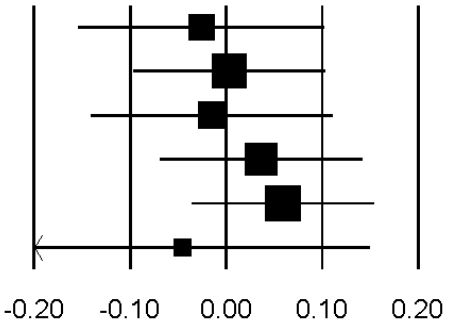
Study	Cmin	n / Total		Risk difference and 95% CI
		Tac-XL	Prograf	Risk difference
Study 158	<=5	9 / 47	11 / 38	-0.098
Study 158	5 or more	20 / 165	18 / 169	0.015
Study 1203	<=5	13 / 50	6 / 28	0.046
Study 1203	5 or more	73 / 272	66 / 299	0.048



5.2.2 HLA-DR Mismatches

There was a statistically significant difference between treatment groups for baseline HLA-DR mismatches in Study 1203. Subgroup analyses by type show no interactions between treatment and HLA-DR type. The event rates were highest for patients with HLA-DR of 2 in Study 1203 with rates of 35% for Tac-XL and 39% for Prograf compared to HLA-DR 0 with rates of 20% for Tac-XL and 16% for Prograf; in Study 158, difference between type 2 and 0 was about 5%.

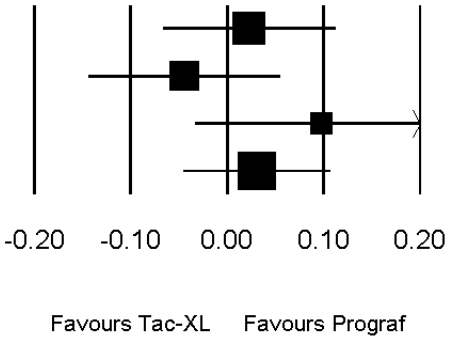
Study	HLA-DR	n / Total		Risk difference and 95% CI
		Tac-XL	Prograf	Risk difference
Study 158	0	5 / 52	5 / 41	-0.026
Study 158	1	15 / 95	17 / 110	0.003
Study 158	2	10 / 67	10 / 61	-0.015
Study 1203	0	18 / 92	18 / 113	0.036
Study 1203	1	53 / 170	44 / 174	0.059
Study 1203	2	22 / 63	15 / 38	-0.046



5.2.3 Donor Type

In Study 158, the types of donor were evenly split between kidneys from live donors and kidneys from deceased donors. In Study 1203, the majority of donors were deceased donors. Both studies show more favorable results for Prograf in patients with live donors than deceased donors though there is no significant interaction (p>0.3).

Study	Donor	n / Total		Risk difference and 95% CI
		Tac-XL	Prograf	Risk difference
Study 158	Alive	14 / 103	12 / 106	0.023
Study 158	Dead	16 / 111	20 / 106	-0.045
Study 1203	Alive	30 / 89	22 / 92	0.098
Study 1203	Dead	63 / 242	56 / 244	0.031

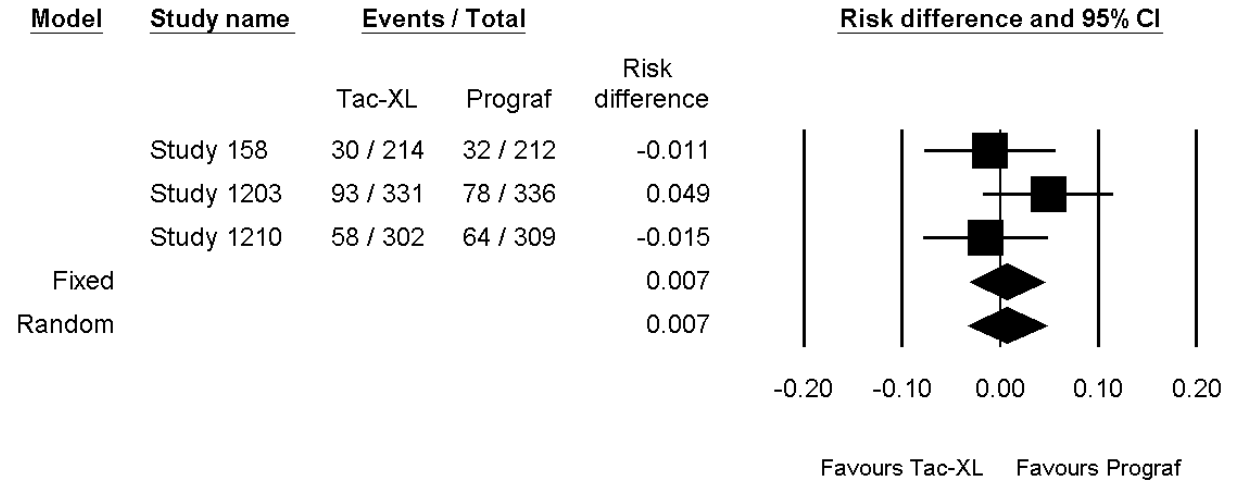


6 SUMMARY AND CONCLUSIONS

6.1 Collective Evidence

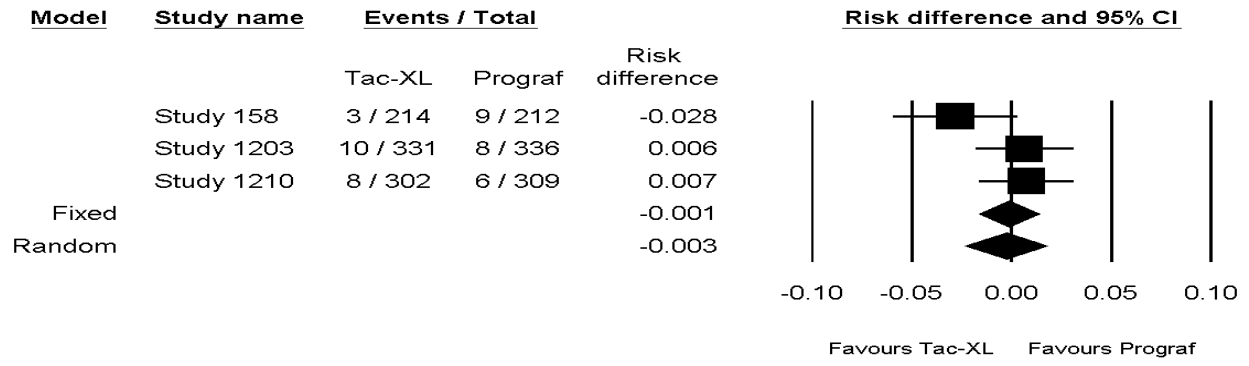
The applicant has provided the results of 3 clinical trials, Studies 158, 1203 and 1210. Study 158 was considered by the applicant as their pivotal trial because dosing comparable to the approved, labeled doses for Prograf were used and also induction was used as well. In addition, Study 158 was conducted predominantly in the US while Studies 1203 and 1210 had no US sites. FDA staff is considering results from both 158 and 1203. Both studies were 12 month studies well-powered to compare Tac-XL to Prograf. Study 1210 was also a large study but of shorter duration, 24 weeks. However, since most of the efficacy failure events occur early in the trial, this reviewer is summarizing the results for all three trials with a meta-analysis (Figure 6.1.1). An overall estimate from all three trials of the difference between Tac-XL and Prograf is about 0.7% (95% CI of -3% to +5%). All three trials show results consistent with this overall estimate and each independently supports the non-inferiority of Tac-XL to Prograf based on an M1 of about 30% and a non-inferiority margin of 11.6% or greater. For more details on the results of each trial, see Tables 3.1.4, 3.2.6 and 3.3.4 in Section 3 of this review.

Figure 6.1.1 Meta-analysis of efficacy failure (locally biopsy-confirmed acute rejection, death, graft loss or lost-to-follow-up)



The mortality rates in transplantation trials tend to be low and thereby the trials are underpowered to show superiority or non-inferiority for deaths. For this application, a meta-analysis provides evidence that Tac-XL and Prograf are comparable with respect to mortality with a treatment difference of -0.3% and CI of about -2% to +2%.

Figure 6.1.2 Meta-analysis of mortality



6.2 Conclusions and Recommendations

The efficacy results from three clinical trials, Studies 158, 1203 and 1210, demonstrated the non-inferiority of Tac-XL, a once a day dosing regimen, to Prograf, a twice a day dosing regimen based on efficacy failure (locally biopsied confirmed acute rejection, death, graft loss or lost-to-follow-up). In all three trials, most of the efficacy failures were due to LBCARs that occurred early in the trial (about half during the first 10 days). Although the event rates differed among the trials, the treatment differences were comparable. Treatment differences were also comparable across many subgroups with no significant treatment by subgroup differences observed.

Safety analyses generally showed no significant differences for adverse events between Tac-XL and Prograf in any of the studies with the exception of gastroenteritis where a higher incidence was seen with Tac-XL (7% in Study 158 and 3% in Study 1203) than Prograf (1% in Study 158 and 1% in Study 1203). Higher doses of Tac-XL compared to Prograf were generally needed to achieve targeted trough levels but there is no evidence from these trials that this resulted in a significant safety risk.

For kidney transplantation, from a statistical perspective, Tac-XL has been shown to have a comparable benefit-risk profile to Prograf, an approved product.

7 APPENDICES

7.1 Justification of a non-inferiority margin for Study 158

To assess the non-inferiority of Tac-XL compared to Prograf in Study 158, the effect of Prograf compared to placebo must be estimated. The goal would be to estimate the difference for the following:

Active control D+MMF+CCS+Prograf 0.1mg BID
Putative placebo D+MMF+CCS

There is no trial that contains these treatment arms so there is no estimate of a head-to-head comparison. There are trials with one of the arms. Publications of these trials consistently report acute rejections but not efficacy failure nor graft loss or death so the computation of the estimates of the active control and putative control are based on acute rejection rates.

An estimate of the active control effect is based on 6 studies shown in Figure 6.1.1. The fixed and random effects from a meta-analysis yielded essentially the same estimate with a rate of 14% and a 95% CI of 12% to 17%. A conservative estimate of the active control effect would be the upper bound of 17%.

An estimate of the putative placebo effect is based on 3 studies shown in the Figure 6.1.2. The fixed and random effects from a meta-analysis yielded similar estimates with a rate of 55% and a 95% CI of 47% to 63%. A conservative estimate of the putative placebo effect would be the lower bound of 47%.

A conservative estimate of the treatment effect of the active control, Prograf, in Study 158 would be 47% minus 17% which equals 30%. The non-inferiority margin may be considered to be some percentage of 30%. For example, if the intention is to conserve 50% of the effect, a margin of 15% would be reasonable.

Figure 7.1.1 Meta-analysis to estimate the acute rejection rate for the active control, D+MMF+CCS+Prograf 0.1mg BID

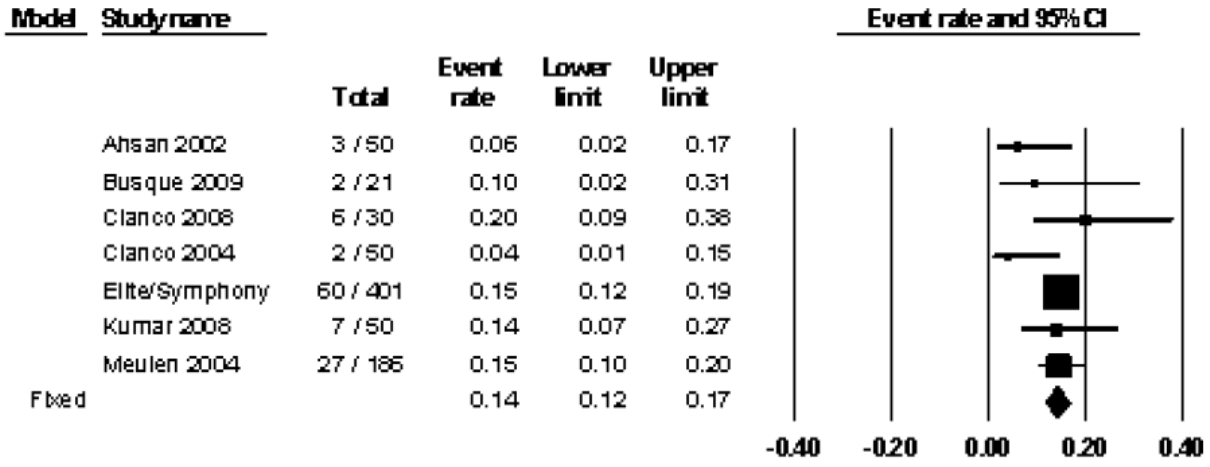
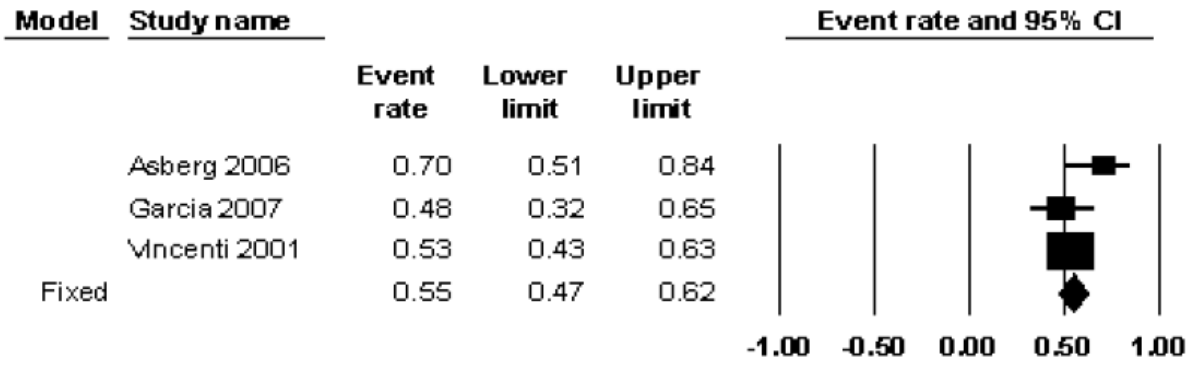


Figure 7.1.2 Meta-analysis to estimate the acute rejection rate for the putative placebo, D+MMF+CCS



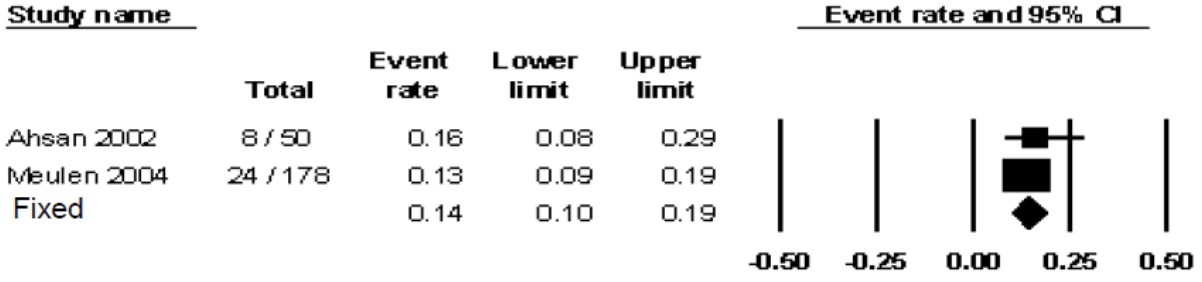
7.2 Justification of a non-inferiority margin for Study 1203

To assess the non-inferiority of Tac-XL compared to Prograf in Study 1203, the effect of Prograf compared to placebo must be estimated. The goal would be to estimate the difference for the following:

Active control MMF+CCS+Prograf 0.1mg BID
Putative placebo MMF+CCS

The results for two trials, identified by this reviewer, which included an arm for MMF+CCS+Prograf are summarized below (Figure 6.2.1). The results from these two trials suggest that a rejection rate of about 19% could be possible (upper limit of the 95% CI) for the active control used in Study 1203.

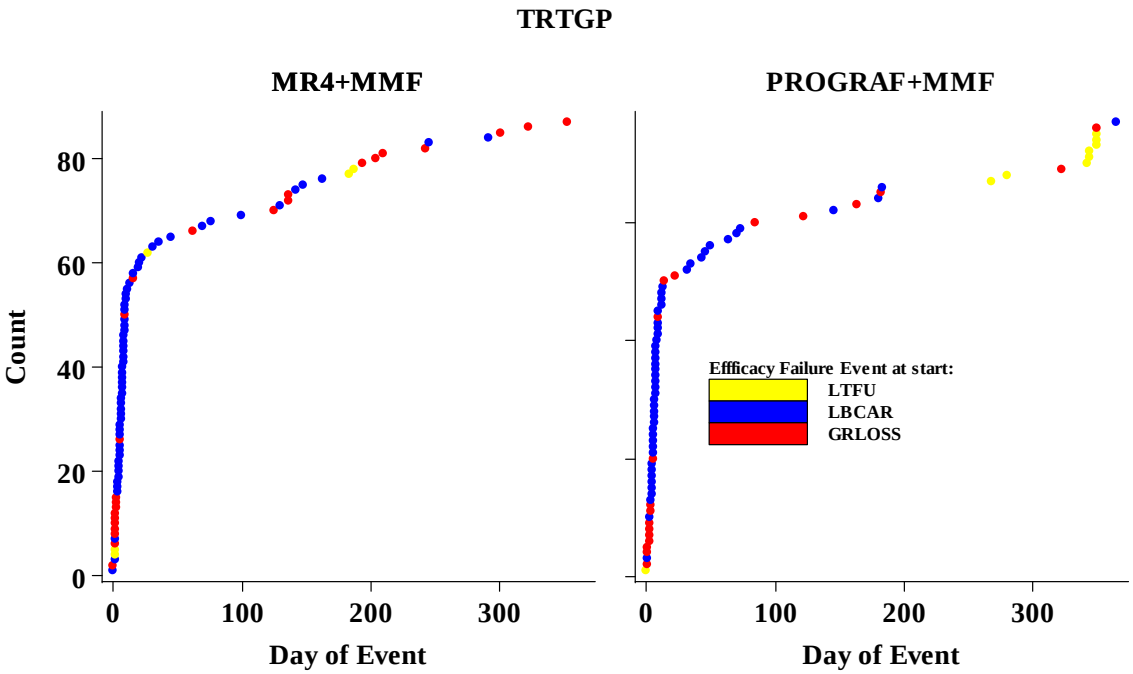
Figure 6.2.1 Meta-analysis to estimate the acute rejection rate for the active control, MMF+CCS+Prograf 0.1mg BID



This reviewer was not able to identify any trials that contained an arm of MMF+CCS, the putative placebo. Additional details regarding a non-inferiority margin for Study 1203 are provided in Section 3.2 of this review.

7.3 Timing of efficacy failures in Study 1203

This graph illustrates the day on which an efficacy failure occurred and the type of failure in Study 1203. Each symbol represents a single patient with an event.



7.4 References

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/s/

JOY D MELE
06/04/2013

KAREN M HIGGINS
06/04/2013
I concur.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 204096 **Applicant: Astellas** **Stamp Date: 9/21/12**

Drug Name: Tacrolimus extended release capsules (Advagraf) **NDA/BLA Type: Standard**

Link to submission: \\cdsesub1\EVSPROD\NDA204096\\0000\
Link to Study 1203: \\cdsesub1\EVSPROD\NDA204096\\0000\m5\datasets\fg-506e-12-03-datasets-full\analysis\datasets\define.pdf

Results from several studies were provided but only new efficacy data is provided for Study 1203. Other studies were reviewed when originally submitted in 2005 and 2007.

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			Also analyzed by donor type
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).		X		Define file cumbersome to use; There is no unique subject ID in study dataset for 1203; these issues are fixable but sponsor should be notified regarding this error

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ____Yes____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

One comment to be sent to the sponsor:
You have provided electronic datasets with define files. Although we do not require that datasets be in a CDISC standardized form at this time, we do expect that analysis datasets will be formatted taking our guidances into consideration (see our guidance page at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm). You have submitted datasets that do not conform to some basic parameters described in our guidances. For example, you have not included a unique subject ID on each dataset and the dataset with the primary efficacy data is not clearly labeled. You have provided a define file for each dataset but links within the define file do not provide information specific for the study making the file more cumbersome to use. For this application, we are not requesting that you fix these problems and others but wish to advise you that as we move closer to accepting only standardized datasets that these types of issues are more likely to result in a request for a new submission.

These responses are based on study 1203

Content Parameter (possible review concerns for 74-day letter)	**Yes**	**No**	**NA**	**Comment**
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			ISS data available
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			Included graft failures, deaths and lost to follow-ups as failures; this is the recommended way to handle missing data for the BPAR outcome

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Reviewing Statistician	Date
Supervisor/Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOY D MELE
11/13/2012
Contains 1 comment to be conveyed to the sponsor

KAREN M HIGGINS
11/14/2012