CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204096Orig1s000

MEDICAL REVIEW(S)

ADENDUM TO CLINICAL REVIEW

Application Type	NDA
Application Number(s)	204096
Priority or Standard	Standard
Submit Date(s)	September 20, 2012
Received Date(s)	September 21, 2012
PDUFA Goal Date	July 21, 2012
Division / Office	DTOP/OAP/OND
Reviewer Name(s)	Marc Cavaillé-Coll, MD, PhD
Addendum Date	July 18, 2013
Established Name	(tacrolimus) extended release capsules
(Proposed) Trade Name	Astagraf XL
Therapeutic Class	Immunosuppressant
Applicant	Astellas Pharma US, Inc.
Formulation(s)	Capsules for oral administration
Dosing Regimen	Fixed initial dose followed by dosing base on therapeutic drug monitoring
Indication(s)	Prophylaxis of organ rejection in adult patients receiving kidney transplants
Intended Population(s)	Renal transplant recipients

Addendum to Clinical Review:

Please refer to Sections 7.3.4.1 Infections on page 132, and the Reviewer's Comments on page 136, as well as recommendations with respect to infections for subsection 6.1 of the Package Insert on page 166 of the Clinical Review, dated June 19, 2013 in DARRTS. Please refer also to the Information Amendment submitted to the NDA by the Applicant on July 18, 2013 (NDA 204096 Document number 48), containing a revised draft package insert and supporting documentation.

In Section 7.3.4.1 Infections under Section 7.3.4 Significant Adverse Events, and Table 56 (Summary of Treatment-Emergent Bacterial, Viral, or Fungal Infections Occurring in ≥ 1%% in Any Treatment Group) and 58 (Incidence of Infections in Study 12-03), of the Clinical Review, dated June 19, 2013 in DARRTS, it was noted that although uncommon (rate < 5%) the observation of a significant increased occurrence of gastroenteritis reported as an infection in the TacXL treatment group compared to the Tac treatment group in both Study 158 (14/214 or 6.5% vs. 1/212 or 0.5%) and Study 12-03 (11/331 or 3.3% vs 3/336 or 09%0, must be interpreted as a truly significant finding, all the more that the rate of gastroenteritis reported as a serious adverse event was significantly greater in the TacXL treatment group (8/214; 4.2%) compared to the Tac or cyclosporine treatment groups in Study 158. Furthermore, it was recommended by this reviewer that subsection 6.1 Clinical Studies Experience in Section 6 ADVERSE REACTIONS should information on selected adverse events, including Infections.

Thus, the Applicant was requested to include information on gastroenteritis in the proposed package insert in a table that summarizes the incidence of infections of interest in Section 6.1 Clinical Studies Experience.

In a submission dated, July 18, 2013 to the NDA (NDA 204096 Document number 48), the Applicant has proposed the following version of Table 3 in Section 6.1 and provided a justification for the table.

Table 3. Overall Infections and Select Infections by Treatment Group in Studies 1 and 2 Through One Year Post-Transplant

	Study 1		Study 2	
	ASTAGRAF XL n (%) (N=214)	Prograf n (%) (N=212)	ASTAGRAF XL n (%) (N=331)	Prograf n (%) (N=336)

All Infections	148 (69)	146 (69)	228 (69)	216 (64)
Serious Infections	48 (22)	49 (23)	79 (24)	64 (19)
Bacterial Infections	18 (8)	25 (12)	125 (38)	137 (41)
Respiratory Infections	73 (34)	65 (31)	75 (23)	74 (22)
Cytomegalovirus Infections	21 (10)	24 (11)	38 (12)	21 (6)
Polyomavirus Infections	6 (3)	10 (5)	7 (2)	1 (0)
Gastroenteritis	16 (7)	6 (3)	16 (5)	8 (2)

The information on gastroenteritis in the table above reflects the number of subjects with any of the following events (MedDRA preferred terms) were used for the Gastroenteritis group: Gastroenteritis, Gastroenteritis Salmonella, Gastroenteritis Staphylococcal, Gastroenteritis Viral, Gastroenteritis Bacterial, Gastroenteritis Clostridial, and Gastroenteritis Cryptosporidial. These numbers are supported by the individual line listings of individual events included in the justification provided by the Applicant.

While Tables 56 and 58 of the FDA Clinical Review, dated June 19, 2013, which were derived and adapted from information and tables in the Study Reports for Study 158 and Study 12-03, represented the numbers by MeDRA Preferred Term “Gastroenteritis” based on the investigator assessment, the numbers now proposed by the Applicant reflect a an assessment of the adverse events as they were reported in the clinical trials, using a cluster of terms for gastroenteritis. This cluster of terms remains more common in the TacXL groups compared to the Tac groups in Studies 158 and 12-03 (Study 1 and Study 2 in the proposed package insert), and this information is adequately represented in the Applicant’s revised package insert Submitted July 18, 2013 to NDA 204096 (Document number 48).

Reviewer’s Conclusion and Recommendation:

The Applicant’s proposed Table 3 - Overall Infections and Select Infections by Treatment Group in Studies 1 and 2 Through One Year Post-Transplant, included in the revised draft Package Insert (NDA 204096, Document number 48, dated 07-18-2013) is acceptable.

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

/s/

MARC W CAVAILLE COLL
07/19/2013

JOETTE M MEYER
07/19/2013

DIVISION OF TRANSPLANT AND OPHTHALMOLOGY PRODUCTS
PEDIATRIC PARTIAL WAIVER AND DEFERRAL JUSTIFICATION

Date:	June 20, 2013
Application:	NDA 204096
Applicant:	Astellas Pharma US Inc.
Drug:	Tacrolimus extended-release capsules
Indication:	Prophylaxis of organ rejection in adult patients receiving a kidney transplant
From:	Joette M. Meyer, Pharm.D. Clinical Team Leader, DTOP
Through:	Renata Albrecht, MD Director, DTOP

Regulatory Background for Tacrolimus

Immediate-release oral and intravenous formulations of tacrolimus (Prograf® and generics) are marketed for the prophylaxis of organ rejection in patients receiving allogeneic liver, kidney or heart transplants. FDA approval occurred in 1994 for liver transplant, in 1997 for kidney transplant; and in 2006 for heart transplant.

Immediate release tacrolimus capsules require twice-daily oral dosing. Tacrolimus XL (Advagraf)[1] was developed as an extended-release formulation of tacrolimus administered once daily and has been studied in kidney, liver and heart transplant patients. Tacrolimus XL is approved in 69 countries, including Canada, Japan and European countries. A granule formulation of tacrolimus was approved for marketing in Japan 2001 for use in pediatric and adult solid organ transplantations (under the name Prograf granules) and was adopted by the European Medicines Agency (EMA) in 2009 for the "prophylaxis of transplant rejection in adult and pediatric kidney, liver, or heart allograft recipients" (under the name Modigraf®).[2] See **APPENDIX A.**

Astellas submitted an NDA on December 19, 2005 proposing the use of tacrolimus XL for once-daily dosing in the prophylaxis of organ rejection following kidney, liver or heart transplantation.

[1] Proposed trade name was not found acceptable by the Division of Medication Error Prevention and Analysis (DMEPA). Final, agreed upon proprietary name is Astagraf XL (DMEPA review May 31, 2013)
[2] EMA Assessment Report for Modigraf: http://www.emea.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000954/WC500030473.pdf

The Agency administratively split the NDA into three separate NDA numbers for each indication: NDA 50811 (kidney), NDA 50815 (liver) and NDA 50816 (heart). On January 19, 2007, the Agency issued an approvable letter for kidney and liver indications and a non-approvable letter for the heart indication. (b) (4) [redacted].

On September 21, 2012, Astellas submitted a new NDA 204096 for following proposed indications for tacrolimus XL:

- Prophylaxis of organ rejection in adult patients receiving kidney transplants.
- Prophylaxis of organ rejection in adult male patients receiving liver transplants.

On February 6, 2013 Astellas requested withdrawal of the liver indication from NDA 204096.

As discussed below, the sponsor is requesting a waiver of pediatric studies under the Pediatric Research Equity Act (PREA) for children aged 0 to < 5 years and a deferral for children aged 5 to 16 years.

The Pediatric Research Committee (PeRC) meeting to discuss the sponsor's request will be held on May 22, 2013.

Currently Approved Products for Use in Kidney Transplantation

Currently approved products for the prophylaxis of organ rejection in kidney transplant recipients include: cyclosporine, tacrolimus, mycophenolate mofetil (MMF), mycophenolic acid (MPA), sirolimus and everolimus. Only mycophenolic acid (Myfortic®) and sirolimus (Rapamune®) contain pediatric dosing regimens in the Dosage and Administration section of the package insert; although the other products do contain information on pediatrics in other sections. For additional information, see the **APPENDIX B**.

Immunosuppressive Regimens Used in Pediatric Kidney Transplant

The Health Resources and Services Administration's (HRSA's) Division of Transplantation administers and oversees two contracts to facilitate the nation's allocation system for organ transplantation. The Organ Procurement and Transplantation Network (OPTN), contracted by the United Network for Organ Sharing (UNOS), is responsible for operating the national network for organ procurement and allocation, and works to promote organ donation. The Scientific Registry of Transplant Recipients (SRTR) provides analytical support for the ongoing evaluation of scientific and clinical status of solid organ transplantation. Together, they publish an annual report focusing on statistics for kidney, pancreas, liver, intestine, heart, and lung transplants in the US regarding data on waiting lists, donation, transplantation, donor-recipient matching, immunosuppression, pediatric transplantation, and center characteristics.

According to the 2011 OPTN/SRTR Annual Data Report[3] the most common initial

[3] OPTN/SRTR 2011 Annual Report: Kidney:

immunosuppressive regimen in adult kidney transplant recipients was tacrolimus plus MMF/MPA with or without corticosteroids (85% of patients transplanted). Data are similar in pediatric kidney transplant recipients.

The numbers of children receiving a kidney transplant between 2009 and 2011 (three year period) are shown below:

Age	**Number (%)**
< 1	5 (0.2)
1 to 5 years	510 (21.5)
6 to 10 years	429 (18.1)
11 to 17 years	1427 (60.2)

Experience with Immediate Release Tacrolimus in Pediatric Kidney Transplant Recipients

Immediate release tacrolimus was approved for use in kidney (and liver) transplant prior to implementation of PREA. The heart indication was added most recently, in 2006, and pediatric studies were waived for this indication due to the small number of pediatric patients who undergo heart transplantation.

There is an extensive amount of data in the literature on the PK of immediate release tacrolimus in pediatric kidney transplant recipients including a comparison with adult kidney transplant recipients.[4] In addition, a multicenter, randomized comparative clinical trial of tacrolimus-based immunosuppression compared to cyclosporine-based immunosuppression in 196 children (mean age 10 years).[5,6] All patients also received azathioprine and corticosteroids. The primary endpoint was incidence and time to first acute rejection (intent-to-treat). At one year, tacrolimus was reported to have a significantly lower incidence of acute rejection (40%) compared with cyclosporine (59%, $p = 0.003$). At four years post-transplant, patient survival was similar (94% vs. 92%, $p = 0.86$) but graft survival significantly favored tacrolimus (86% vs. 69%; $p = 0.025$.

The published PK studies generally report that pediatric patients need higher doses to achieve trough concentrations comparable to adult trough concentrations, as briefly discussed later in the document.

Request for Partial Waiver/Deferral for Tacrolimus XL in Pediatric Kidney Transplant Recipients

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new

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http://srtr.transplant.hrsa.gov/annual_reports/2011/pdf/01_kidney_12.pdf

[4] Wallemacq PE, Verbeeck RK. Comparative clinical pharmacokinetics of tacrolimus in paediatric and adult patients. Clin Pharmacokinet. 2001;40:283-95.

[5] Trompeter R, Filler G, Webb NJ, et al. Randomized trial of tacrolimus versus cyclosporin microemulsion in renal transplantation. Pediatr Nephrol 2002; 17: 141-9.

[6] Filler G, Webb NJ, Milford DV, et al. Four-year data after pediatric renal transplantation: a randomized trial of tacrolimus vs. cyclosporin microemulsion. Pediatr Transplant 2005;9:498-503.

active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. This review will briefly summarize the issues and basis for requesting a waiver for the requirement of pediatric studies in patients 0 to < 5 years and a deferral for children aged 5 to 16 years.

Sponsor's Rationale for Partial Waiver in Pediatric Kidney Transplant Recipients Aged 0 to < 5 Years of Age

The sponsor states the following in the NDA submission for tacrolimus XL:

> Studies to investigate the use of Advagraf [tacrolimus XL] for the prophylaxis of organ rejection in pediatric kidney transplant patients from ages 0 to <5 are highly impractical because the number of pediatric patients is so small (statutory authority: Section 505B(a)(4)(B)(i) of the Act).
>
> Based on the 2010 annual data report [7] of the Scientific Registry of Transplant Recipients (SRTR), over the three year period from 2007 to 2009, there were only seven (7) pediatric kidney transplant patients ages younger than one (1) year and only 478 pediatric kidney transplant patients ages between one (1) to five (5) years old in the United States. By contrast, there were 2,050 kidney transplant patients ages between six (6) to 17 years old in the United States.

Sponsor's Request for Deferral and Proposed Pediatric Plan for Tacrolimus XL in Pediatric Kidney Transplant Recipients from 5 to 16 years

The sponsor states the following in the NDA submission for tacrolimus XL:

> The reason for the deferral request is that adult studies have been completed and are ready for approval.
>
> A Pediatric Plan is included in this NDA submission.
>
> Suggested deferred date for submission of studies: The clinical study PMR-EC-1206 is expected to complete enrollment in May 2013. Astellas proposes to provide the final Clinical Study Report to the FDA within one year of the last patient out.

Sponsor's Pediatric Plan in Kidney Transplant Recipients

The sponsor is conducting a pharmacokinetic study in 10 stable pediatric kidney transplant recipients aged 5 to 16 years of age.

Study PMR-EC-1206: A Phase II, Open-Label, Multi-Center Study to Compare the Pharmacokinetics of Tacrolimus in Stable Pediatric Allograft Recipients Converted from a Prograf® Based Immunosuppressive Regimen to a Tacrolimus Prolonged Release, Advagraf® Based Immunosuppressive Regimen, Including a Long-Term Follow-Up

The following is a summary of the study design, endpoints, and analysis plan.

Study Design:

This is a Phase 2, open label, multicenter study to compare the pharmacokinetics (PK) of tacrolimus in stable pediatric allogeneic recipients converted from a Prograf based

[7] More recent data from 2011 are provided on page 2-3 of this document and show similar numbers of pediatric kidney transplant recipients.

immunosuppressive regimen to a tacrolimus XL-based immunosuppressive regimen

Part A: The initial PK part of the study is from Day -30 to Day 15.
Part B: The long term follow-up is from Day 15 up to 12 months.

Primary Objective:
To compare the tacrolimus steady state $AUC_{0\text{-}24h}$ after dosing with tacrolimus XL to the tacrolimus steady state $AUC_{0\text{-}24h}$ obtained with Prograf in stable pediatric allograft recipients after 1:1 (mg:mg) conversion from Prograf to tacrolimus XL.

Secondary Objectives:
To observe the long-term safety and efficacy profile of tacrolimus in stable pediatric allograft recipients after 1:1 (mg:mg) conversion from Prograf to tacrolimus XL and to evaluate the relationship between $AUC_{0\text{-}24h}$ and C_{24} for tacrolimus XL and for Prograf at each PK profile.

Main Inclusion Criteria:
Stable pediatric subjects who have previously received a single organ liver, kidney, heart, lung or intestinal transplantation (≥ 6 months post-transplant) who are currently being treated with a Prograf based immunosuppressive regimen. The patients must be able to swallow intact study medication capsules.

Patient Population:
Approximately 80 subjects will be enrolled to achieve a total of 72 subjects with two complete evaluable PK profiles required in the following age groups:

Group 1: 5 to 7 years
Group 2: 8 to 10 years
Group 3: 11 to 13 years
Group 4: 14 to 16 years

Number of subjects in each group by type of transplant is specified in the table below:

Transplanted Organ		Kidney	Liver	Other*
Group 1	5 to 7 years	6 (± 2) patients	6 (± 2) patients	6 (± 2) patients
Group 2	8 to 10 years	6 (± 2) patients	6 (± 2) patients	6 (± 2) patients
Total: Group 1 and 2		12	12	12
Group 3	11 to 13 years	6 (± 2) patients	6 (± 2) patients	6 (± 2) patients
Group 4	14 to 16 years	6 (± 2) patients	6 (± 2) patients	6 (± 2) patients
Total: Group 3 and 4		12	12	12
Overall total		24	24	24

*Heart, lung, and intestinal transplantation

DTOP's Comment on Partial Waiver/Deferral Request

Partial Waiver

DTOP agrees with the sponsor's request for a partial waiver pediatric kidney transplant recipients from 0 to < 5 years of age for tacrolimus XL because studies are impossible or highly impractical. As noted above there are only about 500 children between 0 and 5 years that were transplanted between 2009 and 2011 and are dispersed between approximately 200 transplant centers in the US. In addition, tacrolimus XL is an extended release version of tacrolimus that may not be suitable for administration to children below 6 years of age.

In addition, pediatric patients generally need higher doses and more frequent dosing because of higher clearance. Frequent dosing and/or doses requiring multiple capsules may not be feasible with the tacrolimus XL product given its size, as shown below. Also, extemporaneous compounding of the XL capsules into a liquid/suspension formulation may affect the PK properties and stability of the product.

Tacrolimus XL capsules are distinctly larger in size than Prograf capsules:

Deferral

The sponsor's proposed pediatric plan for obtaining PK data in 24 recipients of kidney transplants converted to tacrolimus XL capsules from tacrolimus immediate release capsules after at least 6 months post-transplant is considered to be adequate to compare the PK parameters between children and adults and to establish a dosing regimen in children.

In addition to the tacrolimus XL capsules not being suitable for administration, there are various other reasons why it may be more difficult to determine an appropriate pediatric dosing regimen to children less than 5 years of age:

- Larger interindividual variability in tacrolimus PK in pediatric patients in the 0 to <5 year age subgroup is expected due to developmental changes or physiologic differences in body composition (water/fat), plasma proteins, and metabolic activity, particularly due to

maturational changes in the ontogeny of CYP3A enzymes that are mainly responsible for the metabolism of tacrolimus.

- A greater clearance of tacrolimus in pediatric patients may result in the need for higher drug doses compared to adults in order to achieve similar systemic exposure.[8,9,10]

- Younger children (< 5 to 6 years of age) may also need higher tacrolimus doses than older children.[11,12]

Therefore, DTOP agrees with the sponsor's request for a deferral of pediatric studies for kidney transplant recipients from 5 to 16 years of age for tacrolimus XL.

Pediatric Plan

For the reasons summarized above, we also agree with the sponsor's proposal to conduct Study PMR-EC-1206 in stable kidney transplant recipients between 5 and 16 years of age years to compare the steady state $AUC_{0\text{-}24h}$ of tacrolimus for tacrolimus XL with that of Prograf after 1:1 (mg:mg) conversion from Prograf to tacrolimus XL and to observe the long-term safety and efficacy of conversion from Prograf to tacrolimus XL. The sponsor's proposal to conduct Study PMR-EC-12-06 in stable (≥ 6 months post-transplant) pediatric patients rather than in *de novo* pediatric transplant patients is acceptable because there are early post-transplant patient intrinsic and extrinsic factors that could alter tacrolimus exposures and as such, confound the selection of appropriate doses in the various age subgroups as summarized in the table above. These factors include changes in gastrointestinal absorption during the first 1-2 weeks post-surgery, changes in the type and dosage of concomitant immunosuppressive drugs (e.g., corticosteroid taper) and other medications during the first 6 months post-transplant (including, but not limited to, those used for prophylaxis of infections and for the treatment of acute rejections). In addition, changes to the target tacrolimus trough concentration range occurring during the first 6 months post-transplant may complicate the ability to select the appropriate dosage regimen.

PeRC Meeting May 22, 2013

The PeRC recommended the following modification to the sponsor's partial waiver/deferral request:

- Waiver in patients birth to less than 1 year because studies are impossible or highly impractical

[8] Shishido S, Asanuma H, Tajima E, Honda M, Nakai H. Pharmacokinetics of tacrolimus in pediatric renal transplant recipients. Transplant Proc 2001;33:1066–1068.
[9] Wallemacq PE, Verbeeck RK. Comparative clinical pharmacokinetics of tacrolimus in paediatric and adult patients. Clin Pharmacokinet 2001;40:283–295.
[10] Webb NJA, Stevenson PK, Lewis MA, et al. Pharmcokinetics of tacrolimus in pediatric renal transplant recipients. Transplantation Proceedings 2002;34:1948-50.
[11] de Wildt SN, van Schaik RH, Soldin OP,et al. The interactions of age, genetics, and disease severity on tacrolimus dosing requirements after pediatric kidney and liver transplantation. Eur J Clin Pharmacol. 2011;67:1231-41.
[12] Montini G, Ujka F, Varagnolo C, et al. The pharmacokinetics and immunosuppressive response of tacrolimus in paediatric renal transplant recipients. Pediatric Nephrology 2006;21:719-24.

- Deferred pediatric study under PREA for patients 1 to less than 5 years of age in order to develop a pediatric formulation
- Deferred pediatric study under PREA for patients 5 to 16 years because the product is ready for approval in adults

APPENDIX A:
European Experience with a Pediatric Formulation – Tacrolimus Oral Suspension

Modigraf® is a granule formulation of tacrolimus, as 0.2 mg and 1 mg sachets that was approved for marketing in Japan 2001 for use in pediatric and adult solid organ transplantations (under the name Prograf granules) and was adopted by the European Medicines Agency (EMA) in 2009 for the "prophylaxis of transplant rejection in adult and pediatric kidney, liver, or heart allograft recipients."[13] The sponsor in Europe is Astellas Pharma Europe. According to the EMA document, there has been widespread off-label clinical practice to break the Prograf capsules and use the granules for children and seriously ill adults with difficulties swallowing the capsules. Modigraf also allows fine dose adjustments often needed for pediatric patients. In support of their application, the sponsor conducted PK studies and clinical studies in pediatric liver and kidney transplant recipients below the age of 16 years. One study (FG-506-01-13) was a phase 3 *de novo* multicenter, open-label, prospective, randomized comparative study of Modigraf versus cyclosporine in kidney transplant recipients; all patients received corticosteroids and those in the cyclosporine group also received azathioprine. Numerically more acute rejections, graft losses and deaths occurred in the cyclosporine group compared to the Modigraf group.

[13] EMA Assessment Report for Modigraf: http://www.emea.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000954/WC500030473.pdf

APPENDIX B:
Currently Approved Products for Use in Kidney Transplantation and Pediatric Language in Labeling

Cyclosporine (Sandimmune®)

Sandimmune was approved in kidney transplant recipients in 1983, while not specifically approved for use in children, the package insert (PI) states:

> **PRECAUTIONS**
> **Pediatric Use**
> Although no adequate and well-controlled studies have been conducted in children, patients as young as 6 months of age have received the drug with no unusual adverse effects.
>
> **DOSAGE AND ADMINISTRATION**
> In pediatric usage, the same dose and dosing regimen may be used as in adults although in several studies, children have required and tolerated higher doses than those used in adults.

Neoral® (cyclosporine USP, modified), was approved in kidney transplant recipients in 1995 and has similar wording in the PI to Sandimmune (but no information in DOSAGE AND ADMINISTRATION

> **PRECAUTIONS**
> **Pediatric Use**
> Although no adequate and well-controlled studies have been completed in children, transplant recipients as young as one year of age have received Neoral® with no unusual adverse effects.

Tacrolimus (Prograf® and generics)

Prograf was approved in kidney transplant recipients in 1997 and is specifically indicated for use in pediatric liver, but not kidney transplant patients.

> **2 DOSAGE AND ADMINISTRATION**
> **2.2 Dosage in Pediatric Liver Transplant Patients**
>
> The initial oral dosage recommendations for pediatric patients with liver transplants along with recommendations for whole blood trough concentrations are shown in Table 3. For blood concentration monitoring details see Dosage and Administration (2.6). If necessary, pediatric patients may start on an IV dose of 0.03-0.05 mg/kg/day.
>
> **Table 3. Summary of Initial Oral Dosage Recommendations and Observed Whole Blood Trough Concentrations in Children**

Patient Population	Recommended Prograf Initial Oral Dosage Note: daily doses should be administered as two divided doses, every 12 hours	Observed Tacrolimus Whole Trough Concentrations
Pediatric liver transplant patients	0.15-0.20 mg/kg/day	Month 1-12: 5-20 ng/mL

> Pediatric liver transplantation patients without pre-existing renal or hepatic dysfunction have required and tolerated higher doses than adults to achieve similar blood concentrations.

Experience in pediatric kidney and heart transplantation patients is limited.

8 USE IN SPECIFIC POPULATION

8.4 Pediatric Use

The safety and efficacy of Prograf in pediatric kidney and heart transplant patients have not been established. Successful liver transplants have been performed in pediatric patients (ages up to 16 years) using Prograf. Two randomized active-controlled trials of Prograf in primary liver transplantation included 56 pediatric patients. Thirty-one patients were randomized to Prograf-based and 25 to cyclosporine-based therapies. Additionally, a minimum of 122 pediatric patients were studied in an uncontrolled trial of tacrolimus in living related donor liver transplantation. Pediatric patients generally required higher doses of Prograf to maintain blood trough concentrations of tacrolimus similar to adult patients *[see Dosage and Administration (2.2)]*.

Mycophenolate Mofetil (CellCept® and generics)

CellCept was approved in kidney transplant recipients in 1995 and the PI states

CLINICAL PHARMACOLOGY

Pediatrics

The pharmacokinetic parameters of MPA and MPAG have been evaluated in 55 pediatric patients (ranging from 1 year to 18 years of age) receiving CellCept oral suspension at a dose of 600 mg/m^2 bid (up to a maximum of 1 g bid) after allogeneic renal transplantation. The pharmacokinetic data for MPA is provided in **Table 3**.

The CellCept oral suspension dose of 600 mg/m^2 bid (up to a maximum of 1 g bid) achieved mean MPA AUC values in pediatric patients similar to those seen in adult renal transplant patients receiving CellCept capsules at a dose of 1 g bid in the early posttransplant period. There was wide variability in the data. As observed in adults, early posttransplant MPA AUC values were approximately 45% to 53% lower than those observed in the later posttransplant period (>3 months). MPA AUC values were similar in the early and late posttransplant period across the 1 year to 18 year age range.

CLINICAL STUDIES

Pediatrics

One open-label, safety and pharmacokinetic study of CellCept oral suspension 600 mg/m^2 bid (up to 1 g bid) in combination with cyclosporine and corticosteroids was performed at centers in the US (9), Europe (5) and Australia (1) in 100 pediatric patients (3 months to 18 years of age) for the prevention of renal allograft rejection. CellCept was well tolerated in pediatric patients (see **ADVERSE REACTIONS**), and the pharmacokinetics profile was similar to that seen in adult patients dosed with 1 g bid CellCept capsules (see CLINICAL PHARMACOLOGY: Pharmacokinetics). The rate of biopsy-proven rejection was similar across the age groups (3 months to <6 years, 6 years to <12 years, 12 years to 18 years). The overall biopsy-proven rejection rate at 6 months was comparable to adults. The combined incidence of graft loss (5%) and patient death (2%) at 12 months posttransplant was similar to that observed in adult renal transplant patients.

PRECAUTIONS

Pediatric Use

Based on pharmacokinetic and safety data in pediatric patients after renal transplantation, the recommended dose of CellCept oral suspension is 600 mg/m^2 bid (up to a maximum of 1 g bid). Also see **CLINICAL PHARMACOLOGY, CLINICAL STUDIES, ADVERSE REACTIONS,** and **DOSAGE AND ADMINISTRATION**.

Safety and effectiveness in pediatric patients receiving allogeneic cardiac or hepatic transplants have not been established.

Mycophenolic acid (as mycophenolate sodium) delayed-release tablets (Myfortic®) was approved in kidney transplant recipients in 2004 has information on pediatric use in various sections of the package insert. In the

1 INDICATIONS AND USAGE

1.1 Prophylaxis of Organ Rejection in Kidney Transplant

…Myfortic is indicated for the prophylaxis of organ rejection in pediatric patients 5 years of age and older who are at least 6 months post kidney transplant….

2 DOSAGE AND ADMINISTRATION

2.2 Dosage in Pediatric Kidney Transplant Patients

The recommended dose of Myfortic in conversion (at least 6 months post-transplant) pediatric patients age 5 years and older is 400 mg/m^2 body surface area (BSA) administered twice daily (up to a maximum dose of 720 mg administered twice daily).

2.3 Administration

..Pediatric patients with a BSA of 1.19 to 1.58 m^2 may be dosed either with three Myfortic 180 mg tablets, or one 180 mg tablet plus one 360 mg tablet twice daily (1080 mg daily dose). Patients with a BSA of >1.58 m^2 may be dosed either with four Myfortic 180 mg tablets, or two Myfortic 360 mg tablets twice daily (1440 mg daily dose). Pediatric doses for patients with BSA <1.19 m^2 cannot be accurately administered using currently available formulations of Myfortic tablets.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of Myfortic have been established in pediatric kidney transplant patients 5 to 16 years of age who were initiated on Myfortic at least 6 months post-transplant. Use of Myfortic in this age group is supported by evidence from adequate and well-controlled studies of Myfortic in a similar population of adult kidney transplant patients with additional pharmacokinetic data in pediatric kidney transplant patients [see *Dosage and Administration (2.2, 2.3)* and *Clinical Pharmacology (12.3)*]. Pediatric doses for patients with BSA <1.19 m^2 cannot be accurately administered using currently available formulations of Myfortic tablets.

The safety and effectiveness of Myfortic in *de novo* pediatric kidney transplant patients and in pediatric kidney transplant patients below the age of 5 years have not been established.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Pediatrics: Limited data are available on the use of Myfortic at a dose of 450 mg/m_2 body surface area in children. The mean MPA pharmacokinetic parameters for stable pediatric renal transplant patients, 5 to 16 years, on cyclosporine, USP MODIFIED are shown in Table 6. At the same dose administered based on body surface area, the respective mean C_{max} and AUC of MPA determined in children were higher by 33% and 18% than those determined for adults. The clinical impact of the increase in MPA exposure is not known [see *Dosage and Administration (2.2, 2.3)*].

Sirolimus (Rapamune®)

Rapamune was approved in kidney transplant recipients in 1999. A supplemental new drug application, submitted in response to a Pediatric Written Request, was approved in 2005 which provides the addition of pediatric pharmacokinetics information to the labeling along with results of a clinical study in pediatric patients <18 years of age at high immunologic risk for acute rejection.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and efficacy of Rapamune in pediatric patients < 13 years have not been established.

The safety and efficacy of Rapamune Oral Solution and Rapamune Tablets have been established in children ≥ 13 years judged to be at low-to moderate-immunologic risk. Use of Rapamune Oral Solution and Rapamune Tablets in this subpopulation of children ≥ 13 years is supported by evidence from adequate and well-controlled trials of Rapamune Oral Solution in adults with additional pharmacokinetic data in pediatric renal transplantation patients [see *Clinical Pharmacology (12.3)*].

Safety and efficacy information from a controlled clinical trial in pediatric and adolescent (< 18 years of age) renal transplant patients judged to be at high-immunologic risk, defined as a history of one or more acute rejection episodes and/or the presence of chronic allograft nephropathy, do not support the chronic use of Rapamune Oral Solution or Tablets in combination with calcineurin inhibitors and corticosteroids, due to the higher incidence of lipid abnormalities and deterioration of renal function associated with these immunosuppressive regimens compared to calcineurin inhibitors, without increased benefit with respect to acute rejection, graft survival, or patient survival [see *Clinical Studies (14.6)*].

12 CLINICAL PHARMACOLOGY

12.3 Pharmcokinetcs

Pediatric

Sirolimus pharmacokinetic data were collected in concentration-controlled trials of pediatric renal transplant patients who were also receiving cyclosporine and corticosteroids. The target ranges for trough concentrations were either 10-20 ng/mL for the 21 children receiving tablets, or 5-15 ng/mL for the one child receiving oral solution. The children aged 6-11 years (n = 8) received mean ± SD doses of 1.75 ± 0.71 mg/day (0.064 ± 0.018 mg/kg, 1.65 ± 0.43 mg/m^2). The children aged 12-18 years (n = 14) received mean ± SD doses of 2.79 ± 1.25 mg/day (0.053 ± 0.0150 mg/kg, 1.86 ± 0.61 mg/m^2). At the time of sirolimus blood sampling for pharmacokinetic evaluation, the majority (80%) of these pediatric patients received the Rapamune dose at 16 hours after the once-daily cyclosporine dose.

SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN ± SD) IN PEDIATRIC RENAL TRANSPLANT PATIENTS (MULTIPLE-DOSE CONCENTRATION CONTROL)[a,b]

Age (y)	n	Body weight (kg)	Cmax,ss (ng/mL)	tmax,ss (h)	Cmin,ss (ng/ml)	AUCT,ss (ng•h/mL)	CL/F[c] (mL/h/kg)	CL/Fc (L/h/m^2)
6-11	8	27 ± 10	22.1 ± 8.9	5.88 ± 4.05	10.6 ± 4.3	356 ± 127	214 ± 129	5.4 ± 2.8
12-18	14	52 ± 15	34.5 ± 12.2	2.7 ± 1.5	14.7 ± 8.6	466 ± 236	136 ± 57	4.7 ± 1.9

a: Rapamune co-administered with cyclosporine oral solution [MODIFIED] (e.g., Neoral® Oral Solution) and/or cyclosporine capsules [MODIFIED] (e.g., Neoral® Soft Gelatin Capsules).
b: As measured by Liquid Chromatographic/Tandem Mass Spectrometric Method (LC/MS/MS)
c: Oral-dose clearance adjusted by either body weight (kg) or body surface area (m2).

The table below summarizes pharmacokinetic data obtained in pediatric dialysis patients with chronically impaired renal function.

SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN ± SD) IN PEDIATRIC PATIENTS WITH END-STAGE KIDNEY DISEASE MAINTAINED ON HEMODIALYSIS OR PERITONEAL DIALYSIS (1, 3, 9, 15 mg/m2 SINGLE DOSE)*

Age Group (y)	n	t_{max} (h)	$t_{1/2}$ (h)	CL/F/WT (mL/h/kg)
5-11	9	1.1 ± 0.5	71 ± 40	580 ± 450
12-18	11	0.79 ± 0.17	55 ± 18	450 ± 232

* All subjects received Rapamune Oral Solution.

14 CLINICAL STUDIES

14.6 Pediatrics

Rapamune was evaluated in a 36-month, open-label, randomized, controlled clinical trial at 14 North American centers in pediatric (aged 3 to < 18 years) renal transplant patients considered to be at high-immunologic risk for developing chronic allograft nephropathy, defined as a history of one or more acute allograft rejection episodes and/or the presence of chronic allograft nephropathy on a renal biopsy. Seventy-eight (78) subjects were randomized in a 2:1 ratio to Rapamune (sirolimus target concentrations of 5 to 15 ng/mL, by chromatographic assay, n = 53) in combination with a calcineurin inhibitor and corticosteroids or to continue calcineurininhibitor-based immunosuppressive therapy (n = 25). The primary endpoint of the study was efficacy failure as defined by the first occurrence of biopsy-confirmed acute rejection, graft loss, or death, and the trial was designed to show superiority of Rapamune added to a calcineurin-inhibitor-based immunosuppressive regimen compared to a calcineurin-inhibitorbased regimen. The cumulative incidence of efficacy failure up to 36 months was 45.3% in the Rapamune group compared to 44.0% in the control group, and did not demonstrate superiority. There was one death in each group. The use of Rapamune in combination with calcineurin inhibitors and corticosteroids was associated with an increased risk of deterioration of renal function, serum lipid abnormalities (including, but not limited to, increased serum triglycerides and cholesterol), and urinary tract infections [see *Warnings and Precautions (5.8)*]. This study does not support the addition of Rapamune to calcineurin-inhibitor-based immunosuppressive therapy in this subpopulation of pediatric renal transplant patients.

Everolimus (Zortress®)

Zortress was approved in kidney transplant recipients in 2010.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and efficacy of Zortress has not been established in pediatric patients.

A Pediatric Written Request (PWR), which has now expired, was issued to Novartis on April 25, 2000 for everolimus to obtain information in pediatric transplant patients (b) (4) (b) (4)

The PWR was issued to obtain needed information on safety, tolerability, and basic pharmacokinetics to select an adequate dosing regimen for pediatric transplant patients. (b) (4) (b) (4)

Everolimus was granted a waiver from birth to 16 years of age by the PeRC on January 27, 2010 on the basis that the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

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/s/

JOETTE M MEYER
06/20/2013

RENATA ALBRECHT
07/12/2013

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	204096
Priority or Standard	Standard
Submit Date(s)	September 20, 2012
Received Date(s)	September 21, 2012
PDUFA Goal Date	July 21, 2012
Division / Office	DTOP/OAP/OND
Reviewer Name(s)	Marc Cavaillé-Coll, MD, PhD
Review Completion Date	June 18, 2013
Established Name	(tacrolimus) extended release capsules
(Proposed) Trade Name	Astagraf XL
Therapeutic Class	Immunosuppressant
Applicant	Astellas Pharma US, Inc.
Formulation(s)	Capsules for oral administration
Dosing Regimen	Fixed initial dose followed by dosing base on therapeutic drug monitoring
Indication(s)	Prophylaxis of organ rejection in adult patients receiving kidney transplants
Intended Population(s)	Renal transplant recipients

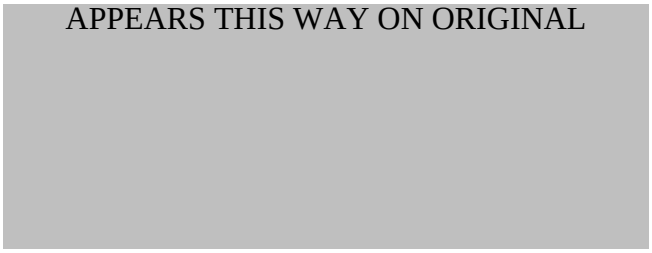
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Table of Contents

1 Recommendations/Risk Benefit Assessment

1. 1 Recommendation on Regulatory Action

The product should be approved for the prevention of rejection in recipients of kidney allograft transplantation. The package insert should reflect how the product may be used with basiliximab induction (lower observed tacrolimus whole blood trough concentrations as in Study 158) and without basiliximab induction (higher observed tacrolimus whole blood trough concentrations as in Study 12-03).

1.2 Risk Benefit Assessment

Astagraf XL provides comparable protection against rejection compared to Prograf (tacrolimus) with a comparable safety profile, as demonstrated by substantial evidence from adequate well controlled trials in combination with basiliximab induction, corticosteroids (Study 158) and MMF and in combination with corticosteroids and MMF without antibody induction (Study 12-03). Small safety differences such as those with respect to increased rate of gastroenteritis (excluding non-infectious causes) are manageable.

There is no substantial evidence of clinical benefit with respect to potential improved patient adherence with once a day dosing of Astagraf XL compared to Prograf.

- Whole blood trough concentrations during maintenance (after week 4) immunosuppression were observed to be the same across treatment groups.
- Occurrence of late rejection (often associated with poor compliance) was not greater in the Prograf groups.
- Discontinuation rates for any reason were similar between Tac and TacXL.
- Modeling of the pharmacokinetic consequences of missing a dose of Astagraf XL versus a dose of Prograf suggests that Astagraf XL may be more forgiving with respect to episodic lapse in compliance.
- Given the prolonged elimination half-life of tacrolimus (12-17 hours) once a day dosing may be feasible with Prograf in stable patients on lower dose maintenance tacrolimus immunosuppression.
- No advantage was seen with Astagraf XL compared to Prograf with respect to tolerance with respect to dose related tacrolimus toxicity associated with C_{max} (tremors).

Introduction of an extended release formulation amidst a number of branded and generic immediate release products on the market in the US, with similar strengths creates a potential for inadvertent substitution between immediate and extended release products. The potential hazards of over or under immunosuppression require attention to potential errors, but these challenges are not unprecedented or

unmanageable. Differences in physical appearance between the branded Prograf and branded Astagraf XL are important. However, one must recognize that there are also multiple generic versions of the immediate release product marketed in the US. Management of the multiple medications needed to support the health of renal transplant recipients have become part of the standard of care in solid organ transplantation. Patient education on adherence to regimens and recognition of individual medications has become part of the standard or care, and integration of the distinction between extended release and immediate release products will be needed. Astagraf XL and Prograf are not interchangeable or substitutable and labeling to that effect is needed.

On February 6, 2013 Astellas requested that NDA 204096 [Original 2 – Liver (Males)] for tacrolimus XL capsules be withdrawn without prejudice to refilling, and this request was acknowledged by the Agency in a letter dated May 14, 2013. (See NDA 204096 memo to file, dated May 13, 2013) Outstanding safety concerns remain from the earlier review of NDA 50-815 for tacrolimus extended release capsules in the indication of prevention of rejection in recipients of liver transplantation, with respect to the observation of a significantly higher rate of mortality in female liver transplantation recipients treated with TacXL compared to female liver transplant recipients treated with Tac. (See Section 7.3.5 of this review) Although a gender-related difference in outcome has not been observed in recipients of kidney transplantation, treated with TacXL compared to Tac, the increased risk of death in female recipients of liver transplantation treated with TacXL needs to be addressed in labeling in the boxed WARNING and in the WARNINGS AND PRECAUTIONS section of the package insert. (See Section 9.2 Labeling Recommendations in this review).

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Astellas had initially proposed a Risk Evaluation and Mitigation Strategy (REMS) that consisted of a communication program to inform healthcare providers and patients about the following potential risks of tacrolimus XL:

- Increased mortality in female liver transplant recipients treated with tacrolimus XL compared to Prograf (tacrolimus XL is not recommended in female patients receiving de novo liver transplants).
- Risk of medication errors with tacrolimus XL due to unintentional conversion or substitution between approved tacrolimus formulations (once-daily extended release and twice-daily immediate-release versions).

As mentioned above, on February 6, 2013 Astellas requested that NDA 204096 [Original 2 – Liver (Males)] for tacrolimus XL capsules be withdrawn without prejudice to refiling. Subsequently, the Review Division (Division of Transplant and Ophthalmology Products – DTOP), in consultation with the Office of Surveillance and Epidemiology (OSE) / Division of Risk Management (DRISK) and the Division of Medication Error

Prevention and Analysis (DMEPA), determined that the medication error issue should be handled outside of a REMS, and this was communicated to the Applicant on January 30, 2013. On April 18, 2013 the Applicant requested that the REMS for NDA 204096 be withdrawn. Since the indication in liver transplantation has been withdrawn and the medication errors can be addressed independent of a REMS, the Review Division agreed that the REMS for NDA 204096 could be withdrawn, and a letter to that effect was sent to the Applicant on May 14, 2013. (See NDA 204096 memo to file, dated May 13, 2013 in DARRTS)

1.4 Recommendations for Postmarket Requirements and Commitments

No clinical post-marketing requirements and commitments are foreseen at this time.

2 Introduction and Regulatory Background

2.1 Product Information

Tacrolimus extended-release capsules (FK506E [MR4]) is a once-a-day formulation of tacrolimus, an immunosuppressant agent. Tacrolimus is a macrolide lactone, calcineurin phosphatase inhibitor produced by *Streptomyces tsukubaensis,* in the class of immunosuppressant drugs called calcineurin inhibitors (CNIs). Tacrolimus inhibits T-lymphocyte activation, although the exact mechanism of action is not known. Experimental evidence suggests that tacrolimus binds to an intracellcular protein, FKBP-12, forming a complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin, and thus inhibiting the phosphatase activity of calcineurin. This effect is thought to prevent the dephosphorylation and translocation of nuclear factor of activated T-cell (NF-AT), a nuclear component thought to initiate gene transcription for the formation of lymphokines (such as interleukin-2, gamma interferon). The net result is the inhibition of T-lymphocyte activation, leading to immunosuppression. [Prograf Package Insert, Mechanism of Action].

Tacrolimus immediate-release capsules (or Prograf) is currently approved for use as prophylaxis against organ rejection in kidney transplantation, liver transplantation, and heart transplantation. In this submission, the Applicant is seeking approval of MR4 as an extended-release capsule of tacrolimus for the indications of prevention of graft rejection in kidney transplantation in men and women.

2.2 Currently Available Treatments for the Proposed Indication of Kidney Transplantation

Currently, several immunosuppressant agents have been approved for the prophylaxis against rejection in organ transplantation (often in combination):

- tacrolimus (immediate release) with corticosteroids and azathioprine – kidney, liver, and heart transplantation

- tacrolimus (immediate release) with corticosteroids and mycophenolate mofetil
- cyclosporine USP and cyclosporine USP MODIFIED – kidney, liver, and heart transplantation
- sirolimus (with cyclosporine and after withdrawing cyclosporine) – kidney transplantation
- mycophenolate mofetil (in combination with cyclosporine) – kidney, liver, and heart transplantation
- mycophenolic sodium (in combination with cyclosporine) – kidney transplantation
- azathioprine (only in combination with cyclosporine and tacrolimus) in kidney and heart transplantation
- corticosteroids (in combination with other drugs)
- daclizumab – induction in kidney transplantation (currently withdrawn from the market)
- basiliximab – induction in kidney transplantation

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

2.3 Availability of Proposed Active Ingredient in the United States

Tacrolimus has been extensively described in previous submissions for Prograf (NDA50-708 [tacrolimus capsules] and NDA 50-709 [tacrolimus injection] and their supplements), which were originally approved for use in the United States in liver transplantation in April 1994, and for kidney transplantation in April 1997. Tacrolimus is also the active ingredient in Protopic (tacrolimus) Ointment (NDA 50-777) approved in December 2000 for the treatment of atopic dermatitis. In May 2006, Prograf was approved for heart transplantation as an orphan drug. In addition, a number of generic equivalents for tacrolimus capsules have been approved and are marketed in the US.

> *Reviewer's Comment: Although the recommended dosing schedule for Prograf (tacrolimus) capsules is twice a day, Prograf is used once a day in clinical practice for maintenance immunosuppression in stable renal transplant recipients in the US, a practice that is consistent with the duration of its pharmacokinetic half-life.*[1]

2.4 Important Safety Issues with Consideration to Related Drugs

Calcineurin-inhibitors, including cyclosporine and tacrolimus are powerful immunosuppressants and their approved labeling contain a boxed WARNING about the increased susceptibility to infections and lymphoma. With the use of

[1] Hardinger KL, Park JM, Schnitzler MA, Koch MJ, Miller BW, and Brennan DC, "Pharmocokinetics of Tacrolimus in Kidney Transplant Recipients: Twice Daily versus Once Daily Dosing," Am J Transplant. 2004; 4: 621-625.

immunosuppressants for prophylaxis of rejection in organ transplantation, the clinician must balance the risks of under and over immunosuppression. Under-immunosuppression may lead to acute rejection, chronic rejection and ultimately, graft loss. Over-immunosuppression, on the other hand, will increase the risks of infections, malignancies, and pre-malignant conditions such as post-transplant lymphoproliferative disorders.

In addition to the risks of infection and malignancies, calcineurin inhibitors are associated with exposure-related toxicities, such as nephrotoxicity, neurotoxicity, glucose metabolism disturbances, gastrointestinal disturbances, hypertension and infections. In particular, a statistically significant relationship between nephrotoxicity, as well as other toxicities, and tacrolimus whole blood trough concentration has been reported in liver transplant recipients.[2] There have also been data demonstrating a significant correlation between tacrolimus whole blood trough concentrations and the incidence of toxicity, with a positive relationship between the maximum posttransplant tacrolimus whole blood trough concentration levels and an increase in serum creatinine ≥0.5 mg/dL above the posttransplant nadir, as well as between the maximum tacrolimus whole blood trough concentrations and the initial incidence of any adverse event that required a reduction in tacrolimus dose for clinical management[3]. Other studies have shown a high correlation between tacrolimus whole blood trough concentrations and glucose metabolism disorders, insulin-dependent diabetes, and tremor in a cohort of renal transplant recipients[4].

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Applicant, Astellas, has met extensively with the FDA since 2002 to discuss their proposed development plan for MR4. The following is a summary of presubmission regulatory activity as it pertains to the indication in renal transplantation and is derived from the administrative record for IND 64,148, and NDA 50811 as well as the Medical Officer's Review of NDA 50-811, dated January 19, 2007, and the Medical Officer Team Leader's memo for NDA 50-811, dated January 19, 2007. Additional reference was made to the Applicant's Regulatory Chronology included in CTD Module 1.6.3 Correspondence Regarding Regulatory Meetings.

March 14, 2002 - response to the PIND, the FDA agreed to the applicant's pharmacokinetic parameters to confirm the new formulation's targeting performance to be adequate in their Phase 2 kidney conversion studies:

- similar AUC24 ratios, AUC within 80% to 125% based on 90% CI,

[2] Venkataramanan R, Shaw LM, Sarkozi, L, et al, "Clinical Utility of Monitoring Tacrolimus Blood Concentrations in Liver Transplant Patients," J Clin Pharmacol 2001; 41:542-551.
[3] Kershner RP, Fitzsimmons WE, "Relationship of FK506 whole blood concentrations and efficacy and toxicity after liver and kidney transplantation," Transplantation 1996;62(7):920-926.
[4] Undre NA, van Hoof J, Christiaans M, Vanrenterghem Y, Donck J, et al. Low systemic exposure to tacrolimus correlates with acute rejection. Transplant Proc 1999;31(Suppl 7A):296-298.

- good correlation of trough concentration to AUC,
- same trough concentration target range, with equal or reduced C_{max},
- safety profile comparable to or better than that of Prograf.

May 30, 2002 – IND 64,148 submitted

July 1, 2003 correspondence, the Division asked the Applicant about plans to determine the potential physicochemical drug-drug interactions following a coadministration of the modified- release tacrolimus formulation and drug products that are frequently used in transplant recipients (e.g. MMF and azathioprine). The Applicant responded that since Prograf does not interact with MMF or azathioprine, there is not basis for drug-drug interaction with the MR4. The Applicant had no plans to address these potential interactions.

> *Reviewer's Comment: The origin of this comment stemmed in part from the fact that at the time the use of tacrolimus in combination with MMF did not yet represent an approved regimen in prevention of rejection in kidney transplantation until the approval of a labeling supplement on May 19, 2009 (NDA 50-708/S-027 and NDA 50-709/S021).*

July 24, 2003 correspondence, The Division requested a formal analysis of all pharmacokinetic data from the MR4 clinical development program to be performed to determine the effect of gender, race, and/or disease (i.e. diabetes) to be included in the NDA.

July 28, 2003 End of Phase 2 meetings Applicant submitted proposal for 11 phase 1 studies in health volunteers, 2 phase 2 studies in kidney and liver transplant patients converted from Prograf-based immunosupppression, 3 phase 2 clinical studies (1 conversion/reconversion kidney transplant study and studies in de novo liver and kidney transplant patients). At this meeting the applicant stated that there would be a separate package insert for the MR4.

The Division commented that an open label study design presented limitations, including the potential for bias in assessing and comparing rates of acute rejection. The Applicant responded that a blinded three-arm study would require triple-dummy dosing, which would result in patients taking an unacceptably high number of tablets and capsules. (Source: Meeting minutes August 27, 2003)

> *Reviewer's Comment: Although the Applicant could not be persuaded to use in Study 02-0-158 a blinded study design, even one limited to the blinding of the two tacrolimus formulations (Prograf and MR4), it was later learned that in clinical studies conducted by the sponsor outside the US did use a double blind design when comparing Prograf to MR4 (Study 12-03).*

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

April 13, 2005 Responses to Meeting Package Questions (Pre-NDA meeting)
The Division agreed to the use of Study 02-0-158 as the primary confirmation of efficacy for MR4 with supportive data being provided in Phase 2 studies.

> *Reviewer's Comment: Study 02-0-158 was a randomized, open label, three arm clinical study in de novo kidney transplantation evaluating three regimens, tacrolimus + MMF, MR4 + MMF and cyclosporine + MMF. The Division's decision to agree to using Study 02-0-158, a Phase 3 study, as the primary confirmation of efficacy for MR4 was influenced at the time by the Applicant's intent to support the use of tacrolimus with Mycophenolate mofetil (MMF) in kidney transplantation, a regimen not yet approved or supported by data from adequate well controlled trials until later. The use of Prograf® (tacrolimus) in combination with mycophenolate mofetil (MMF) in kidney transplantation was approved on May 19, 2009 (NDA 50-708/S-027 and NDA 50-709/S-021). Thus, the Applicant could have chosen an alternate path of supporting the safety and efficacy of the modified release formulation of tacrolimus by providing adequate pharmacokinetic data to characterize and dose of the modified-release formulation of tacrolimus (Please see the Clinical Pharmacology Reviews for additional information).*

December 19, 2005 Astellas submitted an NDA proposing the use of Advagraf for once daily dosing in the prophylaxis of organ rejection following kidney, liver or heart transplantation. The Agency administratively split the NDA into three separate NDA numbers for each indication: NDA 50811 (kidney), NDA 50,815 (liver) and NDA 50816 (heat).

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

January 19, 2007 Approvable action letter for NDA 50811, the indication in kidney transplantation.

> The clinical trials in *de novo* and stable kidney transplant patients do not provide sufficient data to support the safe and effective use of Prograf XL (ntr: Prograf XL was an alternative name used for tacrolimus extended release at the time) for the prevention of graft rejection in kidney transplant patients, and to conclude that the benefit of Prograf XL use outweighs the risks. In addition, the clinical studies

have not demonstrated that there was equivalent daily dosing between Prograf XL and Prograf® on a mg to mg basis over the entire treatment period. The pharmacokinetic results from these studies have not demonstrated similar systemic exposure to tacrolimus (AUC0-24) and C_{trough} between Prograf XL and Prograf® throughout the treatment period.

Specific findings and deficiencies that were of concern included:

1. Following administration of Prograf XL and Prograf® at the same total daily dose on Day 1 post-kidney transplant, the systemic exposure (AUC0-24) and C_{trough} obtained with Prograf XL were approximately 34% and 18% lower, respectively, compared to values obtained with Prograf®. Therefore, at this time there is insufficient information provided in the application to support a safe and effective initial dose of Prograf XL in *de novo* kidney transplant patients.

   Reviewer's Comment: This deficiency was addressed in a subsequent resubmission of NDA 50811 on May 27, 2007. Please see the Clinical Pharmacology Review in DARRTS for further details.

2. Study 02-0-158 provides statistical evidence of the efficacy of a Prograf XL+ CellCept® (MMF), steroid, basilixumab induction regimen in *de novo* kidney transplantation with respect to incidence of acute rejection, death, graft loss, and lost to follow-up. Although the combination of Prograf XL with MMF met the composite efficacy endpoint, the study did not consistently use the protocol-specified MMF dose of 1 gram BID with Prograf XL in kidney transplantation. The doses and pattern of MMF use in combination with Prograf® and Prograf XL were different from the doses and pattern of MMF use in combination with Neoral®. Furthermore, data from this single study do not provide sufficient evidence of safety and efficacy to support an alternative dose of MMF.

   Reviewer's Comment: An acceptable regimen of MMF dosing with tacrolimus in kidney transplantation was subsequently approved May 19, 2009, and is reflected in the approved Prograf® labeling.

3. The safety evaluation from Study 02-0-158 showed that the patients on Prograf XL reported significantly more gastroenteritis and paresthesia compared to subjects in the Prograf® arm. There was also a higher incidence of tremors, although that did not reach statistical significance compared to the Prograf® arm. However, the safety profile was potentially confounded by the higher systemic exposure of mycophenolic acid in both tacrolimus arms compared with the exposures achieved in the currently approved indication using MMF with cyclosporine.

Reviewer's Comment: This finding is addressed in the analyses of safety data from Study 12-03. Please see Section 7.4.1.2 of this review.

4. The Prograf XL+MMF combination had a less favorable safety profile compared with the Neoral®+MMF arm with significantly more diarrhea, gastroenteritis, total infections, sinusitis, diabetes mellitus, blood phosphorous decreased, tremor, chest pain, generalized pruritus, and dysphagia. In addition to those significant events, there was also a higher incidence of loose stools, leukopenia, anemia, and orthostatic hypotension that was likely due to the increased mycophenolic acid levels in the Prograf XL arm compared to the Neoral® arm. Although the renal function was slightly better in the Prograf XL arm, there were several irregularities in Study 02-0-158 that cast doubt as to the robustness of this finding such as:

a. Differences in the baseline characteristics of recipients and donors in the Prograf XL arm compared with the Neoral® arm,
b. The misdiagnosing of acute rejections by the local assessments of the kidney biopsies,
c. The excessive number of treatment crossovers in the Neoral® arm.

Reviewer's Comment: These findings with respect to safety profile of Prograf XL (also referred to as TacXL in this review) are further discussed in Section 7.4.1.1 of this review. Renal function as a secondary efficacy endpoint in Study 158 is discussed in Section 6.1.5.2.1 of this review. The mention of misdiagnosis of acute rejections by local assessments of the kidney biopsies refers to differences in interpretation between the local assessor and a central treatment-blinded review of allograft biopsies. While the word misdiagnosis was used, it should be interpreted as a difference between the interpretation by a local assessor charged with making an assessment that would influence the initiation of therapy intended to save the graft from rejection and a the interpretation of a central assessor whose assessment after the fact would not be used to weigh in on an important treatment decision. In addition, it could not be assured that the sections from individual biopsies reviewed by the local assessor were identical to those reviewed by the central assessor. Thus, given the focal nature of rejection and potential for sampling error, as well as the variability associated with the classification of rejection in allograft histology, which may be the greatest at the threshold between no-rejection and Banff Grade 1A rejection, this reviewer believes the term of misdiagnosis should be replaced by uncertainty in diagnosis. Finally as reflected in Section 6.1.5.2.1 of this review the interpretation of changes in renal function over time in study 158 is impaired by the differences in baseline renal function (Month 1 after transplantation) and greater number

of treatment discontinuations in the Neoral/MMF arm of this open-label study.

5. Furthermore, it is not clear that a modest improvement in glomerular filtration rate between the two arms is clinically significant enough to justify the higher morbidity experienced by the subjects in the Prograf XL+MMF arm.

Reviewer's Comment: Since these findings were highlighted in January 2007 an acceptable regimen of tacrolimus and MMF was approved, and is described in the current Prograf label. Discussion of renal function as secondary endpoint can be found in section 6.1.5.2.2 of this review, including information supporting that comparable renal function is maintained with TacXL or Tac used with MMF in Study 12-03.

6. The results of the Phase 2 stable renal transplant study (Study 02-0-131) show that equal daily mg doses of Prograf XL and Prograf® do not result in comparable systemic exposure to tacrolimus. Instead, the mean tacrolimus AUC0-24 and C_{trough} are 13% and 21% lower, respectively, following Prograf XL compared to Prograf®. The clinical significance of these differences has not been fully characterized.

Reviewer's Comment: It is recognized that TacXL and Tac are not interchangeable or substitutable. This should be addressed by wording to that effect in the package insert. Please see the Clinical Pharmacology Review in DARRTS for further details, including the analysis of Study 02-0-131).

The Applicant was advised that the above deficiencies may be addressed in the following ways:

1. Provide additional pharmacokinetic/pharmacodynamic data and/or efficacy and safety data identifying a safe and effective initial dose of Prograf XL in *de novo* renal transplant patients. Such data may be obtained from Phase 2 studies to evaluate initial doses of Prograf XL that achieve comparable tacrolimus AUC0-24 estimates as Prograf ®. The additional pharmacokinetic data in *de novo* renal transplant recipients are needed to support a dosing regimen which could mimic the exposure to tacrolimus provided by the approved safe and effective dose of Prograf®.

Reviewer's Comment: Such information was provided in a resubmission to NDA 50811 and is included in NDA 204096. The additional pharmacokinetic data in de novo renal transplant recipients submitted in April 2007 and also included in this submission appear to address this deficiency. Please refer to the Clinical Pharmacology Review in DARRTS.

It is noted that the initial dose may be influenced by whether antibody induction is used or not, and the immediate or delayed function of the allograft.

2. In addition, provide results of a prospective, randomized, blinded clinical study in *de novo* renal transplant patients evaluating the safety and efficacy of Prograf XL compared to Prograf®. In this study, you should evaluate Prograf XL in combination with appropriate doses of other immunosuppressants (e.g., MMF) in the prevention of graft rejection in renal transplant recipients. Your ongoing Study FG-506E-12-03 may provide such blinded, comparative safety and efficacy data, without the confounding factors of basiliximab induction and systemic exposures of mycophenolic acid exceeding exposures achieved with the currently approved recommended dose of MMF when used with cyclosporine in renal transplantation.

Reviewer's Comment: A 12-Month Study Report of the results from Study FG-506E-12-03, also referred to as Study 12-3 in this review, has been included in this submission, and is the subject of this review. Please see Sections 5.3.2, 6 and 7 of this review.

May 21, 2007 – Type A meeting "End of Review Conference" to discuss the proposed action plan to address deficiencies identified in the approvable action letter of January 19, 2007.

During the meeting the Applicant presented data from the PK substudy conducted within the double-blind Study FG-506E-12-03. In addition, the applicant discussed specific design issues regarding Study FG-506E-12-03 (choice of control, induction, dosing), and indicated that the full audited study report for this study would not be available in the same time frame as the report for the PK substudy.

In response to the Applicant's request for clarification of the information that would be required in order to address the deficiencies listed in the January 19, 2007 approvable letter the Agency communicated the following information to the Applicant in a letter, dated May 24, 2007:

After further considering this information, we believe the results of the PK substudy may be sufficient to address the deficiency number 1 in our January 19, 2007 approvable letter.

Before making final recommendations on the information that should be included in the resubmission to this application, we have the following additional questions/requests:

1. Does Astellas plan to provide the full 2 week PK substudy report with the accompanying dataset analogous to study FG-506E-12-01 for all subjects participating in the PK substudy? Please elaborate on any information or differences regarding the information available that would be important for us to know.

2. What would be the time expected for the submission of this PK substudy report and supporting information?

3. Does Astellas have subject level data on the incidence of acute rejection at 6 months and patient and graft survival at one-year from the PK substudy?

4. How much information (safety and efficacy) does Astellas have for the subjects participating in the PK substudy?

Further clarification was communicated to the Applicant in an email on July 20, 2007, indicating agreement with the Applicant's proposed approach, and with the understanding that the proposal would not provide for labeling for use of Prograf XL (ntr: tacrolimus extended release) with MMF.

September 12, 2007 Complete response submission

The complete response submission to NDA 50-811, contained new pharmacokinetic data from a subset of patients receiving allogeneic kidney transplants in Study FG-506E-12-03, as well as some limited information on safety and efficacy in this population.

March 13, 2008 - The Agency issued an approvable action letter for NDA 50811.

Before the application may be approved, it will be necessary for you to address the following deficiencies:

After reviewing the PK substudy of Study FG-506E-12-03, the mean AUC0-24 for Advagraf was approximately 20% higher than that for Prograf on Day 7 and Day 14. The mean C_{trough} for Advagraf was 14% higher compared with Prograf on Day 7, but comparable with Prograf on Day 14. The current data in this PK substudy of Study FG-506E-12-03 is not sufficient to determine whether the 20% higher AUC0-24 for Advagraf compare with Prograf on Day 7 and Day 14 is related to a clinically significantly higher incidence of tacrolimus-related adverse events for Advagraf. While reviewing NDA 50-815 (Advagraf for liver transplant), the Division found that there was a substantial gender-related difference in the 12-month mortality between Advagraf and Prograf treatment groups. A gender difference was also found in the onset of post-transplant diabetes mellitus

(PTDM). The Division is concerned that the gender-related difference in mortality and PTDM difference between Advagraf and Prograf treatment groups observed in liver transplant patients may exist in kidney transplant patients receiving Advagraf as part of their treatment regimen.

You may address the above deficiencies in the following ways:

1. Please submit the full study report for Study FG-506E-12-03 and study datasets, including the case reports for all subjects who prematurely discontinued the study or experienced serious adverse events (SAE). Include exposure-response analyses between safety outcomes (i.e., PTDM, renal dysfunction, CMV and other infections, cardiac disorders, glucose intolerance), efficacy outcomes and C_{trough} as a function of gender and treatment group. These exposure-response analyses should be performed in a manner consistent with the exposure-response analyses for the liver transplant Study FG-506E- 11-03. For detailed recommendations, please see the April 16, 2007 and the February 27, 2008 FDA fax comments for NDA 50-815 (Liver transplantation).

   Reviewer's Comment: A full 12-month study report for Study FG-506E-12-03, and study datasets, including the case reports for all subjects who prematurely discontinued the study or experienced serious adverse events (SAE) has been included in this NDA submission. Exposure-responses analyses have also been included (please see the Pharmacometrics Review in DARRTS).

2. Analyze, by gender and treatment group, of all "Adverse events of special interest" (as defined in your submission for NDA 50-815) for all existing Advagraf versus Prograf randomized clinical trials. These should include those events which may have a dosedependent relationship to tacrolimus exposure: renal function impairment, PTDM, infection, neurotoxicity (tremors, headache, insomnia, seizures), and such a relationship should also be analyzed. Please conduct these analyses for Study FG-506E-12-03 and each of the clinical trials in solid organ transplantation, and not just data from studies in kidney transplantation. Analyses should focus on the difference between treatments arms by gender. Provide detailed results and interpretations for all analyses.

   Reviewer's Comment: Reference to NDA 50-815, pertain to the indication for prevention of rejection in recipients of liver allografts, (b) (4) *Analyses of adverse events of special interests in Study FG-506E-12-03 were included in this submission.*

3. Analyze, by gender and treatment groups, of serum electrolytes and liver function tests. Please conduct these analyses for Study FG-506E-12-03 and each of the clinical trials in solid organ transplantation, and not just data from studies in kidney transplantation. Analyses should focus on the difference between treatments arms by gender. Provide detailed results and interpretations for all analyses.

4. Analyze, by gender and treatment group, of mortality, graft loss and acute rejection for all existing Advagraf versus Prograf studies. Please conduct this analysis for Study FG- 506E-12-03 and each of the clinical trials in solid organ transplantation, and not just data from studies in kidney transplantation.

Reviewer's Comment: Analyses by gender and treatment group were included for Study FG-506E 12-03, in this submission.

Although not a deficiency, in order to better understand the potential interaction between gender and tacrolimus use, please provide analyses by gender of mortality, adverse events of interest, and laboratory data, from controlled clinical trials that evaluated Prograf in liver and kidney transplantation, such as the trials submitted for registration. If such analyses are not available, please consider conducting them.

(b) (4)
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September 29, 2009 - A meeting was held to discuss the proposed data to support the NDA for the indication for prophylaxis of organ rejection following kidney transplantation.

Astellas had requested this meeting in light of the recent approval of the use of Prograf® (tacrolimus) in combination with mycophenolate mofetil (MMF) in kidney transplantation (NDA 50-708/S-027 and NDA 50-709/S-021, May 19, 2009) and the availability of the complete results for Study FG-506E-12-03 (Astellas was now able to provide full study reports and complete data sets for this study as specified in the March 13, 2008 Approvable Letter).

Studies to support filing of an NDA submission

It was agreed that Studies 02-0-1258 and FG-506E-12-03 are sufficient to support filing an NDA submission for Advagraf for an indication in kidney transplantation.

In addition, given the safety issues identified in the Advagraf liver transplant program, review of the liver transplantation studies (with particular attention to the different PK profiles exhibited by Advagraf in the liver and kidney patient populations) would be necessary to augment the safety dossier of Advagraf for the indication in kidney

transplantation. It was further anticipated that, if approved, the Advagraf labeling would provide relevant safety information regarding Advagraf in liver transplantation.

The Agency further clarified that failure to meet the primary endpoint in Study 12-03 and absence of a recognized active control would not necessarily represent an impediment to approval, as Astellas does not intend to propose labeling reflective of the regimen used in Study 12-03. The primary value of those data from Study 12-03 would relate to the evaluation of safety issues. If there were sufficient data in the proposed application to support approval, it would be anticipated that information from Study 02-0-158 that would be included in labeling would reflect the whole blood concentrations observed in that study.

> *Reviewer's Comment: The subsequent approval of the use of the combination of Prograf with MMF in kidney transplantation, a combination represented in Study 12-03, allows one to consider the combination of tacrolimus plus MMF as an active control, and to use this study to support the efficacy and safety of TacXL in combination with MMF. Thus, it would be appropriate to include information from Study 12-03 in proposed labeling as it would represent part of the spectrum of the use of tacrolimus with MMF, in regimens that do not include antibody induction with basiliximab.*

Potential risk of mortality with use of Advagraf

With respect to a potential risk of mortality with the use of Advagraf, as part of the review of the Advagraf NDA submission in kidney transplant, the Agency agreed to review analyses of the safety between male and female kidney transplant recipients, as outlined in the March 13, 2008 approvable letter.

Interchangeability between tacrolimus formulations and medication errors

With respect to interchangeability between tacrolimus formulations, the Agency also stated that the Prograf labeling may need to be updated to include information regarding interchangeability with Advagraf and that harmonization between the two labels would be needed to communicate the risk of potential medication errors.

With respect to medications errors reported in countries where Advagraf and Prograf are marketed, the Agency will review the data on dispensing/medication errors the Applicant has collected to date. The Applicant was also requested to provide the labeling and packaging for Advagraf in those countries where errors have occurred. The Agency would like to learn whether or not the Applicant has implemented changes in labeling/packaging in order to reduce errors, and would like to discuss whether these errors may be due to factors other than labeling which would need to be addressed. It was agreed that adequate labeling, including labels, packaging and REMS might address the problem; however, the Agency would need to review in detail the

Applicant's proposed strategies and determine whether they are adequate to prevent medication errors. In particular, the Agency agreed to review, once submitted, information regarding the packaging implemented in the EU to address the potential medication errors with OSE/Division of Medication Error and Prevention Analysis, DMEPA, and provide feedback at the pre-NDA meeting. The Agency further stated that the proposed REMS program to mitigate the risk of potential medication errors should target both prescribers and pharmacists. The proposed REMS should target education of the difference in formulations between Prograf and Advagraf.

> *Reviewer's Comment: During the course of the review of this application and after internal discussion within the Agency it has been concluded that a REMS would not be needed to mitigate the risk of potential medication errors, a risk which can be managed by appropriate labeling, and choice of product name.*

January 31, 2012 – Pre-NDA meeting to discuss the submission of an NDA for Advagraf® (tacrolimus extended-release capsules).

Preliminary responses to the questions posed in the Applicant's briefing package dated December 21, 2011 were communicated on January 27, 2012.

Meeting minutes were sent to the Applicant on February 28, 2012. The following is a summary of the relevant details as they pertain to kidney transplantation.

Study 02-0-158 and supporting studies for an NDA in kidney transplantation

Astellas proposed that Study 02-0-158 would be the primary basis for the efficacy and safety evaluation of Advagraf for prophylaxis of organ rejection in kidney transplant patients to support NDA approval. Studies FG-506E-12-03, PMR-EC-1210 (OSAKA) and FG-506E-12-01 would provide supportive evidence of efficacy.

The Agency agreed that the trials mentioned by the sponsor including Study 02-0-158, can be submitted to support filing of an NDA for an indication in *de novo* kidney transplant patients. The Agency requested that the NDA include a complete non-inferiority (NI) margin justification for Study 02-0-158 and for Study FG-506E-12-03. Study 02-0-158 has two potential controls arms; therefore, the Applicant should provide NI margin justifications for each.

In addition to the trials mentioned above, the Agency would expect that the final reports for Studies 02-0-131, FG 506E-12-02 and FG 506E-KT01 in conversion kidney patients will be submitted which include not only the results of the PK analyses, but also the 12 month results for the BPAR endpoint (including deaths, graft losses, and losses to follow-up imputed as failures). The Agency did not expect that justification of an NI margin in the conversion trials is possible; therefore, a NI justification for these trials would be recommended, but not required.

Reviewer's Comment: These studies in stable patients converted from Prograf to MR4 are single arm, and not randomized. Furthermore, they were not designed to collect systematic long-term information on BPAR, after participation in the clinical pharmacology portion of these studies. Thus, Studies 02-0-131, FG 506E-12-02 and FG 506E-KT01 in conversion kidney patients are not considered adequate well controlled trials for the purpose of supporting a specific conversion indication in proposed labeling.

Proposed recommended dosing with Avagraf in Kidney Transplantation

The Agency agreed with the Applicant's proposal to provide Advagraf dosing recommendations for an initial daily dose in *de novo* kidney transplant patients based on observed data. The initial dosing recommendation for conversion of stable transplant patients from Prograf to Advagraf should also be based on observed data. In addition, the labeling should report whole blood tacrolimus trough concentrations (median, 10th to 90th percentiles) observed at various periods during the initial 12 months post-transplant (i.e., both during the early de novo and later conversion period).

Reviewer's Comment: As mentioned above, the issue of making recommendations for conversion of stable transplant patients from Prograf to TacXL in the proposed label is moot, since Studies 02-0-131, FG 506E-12-02 and FG 506E-KT01, which are single arm and non-randomized, do not represent adequate well controlled studies.

A final recommendation regarding the dosing information to be included in product labeling would be determined after completing NDA reviews of clinical trials, including Study 02-0-158 and FG-506E-12-03.

Foreign labeling

The Agency agreed to the Applicant's proposal to include the current product labeling from the UK, Canada and Japan (translated into English) to serve as representation of the foreign labeling of Advagraf.

Pediatric use

The Applicant will need to submit a request for a waiver or deferral for both the kidney and liver indications separately, as part of the NDA submission. The request will need to address all age groups between 0 and < 17 years.

Advagraf in heart transplantation

Although the Applicant does not intend to pursue an indication in heart transplantation, the Agency requested that they submit the complete study report and electronic data from Study FG-506-15-02 to the NDA.

Waiver for the 120-day update
Assuming the Applicant would not have any new information from ongoing, randomized, controlled trials and any new post-marketing safety signal of serious adverse events (SAEs), the Agency agreed with the Applicant's request for a waiver for the commitment to submit the 120-day safety update. However, at 120-days the Agency requested the Applicant provide a brief summary of ongoing trials including number of patients enrolled and any unexpected SAEs.

2.6 Other Relevant Background Information

Tacrolimus extended release capsules are approved in 69 countries in Europe, Japan and Canada.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The NDA is well organized, and the necessary information is easily located. All of the study reports requested have been included in this submission, including those previously submitted and reviewed under NDA 50-811.

3.2 Compliance with Good Clinical Practices

All studies reported in the NDA were conducted under IRB approval and written informed consent. There were no apparent violations of clinical standards of research. Please see the summary of the inspections conducted by the Division of Scientific Investigations in DARRTS [Finalized – Tedesco-Silva, Helio NDA 204096 CI VAI Foreign (COR-DSICI-06), dated 05-28-2013; Finalized – Kraemer, Bernhard NDA 204096 CI VAI Foreign (COR-DSICI-06), dated 05-28-2013; Finalized – Backman, Lars NDA 204096 CI VAI Foreign (COR-DSICI-06), dated 05-28-2013].

The clinical sites of Dr. Helio Tedesco-Silva, in Sao Paul, Brazil, and of Dr. Harold Yang, in Harrisburg, Pennsylvania who participated in Protocol 02-0-158 entitled "A Phase 3, 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" conducted under the US IND by Astellas Pharma US Inc. were inspected as part of FDA's Bioresearch Monitoring Program. While the FDA inspection revealed regulatory violations of clinical investigator obligations in the conduct of the study, these are considered isolated in nature and unlikely to significantly impact data reliability. The

data derived from Dr. Helio Tedesco-Silva's and from Dr. Harold Yang's site appear reliable in support of the NDA.

The clinical sites of Dr. Berhard Krämer, in Regensburg, Germany, and of Dr. Lars Backman in Gothenburg, Sweden, of who participated in Protocol FG-506E-12-03 entitled "A Multicenter, 1:1 Randomized, Double Blind Two Arm Parallel Group Study to Evaluate and Compare the Efficacy and Safety of Modified Release Tacrolimus FK506 (MR4) vs. Tacrolimus FK506 in Combination with MMF (Cellcept®) and Steroids in Patients Undergoing Kidney Transplantation", conducted by Astellas Pharma Global Development, Inc., outside the US and not under a US IND, were inspected as part of FDA's Bioresearch Monitoring Program. In general, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication. Although regulatory violations were noted, it is unlikely, based on the nature of the violations, that they significantly affect overall reliability of safety and efficacy data from these sites. The data derived from Dr. Bernhard Kraemer's site, and Dr. Lars Backman site are considered reliable in support of the NDA.

3.3 Financial Disclosures

Information on Financial Certification and Disclosure, including Financial Disclosure Investigator Listings for Covered Clinical Studies are submitted in Section 1.3.4 of Module 1 of the NDA Submission. Completed forms FDA 3454 dated August 28, 2012, have been submitted for (b) (6) (Protocol Number (b) (6)), (b) (6) from the (b) (6) (Protocol Numbers (b) (6) and (b) (6)), (b) (6) from the (b) (6) (Protocol Number (b) (6)) and (b) (6) currently an employee of Astellas (Protocol Number (b) (6)) in accordance with 21 CFR part 54. The named individuals have participated in financial arrangements required to be disclosed, described as significant payments made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria.

Overall, due to the size of the clinical studies the relative participation of (b) (6) and (b) (6) is not expected to be significant enough to influence the conduct, analysis and interpretation of the results from Study (b) (6), considered a major adequate well controlled trial intended to support this NDA.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The following Summary is provided by the Chemistry Reviewer, Mark Seggel, Ph.D.

Tacrolimus extended-release capsules is a new solid oral dosage form of tacrolimus intended for once a day administration. Capsules contain the equivalent of 0.5-, 1- or 5-mg of anhydrous tacrolimus. Currently approved formulations of tacrolimus manufactured by Astellas include Prograf Capsules (also in 0.5-, 1- and 5-mg strengths), Prograf Injection, and Protopic Ointment.

As with Prograf immediate-release capsules, an (b) (4) of tacrolimus is prepared (b) (4)

To achieve extended release of tacrolimus, (b) (4) (b) (4) The formulation is otherwise qualitatively the same as that of Prograf Capsules. In addition to tacrolimus and ethyl cellulose, (b) (4)

In the tacrolimus extended-release formulation, the release of tacrolimus is controlled by (b) (4) Based on the previous experience with Prograf Capsules formulation development and because of the low aqueous solubility of tacrolimus (b) (4) hydroxypropyl methylcellulose (b) (4)

Lactose is used to (b) (4)

The manufacture and control of tacrolimus extended-release capsules parallel those of Prograf immediate-release capsules. All aspects of drug product CMC have been adequately documented. Evidence is provided that the product can be consistently manufactured in such a manner as to provide assurance of its identity, strength, quality, purity, potency and bioavailability. The drug product specification further ensures that the product will meet the established quality standard. The manufacturing facilities have acceptable cGMP status.

- The proportions of inactive ingredients and tacrolimus are the same across all three product strengths, the only differences being the amount filled into each capsule and the capsule size.
- The same formulation was used for all clinical samples (single-dose biopharmaceutics studies, repeated-dose biopharmaceutics studies, phase 2 and phase 3 studies), primary stability batches and proposed commercial production batches.
- The product specification includes tests for identification, assay, related substances, content uniformity, microbial limits and dissolution (three-point test: 0.5, 1.5 and 24 hours). The analytical procedures are similar to those employed

for Prograf Capsules, although sodium lauryl sulfate is included in the dissolution medium to facilitate dissolution.

- Dose-dumping in patients who have consumed alcohol near the time of dosage administration is a concern with extended-release products. To evaluate the potential for dose-dumping from Prograf XL, *in vitro* dissolution studies were conducted. While the presence of 20% ethanol in the dissolution medium resulted in a modest increase in the rate of dissolution, the increase (5%-20% higher levels) was not considered clinically significant. Additional *in vitro* dissolution studies, submitted during this review, using higher concentrations of ethanol, up to 40%, resulted in a potentially clinically significant greater increase in rate of dissolution.
- The stability profile of Prograf XL is comparable to that of the immediate-release product. No new degradation products were observed.
- The drug product is packaged in blisters for in-hospital use and in HDPE bottles for outpatient dispensing.

Reviewer's Comment: (b) (4)

owever, after consultation with the FDA CMC Reviewer, it is not expected that the extended release properties would be conserved if the contents of the capsules were to be emptied and suspended in a liquid or mixed with apple sauce. In addition, the size of the capsules may be difficult for a small individual or child to swallow. Thus, there does not appear to be an age appropriate version of the extended-release formulation for pediatric patients, less than 5-7 years old, and there remains some question as to whether children aged less than 13 years old could actually swallow the larger capsules.

While 40% ethanol represents the upper range of ethanol content of potable alcoholic beverages, the increased rate of dissolution observed in vitro, supports the recommendation that alcoholic beverages should not be consumed with TacXL.

4.2 Clinical Microbiology

Not Applicable.

4.3 Preclinical Pharmacology/Toxicology

Because the active moiety is tacrolimus, a product on the market since 1994, the Division and the Applicant agreed to allow for referencing of the original Prograf NDA for information regarding animal pharmacology/toxicology.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Tacrolimus is chemically known as a macrolide. In T-cells, activation of the T-cell receptor normally increases intracellular calcium, which acts via calmodulin to activate calcineurin. Calcineurin then dephosphorylates the transcription factor, nuclear factor of activated T-cells (NF-AT), which migrates to the nucleus of the T-cell and increases the transcription of genes coding for interleukin-2 (IL-2) and other related cytokines. Tacrolimus prevents the dephosphorylation of NF-AT.[5] Specifically, tacrolimus reduces peptidyl-prolyl isomerase activity by binding to the immunophilin, FK506 binding protein (FKBP12) creating a new complex. The tacrolimus-FKBP complex interacts with and inhibits calcineurin, thus inhibiting both T-cell receptor signal transduction and IL-2 transcription, as well as inhibition of other related cytokines.[6] The net result is inhibition of T-lymphocyte activation (i.e. immunosuppression).

4.4.2 Pharmacodynamics

The pharmacodynamic relationships of TacXL are expected to be the same as the pharmacodynamic relationship of Prograf.

4.4.3 Pharmacokinetics

To support the approval of the kidney indication of NDA 204-096, a total of 22 studies with clinical pharmacology or tacrolimus dose and concentration information from *de novo* kidney transplant patients, stable kidney transplant patients and healthy subjects were submitted for FDA review. With the exception of two new drug interaction studies (with ketoconazole and with rifampin) in healthy subjects, two Phase 2 PK studies in stable kidney transplant patients (Study 12-02 and Study KT01), one Phase 3 PK substudy in *de novo* kidney transplant patients (Study 12-03-PK), and two Phase 3 trials in *de novo* kidney transplant patients (Study 12-03 and OSAKA a.k.a. Study 12-10), all these studies were also previously reviewed under NDA 50-811 by Dr. Seong Jang (Clinical Pharmacology reviewer). Note that in previous Clinical Pharmacology reviews and FDA communications, TacXL was also referred to as MR, MR4, FK506E, Prograf XL® and Advagraf®. Recently, FDA made a determination that Astagraf XL® is an acceptable trade name for tacrolimus extended release oral capsules, referred to as TacXL in this review.

Table1 below adapted from the recommendation for labeling in the Clinical Pharmacology Review in DARRTS summarizes the pharmacokinetic (PK) parameters of tacrolimus following oral administration of TacXL in healthy subjects and in kidney

[5] Liu J, Farmer J, Lane W, Friedman J, Weissman I, Schreiber S (1991). Calcineurin is a common target of cyclophilin-cyclosporin A and FKBP-FK506 complexes. *Cell* 66 (4): 807–15
[6] Halloran PF. Immunosuppressive Drugs for Kidney Transplantation. *N Engl J Med* 2004;351:2715-29.

transplant patients. Whole blood tacrolimus concentrations in these pharmacokinetic studies were measured using validated HPLC/MS/MS assays.

Table 1. Pharmacokinetic Parameters of TRADENAME XL Once Daily in Healthy Subjects and in Kidney Transplant Patients (Under Fasted Conditions), and Statistical Comparison of PK Parameters with Prograf® Twice Daily

Population	N	Tac XL Dose[a]	Day[b]	Pharmacokinetic Parameters of TacXL and TacXL XL:Tac ratio (90% CI for ratio)[e]			
				C_{max}[c] (ng/mL)	T_{max}[d] (hr)	AUC_{24}[c] (ng•hr/mL)	C_{24}[g] (ng/mL)
Healthy Subjects	24	4 mg 4 mg	Day 1 Day 10	6.2 ± 2.1 11.6 ± 3.4	2.0 [1.0-5.0] 2.0 [1.0-3.0]	74 ± 22 155 ± 46	2.3 ± 0.8 4.7 ± 1.5
			Ratio (90% CI) Day 1 Day 10	0.67 (0.59 – 0.75) 0.74 (0.69 –0.80)		1.02 (0.91 – 1.13) 0.93 (0.87 – 0.99)	0.81 (0.72 – 0.92) 0.87 (0.81 – 0.94)
Adult Kidney *De novo*[f]	17	0.20 mg/kg 0.19 mg/kg 0.18 mg/kg 0.18 mg/kg	Day 1 Day 3 Day 7 Day 14	26.0 ± 13.7 31.0 ± 13.9 32.2 ± 10.2 32.7 ± 9.0	3.0 [2-24] 2.0 [0.5-20] 2.0 [1-6] 2.0 [1-4]	372 ± 202 437 ± 175 405 ± 117 412 ± 109	12.1 ± 7.2 13.5 ± 5.6 11.4 ± 4.0 11.2 ± 3.9
			Ratio (90% CI) Day 1 Day 3 Day 7 Day 14	0.86 (0.63 – 1.19) 0.93 (0.71 – 1.21) 1.14 (0.95 – 1.38) 1.27 (1.03 – 1.57)		0.84 (0.63 – 1.12) 1.05 (0.82 – 1.33) 1.22 (1.02 – 1.46) 1.21 (1.02-1.42)	0.85 (0.59 – 1.17) 1.04 (0.79 – 1.36) 1.14 (0.90 – 1.44) 0.99 (0.82 – 1.20)
Adult Kidney (stable; ≥ 6 months post-transplant	60	5.2 mg/day	Day 14	16.1 ± 5.3	[1.0 -6.0]	222 ± 64	6.7 ± 1.9
				(b) (4)			

a) Healthy adult subjects (actual administered dose of TRADENAME XL and Prograf); Adult *de novo* kidney transplant patients (actual group mean dose of TRADENAME XL, corresponding doses for Prograf on Days 1, 3, 7 and 14 were 0.20, 0.18, 0.16, and 0.17 mg/kg/day); (b) (4)

b) Day of TacXL
c) Arithmetic means ± S.D.
d) Median [range]
e) Ratio of geometric least square means
f) PK substudy Study 12-03
g) tacrolimus trough concentration before the next dose

The following summary is extracted and adapted from the Summary of Important Clinical Pharmacology Findings in the Clinical Pharmacology Review by Dr. Gerlie Geiser, PhD., and addresses the clinically relevant findings from the Clinical Pharmacology Review (See Clinical Pharmacology Review in DARRTS).

General Clinical Pharmacology and Biopharmaceutics of TacXL

Linearity of Pharmacokinetics (PK)

The pharmacokinetics of tacrolimus was linear from 1.5 mg to 10 mg (equivalent to doses up to 0.2 mg/kg) in healthy subjects who received TacXL as single doses in a crossover fashion.

Diurnal Variation in PK

In healthy subjects, evening dosing of TacXL resulted in a 35% lower $AUC_{0\text{-}inf}$ compared to morning dosing. TacXL daily doses should be taken in the morning.

Food Effect

Concomitant administration of a high-fat meal reduced C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ of TacXL by approximately 25% compared with fasting values. Food delayed the median T_{max} from 2 hours in the fasted state to 4 hours in the fed state; however the terminal half-life remained 36 hours regardless of dosing conditions. The timing of TacXL co-administration with a high-fat breakfast also influenced the food effect, i.e., tacrolimus $AUC_{0\text{-}inf}$ decreased approximately 35% relative to the fasted state when TacXL was administered 1.5 hours after consumption of the meal, and by 10% when administered 1 hour prior to the meal.

> *Reviewer's Comment: Food effects are also significant for the immediate release formulation of tacrolimus, which should be taken at a consistent time with respect to meals. Regarding the extended release formulation, as recommended by the Clinical Pharmacology Reviewer wording on the timing of TacXL dosing with respect to meals should be included in the package insert, such as "To achieve maximum possible tacrolimus exposure, TRADENAME-XL should be taken on an empty stomach, preferably at least 1 hour before breakfast or at least 2 hours after breakfast."*

Nasogastric Administration

In healthy subjects, the *nasogastric* administration of TacXL as an aqueous suspension prepared from the capsule contents resulted in a 30% higher tacrolimus C_{max}, a shorter

T_{max} (by 1 hour), and a 17% lower AUC_{inf} than that following oral administration of the intact TacXL capsules. The *oral* administration of the same aqueous suspension resulted in a comparable $AUCi_{nf}$, a 28% higher C_{max}, and a shorter T_{max} (by 1.5 hours) than that following oral administration of the intact TacXL capsules.

> *Reviewer's Comment: It does not appear that nasogastric administration of the capsule contents conserves the extended-release pharmacokinetic properties of the intact TacXL capsules for oral administration. De novo kidney transplant recipients are usually able to take oral medication on the first day after transplantation; however, it is recognized that the size of the capsule may present a challenge, and limited use of nasogastric administration was allowed in Phase 3 clinical trials. Nevertheless, the following should be reflected in product labeling:*
>
> *Nasogastric administration of the extemporaneously compounded aqueous suspension of TAC-XL from the capsule contents is not recommended at this time because only a limited number of de novo kidney transplant patients received TAC-XL in this manner in the Phase 3 clinical trials, and the stability of the aqueous suspension had not been evaluated. For de novo kidney transplant patients unable to tolerate oral dosing, therapy should be initiated with Prograf for intravenous infusion; conversion to TAC-XL is recommended as soon as oral therapy can be tolerated.*

Alcohol induced dose-dumping

As described above in the Summary of Chemistry Manufacturing and Controls in Section 4.1 of this review, *in vitro* dissolution testing in 40% ethanol at pH 1.2 resulted in accelerated dissolution (i.e., dose-dumping) of tacrolimus from TacXL 0.5 mg and 5 mg capsules. No *in vivo* follow on studies had been conducted.

> *Reviewer's Comment: A concentration of 40% ethanol is within the range of potable alcoholic beverages, and the pH of 1.2 is within the range of physiologic gastric content pH. Therefore, these in vitro findings are clinically relevant and the package insert should specify that TacXL should not be taken with alcoholic beverages, or similar wording to that effect, or wording to that effect.*

Relative Bioavailability

In terms of systemic exposure to tacrolimus, the Day 1 and steady-state tacrolimus AUC_{0-24} for TacXL extended release capsules once daily met the 80-125% criteria for bioequivalence as compared to Prograf immediate release capsules twice daily in healthy subjects and stable kidney transplant patients (≥ 6 months post-transplant) but not in *de novo* kidney transplant recipients.

Reviewer's Comment: From this stemmed a need for data from clinical studies evaluating the efficacy and safety of TacXL in de novo kidney transplant recipients, which are provide in this application.

Drug-Drug Interactions

In healthy subjects, coadministration of a 4 mg dose of TacXL with *ketoconazole* (400 mg/day) for 9 days increased the mean AUC_{inf} and C_{max} of tacrolimus 7.5-fold and 4.6 -fold, respectively. In healthy subjects, coadministration of a single 10 mg dose of TacXL with *rifampin* (600 mg/day) for 12 days decreased the mean AUC_{inf} and C_{max} of tacrolimus by 56% and 46%, respectively.

Reviewer's Comment: TacXL shares the same drug interactions with the immediate release formulation of tacrolimus, which have clinical implications that need to be addressed in labeling, with wording reflecting that adjustment of TacXL doses and frequent monitoring of tacrolimus trough concentrations are recommended when coadministering TacXL with strong CYP3A inhibitors and strong CYP3A inducers.

Correlation of C_{trough} to AUC_{0-24}

For TacXL, tacrolimus trough concentrations measured at 24 hours post-dose (C_{trough} or C_{24}) had a good correlation with the AUC_{0-24} of tacrolimus in healthy subjects (r = 0.987), in stable transplant patients (r= 0.88), and in de novo kidney transplant recipients (r = 0.87).

Reviewer's Comment: Reliance on correlation between whole blood trough concentrations is needed for successful use of therapeutic drug monitoring to guide TacXL dosing. This level of correlation is acceptable and comparable to that observed with the immediate release tacrolimus formulation.

Management of Missed Dose

Based on simulations, taking a missed TacXL dose as soon as remembered but no more than 14 hours after missing the morning administration would result in a tacrolimus C_{trough} considered acceptable from an efficacy perspective, and a C_{max} after the next regular morning dose considered acceptable from a toxicity perspective.

Finding Relevant to Important Subpopulations

At comparable mean tacrolimus trough concentrations over time, African-Americans received, on average, 35% higher mean TacXL daily doses than Caucasians in Study 158. There were not enough African-Americans included in Study 12-03 to warrant a meaningful comparison of TacXL doses with Caucasians.

5 Sources of Clinical Data

The Applicant is seeking approval for tacrolimus XL for the prophylaxis of organ rejection in patients receiving de novo kidney transplants.

The EDR location of the submission is: \\CDSESUB1\EVSPROD\NDA204096\0000.

Module 2.5 contains the Clinical Overview, \\Cdsesub1\EVSPROD\NDA204096\0000\m2\25-clin-over and the Clinical Summary, \\Cdsesub1\EVSPROD\NDA204096\0000\m2\27-clin-sum.

Study 02-0-158 is a primary study used to support efficacy in kidney transplantation and was reviewed in great detail under NDA 50-811. In addition, Study 02-0-158 was also one of the 2 studies that provided support for the approval of Prograf use with MMF in kidney transplant recipients (NDA 50-708/S-027 and 50-709/S021).

Study FG-506E-12-03 is considered a primary study used to support efficacy in kidney transplantation, providing information on the use of TacXL with MMF, without antibody induction.

5.1 Tables of Studies/Clinical Trials

Tacrolimus XL Studies in De Novo Kidney Transplantation:

The primary studies supporting the indication of prevention of rejection in recipients are the 12-month Phase 3 randomized studies that include treatment arms for both TacXL and Prograf (also referred to as Tac in this review), Studies 02-0-158 (Study 158) and FG-506E-12-03 (Study 12-03). Study 158 was previously reviewed by FDA under NDA 50-811 and results from that statistical clinical review are included in this review. Data from 34 evaluable patients from a pharmacokinetic substudy of Study 12-03 were reviewed under NDA 50-811. The full 12-month report of Study 12-03 is included in this submission.

- **Study 02-0-158:** A randomized, 1-year, Phase 3 comparative trial of tacrolimus-XL (0.15-0.20 mg/kg once daily) + MMF + corticosteroids, Prograf (0.075-0.10 mg/kg twice daily) + MMF + corticosteroids, and cyclosporine (Neoral®; 4.5 mg/kg twice daily) + MMF + corticosteroids in de novo kidney transplant recipients (all with basiliximab induction) assessing the efficacy and safety of tacrolimus XL /MMF + corticosteroids. The study included a 1-year primary analysis period [Study 02-0-158 1Y] and a clinical continuation period of treatment for up to 60 months posttransplant [Study 02-0-158 LT].

- **Study FG-506E-12-03:** A randomized**,** Phase 3, double-blind, double-dummy study during the first 24 weeks and continued as an open-label study until the last patient completed the 12-month visit [Study FG-506E-12-03 12M]. The study

compared the efficacy and safety of tacrolimus XL (0.2 mg/kg once daily) and Prograf (0.1 mg/kg twice daily), both in the presence of MMF and steroids. The study included a 2-week pharmacokinetic evaluation period [Study FG-506E-12-03 PK]. Transplant recipients receiving tacrolimus XL were given the option of continuing treatment in [Study FG-506-14-02].

The designs for these two clinical trials are summarized below in Table 2.

Table 2 Overview of Design of Clinical Efficacy and Safety Studies in De Novo Kidney Transplant

Parameter	**Study 02-0-158**			**Study FG-506E-12-03**	
Design	Phase 3, multicenter, 1:1:1 randomized, open-label, comparative, 3-arm parallel group, noninferiority			Phase 3, multicenter, 1:1 randomized, double-blind, double-dummy, 2-arm parallel group, noninferiority	
Advagraf and comparators FAS PPS	**TacXL** (n = 214) (n = 211)	**Tac** (n= 212) (n =	**Neoral§§** (n = 212) (n = 209)	**TacXL** (n = 331) (n = 280)	**Tac** (n = 336) (n = 291)
Timing of preoperative dose, if allowed	NA			Within 12 hours prior to reperfusion†	
Protocol-defined initial preoperative CNI dose (po)	Not permitted			**TacXL** 0.1 mg/kg	**Tac** 0.1 mg/kg
Timing of initial dose	Prior to or within 48 hours of completion of transplant procedure			Not < 4 hours after the preoperative dose or > 12 hours after reperfusion	
Antibody induction	Basiliximab 20 mg iv on day 0 and once between days 3 and 5			Not permitted	
Protocol-defined initial postoperative dose per day	**TacXL** 0.15 to 0.20 mg/kg po (AM)	**Tac** 0.15 to 0.20 mg/kg (2 divided doses)		**TacXL** 0.2 mg/kg po (AM)	**Tac** 0.2 mg/kg po (2 divided doses)
Protocol-defined tacrolimus trough concentration	Days 0 to 90: 7 to 16 ng/mL Thereafter: 5 to 15 ng/mL			Up to day 28: 10 to 15 ng/mL Day 29 to day 168: 5 to 15 ng/mL Thereafter: 5 to 10 ng/mL	
Protocol-defined MMF initial dose	2.0 g/day (2 divided doses) Black/African American patients could receive 3.0 g/day (2 divided doses).			Initial 14 days: 2 g/day (2 divided doses)	
Protocol-defined MMF reduction	Dose changes for adverse events if clinically indicated or withdrawal at the investigator's discretion			After day 14: 1 g/day	

Protocol-defined corticosteroid initial dose	Methylprednisolone (or equivalent) Day 0: 500 to 1000 mg iv Day 1: 200 mg po		Methylprednisolone (or equivalent) Day 0: Up to 1000 mg iv Day 1: 125 mg iv	
Protocol-defined corticosteroid reduction schedule (po)	By day 14: 20 to 30 mg/d By month 1: 10 to 20 mg/d By month 2: 10 to 15 mg/d By month 3 to 12: 5 to 10 mg/d		Days 2 to 14: 20 mg/d Days 15 to 28: 15 mg/d Days 29 to 42: 10 mg/d Days 43 to 84: 5 mg/d	
Patient population	**TacXL** (FAS)	**Prograf** (FAS)	**Advagraf** (FAS)	**Prograf** (FAS)
Male	64.5%	64.2%	61.6%	64.0%
Female	35.5%	35.8%	38.4%	36.0%
Living donor	48.1%	50.0%	26.9%	27.4%
Deceased donor	51.9%	50.0%	73.1%	72.6%
White	74.8%	71.7%	83.7%	81.3%
Black/African American	19.2%	24.1%	4.2%	5.7%
Treatment Duration and Primary Endpoint	Open-label (OL) 1 year Month 12 efficacy failure defined as death, graft failure, biopsy-confirmed acute rejection, or lost to follow-up		Double Blind 24 wks (until last subject completed 24 weeks) Open label thereafter up to Week 52 Week 24 biopsy-proven acute rejection Month 12 efficacy failure was a secondary endpoint	

Source: Adapted from Applicant's Table 1 in Module 2.7.3 Kidney Transplantation, Summary of Clinical Efficacy and Tables 2.1.1 and 2.1.2 in the FDA Statistical Review.

> *<u>Reviewer's Comment</u>: Submission of the complete 12-month Study Report for Study FG-506E-12-03 addresses the need for information on comparative safety between TacXL and Tac, identified as a deficiency in prior Approval and Complete Response Letters, which will be reviewed in Section 7, Integrated Review of Safety, of this review.*

An additional non-US, ex-IND, European, post-marketing study, Study PMR-EC-1210 not previously reviewed by FDA was included in this submission, but is not considered a primary study in this review, because of the short duration of only 24 week, and the complexity of its open-label design, including three different TacXL regimens, as well as concerns over the interpretation of multiple comparisons (See Section 5.2 of this review).

- **Study PMR-EC-1210:** A phase 3b, open-label, randomized, comparative study comparing 4 therapeutic regimens: arm 1, Prograf 0.2 mg/kg + MMF; arm 2, tacrolimus XL 0.2 mg/kg + MMF; arm 3, tacrolimus XL 0.3 mg/kg + MMF; and arm 4, tacrolimus XL 0.2 mg/kg + MMF + basiliximab. The study assessed the efficacy and safety of the 4 immunosuppressive regimens during the 6-month analysis period [Study PMR-EC-1210]. Transplant recipients receiving tacrolimus XL were given the option of continuing treatment in [Study FG-506-14-02].

Table 3 Overview of Design of Study PMR-EC-1210 in De Novo Kidney Transplant

Parameter	Study PMR-EC-1210			
Design	Phase 3b, multicenter, 1:1:1:1 randomized, open-label, comparative, 4-arm parallel group, noninferiority			
TacXL and comparators FAS PP	**TacXL** 0.2 mg/kg (n = 302) (n = 263)	**Tac** 0.2 mg/kg (n = 309) (n = 237)	**TacXL** 0.3 mg/kg (n = 304) (n = 246)	**TacXL** 0.2 mg/kg (n = 283) (n = 230)
Timing of preoperative dose, if allowed	Within 12 hours prior to reperfusion and if possible within 3 hours prior to anesthesia†			
Protocol-defined initial preoperative CNI dose (po)	**TacXL** 0.1 mg/kg	**Tac** 0.1 mg/kg	**TacXL** 0.15 mg/kg	**TacXL** 0.1 mg/kg
Timing of initial dose	Not < 4 hours after the preoperative dose or > 12 hours after reperfusion			
Antibody induction	Not permitted			BAS 20 mg iv on day 0 and once on day 4
Protocol-defined initial postoperative dose per day	**TacXL** 0.2 mg/kg po (AM)	**Tac** 0.2 mg/kg po (2 divided doses)	**TacXL** 0.3 mg/kg po (AM)	**TacXL** 0.2 mg/kg po (AM)
Actual mean dose on day 1‡	**TacXL**(FAS) 0.16 mg/kg	**Tac**(FAS) 0.16 mg/kg	**TacXL**(FAS) 0.22 mg/kg	**TacXL**(FAS) 0.17 mg/kg
Protocol-defined tacrolimus trough concentration	Days 0 to 14: 10 to 15 ng/mL Days 15 to 42: 5 to 12 ng/mL Days 43 to 168: 5 to 10 ng/mL			
Protocol-defined MMF initial dose	1 g preoperatively; 2 g/day (2 divided doses)			
Protocol-defined MMF reduction	After day 14: 1 g/day			
Protocol-defined corticosteroid initial dose	Methylprednisolone (or equivalent) Day 0: up to 500 mg iv Day 1: 125 mg iv			Methylprednisolone (or equivalent) Day 0: up to 500 mg iv
Protocol-defined corticosteroid reduction schedule (po)	Days 2 to 14: 20 mg/d Days 15 to 28: 15 mg/d Days 29 to 42: 10 mg/d Days 43 to 84: 5 mg/d Days 85 to 168: ≤ 5 mg/d			No corticosteroids Days 1to 168.

Patient population	**TacXL** (FAS)	**Tac** (FAS)	**TacXL** (FAS)	**TacXL** (FAS)
Male	68.2%	68.3%	67.1%	65.4%
Female	31.8%	31.7%	32.9%	34.6%
Living donor	11.3%	13.3%	10.9%	12.7%
Deceased donor	88.7%	86.7%	89.1%	87.3%
White	94.0%	95.8%	95.7%	93.6%
Black/African American	4.6%	2.3%	2.3%	3.9%
Treatment duration	Open Label for 24 weeks			
and primary endpoint	Week 24 graft loss, biopsy confirmed acute rejection, or graft dysfunction defined as estimated GFR < 40mL/min/1.73m².			

Source: Adapted from Applicant's Table 1 in Module 2.7.3 Kidney Transplantation, Summary of Clinical Efficacy and Tables 2.1.1 and 2.1.2 in the FDA Statistical Review.

Differences between the primary US Study 02-0-158, primary non-US Study FG-506E-12-03 and the European post-marketing study PMR-EC-1210 are noted in the following areas:

Study populations

- Higher proportion of Black/African-American patients in Study 02-0-158 compared with the other 2 studies
- Higher proportion of recipients of kidneys from living donors in Study 02-0-158 compared with the other 2 studies.

Protocol-defined primary analysis

In Study 02-0-158, the primary analysis was efficacy failure rate (BPAR, graft failure, death or lost to follow-up at 1 year). In Study FG-506E-12-03, the primary analysis was the BPAR event rate within the first 24 weeks posttransplant. In Study PMR-EC-1210, the primary analysis was efficacy failure (incidence and time to first graft loss, BPAR or graft dysfunction defined as estimated GFR < 40mL/min/1.73m²) at week 24**.**

> *<u>Reviewer's Comment</u>: Although different primary endpoints were used in these trials, data for efficacy failures (BPAR, death, graft loss, or loss to follow-up) was collected and analyzed by the statistical reviewer for all three studies.*

Antibody induction

Antibody induction was mandated by the protocol in Study 02-0-158 (basiliximab 20 mg intravenously on day 0 and once between days 3 and 5), but was not used in any of the other studies, except in arm 4 of Study PMR-EC-1210.

> *<u>Reviewer's Comment</u>: Study 02-0-158 is the only study in de novo kidney transplantation included in this submission that includes a regimen of anti-IL2-*

receptor antibody induction, with a regimen of Prograf + MMF that approximates the regimen of Prograf + MMF approved for prophylaxis of rejection in kidney transplant recipients, which also used anti-IL2-receptor antibody induction. Comparison of the observed tacrolimus and MMF doses and exposures in the Prograf and tacrolimus XL arms of Study 02-0-158 to those observed in the ELiTE study, which supported the approval of Prograf + MMF in the prevention of graft rejection in kidney transplant recipients will be considered in this review.

Initial dose of calcineurin inhibitor (Prograf, tacrolimus XL, cyclosporine)

Study 02-0-158 did not permit the use of a preoperative dose of calcineurin inhibitor, while Studies FG 506E-12-03 and PMR-EC-1210 permitted a preoperative dose within 12 hours prior to reperfusion, reflecting the differences in use of antibody induction. In Study 02-0-158, the protocol-defined initial postoperative dose was 0.15 to 0.20 mg/kg in the morning for tacrolimus XL and the same total dose administered in 2 divided doses for Prograf. The protocol-defined initial postoperative dose was 0.2 mg/kg in Studies FG-506E-12-03 and PMR-EC-1210 (in the morning for tacrolimus XL and in 2 divided doses for Prograf). In Study PMR-EC-1210, one of the tacrolimus XL treatment groups had a protocol-defined initial postoperative dose of 0.3 mg/kg.

<u>Reviewer's Comment:</u> In the analyses and interpretation of efficacy and safety data from the clinical studies included in this review, attention will be paid to the observed doses and whole blood trough of calcineurin inhibitors, as well as to the protocol-specified doses.

Protocol-defined MMF reduction

In Study 02-0-158, dose changes of MMF were only made for adverse events if clinically indicated; withdrawal was permitted at the investigator's discretion. In Studies FG-506E-12-03 and PMR-EC-1210, the protocol-defined MMF reduction was from 2 g/day to 1 g/day after day 14.

<u>Reviewer's Comment:</u> In this review the protocol-specified as well as the observed use of MMF in studies 02-0-158 and FG-506E-12-03 will be compared to those of the Symphony-ELiTE trial used to support the use of tacrolimus + MMF (NDA 50-708/S027, NDA 50-709/S021).

Corticosteroid reduction

Corticosteroids could be reduced to 5 to 10 mg/day in Study 02-0-158, but could not be discontinued. In Study FG-506E-12-03, corticosteroids could be discontinued after day 84. In Study PMR-EC-1210, the corticosteroid dose could be reduced to ≤ 5 mg/day after day 84 in arms 1, 2 and 3 and was administered as a single steroid bolus in arm 4.

Reviewer's Comment: Protocol-specified as well as observed corticosteroid use and reductions will be examined in this clinical review.

Active comparator

Study 02-0-158 included an active comparator regimen of Neoral® (cyclosporine USP) MODIFIED + MMF, which represents an approved regimen for the prevention of allograft rejection in *de novo* kidney transplantation. Study FG-506E-12-03 compared two investigational regimens of Prograf + MMF and tacrolimus XL + MMF.

The Applicant believes that Study 02-0-158, which is the primary study used to support efficacy, safety and dosing recommendations for labeling, is more consistent with the US standard of care and population demographics. For this reason, Study 02-0-158 is considered by the Applicant as the primary study to support the demonstration of the efficacy and safety of tacrolimus XL.

Reviewer's Comment: To the extent that Study 12-03 also provides information on a combination of tacrolimus + MMF without the use of antibody induction, which represents part the spectrum of use of this combination, Study 12-03 is also considered by this reviewer a primary study to support the efficacy and safety of tacrolimus XL, as further discussed in Section 5.2 of this review.

Tacrolimus XL Conversion Studies in Kidney Transplantation

- **Study 02-0-131**, a phase 2, open-label study assessing the pharmacokinetics, safety and tolerability of tacrolimus XL in stable kidney transplant recipients converted from a Prograf-based immunosuppressive regimen. The study included a 5-week pharmacokinetic evaluation period [Study 02-0-131 PK] and a clinical continuation period [Study 02-0-131 LT]

- **Study FJ-506E-KT01**, a phase 2, open-label study assessing the pharmacokinetics of tacrolimus XL in stable Japanese kidney transplant recipients converted from a Prograf-based immunosuppressive regimen. This study included a 2-week pharmacokinetic evaluation and 3-month postconversion treatment continuation period [Study FJ-506E-KT01].

- **Study FG-506E-12-02**, a phase 2, open-label, single sequence, 4-period crossover study assessing the pharmacokinetics of tacrolimus XL in stable kidney transplant recipients converted from a Prograf-based immunosuppressive regimen. The study included an 8-week pharmacokinetic evaluation period [Study FG-506E-12-02] and continuation of treatment in [Study FG-506-14-02].

Table 4 - Clinical Pharmacology Conversion Studies

Type of Study	Study No.	Objective	Design/ Control	Product/ Dose/Route	No. of Subjects	Subject Type/ Diagnosis	Treatment Duration
PK LTS Toler-ability	02-0-131 (Study 131)	Compare Tac and TacXL	Phase 2, multi- center, open-label crossover conversion	Prograf/stable bid dose/oral TacXL/equivalent to daily bid dose of Prograf given qd (1 mg and 5 mg capsules)/oral	*PK Period* 70/67 *FAS* 68 *Continuation* § 66 MR4 treated; 59 completed 2 years	Stable kidney transplant recipient treated with Prograf	Prograf: 1 week MR4: 4 weeks PK period report
PK S Toler-ability	FJ-506E-KT01 (Study KT01)	Compare Tac and TacXL	Phase 2, multi- center, open-label, crossover, conversion	Prograf/bid dose equal to previous screening phase dose/oral TacXL/qd dose equal to previous Prograf dose(above)/oral	37/34	Stable Japanese kidney transplant recipient treated with Prograf	Prograf: 1 week MR4: 1 week plus 3-month continuation
PK S Tolerability	FG-506E-12-02 (Study 12-02)	Compare Tac and TacXL	Phase 2, multi-center, open-label, crossover, conversion	Prograf/bid dose equal to previous screening phase dose/ oral TacXL/qd dose equal to previous Prograf dose (above)/oral Prograf/bid dose equal to previous MR4 dose (above)/ oral TacXL/qd dose equal to previous Prograf dose (above)/oral	*PK Period* 73/64 *FAS* 69 *Continuation* § 67 MR4 treated 63 completed 1 year	Stable kidney transplant recipient treated with Prograf	14 days per treatment period, PK period report in submission; optional 1-year continuation for MR4 patients

The pharmacokinetic data from the studies of tacrolimus XL conversion studies will be reviewed in the FDA Clinical Pharmacology Review. The applicant is not seeking a specific conversion indication, but is requesting that (b) (4) afety data from these studies was examined and reviewed under the FDA Clinical Review of NDA 50-811, dated January 19, 2007, and will be referred to as needed in section 6 Summary of Safety of this review.

Reviewer's Comment: These studies do not represent adequate well controlled studies capable of providing substantial evidence of efficacy and safety of a potential "conversion" indication.

5.2 Review Strategy

De Novo Kidney Transplantation

Study 02-0-158, hereto after also referred in this review as Study 158, previously reviewed under NDA 50-811, provides information on efficacy of tacrolimus XL

compared to cyclosporine when used MMF, and is considered a primary study in this clinical reveiw. The design and results of this study will be summarized in Section 5.3 below, based on the previous FDA clinical and statistical reviews. Results from this study will also be summarized in Sections 6, Summary of Efficacy, and 7, Summary of Safety of this review.

Study FG-506E-12-03, hereto after also referred in this review as Study 12-03, provides a comparison of the efficacy and safety of tacrolimus XL + MMF to Prograf + MMF, when used without antibody induction. This study is representative of the spectrum of combination immunosuppression using tacrolimus and MMF, is considered a primary study supporting the safety and efficacy of tacrolimus-XL in the prevention of rejection in recipients of allogeneic renal transplants. Such a comparison was requested in the AE Letter of 2008. The design of this study, which has not been previously reviewed under NDA 50-811, will be described in summary in Section 5.3 of this review and the results presented in greater detail in Sections 6, Summary of Efficacy, and 7, Summary of Safety, of this review.

Study PMR-EC-1210 was a non-US, non-IND, European, open-label post-marketing study, exploring three different regimens using various doses and combination of tacrolimus-XL, compared to tacrolimus + MMF + corticosteroids control arm that resembles the regimen used in the tacrolimus arm of Study 12-03, without antibody induction. Although one of the tacrolimus-XL treatment arms approximates that used in the tacrolimus-XL treatment arm of Study 12-03, the open-label design, the limitation of assessment of efficacy and safety to 24 weeks, and the multiple comparisons involved all limit the utility of this study to support labeling of the efficacy and safety of a tacrolimus-XL regimen in the US. Thus, this study is not considered to be a primary study in this review, but is exploratory at best, due to the multiple comparisons and shorter duration (24 weeks) than studies 12-03 and 158 (12-months).

> *Reviewer's Comment: Analyses comparing the tacrolimus treatment arm in Study 1210 to one of the tacrolimus-XL treatment arms that approximate the ones used in Study 12-03 are included in the FDA Statistical Review.*

No pooling of the results of Study 158 and Study 12-03 will be included in Sections 6 and 7 of this review, as there are too many differences in design and study populations to allow one to draw meaningful conclusions from such pooling. As one will read below, Study 158 is representative of the proposed use of tacrolimus, as an immediate release product, Prograf®, hereafter referred to as Tac, or as an extended-release product (Astagraf XL®), hereafter referred to as TacXL, in combination with mycophenolate mofetil (MMF) and antibody induction immunosuppression with basiliximab (Simulect®). Study 12-03 is representative of the proposed use of tacrolimus, as an immediate release product, Prograf®, hereafter referred to as Tac, or as an extended-release product (Astagraf XL®), hereafter referred to as TacXL, in combination with mycophenolate mofetil (MMF), without antibody induction immunosuppression.

Tacrolimus XL Conversion Studies in Kidney Transplantation

The pharmacokinetic data from the studies of tacrolimus XL conversion studies will be reviewed in the FDA Clinical Pharmacology Review. The applicant is not seeking a specific conversion indication. Safety data from these studies was examined and reviewed under the FDA Clinical Review of NDA 50-811, and will be referred to as needed in section 6 Summary of Safety of this review. These studies were not randomized, and do not represent adequate well controlled studies that could be used to support a formal clinical indication of conversion from tacrolimus to tacrolimus-XL, or vice versa. They are inherently not designed to meet the standard of providing substantial evidence of safety and efficacy of conversion from Prograf to tacrolimus-XL, and will not be reviewed for safety and efficacy in this review.

> *Reviewer's Comment: Although some 12 month follow-up data from these short studies has been submitted by the Applicant, such data is not readily interpretable without a randomized concurrent control group, and did not include systematic collection of safety data, or episodes of allograft rejection, beyond the completion of the short period of pharmacokinetic sampling. In addition, the range of duration from time of transplant to time of conversion renders data on 12 month graft and patient survival even more difficult to interpret in a clinically meaningful way that could inform an individual clinician or patient on the safety or efficacy of such conversion.*
>
> *In as much it is to be expected that clinicians and patients may choose to switch between tacrolimus-XL and Prograf, bidirectionally, if the former becomes available, then wording to the effect that these two products are not interchangeable without physician supervision could be included in labeling. Pharmacokinetic data and from these studies could be included in the Clinical Pharmacology section of the label if based on the FDA Clinical Pharmacology Review such information is judged necessary to alert the practitioner to the need for precautions, including but not limited to monitoring of tacrolimus whole blood concentrations, when switching between the immediate release and extended release formulations.*

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study 02-0-158

Study 02-0-158 **-** "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"

The following is a discussion of Study 02-0-158 adapted from the Clinical and Statistical Reviews of NDA 50-811, dated 01/19/2007 and 01/12/2007, respectively.

Study Design and Objectives

This study enrolled male and female patients who are 12 years of age or older and undergoing primary or re-transplanted non-HLA-identical living or cadaveric kidney transplantation. Previous and current transplants of an organ other than a kidney were basis for exclusion. The study was conducted between July 2003 and April 2005 in 60 clinical sites across the United States, Canada and Brazil. Study duration was one-year followed by a clinical continuation phase for a minimum of 2 years.

Study 02-0-158 was an open-label, randomized, non-inferiority study evaluating the safety and efficacy of TacXL/MMF, Prograf or Neoral all in combination with CellCept (MMF) in *de novo* kidney transplant recipients.

The primary efficacy endpoint of efficacy failure, measured at one-year post-transplant, was efficacy failure, defined as death, graft failure [permanent return to dialysis (> 30 days) or re-transplant], biopsy-confirmed (Banff Grade ≥ I) acute rejection (BCAR) based on local assessment, or lost to follow-up at one year post-transplant. All suspected rejection must be biopsy confirmed before treatment for rejection is initiated or within 48 hours of initiation of treatment for acute rejection.

The study was designed to demonstrate non-inferiority of TacXL /MMF and of Prograf/MMF to Neoral/MMF within a 10% margin. The primary efficacy comparison in Study 158 will be between the TacXl and Neoral arms. The comparison of Tac-XL vs Prograf was a secondary efficacy endpoint.

Patients were randomized to Prograf/MMF, Tac XL /MMF or Neoral/MMF in a 1:1:1 fashion stratified by donor type (living or cadaveric) and transplant history (primary or re-transplant). Starting doses of Prograf and Tac XL were to be between 0.075 and 0.1 mg/kg BID and between 0.15 and 0.2 mg/kg QD, respectively. Subsequent doses of Prograf and TacXL were adjusted based on clinical evidence of efficacy, occurrence of adverse events, and whole blood tacrolimus trough concentrations. For both Prograf and TacXL, the target range for whole blood tacrolimus concentrations was 7 to 17 ng/mL for days 0 through 90, and 5 to 15 ng/mL thereafter. The initial dose of Neoral was to be 4 to 5 mg/kg BID. Subsequent doses of Neoral were also adjusted based on clinical evidence of efficacy, occurrence of adverse events, and whole blood cyclosporine (CsA) trough concentrations. The target range for whole blood CsA concentrations was 125 to 400 ng/mL for days 0 through 90, and 100 to 300 ng/mL thereafter. All MMF doses were to be 1.0 g BID (currently labeled dose); however, African American patients were allowed to receive 1.5 g MMF BID if necessary. MMF dose changes for adverse events were permitted at the investigator's discretion if

clinically indicated. Target trough MMF levels (MPA) were not identified; therefore, dose adjustments were not to be made based on MPA trough concentration.

Time of randomization is unspecified in the study protocol; however, study drug was to be initiated within the first 24 hours post-transplantation. In addition to assigned treatment, all patients were to receive basiliximab induction therapy and corticosteroid treatment.

Justification of the Non-Inferiority Margin

By the time that Study 158 was designed and conducted, substantial information was available to support the justification of the proposed non-inferiority margin. In particular, the inclusion of a calcineurin inhibitor (CNI), namely cyclosporine or tacrolimus, as part of an immunosuppressant regimen in kidney transplantation had led to marked decreases in acute rejection rates and significant improvements in 1-year graft survival. Previous clinical trials comparing regimens of cyclosporine (Sandimmune®, FDA approval 1983) plus steroids to non-CNI regimens (predominantly azathioprine plus steroids) demonstrated statistically significant decreases in number of acute rejection episodes in the cyclosporine treated patients. Acute rejection rates were 4 to 10 times higher in the azathioprine/steroid regimens than in the cyclosporine/steroid regimens. Graft survival was also higher in the cyclosporine treated groups [7]. Neoral® (cyclosporine USP) modified, a formulation of cyclosporine that forms a microemulsion when mixed in an aqueous solution, had been shown to be therapeutically equivalent to cyclosporine and was also FDA approved (NDAs 50-715 and 50-716).

Although clinical experience with a regimen of only antibody induction/MMF/steroids was limited, of the few studies performed rejection rates had been greater than 30%. Incidence of acute rejection was 70% (19/27) in a daclizumab (induction therapy)/MMF/steroids regimen versus 30% (8/27) in a cyclosporine-based MMF/steroids regimen in one randomized comparative study[8]. Due to unacceptable acute rejection rates in the daclizumab group, inclusion of new subjects was halted by the DSMB when 54 of the planned 70 patients had been randomized. Other published results with a non-CNI based MMF regimen in non-controlled studies had suggested rejection rates higher than those observed with CNI-based regimens[9] [10].

[7] The Canadian Multicenter Transplant Study Group. A randomized clinical trial of cyclosporine in cadaveric renal transplantation. N Engl J Med 1983;309(14):809-15.
[8] 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.
[9] Tran HT, Acharya MK, McKay DB, Sayegh MH, Carpenter CB, Auchincloss H, et al. Avoidance of cyclosporine in renal transplantation: Effects of daclizumab, mycophenolate mofetil, and steroids. J Am Soc Nephrol 2000;11:1903-9
[10] Vincenti F, Ramos E, Brattstrom C, Cho S, Ekberg H, Grinyo J, et al. Multicenter trial exploring calcineurin inhibitors avoidance in renal transplantation. Transplantation 2001;71(9):1282-7.

CNI-based immunosuppressive therapy in kidney transplantation was well-established with over 20 years of clinical use. More contemporary studies had suggested increased acute rejection with CNI withdrawal and decreased graft loss when including a CNI in the therapeutic regimen. Thus, it was felt that a 10% non-inferiority margin for the composite of acute rejection, patient and graft loss would be considerably lower than the benefit of immunosuppressive therapy over placebo alone. A more restrictive margin, between 5 and 10%, was typically used to assess the outcome of graft loss and death alone.

> *Reviewer's Comment: A justification of the non-inferiority margin was also submitted as part of NDA 204096. For a further updated discussion and justification of the non-inferiority margin please refer to the FDA Statistical Review of this NDA 204096 in DARRTS. In the FDA Statistical review of NDA 50-811, the randomized controlled study by Asberg et al. [2006] using MMF/steroids and antibody induction with and without CNI (cyclosporine) was judged to be the most relevant Study 158 [11]. A confidence interval around the observed difference was calculated to be (-65.1, -16.4). This excluded a margin of 10% considered appropriate for BCAR, graft and patient survival. The width of the confidence interval is a reflection of the small study size due to the premature halting of patient enrollment due to safety concerns (unacceptable risk of rejection).*

Demographics and Patient Disposition

Six hundred sixty-eight (668) patients were randomized among 60 clinical sites in three countries (US, n=50; Canada, n=5; and Brazil, n=5). Of these 95%, 97% and 95% in the tacrolimus XL/MMF, Prograf/MMF and Neoral/MMF groups respectively received study drug. The largest number of patients enrolled at one site was 42 (Brazil) and one site enrolled only one patient. The mean enrollment was 11 patients per site. The majority (548/668, 82%) of study patients were enrolled in sites within the United States. Ninety-two (13.8%) patients were enrolled in clinical sites in Brazil and the remaining 28 patients were enrolled in Canadian sites.

The table below adapted from table 3.1 the FDA Statistical Review of NDA 50-811, dated 01/12/2007, summarizes the patient disposition in study 02-158-02. MR refers to tacrolimus XL.

Table 5 Study 158 Patient Disposition

[11] 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.

	MR/MMF	Prograf/MMF	Neoral/MMF
Randomized	226	219	223
Full Analysis Set*	214 (94.7)	212 (96.8)	212 (95.1)
Crossover**	10 (4.4)	6 (2.7)	39 (27.5)
Completed 1-yr of therapy	183 (85.5)	179 (84.4)	151 (71.2)
Discontinued Randomized Therapy	31 (14.5)	33 (15.6)	61 (28.8)
AE	19 (8.9)	23 (10.8)	37 (17.5)
Rejection	1 (0.5)	0	16 (7.5)
Non-Compliance	2 (0.9)	4 (1.9)	5 (2.4)
Graft Failure	2 (0.9)	3 (1.4)	1 (0.5)
Withdrawal of Consent	4 (1.9)	0	1 (0.5)
LTF	0	1 (0.5)	0
Other#	3 (1.4)	2 (0.9)	1 (0.5)

** Randomized and received at least one dose of study treatment*
*** Protocol allowed crossover to another study treatment except to MR/MMF regimen*
 # Prograf/MMF: Converted to rapamycin, acute tubular necrosis, MR/MMF: incorrect study drug dispensed, investigator discretion/possible toxicity, improper drug absorption, Neoral/MMF: subsequent pancreas transplant after kidney transplant
Source: Applicant's CSR Tables 13.1.1, 13.1.2, and Appendix 14.4.1.3

Reviewer's Comment: As noted in the 2007 Clinical and Statistical Reviews of NDA 50-811 a higher proportion of patients in the Neoral treatment group discontinued randomized therapy in this open-label study. The protocol allowed for cross-over to another study treatment except to TacXl/MMF. The leading causes of discontinuation were reported as adverse events or rejection; however, comparisons should be interpreted with caution in this open-label study, due to the potential for bias.

The table below, adapted from Table 3.2 in the FDA Statistical Review of NDA 50-811, dated 01/12/2007, summarizes patient and demographic characteristics from study 02-0-158.

Table 6 Study 158 Patient and Demographic Characteristics

Variable	*MR/MMF (n=214)*	*Prograf/MMF (n=212)*	*Neoral/MMF (n=212)*
Country			
Brazil	31 (14.4)	30 (14.1)	30 (14.1)
Canada	10 (4.7)	7 (3.3)	10 (4.7)
United States	173 (80.8)	175 (82.5)	172 (81.1)
Males	138 (34.1)	136 (33.7)	130 (32.2)
Donor Males	113 (52.8)	86 (40.6)	96 (45.3)
Race			
Black	41 (19.1)	51 (24.0)	36 (17.0)
Caucasian	160 (74.8)	152 (71.7)	163 (76.9)
Asian	5 (2.3)	5 (2.3)	8 (3.8)
Other	8 (3.7)	4 (1.9)	5 (2.3)
Mean Age (range)	47.8 (17-77)	48.6 (19-74)	47.6 (17-77)
Mean Donor age (range)	38.2 (2-72)	39.0 (0-68)	39.9 (17-63)
Donor Type			
Cadaver	111 (51.9)	106 (50.0)	101 (47.6)
Living non-related	41 (19.2)	41 (19.3)	37 (17.4)
Living related	62 (29.0)	65 (30.7)	74 (34.9)

Values in parenthesis are percentages unless otherwise noted

Source: Applicant's CSR Tables 13.2.1, 13.2.2, 13.2.4, and Appendix 14.4.1.4.1, 14.4.1.6.

There were no significant differences among treatment groups in any baseline characteristics, including donor type. The majority of randomized patients (614/638; 96.2%) received a primary kidney transplant upon entry into the study, with approximately half receiving a kidney from a deceased donor and half receiving a kidney from a living donor. The majority of patients (491/638; 77.0%) had ≥ 3 HLA mismatches. There were no significant differences across treatment groups in terms of baseline status of hypertension, diabetes type I or II, or hyperlipidemia. There were no clinically significant differences in the history/type or duration of pre-study dialysis between the three treatment groups. The majority of patients (539/638; 84.5%) underwent some form of dialysis (hemodialysis, peritoneal dialysis, or both) prior to study entry, with the median duration of pre-study dialysis being 29 months. There were significantly more male donors in the tacrolimus/MMF group (113/214, 52.8%) compared to the Prograf/MMF group (86/212, 40.6%) (2-sided chi-square p-value=0.011).

There were no significant differences across treatment groups for any of the other donor demographic parameters (race, age, and age group). It was noted that numerically more males in the Prograf/MMF treatment group (85/136; 62.5%) received a kidney from a female donor than males in the tacrolimus XL/MMF treatment group (68/138; 49.3%) or Neoral/MMF treatment group (73/130; 56.2%).

Efficacy Analyses

One year efficacy failure (first occurrence of BCAR, graft loss, death or loss to follow-up) was **14%** (30/214), **15.1%** (32/212) and **17.0%** (36/212) in tac XL/MMF,

Prograf/MMF and Neoral/MMF groups respectively yielding differences of -3.0, 95.2% 2-sided CI [-10.0, 4.0], p-value=0.4 (tac XL-Neoral) and -1.9, 95.2% 2-sided CI [-9.0, 5.2], p-value=0.6 (Prograf-Neoral). The upper 95.2% confidence bound for both comparisons fell below the clinically relevant 10% margin demonstrating non-inferiority of these regimens to Neoral/MMF. 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).

See Table 7 from the FDA Statistical Review of BDA 50-811, dated 01/12/20-07 (Table 3.5), and reproduced below:

Table 7 Study 158 Efficacy Failure at Day 365

Table 3.5 Efficacy Failure at day 365 (study 02-0-158)

Day 365	MR/MMF (n=214)	Prog/MMF (n=212)	Neoral/MMF (n=212)	Difference, 95.2% CI, p-value MR-Neoral	Prograf-Neoral	MR-Prograf
Efficacy failure[1]	**30 (14.0)**	**32 (15.1)**	**36 (17.0)**	**-3.0, [-10.0, 4.0], 0.4**	**-1.9, [-9.0, 5.2], 0.6**	**-1.1, [-7.9, 5.8], 0.8**
Reason for failure:						
BCAR*	22 (10.3)	16 (7.5)	29 (13.7)	-3.4, [-9.7, 2.8], 0.3	-6.1, [-12.2, -0.2], 0.04	2.7, [-2.8, 8.4], 0.4
Graft Failure[2]	4 (1.9)	6 (2.8)	4 (1.9)			
Death[3]*	3 (1.4)	9 (4.2)	5 (2.4)	-0.9, [-4.2, 2.0], 0.5	1.9, [-1.7, 5.8], 0.3	-2.8, [-6.6, 0.3], 0.08
LTF[4]	3 (1.4)	4 (1.9)	1 (0.5)			

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

When adjusting for donor type (living or cadaveric) the 95.2% confidence interval around MR-Neoral difference is (-10.2, 3.6) and around the Prograf-Neoral difference is (-9.1, 4.8).

> *Reviewer's Comment: There were more deaths in the Prograf/MMF group compared to the other treatment groups. Please see Section 7 of this review on the Summary of Safety for further discussion.*

Patient and graft survival

Table 3.6 from the FDA Statistical Review of NDA 50-811, dated 01/12/2007, reproduced as Table 8 below summarizes patient and graft survival in Study 02-0-158:

Table 8 Study 158 Patient and Graft Survival

Table 3.6 Patient and Graft Survival (study 02-0-158)

	MR/MMF (n=214)	Prog/MMF (n=212)	Neoral/MMF (n=212)	Difference, 95.2% CI, p-value MR-Neoral	Prograf-Neoral	MR-Prograf
Day 365 (1 yr follow-up)						
Patient Survival	**208 (97.2)**	**199 (93.9)**	**206 (97.2)**	0, [-3.6, 3.6], 0.99	-3.3, [-7.8, 0.7], 0.1	3.3, [-6.9, 7.8], 0.1
Reason:						
Death*	3 (1.4)	9 (4.2)	5 (2.3)	-0.9, [-4.2, 2.0], 0.5	1.9, [-1.7, 5.8], 0.3	-2.8, [-6.6, 0.4], 0.08
LTF	3 (1.4)	4 (1.9)	1 (0.5)			
Graft Survival	**204 (95.3)**	**194 (91.5)**	**202 (95.3)**	0, [-4.3, 4.4], 0.99	-3.8, [-8.9, 1.0], 0.1	3.8, [-1.0, 8.9], 0.1
Reason						
Death	3 (1.4)	9 (4.2)	5 (2.3)			
Graft Failure[1]	5 (2.3)	9 (4.2)	4 (1.9)			
LTF[2]	3 (1.4)	4 (1.9)	1 (0.5)			
Day 547 (1.5 yr follow-up)						
Patient Survival	**207 (96.7)**	**195 (92.0)**	**204 (96.2)**	0.5, [-3.3, 4.4], 0.8	-4.2, [-9.2, 0.3], 0.06	4.7, [0.3, 9.6], 0.03
Reason:						
Death*	4 (1.9)	12 (5.7)	7 (3.3)	-1.4, [-5.0, 1.8], 0.5	2.4, [-1.7, 6.7], 0.2	-3.8, [-7.9, -0.2], 0.04
LTF	3 (1.4)	5 (2.3)	1 (0.5)			
Graft Survival	**202 (94.4)**	**190 (89.6)**	**198 (93.3)**	1.0, [-3.8, 5.9], 0.7	-3.8, [-9.4, 1.6], 0.2	4.8, [-0.4, 10.3], 0.07
Reason						
Death	4 (1.9)	12 (5.7)	7 (3.3)			
Graft Failure[1]	6 (2.8)	9 (4.2)	6 (2.8)			
LTF[2]	3 (1.4)	5 (2.3)	1 (0.5)			
Day 780 (2 yr follow-up)						
Patient Survival	**206 (96.3)**	**195 (92.0)**	**204 (96.2)**	0, [-3.9, 4.0], 0.99	-4.2, [-9.2, 0.3], 0.06	4.3, [-0.2, 9.2], 0.06
Reason:						
Death	5 (2.3)	12 (5.7)	7 (3.3)	-1.0, [-4.6, 2.5], 0.6	2.4, [-1.7, 6.7], 0.2	-3.8, [-7.9, -0.2], 0.04
LTF	3 (1.4)	5 (2.3)	1 (0.5)			
Graft Survival	**198 (92.5)**	**190 (89.6)**	**196 (92.4)**	0, [-5.2, 5.3], 0.99	-2.8, [-8.5, 2.7], 0.3	2.9, [-2.6, 8.6], 0.3
Reason						
Death	5 (2.3)	12 (5.7)	7 (3.3)			
Graft Failure[1]	9 (4.2)	9 (4.2)	8 (3.8)			
LTF[2]	3 (1.4)	5 (2.3)	1 (0.5)			

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

The lower bounds around the 95% confidence interval closely approach -10% for the difference in patient and graft survival between Prograf/MMF and Neoral/MMF (Table 3.6). Additionally, at day 365 three times more deaths, 9/212 (4.2%) vs. 3/214 (1.4%) occurred in the Prograf/MMF group compared to the tac XL/MMF groups, which is clinically and near statistically relevant (Please see the Summary of Safety in Section 7 for further discussion of the deaths in Study 158). This difference is more notable given the open-label nature of this study where patients were given the option to switch to an

alternative therapy. In the Neoral/MMF group, five patients died at one year of follow-up. Sepsis was more commonly the cause of death in the Prograf/MMF group compared to the other two groups. There were no notable differences in death rates among countries or clinical sites.

Rates of premature treatment discontinuation and treatment crossover were considerably larger in the Neoral/MMF group compared to the two tacrolimus groups. These rates are inconclusive and potentially biased given the open-label nature of this study and the clinical preference to use tacrolimus in *de novo* kidney transplantation that prevailed at the time.

MMF Exposure

The study protocol specified 2 g/day (1 g/BID) was not consistently achieved in either of the tacrolimus treatment groups, which appears to be a reflection of dose adjustments needed for adverse events or poor tolerance. As discussed in greater detail in the clinical pharmacology review of NDA 50-811 and this NDA 204096, calculated mean daily doses of MMF in both the Prograf and MR groups were consistently less than 2 g/day; however, mycophenolic acid (MPA) trough concentrations for Prograf and tac XL were consistently higher than MPA concentrations in the Neoral arm at 30, 192 and 365 days. Specifically, MPA trough concentrations in both tacrolimus groups were approximately 76% higher at one month and 29% higher at 12 months than in the Neoral arm.

> *Reviewer's Comment: Appropriate doses of MMF to be given with Tac XL could not be fully assessed from these data. Data obtained subsequently from the ELiTE-SYMPHONY study provided additional information needed to assess the appropriate dose of MMF to be used with Prograf (NDA 50-708/S027 and NDA 50-509/S021), and demonstrated superiority with respect to efficacy failure compared to an active control. Information from Study 158 regarding the use of MMF with tacrolimus was then included in the Clinical Studies section following the approval of the use of Prograf with MMF in the prevention of rejection in recipients of kidney transplantation.*

Evaluation of Safety

Safety analysis was performed in all randomized patients who received at least one dose of study drug and were on therapy or had discontinued (or crossed over to an alternate therapy) within 10 days.

Differences in safety between the arms containing tacrolimus + MMF compared to the Neoral + MMF control arm were dominated by gastrointestinal adverse events, which are know hazards of MMF and mycophenolic acid (MPA) exposure.

The incidence (by patient) of diarrhea was statistically significantly higher in both the TacXL/MMF group (100/214, 47%, p-value <0.0001, 95% CI 7.3, 25.5) and Prograf/MMF group (94/212, 44%, p-value 0.0001, 95% CI 5.0, 23.1) compared to Neoral/MMF (64/212, 30%). Median duration and grade of severity of these events were greater in the tacrolimus groups compared to the Neoral group, as described in Table 3.10 from the FDA Statistical Review of NDA 50-811, dated 01/12/2007, reproduced below as Table 9:

Table 9 Study 158 Incidence of Diarrhea up to 365 Days

Table 3.10: Incidence of Diarrhea up to 365 days (study 02-0-158)

	MR/MMF N=214	Prograf/MMF N=212	Neoral/MMF N=212
Diarrhea			
Patients	100 (46.7)	94 (44.3)	64 (30.2)
P-value, 95% CI (vs. Neoral)	*<0.001, (7.3, 25.5)*	*0.001, (5.0, 23.1)*	
Events*	141 (6)	135 (2)	89 (19)
Duration of diarrhea (by event)			
Mean no. of days	27.3	22.1	18.0
Median no. of days	8	9	5.5
Severity of Diarrhea (by event)			
Mild	96	90	55
Moderate	42	40	31
Severe	3	5	3

** Events occurring after treatment cross-over in parenthesis*

MR = TacXL
Prograf = Tac

In addition, adverse events reported as gastroenteritis were more common in the tac XL+MMF group compared to the Neoral + MMF and Prograf + MMF group.

> *<u>Reviewer's Comment</u>: These differences in safety profile suggested higher exposure to MMF and MPA in the TacXL group, and Prograf group compared to the Neoral group, and may be explained in part by the effect of cyclosporine's inhibition of enterohepatic recirculation of MPA, which is not share by tacrolimus, meaning that higher MPA exposures result when the same dose of MMF is given with tacrolimus compared to when given with cyclosporine. The issue of the appropriate dose of MMF to be given with tacrolimus in de novo kidney transplant recipients was addressed in the review of NDA 50-508/S027 and NDA 50-709/S021. Further assessment of the safety of TacXL compared to Prograf is needed and will be provided by data from Study FG-506E-12-03 as requested in the Approvable Letter for NDA 50-811, dated January 19, 2007.*

5.3.2 Study FG-506-12-03

Study FG-506E-12-03 – 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.

> *Reviewer's Comment: This section is based on the report of the 12 month analysis of this study, which was conducted as a non-US post-marketing study not under a US IND.*
>
> *Unlike Study 158, which was conducted under the US IND and reflects input in study design, received from FDA along the course of its development, Study 12-03 is a non-US study, which was not conducted under the US IND. Thus, greater detail is provided below on the Study design of Study 12-03, including Reviewer's Comments on the acceptability of significant aspects of the study design and conduct.*

5.3.2.1 Study Design and Objectives

The objective of this study was to evaluate and to compare the efficacy and safety of a triple regimen of TacXL/mycophenolate mofetil (MMF)/steroid with a triple standard regimen of Tac/MMF/steroid in patients undergoing kidney transplantation. The study was double-blind until the last randomized subject had completed 24 weeks on study drug and open-label thereafter. The intent was to demonstrate that tac XL was non-inferior to tac with respect to the primary endpoint: event rate of patients with biopsy-proven acute rejection within the first 24-weeks following transplantation.

5.3.2.1.1 Primary Endpoints

The primary endpoint of the study was the event rate of patients with biopsy-proven acute rejection within the first 24 weeks following transplantation.

> *Reviewer's Comment: This study was not conducted under the US IND and did not include the preferred endpoint of efficacy failure defined as biopsy-proven acute rejection, graft loss, death or loss to follow-up. However, data needed to assess this endpoint was collected in the prespecified secondary endpoints, and the Applicant was requested to perform analyses evaluating this endpoint.*

Applicant was

5.3.2.1.2 Secondary Endpoints

Efficacy:

- Event rate of patients with biopsy-proven acute rejection within the first 12 months following transplantation.
- Incidence of and time to acute rejection and biopsy-proven acute rejection as well as corticosteroid resistant acute rejection and biopsy-proven corticosteroid resistant acute rejection within the first 24 weeks and 12 months following transplantation.
- Overall frequency of acute rejection and biopsy-proven acute rejection as well as corticosteroid resistant acute rejection and biopsy-proven corticosteroid resistant acute rejection within the first 24 weeks and 12 months following transplantation.
- Severity of biopsy-proven acute rejection.
- Patient and graft survival within the first 24 weeks and 12 months following transplantation.
- Renal function assessed by calculated creatinine clearance (Cockcroft-Gault's formula) and serum creatinine within the first 24 weeks and 12 months following transplantation.

Safety:

- Incidence of adverse events.
- Incidence of adverse events of special interest (renal function, diabetes mellitus, neurological adverse events, and hypertension).
- Laboratory assessments.

5.3.2.2 Study Design and Plan Description

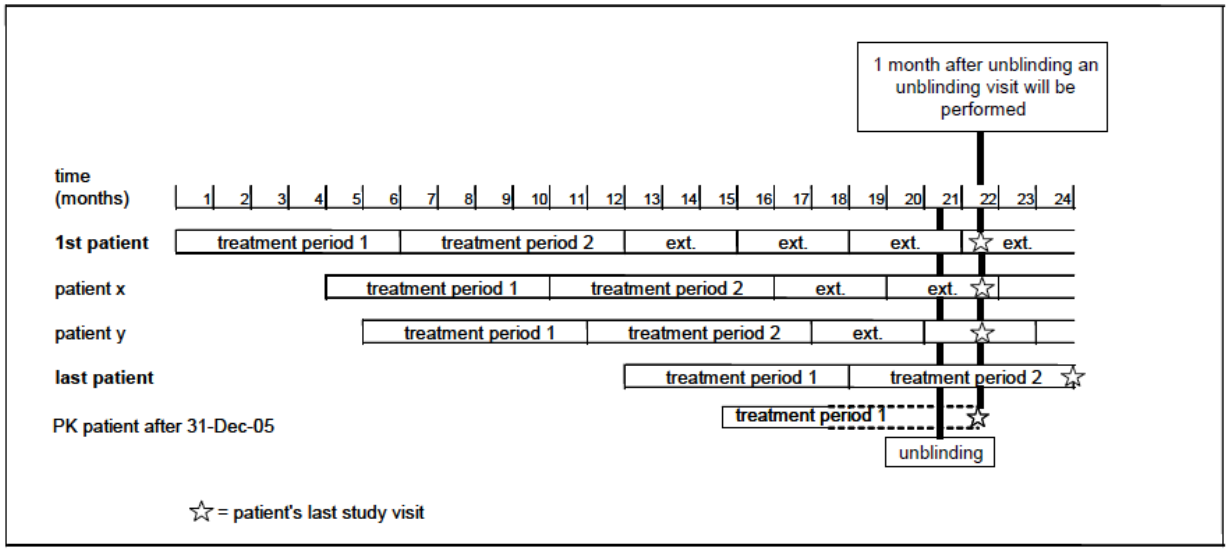
Overview:

This was a multicenter, 1:1 randomized, double blind, double dummy, two arm parallel group Phase III study comparing a TacXL/MMF/steroid regimen with a Tac/MMF/steroid regimen, over a period of at least 12 months. During the first 24 weeks of study duration a double blind, double dummy design was maintained and after the 24-week data were cleaned, the study was unblinded and continued in an open design extension period until the last patient completed his/her 12-month visit.

> *<u>Reviewer's Comment</u>: In the 12 month study report, as the blind was to be maintained until the last subject had completed 24-weeks and the 24-week data had been cleaned, it can be deduced that most of the 12 month data was collected under blinded conditions. Moreover, most of the events of interest with respect to safety would have occurred early in the study and been reported for the most part when treatment assignment was still blinded. This is a particular strength of this study when addressing comparative safety issues between TacXL and Prograf.*

A schematic overview of the study design is presented in the figure below (Source: Applicant's Study Report Figure 1)

Figure 1: Schematic Overview of Study Design



Schematic overview of study design according to Amendment 03

Patients about to undergo kidney allograft transplantation were randomized to one of the following treatment arms:

Treatment Arm 1: tacXL-Placebo/tac/MMF/steroids

Treatment Arm 2: tacXL/tac-Placebo/MMF/steroids

The 12-month analysis includes all data collected during Treatment Periods 1 and 2, i.e. up to Month 12 / End of study (Visit 11) for the completers, and up to Month 12 follow-up for withdrawals. It also includes further data from the treatment period extension visits where appropriate.

Major Protocol Amendments:

Protocol Amendment 1 (dated 30 September 2004) increased the number of planed study centers from 50 to 80 centers.

Protocol Amendment 3 (dated 5 December 2013)

- Increase in the number of patients to be studied from 600 patients to approximately 680 patients in order to ensure enough evaluable pharmacokinetic patients were enrolled in the pharmacokinetic substudy.
- Change of timelines to reflect the increase in patient numbers.

- Change of study design such that patients enrolled after a cutoff date for inclusion in the pharmacokinetic substudy were not required to complete the 24-week period prior to unblinding.
- The definition of the full analysis set was changed to only include patients who were enrolled prior to 31 December 2005.
- A modified full analysis was added as an additional analysis set and included patients in the full analysis set (enrolled prior to 31 December 2005) and patients who enrolled after 31 December 2005 and received at least one dose of study medication.

5.3.2.3 Selection of Study Population

In order to ensure a complete number of evaluable patients in the pharmacokinetic substudy, the planned number of patients was increased by protocol Amendment 03 to approximately from 300 to 680 patients (340 patients per treatment arm) in from approximately 50 increased to 80 centers.

Inclusion Criteria

1. Patients aged between 18 and 65 years.
2. Female patients of child bearing potential must have had a negative serum pregnancy test prior to enrolment and must have agreed to practice effective birth control during the study.
3. Patients receiving a kidney transplant from a cadaveric donor or a living non-Human Leukocyte Antigen (HLA) identical donor between 5 and 65 years of age with compatible AB0 blood type.
4. Patients with end stage kidney disease who were suitable candidates for primary renal transplantation or re-transplantation (unless the graft was lost because of immunological reasons within 12 months).
5. Patients capable of understanding the purpose and risks of the study, who had been fully informed and who had given written informed consent to participate in the study.

Exclusion Criteria

1. Patients receiving or having previously received an organ transplant other than a kidney.
2. Patients with a high immunological risk, defined as a PRA grade >50% in the previous 6 months and/or with a previous graft survival of less than 12 months due to immunological reasons.
3. Cold ischemia time of the donor kidney >30 hours.
4. Patients receiving a graft from a non-heart-beating donor other than of Maastricht category 3 (withdrawal of support awaiting cardiac arrest).

5. Patients allergic or intolerant to HCO-60 or structurally related compounds, steroids, macrolide antibiotics, mycophenolate mofetil, or tacrolimus.
6. Patients with malignancies or a history of malignancy within the last 5 years, with the exception of those with basalioma or squamous cell carcinoma of the skin that had been treated successfully.
7. Patients with significant, uncontrolled concomitant infections and/or severe diarrhea, vomiting, active upper gastrointestinal tract malabsorption or active peptic ulcer.
8. Patients with significant liver disease, defined as having continuously elevated SGPT/ALT and/or SGOT/AST and/or total bilirubin levels during the previous 28 days of greater than or equal to 2 times the upper value of the normal range of the investigational site.
9. Patients with liver cirrhosis.
10. Patients requiring initial sequential or parallel therapy with immunosuppressive antibody preparation(s).
11. Patients with any form of substance abuse, psychiatric disorder or condition which, in the opinion of the investigator, may have complicated communication with the investigator.
12. Patients participating or having participated in another clinical trial and/or those taking or having taken an investigational/non-registered drug in the previous 28 days.
13. Patients requiring ongoing dosing with a systemic immunosuppressive drug prior to transplantation. Low dose steroids (<20 mg/day prednisolone equivalent) were acceptable.
14. Patients who were pregnant or breast-feeding.
15. Patients or donors known to be HIV positive.
16. Patients unlikely to comply with the visits scheduled in the protocol.

5.3.2.4 Treatments

Treatments Administered and Selection and Timing of Doses

The immunosuppressive therapy with TacXL-Placebo/Tac or TacXL/Tac-Placebo started within 12 hours prior to reperfusion. The initial post-operative dose of TacXL-Placebo/Tac or TacXL/Tac-Placebo was not to be administered less than 4 hours after the pre-operative dose or more than 12 hours after reperfusion.

Recipients of a living donor organ could receive pre-dosing with TacXL/TacXL-Placebo or
Tac/Tac-Placebo provided the dosing was not more than 72 hours prior to reperfusion and the dose did not exceed 0.2 mg/kg/day.

TacXL/TacXL-Placebo was always administered together with tac/tac-Placebo every morning, whereas the evening dose of tac/tac-Placebo was given without the corresponding TacXL-Placebo dose. Study drug was given in a blinded manner, according to the randomized treatment assignment for at least the first 24 weeks of treatment.

> *Reviewer's Comment: The total pill burden was the same across treatment groups, which is important for maintaining the study blind but would not allow one to assess the effect of the number of daily doses on compliance. Since the study did not use induction immunosuppression with antibody preparations, it is acceptable to allow predosing in individuals recipients of living donor organ.*

Initial TacXL/TacXL-Placebo and Tac/Tac-Placebo Dosing

The pre-operative dose of *TacXL* / *TacXL* -Placebo was 0.1 mg/kg given orally in one dose, at any time of the day. The initial post-operative *TacXL* / *TacXL* -Placebo dose was 0.2 mg/kg/day given orally in one dose, preferably in the morning. In case the initial dose had to be administered in the evening, the dose might have been reduced to 0.1 mg/kg. All subsequent doses were taken once daily in the morning only.

The pre-operative dose of *Tac*/ *Tac*-Placebo was 0.1 mg/kg given orally in one dose, at any time of the day. The initial post-operative *Tac*/ *Tac*-Placebo dose was 0.2 mg/kg/day given orally in two equal doses, starting in the morning or in the evening.

All subsequent doses were taken twice daily, once in the morning and once in the evening.

Patients unable to swallow capsules at the time of the first dose could be administered study drug via nasogastric tube.

> *Reviewer's Comment: This practice was expected to be needed rarely and was allowed only for the first dose; however, there is uncertainty as to whether the fill of the extended release capsules would retain its extended release pharmacokinetics when administered via a nasogastric tube.*

Tacrolimus Dose Modification

The investigator was able to adjust subsequent doses of TacXL/TacXL-Placebo and Tac/Tac-Placebo on the basis of clinical evidence of efficacy, occurrence of adverse events and according to whole blood tacrolimus trough concentration measurements using a microparticle enzyme immunoassay (IMx)®, Enzyme-Multiplied Immunoassay Technique (EMIT®) or Liquid Chromatography/Mass Spectrometry/Mass Spectrometry (LC/MS/MS).

The following trough concentration ranges were recommended:

- from transplantation to Day 28: 10 to 15 ng/mL
- from Day 29 to Day 168: 5 to 15 ng/mL
- Thereafter 5 to 10 ng/mL.

To ensure the double blind, double dummy design of the study, dose adjustments for only TacXL/TacXL-Placebo without adjustment of tac/tac-Placebo, or vice versa, or temporary discontinuation of only one of these study medications, was prohibited.

Concomitant Immunosuppressive Therapy

Corticosteroids - An intravenous (i.v.) bolus of up to 1000 mg methylprednisolone (or equivalent) was given perioperatively (Day 0) with a second i.v. bolus of 125 mg being administered 1 day after reperfusion (Day 1). Thereafter oral prednisone (or equivalent) was administered on: Days 2 to 14, 20 mg/day; Days 15 to 28, 15 mg/day; Days 29 to 42, 10 mg/day; Days 43 to 84, 5 mg/day; thereafter, 0 to 5 mg/day.

Steroid withdrawal was confined to patients showing good kidney function (serum creatinine < 200 µmol/L), adequate tacrolimus exposure (within the protocol target ranges), absence of signs and symptoms of acute or chronic rejection and not at risk of recurrence of an autoimmune disease (systemic lupus erythematosus, Goodpasture's disease, scleroderma, panarteritis nodosa).

Mycophenolate Mofetil - The initial dose of mycophenolate mofetil (MMF, Cellcept®) was 2 g/day (split into two doses) starting pre-operatively and given for the first 14 days of the study. Thereafter the MMF dose was reduced to 1 g/day (split into two doses) to be maintained throughout the study.

> *<u>Reviewer's Comment</u>: The chosen regimen for MMF for use with tacrolimus is less than the recommended dose of MMF when administered with cyclosporine, but is similar to others arrived at empirically in combination with tacrolimus. It appears to take into consideration the lack of effect of tacrolimus on enterohepatic recirculation of MPA seen with cyclosporine, meaning that higher mycophenolic acid (MPA) exposures are expected when MMF is administered in combination with tacrolimus compared to cyclosporine. In addition, the proposed MMF regimen also appears to take into consideration that the MPA exposure as measured by AUC to oral dose increases over time, meaning that MMF dosing at 1 g twice a day for 14 days may be considered to represent a loading regimen that allows one to reach steady state levels expected at 1 g per day by the end of week 2.*

Prohibited immunosuppressants - Administration of other immunosuppressants (e.g. azathioprine or sirolimus and analogues, and mycophenolic acid [(MPA; Myfortic®)]) was not permitted, with the exception of antibody rejection therapy for severe (Banff IIB

or III) or corticosteroid resistant rejection episodes. Antibody induction therapy was not allowed.

Treatment of Rejection

First-line therapy for an acute rejection episode was corticosteroids according to local practice. It was suggested to keep methylprednisolone doses between 100 mg to 1000 mg per day.

If a biopsy indicated a severe vascular rejection (Banff IIB or III) antibodies could be given as first-line therapy.

If the rejection episode did not respond to corticosteroids, additional agents such as mono and/ or polyclonal antibodies could be used according to study center's common practice.

> *Reviewer's Comment: These regimens are acceptable and consistent with current practice in the US, meaning that a more profound increase in overall immunosuppression using lytic antilymphocyte antibodies is reserved for the treatment of higher grades of rejection. The increased severity of the rejection is commensurate the increased risks and morbidity resulting from the level of immunosuppression and adverse events associated with the use of these products.*

Prophylactic Antiviral Treatment

Prophylactic antiviral treatment was required for cytomegalovirus (CMV) in cases where a CMV positive donor graft was transplanted into a CMV negative recipient. The treatment consisted of oral ganciclovir or equivalent antiviral therapy.

> *Reviewer's Comment: During the period the study conduct, valganciclovir (Valcyte®) came to replace oral ganciclovir as the drug of choice for CMV prophylaxis in seronegative recipients of kidneys from seropositive donors, and has become the standard of care. In addition, the duration of prophylaxis has evolved towards longer periods after transplantation or prolongation of prophylaxis after early episodes of rejection, needing treatment with intensification of immunosuppression.*

Identity of investigational products

Detailed description of the study treatments, including composition, packaging, labeling, and storage of study drugs, is found in the written protocol (Appendix 15.1.1). For each strength of TacXL and Tac study medication, an identical Placebo medication was provided.

Method of Assigning Subjects to Treatment Groups

Allocation of the patients to treatment was performed in a blinded manner according to a randomization schedule provided by the Astellas Pharma GmbH Data Operations department. The randomization involved 1:1 randomization stratified by center. Each center was allocated a unique sequence of patient numbers. Prior to the first dose of tacrolimus the patient was randomized to treatment and given the lowest available patient number in the respective center.

Blinding

The following controls were employed to maintain the double blind status of the study:

- Placebo capsules identical in size and appearance to each strength of TacXL/Tac were used
- Packaging and labeling for Placebo capsules was identical to that of the respective active study drug
- Adjustment of TacXL/TacXL-Placebo dose without adjusting tac/tac-Placebo dose or vice-versa (or stopping only one of them temporarily) was prohibited due to the double blind, double dummy design
- The TacXL/TacXL-Placebo and Tac/Tac-Placebo total daily dose was always to remain in a 1:1 ratio

The investigator and other personnel involved with the study remained blinded to the treatment randomization until unblinding of the study. The study was unblinded after the clean data were available from the 24-week period (Treatment Period 1) for all patients included in the study. Those patients who were in Treatment Period 2 (between 24 weeks and 12 months) at the time of unblinding were switched to receive open medication and continued with their active medication only, i.e. without placebo.

Patients whose 12-month visit was conducted under blinded conditions were allowed to continue until unblinding (treatment period extension visits) to maintain the opportunity of continuing their TacXL treatment in a long-term extension study.

Sealed emergency envelopes were provided with every set of numbered study medication, containing the identity of the treatment arm to which the patient was allocated.

In case of an emergency, the investigator needed to decide whether to open the envelope and thus break the blinding. Unblinding of a patient was to be reported to the sponsor within 48 hours and the patient needed then to be withdrawn from the study. Date of emergency decoding, together with the reason for decoding and the signature of the person opening the envelope, was recorded on the treatment code sheet.

Note that the protocol indicated that a medical need to switch to another immunosuppressant medication was not considered a reason to unblind a patient.

> *Reviewer's Comment: One of the strengths of the study design is that adequate precautions appear to have been taken to protect the blinding of randomized treatment assignment. This period of protection extends substantially beyond the first 6 months after transplantation, a period where most events and interventions are expected to occur.*

Treatment Adherence

There was no formal analysis of treatment compliance. The number of capsules of returned study drug medication was counted. Tacrolimus whole blood trough concentration measurements were used as a rough guide for assessing patient compliance during the study.

> *Reviewer's Comment: Treatment compliance is adequately addressed in the protocol. The study design does not lend itself to comparative analyses of compliance across treatment groups based on QD versus BID dosing.*

5.3.2.5 Assessments – Endpoints

5.3.2.5.1 Overview of Schedule and Procedures

A patient's participation in the study was to be for a minimum of 12 months. All visits were calculated from the day of transplantation, which was the day of reperfusion and defined as Day 0.

A summary of the planned visits and assessments and their timing in the study is provided in the Applicant's Table 1 copied below as Table 10:

Table 10 Study 12-03 Visits and Assessments

Table 1 Visits and Assessments

	Treatment period 1									Treatment period 2[6]		Treatment period Extension visits[7]
Assessment	Visit 1 Baseline	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11 EOS	every 3 months[5] ± 14 days[5]
Day	0	1	3	7	14 ± 3	28 ± 3	56 ± 3	84 ± 3	168 ± 7	274 ± 14	365 ± 14	
Week[8]				1	2	4	8	12	24			
Month[8]						1	2	3	6	9	12	
Informed consent[1]	x											
Inclusion / exclusion criteria	x											
Randomization and patient number allocation	x											
Surgical details, donor and donor organ data	x											
Primary diagnosis / secondary diagnoses	x											
Medical history / pre-study medication	x											
Physical examination	x					x	x	x	x	x	x	x
Body weight	x	x	x	x	x	x	x	x	x	x	x	x
ECG	x								x		x	
Vital signs	x	x	x	x	x	x	x	x	x	x	x	x
Laboratory assessments	x[2,4]	x	x	x	x	x	x	x	x[4]	x	x [2,4]	x
Tacrolimus whole blood trough levels[3]		x	x	x	x	x	x	x	x	x	x	x
Rejection episodes, adverse events, tacrolimus dose, concomitant medication, days of dialysis, days hospitalized – Continuous assessment												

1. Informed consent was obtained during the waiting period for transplantation; patients might have signed the patient informed consent form after receiving notice that the organ is currently available. Where informed consent was obtained more than 3 months prior to transplantation, it was recommended to obtain a second informed consent.
2. Urine or serum pregnancy test (ß-HCG) in females of childbearing age (Baseline and Visit 11/EOS)
3. Tacrolimus whole blood trough level measurements were performed daily during the first week post-transplant, thereafter three times per week until discharge from hospital and thereafter at all scheduled visits, and as clinically indicated.
4. Including glycosylated haemoglobin, HDL, LDL, triglycerides, cholesterol
5. Until unblinding of the study.
6. An additional unblinding visit for exchanging the study medication should ensue one month at the latest after the investigator has been informed by the sponsor in writing about the unblinding. Assessments as described in Visit 10 can be performed if deemed necessary from a clinical point of view.
7. An additional unblinding visit should ensue one month at the latest after the investigator has been informed by the sponsor in writing about the unblinding. All assessments as described in treatment period Extension visits should be performed.
8. For orientation purposes only

A summary of the planned laboratory assessments and their timing in the study is provided in the Applicant's Table 2 copied below as Table 11:

Table 11 Study 12-03 Laboratory Assessment Schedule

Table 2 Laboratory Assessment Schedule

	Treatment period 1									Treatment period 2		Treatment period Extension visits
Value	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	every 3 months ± 14 days
Day	0	1	3	7	14 ± 3	28 ± 3	56 ± 3	84 ± 3	168 ± 7	274 ± 14	365 ± 14	
Week				1	2	4	8	12	24			
Month						1	2	3	6	9	12	
Urine or serum pregnancy test	x										x	
Haematology: - Red blood cells - Haemoglobin - Hematocrit - White blood cells - Platelets	x	x	x	x	x	x	x	x	x	x	x	x
Biochemistry: - Sodium - Potassium - Glucose[1] - Serum creatinine[1] -Aspartate aminotransferase (AST) / Serum glutamyl oxaloacetic transaminase (SGOT) - Alanine aminotransferase (ALT) / Serum glutamyl pyruvate transaminase (SGPT) - Gamma glutamyl transferase (γ-GT) - Alkaline phosphatase - Total bilirubin - Albumin	x	x	x	x	x	x	x	x	x	x	x	x
- Glycosylated haemoglobin - High density lipoprotein (HDL) - Low density Lipoprotein (LDL) - Cholesterol - Triglyceride	x								x		x	

5.3.2.5.2 Efficacy Assessment

The stated primary efficacy variable in the written protocol was event rate of patients with biopsy-proven acute rejection (local assessment) within the first 24 weeks following transplantation.

> *Reviewer's Comment: FDA analyses will focus on biopsy-proven rejection, death, graft loss, or loss to follow-up, meaning that death, graft loss and loss to follow-up are not to be considered as successes when evaluating the acute rejection endpoint. (See Section 6.1.4.2 of this review)*

Diagnosis and Grading of Rejection Episodes

A biopsy was to be performed if clinical and/or laboratory signs indicated the occurrence of a rejection episode, a kidney. The biopsy was to be performed prior to the initiation of any anti-rejection therapy and as soon as possible after the onset of clinical/laboratory signs indicative of possible rejection. The histological evaluation of the biopsy was performed by the local histopathologist following the Banff 97 Working Classification of Renal Allograft Pathology[12]. The slides were stored locally for subsequent central evaluation.

An independent central biopsy review for assessment of acute rejection was performed in order to confirm the results of the local biopsy assessments. It is noted that the central review was not necessarily performed on the same section of the biopsy as the local assessment, which may introduce some variability and potential for sampling error in the assessment of focal biologic phenomena.

The protocol specified two scenarios for processing of the central biopsy review data which were to be followed in order to account for potentially missing biopsies, not evaluable biopsies and biopsies taken for reasons other than to confirm or reject the clinical diagnosis of acute rejection (e.g. surveillance, site-specific protocol or intra-operative biopsies):

- Scenario A:
  - Only biopsies associated with an acute rejection episode by signs and symptoms reviewed.
  - If a biopsy was 'not available' or 'not evaluable', then the result was recorded as 'missing' (no imputation).
- Scenario B (primary analysis for central review data):
  - All available biopsies reviewed.
  - If a biopsy was 'not available', then no central review could be performed and the local biopsy result was imputed.

[12] Racusen LC, Solez K, Colvin RB, et al. The Banff 97 working classification of renal allograft pathology. Kidney Int, 1999; 55: 713–723

If a central review was performed; however, no result was given (e.g. due to insufficient material) then this was 'not evaluable' and the result was recorded as 'missing' (no imputation).

> *Reviewer's Comment: It is noted that the central review was not necessarily performed on the same section of the biopsy as the local assessment. A difference in sections is a potential source of variation between the central and local assessments of rejection. Furthermore, to the extent that local biopsies are used to make immediate local treatment decisions these may be read more conservatively to avoid missing treatable rejection. Thus, for the purpose of assessment of efficacy the local reading is what will be considered part of the primary endpoint in this review, all the more that it is the one that dictates treatment with a direct clinical effect on the patient.*

Classification of Acute Rejection Episodes

The protocol provides for classification of acute rejection episodes into one of the following categories for protocol-defined endpoints:

- Spontaneously-Resolving Acute Rejection.
- Corticosteroid-Sensitive Acute Rejection.
- Corticosteroid-Resistant Acute Rejection.
- Other Acute Rejection.

The time to the first acute rejection episode was defined as the number of days from reperfusion to the first clinical, laboratory or histological signs that were considered to be related to the first acute rejection episode. The acute rejection was considered to have resolved when the laboratory or clinical signs indicated that no further rejection treatment was necessary and graft function had stabilized.

> *Reviewer's Comment: Repeat biopsy was not systematically required after treatment of rejection episodes.*

Graft Loss

Graft loss was defined as re-transplantation, nephrectomy or death, or as dialysis ongoing at study end or withdrawal of the patient from the study unless superseded by follow-up information. The date of graft loss was the earliest date of any of these events. In case of dialysis the date of graft loss was the first day of the last dialysis period reported.

> *Reviewer's Comment: The proposed definition of graft loss is acceptable.*

5.3.2.5.3 Safety Assessment

Adverse Events

The protocol defined adverse events as: “Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product.”

Reviewer’s Comment: The definition used in this study is acceptable.

A severity rating (mild, moderate, or severe) and a causality rating (highly probable, probable, possible, unlikely, definitely not, or not assessable) to study medication were assigned for each event by the investigators.

Serious Adverse Events

According to the study protocol, a serious adverse event was defined as any adverse event that at any dose:

- Resulted in death.
- Was life-threatening.
- Required patient hospitalization or prolongation of existing hospitalization.
- Resulted in persistent or significant disability/incapacity.
- Resulted in a congenital anomaly/birth defect.
- Required intervention to prevent one of the above.

Additionally manifested signs and symptoms caused by overdose and reports of cancer were to be handled in the same manner as serious adverse events.

Hospitalization was not assessed as a serious adverse event if hospitalization:

- Occurred due to protocol related procedures (e.g. blood collection for PK profiles).
- Occurred due to routine procedures (e.g. T-tube removal).

Furthermore, hospitalizations occurring under the following circumstances were not considered as serious adverse events:

- Hospitalizations that were planned before study entry or occurred without being scheduled before study entry for a pre-existing, non-worsening condition.
- Situations not fulfilling the criterion of untoward medical occurrence (e.g. hospitalizations for cosmetic elective surgery, social and/or convenience admissions).

Serious adverse events were to be reported to the sponsor within 24 hours.

Reviewer's Comment: The proposed definition of serious adverse events is acceptable.

Vital Signs

Heart rate and blood pressure were assessed at each visit after 5 minutes of rest according to local hospital routine.

Electrocardiograms

12-lead ECGs were performed at Visit 1, Visit 9 and Visit 11/EOS according to local hospital routine.

Physical Examinations

A physical examination was performed at all scheduled visits except visits 2 through 5 (days 1, 3, 7, and 14).

Body Weight

Body weight was measured at all visits.
Laboratory Evaluations

The following routine laboratory assessments were performed at each visit by the local laboratory. Additional values for glucose and serum creatinine may have been recorded in the eCRF if assessed for medical reasons.

Hematology: red blood cells, hemoglobin, hematocrit, white blood cells, platelets.

Biochemistry: sodium, potassium, glucose, serum creatinine, AST/SGOT, ALT/SGPT, γ-GT, alkaline phosphatase, total bilirubin, albumin, glycosylated hemoglobin*, LDL*, HDL*, cholesterol*, triglycerides* (* Visits 1, 9 and 11/EOS only).

A urine or serum pregnancy test (beta human choriongonadotropin [β-HCG]) was performed in females of childbearing potential at Visit 1 and at Visit 11/EOS.

Reviewer's Comment: These planned assessments are acceptable. In particular, assessment of fasting glucose and glycosylated hemoglobin, needed to monitor for new onset of diabetes after transplantation (NODAT), a potential hazard of tacrolimus use are appropriately included.

5.3.2.5.4 Schedule and Methods for Drug Concentration Measurements

Whole Blood Tacrolimus Trough Concentrations

Whole blood tacrolimus trough levels were routinely monitored using IMX, EMIT, or LC/MS/MS in the local laboratories. Blood samples were drawn in the morning before administration of study drug according to the visits and assessments (i.e., daily during the first week post-transplant; thereafter, three times per week until discharge from hospital and thereafter at all scheduled visits and as clinically indicated).

> *Reviewer's Comment: The protocol-specified schedule for monitoring whole blood tacrolimus trough concentrations is acceptable; however, it is noted that no specific provisions were included for measurement of "for cause" tacrolimus concentrations in the setting of episodes of rejection or the occurrence of an adverse event. This may represent a limitation in performing exploratory exposure/response analyses.*

Pharmacokinetic Assessments

Pharmacokinetic assessments were performed as part of a pharmacokinetic substudy (Protocol Amendment 1). Results from this substudy are presented in Report FG-506E-12-03-R-PK.

> *Reviewer's Comment: This will be addressed in the FDA Clinical Pharmacology Review. Portions of the information obtained from this report were reviewed during a previous NDA review cycle.*

5.3.2.6 Statistical Issues

5.3.2.6.1 Planned Sample Size

The planned sample size was based on the primary objective which was to compare the efficacy of both treatment groups during the first 24 weeks following kidney transplantation. The primary endpoint was the event rate of patients with biopsy-proven acute rejection within this time period. The comparison of both treatment groups was performed by testing for non-inferiority. The level of significance was 2.5% for the one-sided test, confidence intervals were displayed two-sided at the 95% level. Based on an estimated event rate of biopsy-proven acute rejection of 20% and the Applicant's assumption that a difference in event rate of 10% between both treatment groups would be considered a clinically meaningful margin for non-inferiority, and on a 1:1 randomization, the Applicant concluded that a total of 504 patients (252 per treatment arm) would be needed to reach a power of 80%.

In order to account for an anticipated rate of about 16% to be excluded from the per protocol set, a total of 600 patients (300 patients per treatment arm) were planned to be randomized. This was subsequently increased to a total of 680 patients (340 patients

per treatment arm) by Protocol Amendment 3 in order to ensure a complete number of evaluable patients in the pharmacokinetic substudy.

> *Reviewer's Comment: The protocol was adequately powered to detect a clinically meaningful difference in rates of the proposed primary endpoint. For discussion on the adequacy of the justification for the proposed non-inferiority margin, please see the FDA Statistical Review in DARRTS.*

5.3.2.6.2 Populations for Analysis

Four populations were prospectively identified for analysis:

Four populations were identified for analysis:

- Modified Full Analysis Set

The modified Full Analysis Set includes all randomized patients who received at least one dose of study medication (i.e. all patients from the extended Full Analysis Set and all patients randomized after the cut-off date who received at least one dose of study medication).

- Extended Full Analysis Set

The extended Full Analysis Set includes all randomized patients randomized until the cutoff date for the pharmacokinetic substudy (Protocol Amendment 3) who received at least one dose of study medication (MR4 or FK506).

- Full Analysis Set

The Full Analysis Set includes all patients of the extended Full Analysis Set who were actually transplanted.

This was an expansion of the specification in the protocol. The extended Full Analysis Set corresponds to the original Full Analysis Set in the protocol, whereas the new definition of the Full Analysis Set is now restricted to the actually transplanted patients from the extended Full Analysis Set. This expansion was introduced as the administration of study drug before transplantation (pre-dosing for living donation and possible pre-operative dosing on the day before the transplantation) may have resulted in treated but not transplanted patients who contributed to safety but not to efficacy endpoints.

5.3.2.6.3 Statistical Methodology

The data presented in this report were generated according to the Inferential Analysis Plan (IAP) dated 25 July 2005 and the amended IAP (dated 28 July 2006), included in Appendix 15.2 of the Study Report.

> *Reviewer's Comment: Please see the FDA Statistical Review in DARRTS for a more detailed discussion of the planned statistical methodology, including the timing of the IAP and its amendments with respect to initiation and completion of the study, as well as unblinding of the treatment assignment and other data.*

Time definitions

Days used for analysis were relative to the date of reperfusion (Day 0), which was considered to be the day of transplantation. Randomization occurred immediately prior to administration of the first dose of study medication, which should have started within 12 hours prior to reperfusion, and up to 72 hours prior to reperfusion for recipients of a living donor organ.

Analysis of medication, rejections, graft survival, patient survival, adverse events, and hospitalization were based on dates and days relative to Day 0. Time-to-event analysis was performed on a day basis. The analysis of laboratory data and vital signs was visit based.

"End of study" (EOS) was defined in the protocol as Visit 11 (Month 12). 'End of study', with regard to a considered analysis period, was the day of the latest visit (any completer) or assessment (any withdrawn patient; excluding follow-up assessments) performed for the respective period - over all patients. In the tables and listings, EOS still denotes 'End of study' = 'End of Treatment Period 2' (Month 12), whereas EOS-24W denotes 'End of study – 24-week period' = 'End of Treatment Period 1', and EOS-EP denotes 'End of study – extension period'.

"End of treatment" (EOT), with regard to a considered analysis period, was the day of the last intake of study medication prior to or at the day of the latest visit (completers) or assessment (withdrawn patients; excluding follow-up assessments) performed for a patient for the respective period.

"Analysis period assessment" was the day of the last visit or evaluation performed for a patient for the considered analysis period. 'Week 24 assessment' and 'Month 12 assessment' denotes the respective analysis periods. For patients completing the respective period, this was either the day of the last visit performed for this period, or the day of any blood sample taken at this visit, whichever was the latest. For patients who discontinued prematurely, this was the day of the respective follow-up visit or, where no follow-up visit was done, the day of the latest visit or evaluation for this period.

The following event and censor times were used for the Kaplan-Meier analyses of the corresponding endpoints:

Table 12 Study 12-03 Event and Censor Times

Parameter	Event Time	Censor Time
Patient survival	Day of death	'Analysis period assessment'
Graft survival	Day of graft loss	'Analysis period assessment'
Rejection	Onset of first rejection	'End of treatment'

Additional provisions for estimation of partial dates suing the worst case scenario were also provided.

> *Reviewer's Comment: The prospectively defined time definitions are acceptable. The timing of randomization as close as possible to the administration of the first dose of study medication is a desirable feature.*

Efficacy Endpoints

Biopsy Proven Acute Rejections
An acute rejection was considered to be biopsy-proven if it was associated with a positive biopsy finding (Banff grade I, II or III). Only the results from biopsies performed during the treatment phase + 1 day were considered in order to assess whether an acute rejection which started during the treatment phase was biopsy-proven or not.

The Applicant proposed to calculate the two-sided 95% confidence intervals for the estimated survival rates at 24 weeks or 12 months for each treatment group and their difference using the normal approximation with the standard error calculated according to Greenwood's formula.

Differences between treatment groups were assessed using the Wilcoxon Gehan test.

The primary endpoint of the study was the event rate of patients with biopsy-proven acute rejection within the first 24 weeks following transplantation. Kaplan-Meier methods were used to analyze the primary endpoint. The event rate of patients with biopsy-proven acute rejections at 24 weeks was calculated as (1 – the survival function at 24 weeks).

As specified by the Applicant, the comparison of both treatment groups was done by testing for non-inferiority. The non-inferiority test was performed by means of confidence intervals for the difference in these event rates between the treatment arms, i.e. for MR4 – FK506. The confidence intervals were displayed two-sided at the 95% level, i.e. the level of significance was 2.5% for the one-sided test. If the two-sided 95% confidence

interval for the difference lies entirely below 10%, non-inferiority was shown for the respective comparison.

> *Reviewer's Comment: No substantial justification of the prospectively proposed non-inferiority margin is provided in the study report, other than a difference in biopsy-proven acute rejection rate greater than 10% at 24 months after transplantation would be clinically meaningful. This margin in the study's original statistical analysis plan 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).*
>
> *Documentation from the Applicant to support the non-inferiority margin of 10% for Study 1203, with respect to the endpoint of efficacy failure at 12 months (defined as BPAR, graft loss, or death) is provided in Attachment 3 of the Summary of Clinical Efficacy. Please see Section 3.2 of the FDA Statistical Review in DARRTS for further details and discussion of the non-inferiority margin. The FDA Statistical Review arrives at an estimate of 28% for the effect of Prograf over placebo, which is considered an estimate of M1. The non-inferiority margin should be equal to or less than M1. A 50% retention of the Prograf effect over placebo would result in a margin of 14%. Thus, the post hoc justification of an NI margin of 10% for the 12-month endpoint is acceptable, for the purpose of evaluating the efficacy of TacXL in the prevention of rejection in Study 12-03.*

Proposed statistical analyses of the secondary efficacy endpoints were prospectively described by the Applicant. As described earlier in this review, secondary efficacy endpoints were the event rate of patients with biopsy-proven acute rejections within the first 12 months following transplantation, the incidence of and time to acute rejections and biopsy-proven acute rejections as well as corticosteroid resistant acute rejections and biopsy-proven corticosteroid resistant acute rejections within the first 24 weeks and 12 months following transplantation. Kaplan-Meier estimates and confidence intervals for the treatments and their difference were calculated. Treatments were further compared using the Wilcoxon Gehan test.

The overall frequency of acute rejections and of biopsy-proven acute rejections and their respective main clinical categories within the first 24 weeks and within 12 months following transplantation as well as the severity of biopsy-proven acute rejection were further secondary efficacy endpoints. These endpoints were assessed descriptively by chi-square- or Fisher's exact test. To assess the consistency of the results, Cochran-Mantel-Haenszel test adjusted for center was applied in addition.

The Applicant further specifies that any comparison of secondary endpoints was explorative.

Patient and Graft Survival

Graft loss was defined as re-transplantation, nephrectomy, death, or as dialysis ongoing at study end or at withdrawal of the patient from the study unless superseded by follow-up information. The date of graft loss was the earliest date of any of these events.

Patient and graft survival were analyzed using Kaplan Meier procedures.

The two-sided 95% confidence intervals for the estimated rates of patients alive and patients free from graft failure at 24 weeks and 12 months were calculated for each treatment group and their difference using Greenwood's formula. Furthermore, the Wilcoxon-Gehan test was used to test for a difference between treatment groups in cumulative patient and graft survival rates over time.

Frequency tables of deaths and of graft losses by treatment arm are provided. Reasons for deaths and graft losses were classified during a blinded data review.

Efficacy Failure

Efficacy failure, defined as any patient who had a biopsy-proven acute rejection, graft loss, death or whose outcome at the end of the considered analysis period was unknown, was analyzed using Kaplan-Meier procedures and providing frequency tables.

> *<u>Reviewer's Comment</u>: The definitions of the proposed primary and secondary efficacy endpoints appear to be lacking as to how missing data due to loss to follow-up would be handled in the proposed analyses. Over a period or 24 weeks and even 12 months, the expectation is that there would be very little or no loss to follow-up with respect to patient and graft survival; however, assessment of acute rejection status after loss-to-follow-up remains problematic. In the FDA analyses missing data with respect to rejection endpoints for any reason including loss-to-follow-up will be considered as failures. Note that in the Pre-NDA meeting with the Applicant, FDA requested a 12-month analysis of efficacy failure (defined as BPAR, graft loss, death or loss-to-follow-up), even though the analysis had not been pre-specified.*

Renal Function

The Applicant has prospectively described how renal function was analyzed.

Renal function was assessed through analysis of serum creatinine, creatinine clearance, long-term dialysis, delayed graft function, and never functioning graft.

Long-term dialysis was defined as return to maintenance (permanent) dialysis at any time point during the study. Maintenance dialysis was defined as dialysis episode ongoing within the first 24 weeks and 12 months following transplantation, or as ongoing

at retransplantation, at nephrectomy, or at death. The start date of long-term dialysis was defined as the onset date of the earliest maintenance dialysis episode. Number of patients and duration of dialysis was also analyzed by time period.

Prior to counting the days of dialysis dependence, individual dialysis episodes were combined to one episode if they were up to 5 days apart. An episode of dialysis occurring more than 5 dialysis-free days after the last dialysis was considered as a new episode.

Delayed graft function was defined as the patient having dialysis for more than 1 day within the first 7 days post-transplantation (Day 0 to Day 7). A never functioning graft was defined as a graft which displayed no function as of the moment of reperfusion and whose recipient had been on dialysis ever since.

> *Reviewer's Comment: These prospectively proposed definitions and methods for counting days on dialysis are acceptable. It is noted that no prospective definition for slow graft function was intended to be used in this study.*

Renal function was assessed by values of serum creatinine. Values of serum creatinine were summarized based on both one value per patient on selected days and on mean values per patient during time periods. Additionally, the last visit during the considered analysis period (Visit 9 for the 24-week analysis) was analyzed for completers only.

Creatinine clearance was calculated using the Cockcroft-Gault formula or MDRD formula and was summarized as for serum creatinine.

Additionally, serum creatinine and creatinine clearance were analyzed by displaying number and percent of patients meeting the following threshold criteria at each time point:

Serum Creatinine <1.5, 1.5 to 2.0, >2.0 mg/dL
Creatinine Clearance <40, 40 to 75, >75 mL/min

The percentage of patients with creatinine clearance values <40 mL/min at the end of the considered analysis period were compared between treatment groups using a Cochran-Mantel-Haenszel test stratified by center and donor type.

Reviewer's Comment: Additional analyses of renal function variables will be discussed in the review of the study results further below.

Safety

Adverse Events

Adverse events were coded using the MedDRA dictionary, version 6.1. Events were summarized per treatment group, grouped by their primary system organ class, high level term and preferred term.

An overall adverse event summary displays number of events and patient counts and percentages for any adverse event, serious, causally related and serious-causally related adverse events.

Causally related adverse events are prospectively defined to be those having a highly probable, probable, possible, not assessable or missing relationship to treatment assessed by the investigator.

The incidence of adverse events during the analysis period (based on patients, not events) was compared between treatments using descriptive p-values of Fisher's exact test.

Only treatment emergent adverse events are included in the summaries. Adverse events were defined to be treatment emergent if the start date was between the first intake of study medication (Tac XL or Tac) and the last intake of study medication + 7 days. For the 24- week analyses, only adverse events with a documented or estimated start date before or at the day of the 24- week assessment were included for analysis.

> *Reviewer's Comment: For most adverse events with a readily identifiable start date, the use of the last intake of Tac XL or Tac plus seven days is acceptable, given the pharmacokinetic half-life of tacrolimus; however, such a cut-off may be a little short for adverse events with a more insidious time of onset including some infections or malignancies.*

Since events of acute transplant rejection are the primary efficacy endpoint in this study, events coded as MedDRA preferred term "Kidney transplant rejection" or "Transplant rejection" do not appear in the adverse event tables, but are included in the by patient listings.

Clinical Laboratory Data

Analyses of laboratory results are based on the visits rather than the actual days and were summarized using descriptive statistics. The last visit in the considered analysis period were analyzed for all patients and for completers only.

Changes from Planned Analyses

Based on the results of analyses planned in the statistical analysis plan, additional exploratory analyses were performed to examine:

- Effect of HLA DR mismatch on efficacy

- Effect of early exposure to tacrolimus on local biopsy-confirmed acute rejection
- Effect of early exposure to tacrolimus on viral infection
- Incidence of polyoma virus infection.

Reviewer's Comment: The efficacy and safety results from Study 12-03 will be discussed in detail in Sections 6 and 7 of this review, respectively.

6 Review of Efficacy

Efficacy Summary

TacXL is an extended release oral formulation of Prograf (tacrolimus), the immediate release oral formulation, which is approved for the prophylaxis of organ rejection in patients receiving allogeneic kidney transplants. TacXL taken once daily is intended to provide tacrolimus exposure and immunosuppression comparable to that delivered with Prograf taken twice daily, resulting in comparable protection against rejection, without clinically significant differences in the safety profile of tacrolimus. The efficacy of TacXL in the prevention of rejection in recipients of kidney transplantation is based on comparison of the pharmacokinetics of TacXL to those of Prograf, as well as on comparable efficacy, as demonstrated by non-inferiority compared to cyclosporine (Study 158) or to Prograf (Study 12-03) with respect to rate of efficacy failure at 12 months, defined as BPAR, graft loss, death or loss to follow-up, in two Phase 3 clinical trials. The first clinical trial, Study 158, evaluated TacXL in combination with induction immunosuppression using basiliximab (an IL-2 Receptor alpha-chain or CD25 blocker) and maintenance immunosuppression in combination with MMF and corticosteroids. The second trial, Study 12-03 evaluated TacXL compared to Prograf, without antibody induction immunosuppression, in combination with MMF and corticosteroids. MMF dosing was different in the two clinical studies, but is representative of the spectrum of MMF use with tacrolimus in the prevention of rejection in kidney transplantation in the US. While the optimal combination of tacrolimus/MMF may need to be individualized based on tolerance, degree of immunologic risk, and/or allograft rejection status, the regimens evaluated in Studies 158 and 12-03, with or without antibody induction provide information on efficacy and safety that may be used in making individual treatment decisions.

A putative advantage of once daily dosing compared to twice daily dosing with tacrolimus is the potential to enhance adherence to the immunosuppressive regimen; however, no evidence from adequate well controlled clinical trials is included in this submission to support such a clinical efficacy claim for TacXL.

Study 158 was largely a US study (80% of the subjects were from the US) while Study 12-03 was a multinational study conducted outside the US; however, the development

of immunosuppressants for the prevention of rejection in kidney transplantation is historically a global endeavor, and Study 12-03 provides a valuable confirmation of the adequate protection of efficacy demonstrated in Study 158, balance by an acceptable safety profile.

The open-label design of Study 158 represents a limitation with respect to protection of the clinical study from the potential for bias. Study 12-03 was double-blind until the last subject had completed 24 weeks, which represents a strength of that study. The overall, completeness of the assessment of the 12-month primary endpoints in both studies represents a particular strength with respect to the evaluation of efficacy. Availability of efficacy information on dosing of TacXL with or without the use of basiliximab induction immunosuppression is also considered a strength of this application.

No conclusions can be made with respect to the comparative efficacy of TacXL compared to cyclosporine, or to the use of other approved immunosuppressants approved for the prophylaxis of rejection in recipients of kidney transplantation, other than that TacXL provided protection against rejection comparable to cyclosporine when used with basiliximab, MMF and corticosteroids.

6.1 Indication – Prevention of Rejection in Kidney Transplantation

6.1.1 Methods

The primary phase 3 study submitted by the Applicant in NDA 50-811 and resubmitted in NDA 204096 was Study 02-0-158, a large phase 3 study in de novo kidney transplantation comparing 3 treatment arms: Tac+MMF, TacXL+MMF, and cyclosporine (Neoral+ MMF (the putative active control). The primary indications sought by the Applicant under NDA 50-811 in 2007 had been for the use of TacXL in the prophylaxis of organ rejection in kidney transplantation and the concomitant use of tacrolimus (as immediate-release or extended-release capsules) with mycophenolate mofetil (MMF). Since the Applicant had submitted comparative clinical pharmacology data that would support the efficacy of TacXL, the primary focus of the review of Study 02-0-158 under NDA 50-811 was to evaluate the use of tacrolimus with MMF and compare the safety profiles of TacXL and Tac. Subsequent approval of MMF use with tacrolimus, led to labeling that described the use of tacrolimus with MMF in Study 02-0-158, without mention of TacXL+MMF.

This Review of Efficacy will address the efficacy of TacXL when used with MMF. Study 158 was open-label and used antibody induction with basiliximab, and MMF dosing of 2 g/day. Study 12-03 did not use antibody induction, was double blind and used MMF dosing of 2 g/day for 14 days reduced to 1 g/day thereafter.

To the extent that Study 158 has already been reviewed in 2007 under NDA 50-811, this section will refer to Statistical and Clinical Reviews of that NDA, when presenting the results of Study 158 in this section of the current review, as well as to the FDA Statistical Review of this NDA (NDA 204096). The sections below will not pool the information from both studies but will present them side by side or in separate paragraphs as needed. More details are provided for Study 12-03 as this study has not been previously reviewed, while a more detailed review of Study 158 is included in the review of NDA 50-811.

6.1.2 Demographics

Demographics for Study 158

A summary of patient demographics is presented for Study 158 in the table below:

Table 13 Study 158 Patient Demographics [1]

	Tac-XL (n=214)	Tac (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%
	44%	52%	51%

1 2	31%	35%	25%

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

Demographics for Study 12-03

A summary of recipient demographics and viral status at baseline is presented for Study 12-03 in the table below:

Table 14: Study 12-03 Summary of Patient Demographics and Viral Status

Per Protocol Set			
	Tac (N=291)	**TacXL (N=280)**	**p-value**
Male Female	189 (64.9) 102 (35.1)	174 (62.1) 106 (37.9)	0.486†
Age (years)* Weight (kg)*	45.2 (12.0) 70.5 (13.5)	44.6 (11.9) 70.1 (16.1)	0.547‡ 0.713‡
Caucasian Black Asian Other	234 (80.4) 18 (6.2) 5 (1.7) 34 (11.7)	233 (83.2) 11 (3.9) 5 (1.8) 31 (11.1)	0.663§
Viral status at baseline: CMV negative HBV positive HCV positive EBV negative	 73 (25.3) 8 (2.8) 10 (3.4) 23 (10.5)	 87 (31.2) 5 (1.8) 15 (5.4) 34 (15.1)	 0.123† 0.440† 0.266† 0.142†
Full Analysis Set			
	FK506 (N=336)	**MR4 (N=331)**	**p-value**
Male Female	215 (64.0) 121 (36.0)	204 (61.6) 127 (38.4)	0.529†
Age (years)* Weight (kg)*	45.5 (12.0) 70.3 (13.3)	44.9 (12.1) 70.4 (15.8)	0.489‡ 0.939‡
Caucasian Black Asian Other	273 (81.3) 19 (5.7) 7 (2.1) 37 (11.0)	277 (83.7) 14 (4.2) 5 (1.5) 35 (10.6)	0.768†
Viral status at baseline: CMV negative HBV positive HCV positive EBV negative	 88 (26.4) 10 (3.0) 14 (4.2) 27 (10.6)	 107 (32.4) 5 (1.5) 16 (4.8) 34 (12.9)	 0.090† 0.202† 0.684† 0.418†

Patients (%)

† Chi-square test (excluding not recorded/not done); ‡ Student's t-test; § Fisher's exact test;
* Mean (SD)
CMV = cytomegalovirus; EBV = Epstein-Barr virus; HBV = hepatitis B virus; HLA = human leucocyte antigen; HCV = hepatitis C virus
Source: Applicant's Study Report Table 3 and Post Text Tables 13.2.1.1, 13.2.1.3, 13.2.2.1, and 13.2.2.3

Although there were numerically more patients in the TacXL treatment group who were CMV negative at baseline, there were not statistically significant differences between treatment groups with respect to cytomegalovirus (CMV), hepatitis B (HBV), hepatitis C (HCV), or Epstein-Barr virus (EBV) status at baseline. Treatment groups were comparable with respect to patient demographics and viral status at baseline.

> *Reviewer's Comment: As study 12-03 was conducted outside the US, the racial distribution of the study subjects is not representative of the US renal transplant recipients. The absence of Hispanic Americans as well as of African Americans, a population at increased risk for post-transplant diabetes mellitus, a known hazard associated with the use of tacrolimus in renal transplantation, should be considered when interpreting measures of new onset diabetes after transplantation (NODAT) in the safety review of this study.*

The most common primary diagnoses were glomerulonephritis (37.5% TacXL, 29.2% Tac), unknown cause (11.4% TacXL, 15.5% Tac), polycystic disease (10.7% TacXL, 16.2% Tac),nephrosclerosis (10.0% TacXL, 11.7% Tac) and diabetic nephropathy (6.2% Tac, 7.5% TacXL) with no relevant differences between the treatment groups in the pattern of primary diagnoses (Source: Applicant's Study Report Post Text Table 13.2.1.4).

> *Reviewer's Comment: Diabetes mellitus and hypertension and are leading causes of end-stage kidney disease in the US, leading to neprhosclerosis, particularly in African American and Hispanic patients.*

A summary of donor demographics and viral status for Study 12-03 is presented in the table below.

Table 15: Study 12-03 Summary of Donor Demographics and Viral Status

Per Protocol Set			
	Tac (N=291)	**TacXL (N=280)**	**p-value**
Male Female	169 (58.1) 122 (41.9)	160 (57.1) 120 (42.9)	0.822†
Age (years)*	44.6 (14.1)	44.1 (13.7)	0.673‡

Viral status at baseline: CMV negative HBV positive HCV positive EBV negative	 93 (33.7) 4 (1.4) 3 (1.0) 32 (24.6)	 86 (32.2) 3 (1.1) 4 (1.4) 34 (25.0)	 0.713† 1.000§ 0.720§ 0.942†
Full Analysis Set			
	Tac (N=336)	**TacXL (N=331)**	**p-value**
Male Female	194 (57.7) 142 (42.3)	193 (58.3) 138 (41.7)	0.881†
Age (years)*	44.6 (14.0)	44.5 (13.8)	0.888‡
Viral status at baseline: CMV negative HBV positive HCV positive EBV negative	 111 (34.9) 6 (1.8) 3 (0.9) 35 (24.0)	 106 (33.4) 3 (0.9) 4 (1.2) 37 (24.2)	 0.697† 0.505§ 0.724§ 0.966†

Patients (%)
† Chi-square test (excluding not recorded/not done); ‡ Student's t-test; § Fisher's exact test;
* Mean (SD)
CMV = cytomegalovirus; EBV = Epstein-Barr virus; HBV = hepatitis B virus; HLA = human leucocyte antigen; HCV = hepatitis C virus
Source: Applicant's Study Report Table 6 and Post Text Tables 13.2.1.7, 13.2.1.8, 13.2.2.7, and 13.2.2.8

A summary of donor/recipient mismatch and donor organ characteristics is presented for Study 12-03 in the table below.

Table 16: Study 12-03 Summary of Donor/Recipient Mismatch and Donor Organ Characteristics

Per Protocol Set			
	Tac (N=291)	**TacXL (N=280)**	**p-value**
AB0 mismatch: dentical Compatible	 268 (92.1) 23 (7.9)	 266 (95.0) 14 (5.0)	 0.159†
HLA type mismatch: Mean A Mean B Mean DR§	 0.9 1.2 0.8	 1.0 1.1 0.9	 0.866‡ 0.164‡ 0.017‡
CMV status (recipient/donor) Negative/Positive	 36 (13.2)	 45 (16.9)	0.513†
Donor type: Living Cadaveric	 85 (29.2) 206 (70.8)	 79 (28.2) 201 (71.8)	 0.793†

Cold ischemia time (hours)*	16.1 (5.7)	16.7 (6.3)	0.635‡
Full Analysis Set			
	Tac (N=336)	**TacXL (N=331)**	**p-value**
AB0 mismatch: dentical Compatible ncompatible	 310 (92.3) 25 (7.4) 1 (0.3)	 316 (95.5) 15 (4.5) 0	0.123°
HLA type mismatch: Mean A Mean B Mean DR§	 1.0 1.2 0.8	 1.0 1.1 0.9	 0.857‡ 0.267‡ 0.009‡
CMV status (recipient/donor) Negative/Positive	 43 (13.7)	 54 (17.1)	0.439†
Donor type: Living Cadaveric	 92 (27.4) 244 (72.6)	 89 (26.9) 242 (73.1)	0.886†
Cold ischemia time (hours)*	16.2 (5.8)	16.8 (6.5)	0.545‡

Patients (%)
† Chi-square test (excluding not recorded/not done); ‡ Wilcoxon rank sum test; ° Fisher's exact test (excluding not recorded/not done)
* Mean (SD) for cadaveric donors only; § Further details of HLA DR mismatch in Table XXXX
CMV = cytomegalovirus; EBV = Epstein-Barr virus; HBV = hepatitis B virus; HLA = human leucocyte antigen; HCV = hepatitis C virus
Source: Applicant's Study Report Table 6 and Post Text Tables 13.2.1.6, 13.2.1.9, 13.2.1.10, 13.2.2.6, 13.2.2.9, and 13.2.2.10.

Numerically more cytomegalovirus (CMV) negative patients in the TacXL treatment group received an organ from a CMV positive donor than patients in the Tac treatment group. Donor/recipient mismatch, donor type and cold ischemia time were comparable across treatment groups, with the exception of HLA DR mismatch, which was significantly higher in the TacXL group compared to the FK506 group (See table below).

Table 17: Study 12-03 Summary of HLA DR Donor/Recipient Mismatch

Per Protocol Set		
	Tac (N=291)	**TacXL (N=280)**
HLA type mismatch: DR: 0 DR: 1 DR: 2 Not recorded	 98 (35.0) 148 (52.9) 34 (12.1) 11	 74 (26.9) 153 (55.6) 48 (17.5) 5
Mean DR	0.8	0.9†
Full Analysis Set		
	Tac (N=336)	**TacXL (N=331)**

HLA type mismatch: DR: 0 DR: 1 DR: 2 Not recorded	 113 (34.8) 174 (53.5) 38 (11.7) 11	 92 (28.3) 170 (52.3) 63 (19.4) 6
Mean DR	0.8	0.9‡

Patients (%)
Percentage calculations: Due to the patients not recorded, the denominator for the percentage calculations is n=280 for FK506 and n=275 for MR4 in the Per Protocol Set and n=280 for FK506 and n=274 for MR4 in the Full Analysis Set.
HLA-DR = human lecocyte antigen D-related. HLA-DR is a major histocompatibility complex, cell surface receptor encoded by the human leukocyte antigen complex on chromosome 6.
† p=0.017, ‡ p=0.009 [Wilcoxon rank sum test (comparing distributions, excluding not recorded)] Source: Applicant's Study Report Table 8 and Post Text Tables 13.2.1.6 and 13.2.2.6

Reviewer's Comment: HLA DR mismatch is associated with increased risk for rejection and decreased long-term graft survival in kidney transplantation. In the Full Analysis Set the proportion of 2 DR mismatches is higher in the TacXL group, and the proportion of zero DR mismatches greater in the Tac group (p=0.009; Wilcoxon rank sum test) . Similar findings were observed for the Per Protocol Set (p=0.017; Wilcoxon rank sum test). This probably justified the need for an unplanned additional analysis of effect of HLA DR mismatch on efficacy, mentioned in the Applicant's Report, among the Changes from Planned Analyses.

6.1.3 Subject Disposition

Disposition of Subjects and Analysis Sets for Study 158

A total of 668 patients were randomized to treatment (Table 18) with the majority of patients (81%) treated at US sites. 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 18: Study 158 Patient Disposition

	Tac-XL	Tac	CYC
Randomized	226	219	223
Crossover*	10 (4%)	6 (3%)	39 (17%)
Completed 1-yr	183 (86%)	179 (84%)	151 (71%)
ITT (Full Analysis Set)**	214 (95%)	212 (97%)	212 (95%)
Discontinued Rand. Treatment ADE Rejection Graft Loss	 31 (15%) 9% 0.5% 0.9%	 33 (16%) 11% 0% 1.4%	 61 (29%) 18% 8% 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 of NDA 50-811.
**Protocol allowed crossover to another study treatment except to TacXL/MMF regimen*
*** Randomized and received at least one dose of study treatment*

Reviewer's Comment: The FDA's primary efficacy analysis is on the ITT (Full Analysis Set), as are the safety analyses.

Disposition of Subjects and Analysis Sets for Study 12-03

A total of 699 (353+346) 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 19). About 99% (667) of these 676 patients composed the full analysis population (Full Analysis Set in the table below) for this study where this population is defined as patients randomized, transplanted and treated with at least one dose (Randomized to treatment until cut-off in the table below). Among patients randomized to treatment, about 74% of Tac-XL patients and 78% of Tac patients completed one year on treatment.

Table 19: Study 12-03 Patient Disposition and Populations for Analysis

	Tac (N=353) Patients (%)	**TacXL (N=346) Patients (%)**
Randomized to treatment	353 (100.0)	346 (100.0)
Randomized but not having received at least one dose of study medication	1 (0.3)	2 (0.6)
Modified Full Analysis Set*	352 (99.7)	345 (99.7)
Randomized to treatment until cut-off	340 (96.3)	336 (97.1)
Randomized until cut-off date~ but not having received at least one dose of study medication	1 (0.3)	1 (0.3)
Extended Full Analysis Set^	339 (96.0)	335 (96.8)
Number of patients in the Extended Full Analysis Set who were not transplanted	3 (0.8)	4 (1.2)
Full Analysis Set†	336 (95.2)	331 (95.7)
Per Protocol Set‡	291 (82.4)	280 (80.9)
Completed 24 weeks	292 (82.7)	269 (77.7)
Completed 1 year	275 (77.9)	257 (74.3)

* Modified Full Analysis Set includes all randomized patients who received at least one dose of study medication (i.e. all patients from the extended Full Analysis Set and all patients randomized after the cut-off date who received at least one dose of study medication).
~ Cut-off date is the 31st December 2005. Patients enrolled after the cut-off date were enrolled for the PK substudy only, and considered in the non-PK analysis only for safety summary and for listing.

^ Extended Full Analysis Set includes all patients randomized until cut-off date who have received at least one dose of study medication (TacXL or Tac).
† All randomized patients who were enrolled until cut-off date, who received at least one dose of study medication and were transplanted (subset of patients participating in the pharmacokinetic study and enrolled after cut-off date are excluded).
‡ All Full Analysis Set patients without major protocol deviations defined as: violation of inclusion/exclusion criteria; randomization code broken; periodic exchange of randomization numbers (in case of different treatments only); >7 days stop of study medication (except for adverse event or trough level); >7 days prohibited immunosuppressive co-medication; withdrawal before biopsy-confirmed acute rejection.
Source: Applicant's Study Report Table 3 and Post-Text Table 13.1.1.

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.

Table 20: Study 12-03 Discontinuation from Randomized Treatment before One Year

	Tac (N=353) Patients (%)	**TacXL (N=346) Patients (%)**
Randomized for primary analysis population*	340 (100%)	336 (100%)
Discontinuation of rand. treatment prior to 12 mos	61 (18%)	74 (22%)
Reasons for Discontinuing		
ADE	39 (11%)	43 (13%)
Death	2 (~1%)	4 (~1%)
Withdrawal of consent	5 (~1%)	5 (~1%)
Non-compliant	5 (~1%)	4 (~1%)
Excl/incl violation	3 (~1%)	6 (2%)
Other	7 (2%)	12 (4%)

*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 agrees with the FDA statistical reviewer who 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.

Reviewer's Comment: The Applicant's primary efficacy analysis is based on the Per Protocol Set, while the FDA's Analysis is on the Full Analysis Set (Full Analysis Population). The Safety Analysis was also based on the Full Analysis Set. The numbers in these tables are consistent with those computed by the FDA statistical reviewer and summarized in Table 3.2.2 Study 1203 Patient Disposition in the FDA Statistical Review of NDA 204096 in DARRTS.

Information on the other populations defined by the Applicant in the tables above are provided for completeness and to aid as needed in the understanding of some of the exploratory safety analyses performed by the Applicant.

6.1.4 Analysis of Primary Endpoint(s)

Reviewer's Comment: In order to assist the understanding and interpretation of the analyses of efficacy, the reader is encouraged to refer to the information on study drug exposure and concomitant immunosuppressive drugs in Section 7.2.1 of this review.

6.1.4.1 Analysis of the Primary Endpoint(s) for Study 158

The Month 12 results for efficacy failure, defined as death, graft loss, biopsy confirmed acute rejection (BCAR) or loss to follow-up, are presented in the Table X below (adapted from Table 3.1.4 in the FDA Statistical Review). The results show that TacXL is comparable to both Tac and cyclosporine with upper bounds of the confidence intervals of 6% or less; well within a non-inferiority boundary of 10%. As would be expected, most of the events of efficacy failure are acute rejection. No notable differences are observed between TacXL and Tac.

Table 21: 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)	Tac (n=212)	Neoral (n=212)	Tac-XL minus Tac[2] 95.2% 2-sided CI	Tac-XL minus Neoral[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%)		
Lost-to-FU	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

Analyses of time to efficacy failure performed by the FDA statistical reviewer yield 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 (See Table X below adapted from Table 3.1.5 in the FDA statistical review). Both a log rank test and Wilcoxon test produced essentially the same p-values of about 0.8. As note in the FDA statistical review, no non-inferiority margin based on the HR was named a priori so interpretation of these results is not straight-forward, but does not affect the overall conclusions.

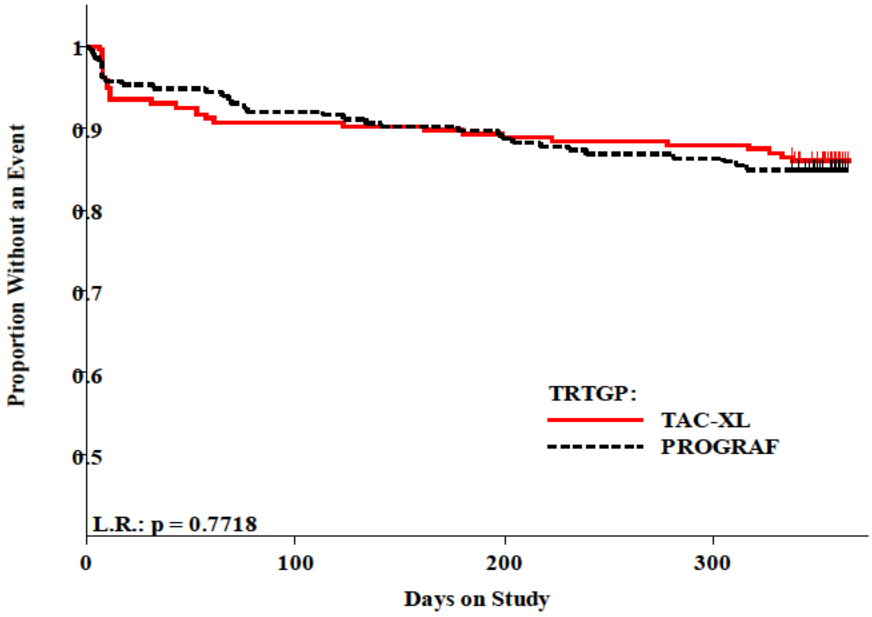
Table 22: Study 158 FDA Statistical Reviewer's results for efficacy failure defined as death, graft loss, BCAR or lost-to-follow-up (ITT population) based on a Cox proportional hazards model analysis

	Tac-XL (n=214)	Tac (n=212)	Risk Difference	HR Tac-XL/Tac[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

In the figure below (adapted from Figure 3.1.1 in the FDA statistical review) the Kaplan-Meier plot of time to efficacy failure illustrate the similarity between the treatment responses for the duration of the trial in the Tac and Tac-XL groups.

Figure 2 Study 158 Kaplan–Meier plot of time to efficacy failure



Reviewer's Comment: Based on an estimate of M1 of about 30%, corresponding to the contribution to protection against rejection provided by tacrolimus-mediated calcineurin inhibition, and a prespecified and adequately justified non-inferiority margin of 10%, this reviewer concludes that the efficacy results from Study 158 show that TacXL is non-inferior to Tac.

Reviewer's Comment: An imbalance in mortality at 12 months is observed in those patients receiving Tac/MMF (4.2%) compared to those receiving cyclosporine/MMF 2.3%) and those receiving TacXL/MMF (1.4%). The

difference between Tac/MMF and cyclosporine/MMF is currently described in the Kidney Transplantation subsection of the CLINICAL STUDIES Section of the approved Prograf Label (See Table 20 of the Prograf Label). Such an imbalance is not observed in those receiving TacXL. Patient and graft survival in those receiving TacXL/MMF is comparable to those receiving cyclosporine/MMF.

6.1.4.2 Analysis of the Primary Endpoint(s) for Study 12-03

The stated primary endpoint for Study 12-03 was BCAR (biopsy confirmed acute rejection by local assessment) measured at 24 weeks after transplantation; however the results at Month 12 represent an important secondary endpoint. Thus, the emphasis of the FDA review for Study 12-03, as for Study 158 is on Month 12 results for efficacy failure.

The table below (adapted from the FDA statistical review Table 3.2.5) summarizes the Applicant's Week 24 results.

Table 23: Study 12-03 Applicant's Week 24 primary endpoint (BCAR) results

	TacXL	Tac	TacXL minus Tac[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 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 of +4.5% with a 95% CI of -1.8% to +10.9% for the per-protocol population. Thus, the results for the protocol defined 24 week BCAR primary endpoint met the Applicant's pre-defined, though not justified, non-inferiority margin of 10% using the full analysis population but not using the per-protocol population. Nevertheless, it remains clear that the results for both populations are virtually the same and show that TacXL is non-inferior to Tac. The ITT population is considered by FDA the standard analysis population. If one believes, as does this reviewer, that the ITT population should be the primary population, since it best represents the randomized population, the primary endpoint results at Week 24 meet the margin of 10%.

The table below (adapted from the FDA statistical review Table 3.2.6) summarizes the efficacy failure results at both Week 24 and Month 12.

Table 24: Study 12-03 Results for efficacy failure defined as death, graft loss, BCAR or lost-to-follow-up (ITT population)

	TacXL (n=331)	Tac (n=336)	TacXL minus Tac[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%)	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 TacXL
[2]Results based on applicant's Kaplan-Meier analyses which produced KM estimates and difference in estimates
[3]Computed by the FDA statistical reviewer.

The results at both Week 24 and Month 12 show a higher rate of failure, by about 5%, for the TacXL group compared to the Tac group. While the upper bound for the confidence interval of the treatment difference exceeds a 10% margin, the confidence interval supports that TacXL would have been better than placebo, based on a computed M1 of 28% described in Section 3.2 the FDA Statistical Review in DARRTS.

It is noted that the 5% treatment difference appears to be driven by the difference in BCAR rates (based on local assessment), which explains the consistency between the findings in the analyses of 24 week and 12 month BCAR and of 12 month efficacy failure.

A time to event analysis performed by the FDA statistical reviewer using a Cox proportional model yielded an hazard ratio of about 1.25 (See Table below adapted from Table 3.2.7 in the FDA statistical review) with an upper limit to the 95% confidence interval of about 1.7 (for Study 158, the upper limit was 1.5). Thus, 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).

Table 25: Study 12-03 Results for efficacy failure defined as death, graft loss, BCAR or lost-to-follow-up (ITT population)

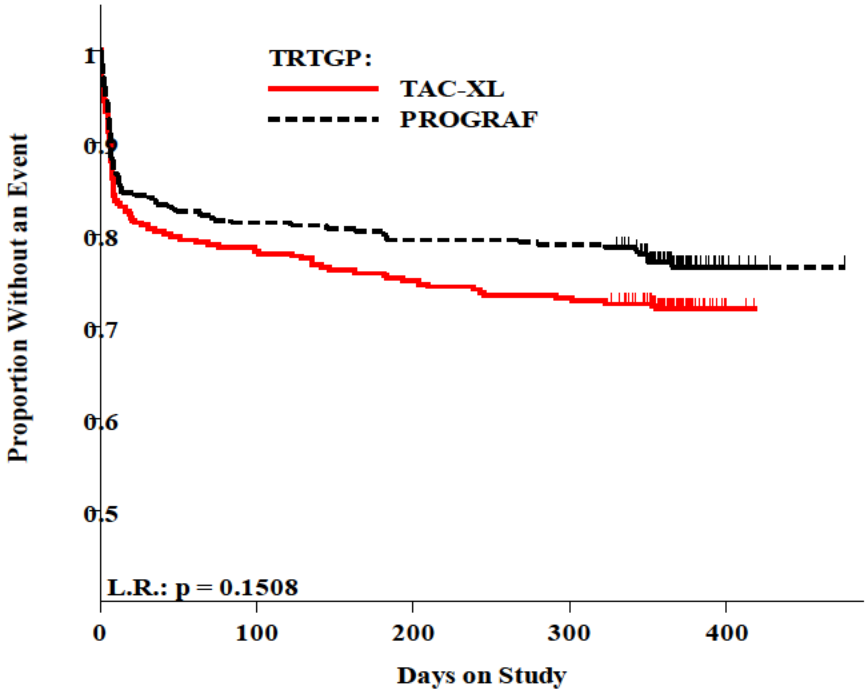
	Tac-XL (n=331)	Prograf (n=336)	Hazard ratio Tac-XL/Prograf[1]

			95% 2-sided CI
Month 12 events Efficacy Failures	93 (28%)	78 (23%)	1.25 (0.9, 1.7)[2]

[1]Values under 1 favor Tac-XL
[2]Computed by the FDA statistical reviewer.

The figure below adapted from the FDA statistical review depicts a Kalplan-Meier plot of time to efficacy failure, which illustrates that most of the events occur within the first month, about half of them within 10 days after transplantation. Virtually all of these events represent acute rejection episodes confirmed by local assessment blinded to treatment assignment.

Figure 3 Study 1203 Kaplan–Meier plot of time to efficacy failure; inset shows events up to Day 30 (adapted from Figure 3.2.1 in the FDA statistical review).



It is further noted, that the incidences at Month 12 are essentially the same as the Kaplan-Meier estimates computed using time to event data in the table above, and that therefore both the treatment differences and confidence intervals are essentially the same. This similarity is due the lack of censoring when counting all discontinuations as failures. Patients not having events are censored at the end of the study (after Month12). Thus, all censoring as illustrated by censor marks on the graph above are at the end of the study (at or beyond Month12).

Effect of HLA-DR mismatch

A statistically significant imbalance of HLA-DR was reported more frequently in the TacXL group compared to the Tac group, and could have contributed an increased risk for rejection in the TacXL arm. Thus, the sponsor has performed an exploratory analysis adjusting for this imbalance which produced a treatment difference (95% CI) of 1.9% (-4.4% to 8.3%) in the Per Protocol Set and of 2.4% (-3.5% to 8.4%) in the Full Analysis Set.

> *Reviewer's Comment: The Applicant's analyses adjusting for imbalance of HLA-DR, are somewhat reassuring, and strengthen the overall conclusion of this reviewer that TacXL when used with MMF provided acceptable protection against rejection, comparable to that provided by Tac used with MMF in Study 12-03.*

6.1.5 Analysis of Secondary Endpoints(s)

Deaths and graft loss will be discussed in greater detail as safety endpoints in Section 7.3.1 of this review. This section will address some of the clinically relevant observations with respect to secondary endpoints related to acute rejection and renal function.

6.1.5.1 Graft and Patient Survival

6.1.5.1.1 Graft and Patient Survival in Study 158

Table 26 below adapted from Table 29 in the FDA Clinical Review of NDA 50-811 summarizes 1-year patient and graft survival in Study 158, where loss to follow-up (LTF) is imputed as a failure.

Table 26: Study 158 Patient and Graft Survival at 1-year Post-Transplantation (Intent-to-Treat)

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

Graft Failure1	9 (4.2)	5 (2.3)	4 (1.9)			
LTF2	4 (1.9)	3 (1.4)	1 (0.5)			
1Permanent (>30 days) return to dialysis or re-transplant not resulting in death. Note: 1 patient in MR/MMF and 3 patients in Prograf/MMF died after experiencing graft failure 2 Note that 1 subject in the Prograf/MMF was LTF after experiencing graft failure.						

Reviewer's Comment: An imbalance in mortality at 12 months is observed in those patients receiving Tac/MMF (4.2%) compared to those receiving cyclosporine/MMF 2.3%) and those receiving TacXL/MMF (1.4%). The difference between Tac/MMF and cyclosporine/MMF is currently described in the Kidney Transplantation subsection of the CLINICAL STUDIES Section of the approved Prograf Label (See Table 20 of the Prograf Label). Such an imbalance is not observed in those receiving TacXL. Patient and graft survival in those receiving TacXL/MMF is comparable to those receiving cyclosporine/MMF.

Deaths reported in Study 158 are further discussed in Section 7.3.1.1 of this review.

6.1.5.1.2 Graft and Patient Survival in Study 12-03

Deaths and graft loss reported up to 12-months after transplantation are tabulated in Section 6.1.4.2 of this review. There were 28 (9%) graft losses in the Tac group and 24 (7%) in the TacXL group. Deaths occurring up to month 12 in Study 12-03 are further discussed in Section 7.3.1.2 of this review. There were 8 (2%) deaths in the Tac group and 10 (3%) deaths in the TacXL group.

Reviewer's Comment: No particular imbalance with respect to death or graft loss was observed between treatment groups. The numerical difference with respect to mortality observed in Study 158 was not observed in Study 12-03, which used higher initial tacrolimus exposures, and lower overall MMF dosing than Study 158 as summarized in Sections 7.2.1.1 and 7.2.1.2 of this review.

6.1.5.2 Acute Rejection

6.1.5.2.1 Acute Rejection in Study 158

In Study 158, which was open-label, biopsies performed for assessment of rejection received a local assessment, which was used as a component of the efficacy failure endpoint, as well as a central review, by a pathologist blinded to treatment assignment.

The central assessment, blinded to treatment assignment found about 50% fewer acute rejection events and a similar number of clinically significant (Banff Grade ≥ 2a) rejections across the three treatment arms.

Table 27: Study 158 Acute Rejections at 1-year Post-Transplantation (Adapted from Table 35 in Clinical Review of NDA 50-811 in 2007)

Acute Rejections	Tac (%)	TacXL (%)	Cyclosporine
	n = 212	n = 214	n = 212
Local Assessment	16 (7.5)	22 (10.3)	29 (13.7)
Blinded, Central Assessment	8 (3.8)	10 (4.7)	14 (6.6)

Source: Study 158 Report Table 14.3.5.5.1

Table X : Study 158 Maximum Grade of Acute Rejection at 1-year Post-Transplantation by Treatment Group and Local versus Central Assessment

Max Grade of Acute Rejection	Tac		TacXL		Cyclosporine	
	Central	Local	Central	Local	Central	Local
Grade IA	1	8	0	10	3	14
Grade IB	1	4	1	3	1	6
Grade IIA	6	3	5	6	7	6
Grade IIB	0	1	3	1	2	1
Grade III	0	0	1	2	1	2
Total	8	16	10	22	14	29

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

> *Reviewer's Comment: Again, due to the open-label design of the study comparisons with respect to rates of biopsy confirmed acute rejection across treatment groups need to be interpreted with caution. Differences between the result of local assessment and the blinded central review are not unexpected, to the extent that a local reviewer may feel compelled by the risk of missing an episode of rejection that requires treatment to make the diagnosis of rejection, while a central reviewer is not. Such a difference between local and central assessment has been observed in other clinical trials. Nevertheless, the local diagnosis of acute rejection remains the one that dictates treatment, which is associated with its own morbidity.*

6.1.5.2.2 Acute Rejection in Study 12-03

The frequency of acute rejections confirmed by local biopsy for the Per Protocol Set and Full Analysis Set, including overall acute rejections, spontaneously resolving, corticosteroid sensitive and corticosteroid resistant acute rejections is presented in Table 28 below (Adapted from Study Report Table 14).

Table 28: Study 12-03 Frequency of Local Biopsy-confirmed Acute Rejection

Per Protocol Set				
	Tac (N=291)		**Tac XL (N=280)**	
	Patients (%)	**Episodes**	**Patients (%)**	**Episodes**
Acute rejections	49 (16.8)	52	59 (21.1)	65
Spontaneously resolving†	1 (0.3)	1	0	0
Corticosteroid sensitive‡	32 (11.0)	32	37 (13.2)	38
Corticosteroid resistant§	19 (6.5)	19	25 (8.9)	25
Other	0	0	2 (0.7)	2
Full Analysis Set				
	Tac (N=336)		**TacXL (N=331)**	
	Patients (%)	**Episodes**	**Patients (%)**	**Episodes**
Acute rejections	50 (14.9)	53	59 (17.8)	65
Spontaneously resolving†	1 (0.3)	1	0	0
Corticosteroid sensitive‡	32 (9.5)	32	37 (11.2)	38
Corticosteroid resistant§	20 (6.0)	20	25 (7.6)	25
Other	0	0	2 (0.6)	2

† An acute rejection episode that was not treated with new or increasing corticosteroid medication, antibodies or any other medication and resolved, irrespective of any tacrolimus or MMF dose changes
‡ An acute rejection episode that was treated with new or increased corticosteroid medication only and resolved, irrespective of any tacrolimus or MMF dose changes
§ An acute rejection episode that did not resolve following treatment with corticosteroids only, or was not treated with corticosteroids first but only with antibodies, irrespective of any tacrolimus or MMF dose changes
Source: Study Report Post Text Tables 13.5.1.1.3 and 13.5.2.1.3

In both analyses sets, the frequency of local biopsy-confirmed acute rejection and of biopsy-confirmed corticosteroid-resistant acute rejection was similar in both TacXL and Tac treatment groups. This was the case for both the Per Protocol and the Full Analysis Sets.

The histological grade of acute rejections (according to the Banff grading system) based on local biopsy and of the local biopsies taken during rejection episodes were also comparable for both TacXL and Tac. This was confirmed for both the Per Protocol and Full Analysis Sets.

6.1.5.2 Renal Function

In both Study 158 and Study 12-03, renal function was defined as a secondary efficacy endpoint along with 10 other endpoints; however, there were no predefined criteria demonstrating efficacy with respect to any measure of renal function, namely non-inferiority with respect to renal function endpoints.

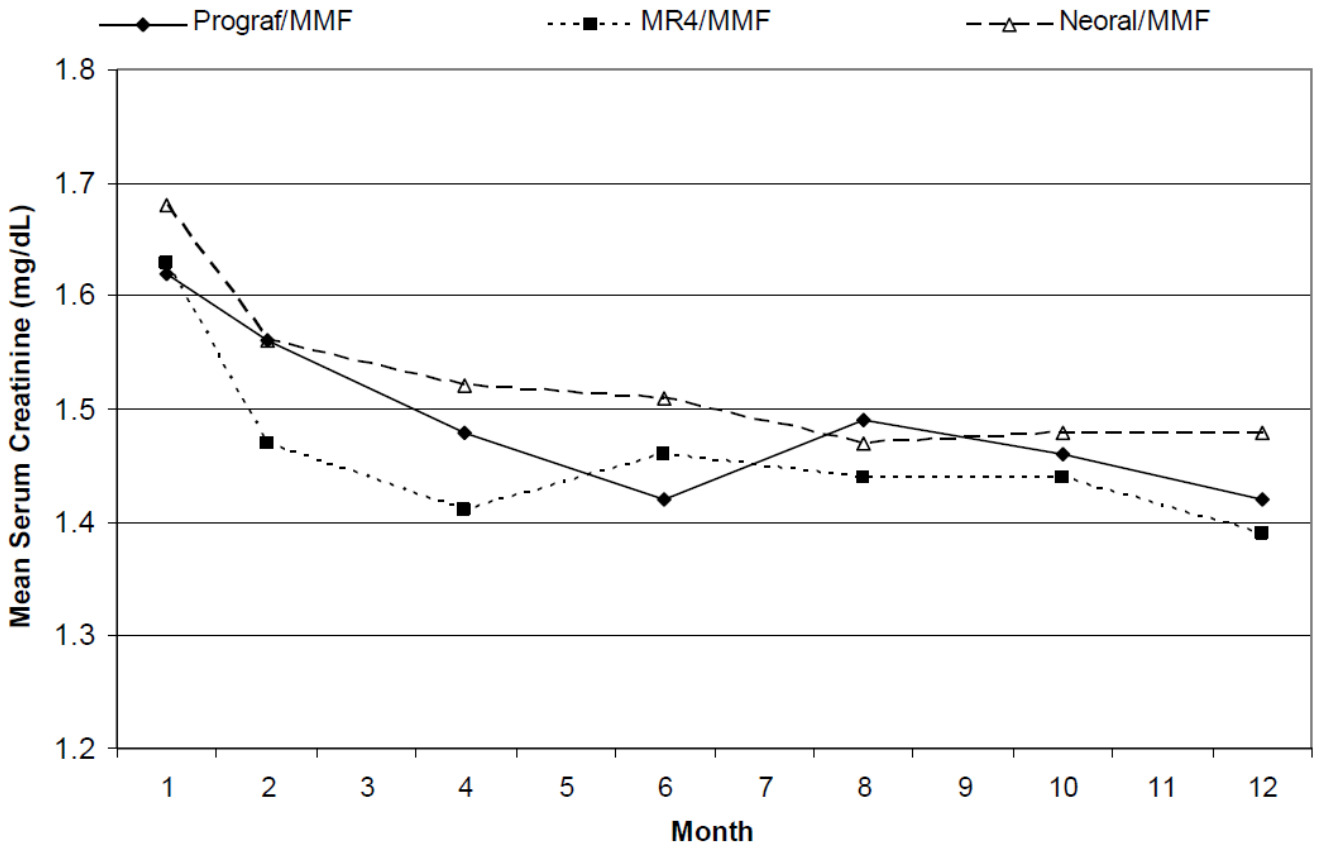
6.1.5.2.1 Renal Function in Study 158

Evaluation of renal function was considered a secondary endpoint in Study 158.

The figure below adapted from the Applicant's Figure 5 (Figure 4 in this review) in the 1-year study report summarizes the mean serum creatinine values from baseline (one month after transplantation) through one year.

Figure 4: Study 158

Figure 5: Summary of Mean Serum Creatinine Values from Baseline Through 1 Year



Patient base: Full analysis set; all randomized patients who received at least one dose of study drug.
Baseline: Month 1 visit.
MMF: Mycophenolate mofetil.
MR4: Tacrolimus modified-release formulation.
Source: Table 13.4.7.1.

Prograf=Tac, MR4= TacXL, Neoral=CYC

Mean serum creatinine in Study 158 is summarized in the Applicant's Study Report Table 22 copied below (Table 29 of this review):

Table 29: Study 158

Table 22: Summary of Mean ± SD Serum Creatinine Values at Month 1, Month 6, and Month 12

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

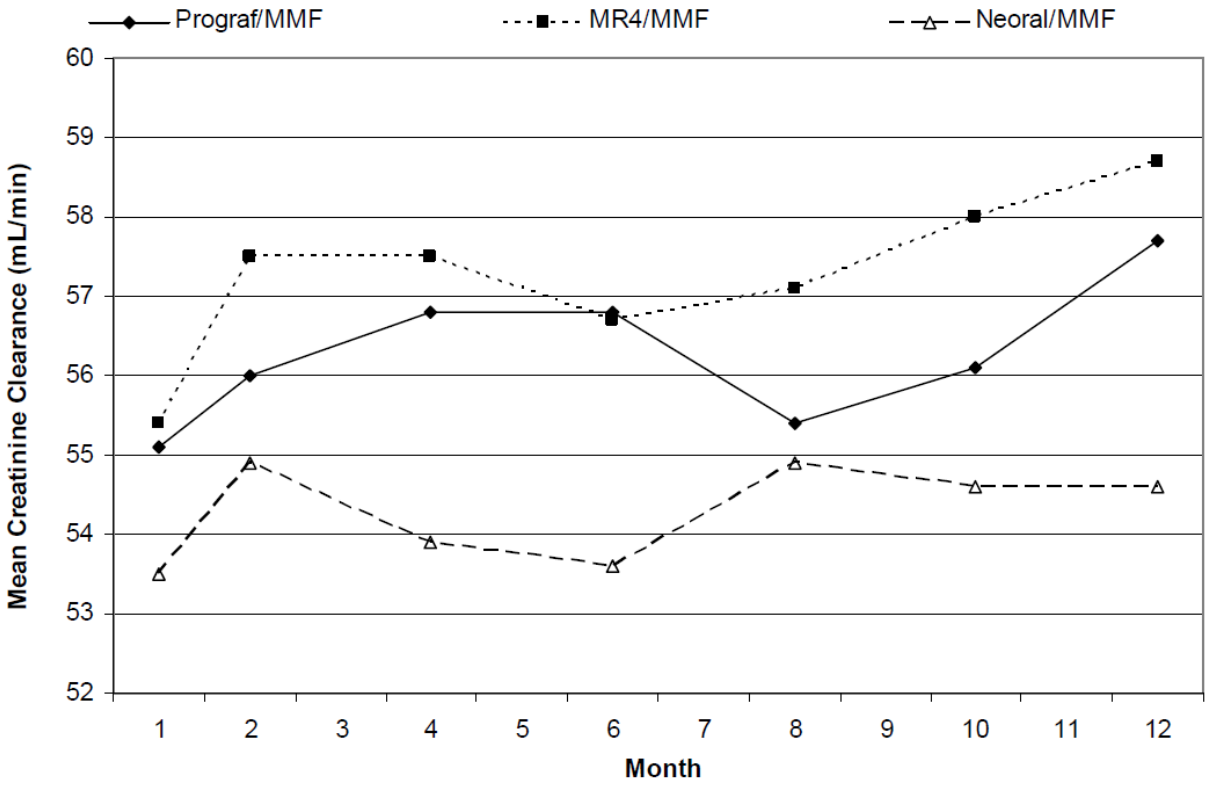
Patient base: Full analysis set; all randomized patients who received at least one dose of study drug.
* Statistical significance of $p < 0.05$ versus Neoral using two-way analysis of variance (ANOVA) with treatment and center as factors.
MMF: Mycophenolate mofetil.
MR4: Tacrolimus modified-release formulation.
SD: Standard deviation.
Source: Table 13.4.7.1.

Prograf=Tac, MR4= TacXL, Neoral=CYC

Mean creatinine clearance in Study 158 from baseline (month 1) through 1 year is summarized in the Applicant's Study Report Figure 7 (Figure 5 of this review) and Study Report Table 24 reproduced below (Table 31 in this review):

Figure 5: Study 158 Mean Creatinine Clearance from Baseline

Figure 7: Summary of Mean Creatinine Clearance Values from Baseline Through 1 Year



Patient base: Full analysis set; all randomized patients who received at least one dose of study drug.
Creatinine clearance calculated using Cockcroft-Gault formula using ideal body weight.
Baseline: Month 1 value.
MMF: Mycophenolate mofetil.
MR4: Tacrolimus modified-release formulation.
Source: Table 13.4.7.1.

Prograf=Tac, MR4= TacXL, Neoral=CYC

Table 31: Study 158 Mean Creatinine Clearance from Baseline

Table 24: Summary of Mean ± SD Creatinine Clearance Values at Month 1, Month 6, and Month 12

Time Point Statistic	Treatment Group Prograf/MMF (n = 212)	 MR4/MMF (n = 214)	 Neoral/MMF (n = 212)
Month 1			
n Mean ± SD	202 55.1 ± 20.73	199 55.4 ± 20.61	193 53.5 ± 21.01
Month 6			
n Mean ± SD	189 56.8* ± 17.25	188 56.7* ± 18.24	171 53.6 ± 15.92
Month 12			
n Mean ± SD	175 57.7* ± 18.81	185 58.7* ± 18.26	148 54.6 ± 17.6

Patient base: Full analysis set; all randomized patients who received at least one dose of study drug.
* Statistical significance of $p < 0.05$ versus Neoral using two-way analysis of variance (ANOVA) with treatment and center as factors.
MMF: Mycophenolate mofetil.
MR4: Tacrolimus modified-release formulation.
SD: Standard deviation.
Source: Table 13.4.7.1.

Prograf=Tac, MR4= TacXL, Neoral=CYC

> *Reviewer's Comment: The Applicant's statistical analyses, and comparisons in this open-label study need to be interpreted with caution since it appears by the numbers of subjects assessed at each time point that there is missing data which is adjusted for by any pre-specified method of imputation. The clinical significance of the differences between treatment groups, which are small, is uncertain; all the more if one were to adjust the comparisons by baseline renal function (one month after transplantation). This reviewer concludes that at best, renal function as measured by serum creatinine and creatinine clearance was comparable across treatment groups. No comparative competitive claims with respect to renal function are supported by such data and analyses.*

Renal function was also evaluated as a safety measure, and will be discussed further in section 7 of this review.

6.1.5.2.2 Renal Function in Study 12-03

Renal function assessed by calculated creatinine clearance (Cockcroft-Gault's formula and also MDRD) and serum creatinine within the first 24 weeks and 12 months following transplantation was a stated secondary efficacy endpoint in Study 12-03. Renal function was assessed based on delayed graft function, serum creatinine and creatinine clearance (Cockcroft&Gault formula).

Delayed graft function was defined as the patient having dialysis for more than one day within the first seven days post-transplantation (Day 0 to Day 7). The incidence of initial renal dysfunction was comparable between TacXL and Tac groups, with the incidence of delayed graft function in the Per Protocol Set being 15.0% and 16.2%, respectively.

Table 32 below adapted from the Applicant's Study Report Table 39 summarizes renal function in Study 12-03 through 12 months after transplantation.

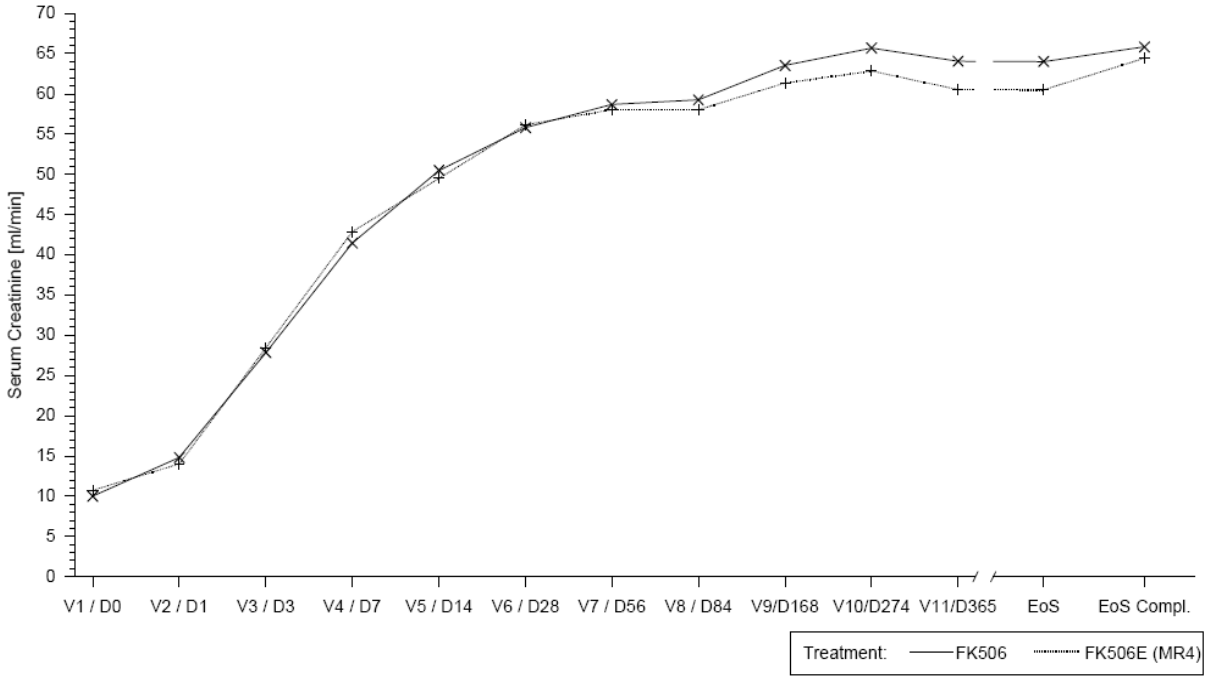
Table 32: Study 12-03 Summary of Renal Function

	N	FK506 (N=336)	N	MR4 (N=331)
Serum creatinine (µmol/L)				
Visit 1/Day 0	334	771.9 ± 284.8	330	736.5 ± 251.9
Visit 3/Day 3	326	398.3 ± 305.5	315	397.3 ± 304.4
Visit 4/Day 7	318	322.2 ± 283.2	309	318.1 ± 284.2
Visit 5/Day 14	310	224.2 ± 198.2	301	224.6 ± 200.0
Visit 6/Day 28	306	152.2 ± 85.7	296	159.1 ± 106.9
Visit 7/Day 56	301	138.3 ± 48.7	285	144.9 ± 57.6
Visit 9/Day 168	292	133.9 ± 46.1	267	133.5 ± 40.3
End of 12 months period†	332	161.6 ± 134.2	329	182.8 ± 179.4
Creatinine clearance				
Visit 1/Day 0	334	11.3 ± 5.0	330	11.6 ± 5.0
Visit 3/Day 3	326	34.4 ± 23.9	315	33.6 ± 22.7
Visit 4/Day 7	318	40.7 ± 23.7	309	40.8 ± 22.9
Visit 5/Day 14	310	49.5 ± 22.9	301	47.9 ± 20.8
Visit 6/Day 28	306	57.3 ± 19.4	296	56.0 ± 18.6
Visit 7/Day 56	301	59.9 ± 18.1	285	57.9 ± 18.6
Visit 9/Day 168	292	63.7 ± 17.7	267	62.6 ± 19.1
End of 12 months period†	332	62.6 ± 22.9	329	60.0 ± 25.8

Full Analysis Set; Mean ± SD; Normal ranges: Serum creatinine <133 µmol/L; Creatinine clearance 91 to 130 mL/min;
† Completers only
Source: Applicant's Study Report Table 13.6.3.1

Median serum creatinine clearance (Cockcroft-Gault) is also summarized in the Applicant's Study Report Figure 6 reproduced below (Figure 6 in this review).

Figure 6: Study 12-03 Median Creatinine Clearance (Cockcroft-Gault)



Full Analysis Set
Source: Applicant's Figure 14.3.2

Renal function, as assessed by serum creatinine and creatinine clearance, is discussed in detail in the Review of Safety, section 7 of this review.

> *<u>Reviewer's Comment</u>: Comparable allograft renal function, as measured by serum creatinine, mean creatinine clearance, and median creatinine clearance was maintained with TacXL and Tac used with MMF in Study 12-03, which was largely conducted as a double blind study (until the last subject had completed 24 weeks).*

6.1.6 Other Endpoints

No other clinically relevant efficacy endpoints will be discussed in this review.

6.1.7 Subpopulations

6.1.7.1 Subpopulations in Study 158

For the composite endpoint for BCAR, graft failure and death, there were no differences by age (16 to < 65 years and ≥ 65 years) or baseline of diabetes in Study 158. Differences in efficacy were noted by sex, race, ethnicity, and donor type as described in the Table below adapted from Table 28 in the clinical review of NDA 50-811 by Dr. Wong.

Table 33: Study 158 Summary of 1-year Composite Endpoint Failure Rate by Recipient Sex, Race, Ethnicity, and Donor Type

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

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

Reviewer's Comment: Due to the open-label design of this study, comparisons across treatment groups need to be interpreted with caution. Within treatment groups there consistently higher rates of efficacy failure (driven by episodes of rejection) in Black subjects compared to White subjects, which is not unexpected based on registry data. Female subjects receiving TacXL or Tac had numerically higher rates of efficacy failure, again driven by episodes of rejection. Ultimately, there were few clinically relevant (Banff Grade ≥ 2a) episodes observed in this study, making it difficult to conclude that these differences are clinically significant.

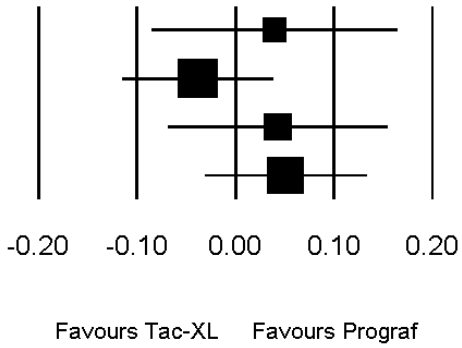
6.1.7.1 Subgroup Analyses of Efficacy

Analyses of efficacy failure results by subgroups of sex, age, race and geographic region were performed by the FDA statistical reviewer and are summarized here. Please see Section 4.1 of the FDA statistical review in DARRTS for further details. In the figures below the black squares are proportionate to the size of the subpopulation and centered on the risk difference, while the lines span the 95% CI of the risk difference.

6.1.7.1.1 Sex

As noted above in Study 158, the efficacy failure results for female patients appear more favorable for Tac while the results in male patients appear more favorable in the TacXL group; however, this difference in treatment effects is not significant with a treatment by sex interaction p-value of 0.27 by the FDA statistical analysis.

Study	Sex	n / Total		Risk difference and 95% CI
		Tac-XL	Prograf	Risk difference
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

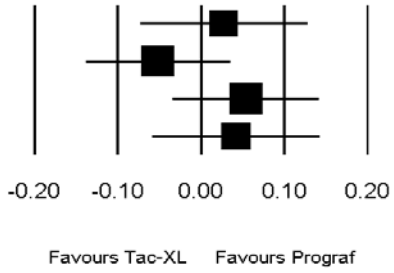


Source: Section 4.1.1 of the FDA statistical review.

6.1.7.1.2 Age

Since there were too few patients 65 years or older in either study, the median age was used to evaluate whether age had an impact on outcome. In Study 158, the results for older patients appear more favorable in the Tac-XL group while the opposite appears true for younger patients; however, the interaction is not significant for treatment by age.

Study	Age	n / Total		Risk difference and 95% CI
		Tac-XL	Prograf	Risk difference
Study 158	<50	20 / 111	15 / 98	0.027
Study 158	50+	10 / 103	17 / 114	-0.052
Study 1203	<50	56 / 195	43 / 184	0.053
Study 1203	50+	37 / 136	35 / 152	0.042

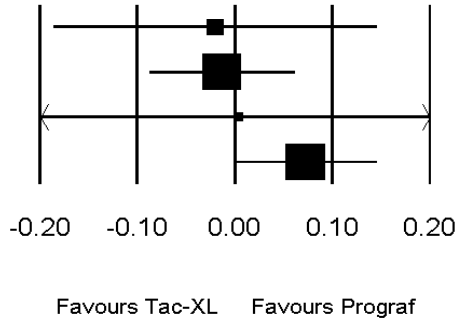


Source: Section 4.1.2 of the FDA statistical review.

6.1.7.1.3 Race

To the extent that Study 158 included US centers, and Study 12-03, the number of Black subjects included in the latter study was limited. The majority of the patients in both trials were Caucasian.

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

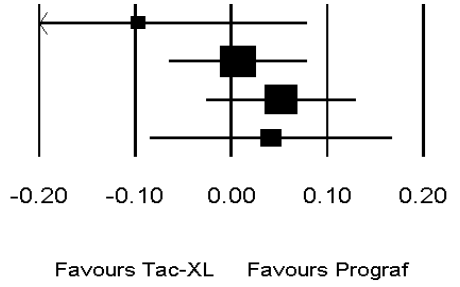


Source: Section 4.1.3 of the FDA statistical review.

6.1.7.1.4 Geographic Region

As noted earlier in this review, Study 158 was primarily conducted in the US while Study 1203 was primarily conducted in Europe, and did not include sites in the US. As summarized below, 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



Source: Section 4.1.4 of the FDA statistical review

Reviewer's Comment: Overall there is considerable overlap between the 95% confidence intervals of the risk differences, and no clear pattern of increased risk could be identified across the subgroups evaluated here. The observation that the risk difference between Tac-XL and Tac (Prograf in the figures above) in US population in Study 158 is small and that the 95% CI for the risk difference excludes 10% is reassuring.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Exploratory exposure/responses are described in the FDA Pharmacometrics and Clinical Pharmacology Reviews in DARRTS.

The observed tacrolimus doses and exposure in Studies 158 and 12-03 are summarized in Section 7.2.1.1 of this review.

> *Reviewer's Comment: The small number of events and narrow range of observed doses and whole blood concentrations limit the ability of such analyses to detect clinically meaningful relationships. The observed whole blood concentration ranges of TacXL used in Study 158 and Study 12-03 reflect the cumulative experience with therapeutic drug monitoring if tacrolimus. The observed doses and whole blood concentrations from Study 158 and Study 12-03 should be represented in the product labeling, in order to inform the practitioner as to what overall exposure was associated with the observed efficacy outcomes that is described in the Clinical Studies section of labeling.*

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable

6.1.10 Additional Efficacy Issues/Analyses

Not applicable

7 Review of Safety

Safety Summary

TacXL is an extended release formulation of tacrolimus and its safety profile is dominated by the well-known potential hazards associated with the use of tacrolimus.

The safety of TacXL was evaluated in two large 12 month phase 3 clinical trials, as described below, Study 158 was open-label and used basiliximab induction and Study 12-03 was largely double blind until the last patient had completed 24 weeks on study medication. Although there is considerable overlap between the doses and exposures of tacrolimus used in the two clinical trials, higher doses and whole blood concentrations were observed in the study without basiliximab induction (Section 7.2.1.1 of this review). In addition, these two studies used different regimens of concomitant immunosuppression with MMF (Section 7.2.1.2 of this review).

Overall, the safety profile of TacXL was comparable to that of the immediate release formulation, Prograf.

Lymphomas and malignancies, as well as serious infections are important potential hazards of tacrolimus and continue to justify the requirement of a boxed warning to that effect, although few were observed in the clinical studies reviewed in this application, and there were no significant differences between TacXL and Tac with respect to causes of death or serious adverse events.

The most common adverse events reported with a frequency of greater than 30% in any study were tremor, hypertension, diarrhea, constipation, nausea, peripheral edema, and anemia (Section 7.4.1 of this review).

Adverse events of interest were evaluated in the clinical trials and should be reflected in labeling (Section 7.3.4 of this review).

Infections are a consequence of immunosuppression with tacrolimus and were observed with TacXL at frequencies comparable to tacrolimus ., with the exception of a slightly higher rate of gastroenteritis (reported as an infection) observed in the TacXL group in both studies and reaching statistical significance by the Applicant's analysis ($p < 0.5$) (Section 7.3.4.1 of this review).

The use of tacrolimus like other calcineurin inhibitors is associated with renal function impairment. Renal failure and impairment reported as an adverse event was not uncommon but occurred at comparable rates across TacXL and Tac treatment groups (Section 7.3.4.2 of this review).

Glucose metabolism disorders, including new onset diabetes after transplantation are associated with the use of tacrolimus and occurred with comparable frequency across TacXL and Tac treatment groups (Section 7.3.4.3 of this review).

Neurologic disorders are known hazards associated with the use of tacrolimus. The most common neurologic adverse events reported in the clinical trials were tremor, headaches and to a much lesser extent paresthesias (Section 7.3.4.4 of this review). While there may have been an expectation that differences between the PK profile of the once daily extended release formulation (single daily Cmax) and that of the immediate release formation (two daily Cmax) could have resulted in less acute neurotoxicity, no advantage was observed for TacXL compared to Tac with respect to neurologic adverse events.

Hypertension is a common adverse event associated with the use of tacrolimus, as reflected in the approved Prograf packages insert and was observed with comparable frequency in patients treated with TacXL (Section 7.3.4.5 of this review).

Overall, no new hazards associated with the use of TacXL were identified in clinical studies that had not been previously identified in association with the use of the tacrolimus immediate release product in kidney transplantation recipients.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary sources used for safety assessment were the open-label Phase 3 Study 158 which was previously reviewed under NDA 50-811 and 12-month report of Study 12-03 which was requested in the Complete Response Letter to NDA 50-811, providing a largely double blind comparison of TacXL to Tac. Because Astagraf XL (tacrolimus extended release) is not considered a new molecular entity and that tacrolimus is a product that has been on the market for almost two decades, certain safety events of interest were targeted for special consideration, including new onset diabetes mellitus after transplantation, hypertension, hyperlipidemia, renal function, gastrointestinal disorders and infections. Safety results from these studies will be described separately and not pooled, as there were significant differences between the two studies with respect to starting doses of tacrolimus, concomitant immunosuppressive medications, including differences in use of induction antibody in Study 158 and not in Study 12-03, and with respect to geographic origins of study populations. Thus, Study 158, which was conducted largely in the US may be more representative of the safety of the products when used with induction immunosuppression in a US population, while Study 12-03 provides a double-blind view of comparative safety between Tac (Prograf) and TacXL (Astagraf XL) in a non-US population.

7.1.2 Categorization of Adverse Events

The Applicant used the MedDRA dictionary of preferred terms to categorize adverse events, grouping closely related investigator-reported verbatim terms. Applicant's categorization of events was assessed by comparing the verbatim terms used by the investigators when reviewing events leading to death and dropouts.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Pooling of data across studies was judged by this reviewer as not appropriate, given the differences in regimens and populations (geographic regions, and consequent differences in demographics and relative proportion of deceased to living donor transplants).

7.2 Adequacy of Safety Assessments

All tests reasonably applicable were conducted to assess the safety of TacXL.

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

Tacrolimus is not a new molecular entity. Overall adequate numbers of subjects were evaluated to assess the safety of TacXL in populations which were representative of the US kidney transplant population in Study 158, and adequate numbers were exposed in Study 12-03, which remained double blind until the last subject had completed 24 weeks of study drug, to allow a more objective assessment of comparative safety between TacXL and Tac. The sections below describe in greater detail the measures of tacrolimus exposures observed in these studies.

In addition, since tacrolimus is used in combination with other immunosuppressive agents which may influence the safety profile observed with the use of tacrolimus, a summary of the mycophenolate dosing observed in these studies is also provided in Section 7.2.1.2 of this review.

7.2.1.1 Tacrolimus Exposure

7.2.1.1.2 Tacrolimus Exposure in Study 158

The table below using results extracted from the Applicant's Study Report summarizes the exposure to tacrolimus in the TacXL and Tac arms of Study 158, as well as the cyclosporine exposure in the cyclosporine+MMF arm.

Table 34: Study 158 Study drug exposures[1]

	TacXL (n=214)	Tac (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	8.9	9.7	250
Month 1	10.5	10.5	302
Month 6	7.7	8.0	194
Month 12	7.2	7.2	169

[1]Results extracted from applicant's study report

7.2.1.2.3 Tacrolimus Exposure in Study 12-03

The table below using results extracted from the Applicant's Study Report summarizes the exposure to tacrolimus in the TacXL and Tac arms of Study 12-03.

Table 35: Tacrolimus Exposure in Study 12-03

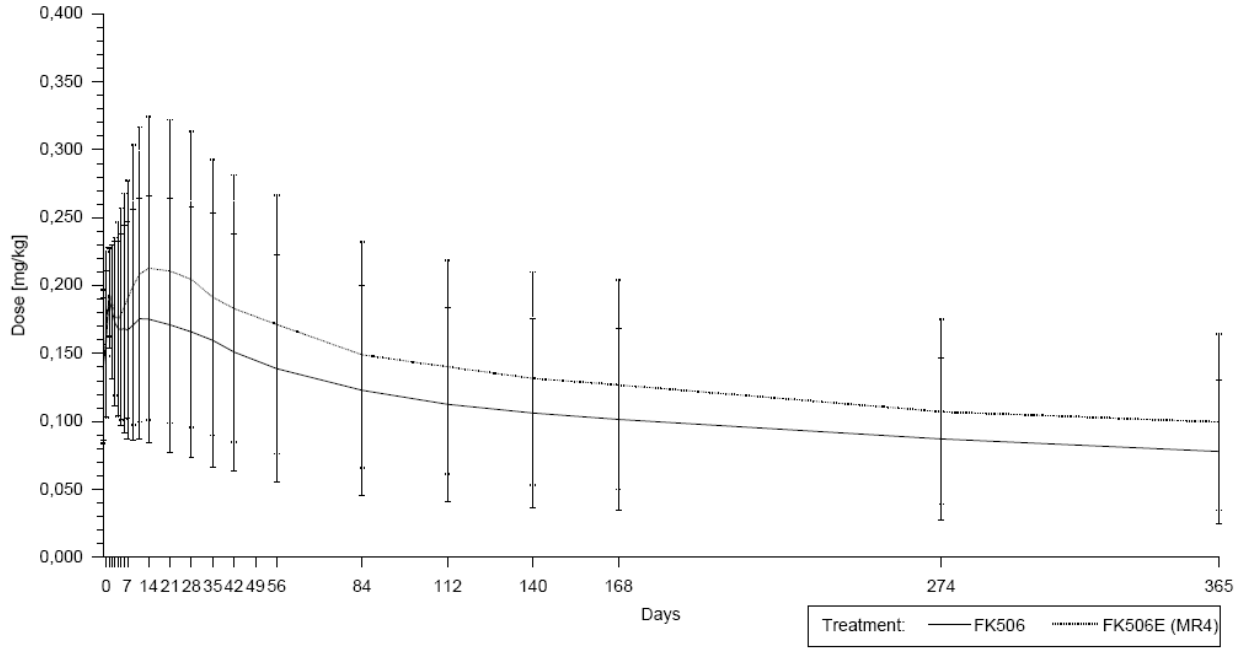
	TacXL (n=331)	Tac (n=336)
Randomized Treatment Days of Exposure Median	365.5	366
Daily dose of randomized treatment (mg/kg) Median		
Day 7	0.18	0.15
Month 1	0.18	0.14
Month 6	0.11	0.08
Month 12	0.09	0.07
Trough conc. rand. trt. Median		
Day 7	10.2	12.0
Month 1	12.0	12.6
Month 6	9.3	8.6
Month 12	8.1	8.1

Extracted from applicant's study report

Tacrolimus Administration in Study 12-03

The mean daily tacrolimus doses for the Per Protocol Set are summarized in the Applicant's Study Report Figure 2 (Figure 7 in this review) reproduced below.

Figure 7: Study 12-03 Mean Daily Tacrolimus Dose (mg/kg) (Per Protocol Set)



Source: Study 12-03 Applicant's Study Report Figure 14.1.1
FK-506 = Tac, and FK506E (MR4) = TacXL

The median and mean total daily tacrolimus dose was higher in the TacXL group compared to the Tac group.

> *Reviewer's Comment: While targeting similar trough whole blood concentrations, higher doses of TacXL appear to have been needed. Please see the FDA Clinical Pharmacology Review in DARRTS for further details.*

Mean whole blood tacrolimus trough levels for the Per Protocol Set in Study 12-03 are summarized in the Applicant's Study Report Table 11 reproduced below (Table 36 in this review).

Table 36: Study 12-03 Tacrolimus Trough Levels (ng/mL)

Time†	N	Tac (N=291)	N	TacXL (N=280)
Week 1	291	15.3 ± 5.7	280	12.9 ± 4.8
Week 2	278	12.4 ± 4.0	269	11.1 ± 4.0
Week 3	250	13.0 ± 4.3	226	12.0 ± 4.2
Week 4	244	12.9 ± 3.9	236	12.2 ± 3.9
Week 5	223	12.4 ± 3.9	216	12.6 ± 4.1
Week 6	182	12.3 ± 4.5	161	12.4 ± 4.2
Week 7 - 8	245	12.1 ± 3.7	234	12.1 ± 4.2
Week 9 - 12	275	11.6 ± 3.5	256	11.3 ± 3.3

Week 13 – 16	238	10.6 ± 3.1	206	10.6 ± 3.4
Week 17 - 20	188	10.0 ± 3.1	175	10.1 ± 3.1
Week 21 - 24	219	9.4 ± 3.3	219	9.8 ± 3.3
Week 25 - 26	160	9.0 ± 3.2	139	9.4 ± 3.2
Month 7 - 9	259	9.3 ± 3.2	234	9.5 ± 3.5
Month 10 – EOS-12M	264	9.0 ± 2.9	255	8.8 ± 2.7

Per Protocol Set
EOS = End of study, 12M = 12 months
Mean ± SD
† Mean during time period
Source: Study 12-03 Applicant's Study Report Table 13.4.2.1.4.1

Although the mean whole blood tacrolimus trough levels were slightly lower for TacXL compared to Tac at by 2.4 ng/mL at Week 1, by 1.2 ng/mL at Week 2, and still by 1.0 ng/mL at Week 3, the whole blood tacrolimus trough levels for MR4 and FK506 were generally comparable from Week 4 and on.

> *Reviewer's Comment: While tacrolimus dosing was started in Study 12-03 at a same mg/kg dose across treatment groups (pre-op dose of 0.1 mg/kg, followed by 0.2 mg/kg post-op), increases in tacrolimus dosing were needed to achieve similar whole blood concentrations, a goal that was only completely achieved at Week 4. Please see the Clinical Pharmacology Review in DARRTS for further discussion on compliance with targeted whole blood tacrolimus concentrations in this study.*
>
> *Recalling that the recommended trough whole blood tacrolimus concentrations in Study 12-03 were 10-15 ng/mL from transplantation to Day 28, 5-15 ng/mL from Day 29 to Day 168, and 5-10 ng/mL thereafter, this represents acceptable compliance with recommended target ranges across treatment groups in this study, which remained double-blind until the last subject had completed Week 24.*

Pharmacokinetic data from a subset of patients are presented in a separate report [FG-506E-12-03-R-PK] which is discussed in the FDA Clinical Pharmacology Review in DARRTS.

> *Reviewer's Comment: Overall, higher trough tacrolimus levels appear to have been maintained in Study 12-03 compared to Study 158, which may reflect in part the use of lower doses of MMF in Study 12-03 compared to those used in Study 158 as well as the ELiTE Study, described in Table 18 of the approved Prograf Package Insert copied below (Study 1 = ELiTE Study).*

Table 18. Tacrolimus Whole Blood Trough Concentrations (Study 1)

Time	**Median (P10-P90a) tacrolimus whole blood trough concentrations (ng/mL)**

Day 30 (N=366)	6.9 (4.4 – 11.3)
Day 90 (N=351)	6.8 (4.1 – 10.7)
Day 180 (N=355)	6.5 (4.0 – 9.6)
Day 365 (N=346)	6.5 (3.8 – 10.0)

7.2.1.2 Mycophenolate Mofetil Exposure

7.2.1.2.1 Mycophenolate Mofetil Exposure in Study 158

The recommended dosing of MMF in Study 158 was 2 grams per day split in two daily doses in accordance with the usage information from the Package Insert of CellCept®(mycophenolate mofetil). Because cyclosporine interferes with the enterohepatic recirculation of mycophenolic acid, but tacrolimus does not, it would be anticipated that equals doses of MMF would produce increased MPA exposure when used with tacrolimus compared to cyclosporine. [13] Thus, the pattern of MMF use across treatment arms was examined in Study 158. The Table below was generated with the assistance of the FDA Clinical Pharmacology Reviewer, during the review of Study 158 under NDA 50-811 in 2007 (Adapted from Table 39 in the Clinical Review of NDA 50-811, in DARRTS).

Table 37: Study 158 Average daily dose (mg/day) of MMF for the TacXL+MMF, Tac+MMF, and CYC+MMF treatment arms during different treatment periods

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

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

[13] Van Gelder T, Klupp J, Barten MJ, et al. Comparison of the effects of tacrolimus and cyclosporine on the pharmacokinetics of mycophenolic acid. Ther Drug Monit 2001;23:119-28.

Average daily dose for Days 31-90 = (2g * (45 -30) + (1.5g * (90-45)) /(90-30)=1.625 g
Average daily dose for Days 91-183 = (1.5g*(183-91))/(183-91)=1.5g
Average daily dose for Days 183-365 = (1.5g * (210-183))/(210-183)=1.5g
If MMF dose was stopped while Prograf, MR4 or Neoral was given, then MMF dose was considered 0.

Reviewer's Comment: Although there was considerable overlap with respect to average MMF daily dose across treatment groups, MMF dosing tended to be lower in the TacXL and Tac arms compared to the cyclosporine arm after Day 90 and more noticeably so after month 6.

7.2.1.2.2 Mycophenolate Mofetil Exposure in Study 12-03

As mentioned earlier in this review, the protocol for Study 12-03 recommended an initial dose of mycophenolate mofetil (MMF, Cellcept®) of 2 g/day (split into two doses) starting pre-operatively and given for the first 14 days of the study. Thereafter the MMF dose was reduced to 1 g/day (split into two doses) to be maintained throughout the study.

Total daily mycophenolate mofetil administration as maintenance therapy over the 12 months post-transplant is summarized in the Applicant's Study Report Table 12 reproduced below (Table 38 in this review):

Table 38: Study 12-03 Mean Daily Mycophenolate Mofetil Administration (g)

	N	Tac (N=336)	N	TacXL (N=331)
Day 0	291	1.65 ± 0.53	280	1.61 ± 0.55
Day 1	290	1.96 ± 0.24	280	1.95 ± 0.25
Day 3	290	1.96 ± 0.20	280	1.95 ± 0.27
Day 7	290	1.94 ± 0.24	280	1.92 ± 0.32
Day 14	288	1.73 ± 0.45	278	1.71 ± 0.49
Day 21	289	1.19 ± 0.41	276	1.23 ± 0.47
Day 28	289	1.15 ± 0.38	276	1.17 ± 0.42
Day 35	288	1.11 ± 0.34	274	1.10 ± 0.35
Day 42	288	1.10 ± 0.30	273	1.09 ± 0.35
Day 56	288	1.05 ± 0.28	272	1.07 ± 0.32
Day 84	286	1.03 ± 0.29	272	1.02 ± 0.30
Day 112	286	1.00 ± 0.28	272	1.00 ± 0.28
Day 140	285	0.99 ± 0.28	270	0.98 ± 0.30
Day 168	285	0.99 ± 0.28	266	0.97 ± 0.29
Day 274	275	0.97 ± 0.28	260	0.95 ± 0.32
Visit 11†	264	0.96 ± 0.27	252	0.95 ± 0.30

Per Protocol Set; Mean ± SD
† Completers only
Source: Applicant's Table 13.4.1.3

Reviewer's Comment: During the 12 months post-transplant, the observed mean doses of MMF (mean ± SD) were comparable across treatment groups, and there appears to have been reasonably good compliance in Study 12-03 with the protocol specified MMF doses of 1g BID, Day 1-14, and 0.5 g BID thereafter.

The current tacrolimus package insert contains information on time-averaged MMF dosing when used with tacrolimus from Study 158 (Table 22 in the Prograf® package insert includes information from the Tac treatment arm) and from the ELiTE Study (Table 19 in the Prograf® package insert) which are adapted below:

Table 39: MMF Dose Over Time in the Prograf/MMF Group (Study 158)

Time period (Days)	Time-averaged MMF dose (g/day)a		
	Less than 2.0	2.0	Greater than 2.0
0-30 (N=212)	25%	69%	6%
0-90 (N=212)	41%	53%	6%
0-180 (N=212)	52%	41%	7%
0-365 (N=212)	62%	34%	4%
Key: Time-averaged MMF dose=(total MMF dose)/(duration of treatment)			

a) Percentage of patients for each time-averaged MMF dose range during various treatment periods. Two grams per day of time-averaged MMF dose means that MMF dose was not reduced in those patients during the treatment periods.

Table 40: MMF Dose Over Time in Prograf/MMF (Group C - ELiTE-SYMPHONY Study)

Time period (Days)	Time-averaged MMF dose (grams per day)a		
	Less than 2.0	2.0	Greater than 2.0
0-30 (N=364)	37%	60%	2%
0-90 (N=373)	47%	51%	2%
0-180 (N=377)	56%	42%	2%
0-365 (N=380)	63%	36%	1%
Key: Time-averaged MMF dose = (total MMF dose)/(duration of treatment)			

a) Percentage of patients for each time-averaged MMF dose range during various treatment periods. Two grams per day of time-averaged MMF dose means that MMF dose was not reduced in those patients during the treatment periods.

Reviewer's Comment Continued: For the purpose of potential labeling, a table summarizing the MMF dosing in the TacXL groups of Studies 158 and 12-03 has been generated and is adapted below:

Table 41: MMF Dose Over Time in the Tac XL/MMF Group

Time period	Study 12-03	Study 158

(Days)	Time-averaged MMF dose (g/day)[a]			Time-averaged MMF dose (g/day)[a]		
	Less than 2.0	2.0	Greater than 2.0	Less than 2.0	2.0	Greater than 2.0
1-30	82%	17%	0	30%	64%	6%
1-90	93%	7%	0	42%	52%	7%
1-180	94%	6%	0	52%	44%	4%
1-365	95%	5%	0	56%	41%	3%
Key: Time-averaged MMF dose=(total MMF dose)/(duration of treatment)						

From day 14 on MMF doses in Study 12-03 remained substantially less than those used in Study 158 and is reflected in the choice of higher doses and trough concentrations of tacrolimus used in Study 12-03 compared to Study 158.

While the optimal combination of tacrolimus dosing (in the form of tacrolimus extended release or immediate release tacrolimus) and MMF dosing may remain to be determined, the combinations used and observed in Study 158 and Study 12-03, may represent reasonable alternatives, where increased doses of one agent compensate decreased doses of the other.

7.2.1.3 Other Concomitant Immunosuppression

In Study 158 as noted above all subjects received basiliximab induction immunosuppression as per the Simulect® label.

As mentioned earlier in this review, in Study 12-03 antibody administration was only permitted as rejection therapy. During the 12 months post-transplant including the extension period, administration of antibodies was comparable in the TacXL (8.5%) and Tac (6.3%) treatment groups [Source Applicant's Appendix 15.3.6.2.4.1], and is further summarized in the Applicant's Table 13.4.2.4.1 copied below (Table 42 in this review).

Table 42: Study 12-03 Antibody Administration

TABLE 13.4.2.4.1

ANTIBODY ADMINISTRATION^

	Number of Patients (%)					
	FK506 N=336			FK506E (MR4) N=331		
	N#	n	(%)	N#	n	(%)
Receiving treatment during:						
Week 1	336	12	(3.6)	331	13	(3.9)
Week 2	320	13	(4.1)	310	18	(5.8)
Week 3	312	9	(2.9)	301	14	(4.7)
Week 4	310	3	(1.0)	298	5	(1.7)
Week 5	308	0	(0.0)	297	1	(0.3)
Week 6	306	0	(0.0)	293	0	(0.0)
Week 7 - 8	303	0	(0.0)	292	1	(0.3)
Week 9 - 12	302	0	(0.0)	289	1	(0.3)
Week 13 - 16	299	0	(0.0)	281	1	(0.4)
Week 17 - 20	298	0	(0.0)	277	0	(0.0)
Week 21 - 24	293	0	(0.0)	275	0	(0.0)
Week 25 - 26	292	0	(0.0)	270	0	(0.0)
Month 7 - 9	290	0	(0.0)	266	0	(0.0)
Month 10 - EOS-12M	281	0	(0.0)	262	1	(0.4)
At any time during study		21	(6.3)		28	(8.5)

^ Only allowed as rejection therapy, but all cases of antibody administration are displayed
# Number of patients still in study at the beginning of time period

FK506 = Tac, FK506E (MR4) = TacXL

Reviewer's Comment: Most of the use of antibody in Study 12-03 appears to have been confined to the first 4 weeks after transplantation, which corresponds to the period of highest risk of rejection, during which treatment assignment was still blinded. Although only allowed as rejection therapy, one cannot exclude the possibility that some in some cases antibody therapy may have been used as adjunct to induction tacrolimus/MMF/corticosteroid therapy in patients who would have experienced early graft dysfunction. The slightly greater use of antibody in the TacXL group could be related the higher rates of steroid resistant rejection in the TacXL group and could reflect the numerically lower tacrolimus whole blood trough concentrations in the TacXL group during the first three weeks after transplantation.

Reviewer's Comment: The overall clinical experience, with respect to exposure, as measured by dosing, duration of dosing, number of patients and

demographics of target populations, is adequate to evaluate the safety of tacrolimus extended release capsules in the intended population of renal allograft recipients.

7.2.2 Explorations for Dose Response

Exploratory exposure/responses are described in the FDA Pharmacometrics and Clinical Pharmacology Reviews in DARRTS.

Reviewer's Comment: The small number and incidence of events of interest and narrow range of observed doses and whole blood concentrations (since TDM based on prespecified target ranges were used in all clinical studies) limited the ability of such analyses to detect clinically meaningful exposure response relationships.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

7.2.4.1 Routine Clinical Testing in Study 158

As per the Clinical Review of NDA 50-811 in DARRTS the following procedures were followed in Study 158:

Procedures Performed on Day 1
The following procedures were to be completed on day 1:

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

Procedures Performed on Day 2 Through Month 10

- Clinical assessment of patient and graft status was performed at all study visits.
- Vital signs.
- Adverse events were recorded at all study visits.

- Routine clinical laboratory assessments were obtained per the schedule provided in the protocol.
- Samples for whole blood tacrolimus or cyclosporine trough levels were obtained at all study visits.
- Samples for mycophenolic acid trough levels were obtained at months 1 and 6.
- Quality of Life Questionnaire was completed by patients at months 1 and 6.
- ECG was performed on day 14.
- Samples for anti-HLA antibodies (class I and II), TGF-beta, HbA1C, and CRP levels were obtained at month 6.
- Study drug dosing information was recorded at all study visits.
- Concomitant medication information was recorded at all study visits.
- If warranted, and based on clinical assessments, additional samples for evaluation may have obtained at any study visit.

Procedures Performed at Month 12 or Last Day of Study Drug Dosing

- Clinical assessment of patient and graft status was performed.
- Physical examination was performed.
- All adverse events and concomitant medication information were recorded.
- ECG was performed.
- Vital signs, including oral body temperature, pulse rate, blood pressure, and weight were obtained.
- Samples for routine clinical laboratory testing were obtained.
- Sample for whole blood tacrolimus or cyclosporine trough level was obtained.
- Sample for mycophenolic acid trough level was obtained.
- Patient and graft survival information was documented for all patients at month 12.
- Quality of Life Questionnaire was completed by patient.
- Samples for anti-HLA antibodies (class I and II), TGF-beta, HbA1C, and CRP levels were obtained.
- Drug accountability was completed.
- Patients randomized to receive Prograf or Neoral were converted to commercial drug supplies.
- Patients randomized to receive MR4 who were continuing into the clinical continuation phase of the study were provided with MR4 supplies.

Unscheduled Study Visits

All unscheduled visits involving adverse events were to be documented on the patient's CRF. Samples for study drug trough levels were to be obtained at all unscheduled visits, prior to receiving the next dose of study drug.

> *<u>Reviewer's Comment</u>: The protocol specified procedures for Study 158, including but not limited to routine clinical testing, are acceptable.*

7.2.4.2 Routine Clinical Testing in Study 12-03

A patient's participation in Study 12-03 was to be for a minimum of 12 months. All visits were calculated from the day of transplantation, which was the day of reperfusion and defined as Day 0.

A summary of the planned visits and assessments and their timing in Study 12-03 is provided in the Applicant's Table 1 copied below (Table 43 in this review):

Table 43: Study 12-03 Visits and Assessments

Table 1 Visits and Assessments

	Treatment period 1									Treatment period 2[6]		Treatment period Extension visits[7]
Assessment	Visit 1 Baseline	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11 EOS	every 3 months[5] ± 14 days[5]
Day	0	1	3	7	14 ± 3	28 ± 3	56 ± 3	84 ± 3	168 ± 7	274 ± 14	365 ± 14	
Week[8]				1	2	4	8	12	24			
Month[8]						1	2	3	6	9	12	
Informed consent[1]	x											
Inclusion / exclusion criteria	x											
Randomization and patient number allocation	x											
Surgical details, donor and donor organ data	x											
Primary diagnosis / secondary diagnoses	x											
Medical history / pre-study medication	x											
Physical examination	x					x	x	x	x	x	x	x
Body weight	x	x	x	x	x	x	x	x	x	x	x	x
ECG	x								x		x	
Vital signs	x	x	x	x	x	x	x	x	x	x	x	x
Laboratory assessments	x[2,4]	x	x	x	x	x	x	x	x[4]	x	x[2,4]	x
Tacrolimus whole blood trough levels[3]		x	x	x	x	x	x	x	x	x	x	x
Rejection episodes, adverse events, tacrolimus dose, concomitant medication, days of dialysis, days hospitalized – Continuous assessment												

1. Informed consent was obtained during the waiting period for transplantation; patients might have signed the patient informed consent form after receiving notice that the organ is currently available. Where informed consent was obtained more than 3 months prior to transplantation, it was recommended to obtain a second informed consent.
2. Urine or serum pregnancy test (ß-HCG) in females of childbearing age (Baseline and Visit 11/EOS)
3. Tacrolimus whole blood trough level measurements were performed daily during the first week post-transplant, thereafter three times per week until discharge from hospital and thereafter at all scheduled visits, and as clinically indicated.
4. Including glycosylated haemoglobin, HDL, LDL, triglycerides, cholesterol
5. Until unblinding of the study.
6. An additional unblinding visit for exchanging the study medication should ensue one month at the latest after the investigator has been informed by the sponsor in writing about the unblinding. Assessments as described in Visit 10 can be performed if deemed necessary from a clinical point of view.
7. An additional unblinding visit should ensue one month at the latest after the investigator has been informed by the sponsor in writing about the unblinding. All assessments as described in treatment period Extension visits should be performed.
8. For orientation purposes only

A summary of the planned laboratory assessments and their timing in Study 12-03 is provided in the Applicant's Table 2 copied below (Table 44 in this review):

Table 44: Study 12-03 Laboratory Assessments

Table 2 Laboratory Assessment Schedule

	Treatment period 1									Treatment period 2		Treatment period Extension visits
Value	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	every 3 months
Day	0	1	3	7	14 ± 3	28 ± 3	56 ± 3	84 ± 3	168 ± 7	274 ± 14	365 ± 14	± 14 days
Week				1	2	4	8	12	24			
Month						1	2	3	6	9	12	
Urine or serum pregnancy test	x										x	
Haematology: - Red blood cells - Haemoglobin - Hematocrit - White blood cells - Platelets	x	x	x	x	x	x	x	x	x	x	x	x
Biochemistry: - Sodium - Potassium - Glucose[1] - Serum creatinine[1] -Aspartate aminotransferase (AST) / Serum glutamyl oxaloacetic transaminase (SGOT) - Alanine aminotransferase (ALT) / Serum glutamyl pyruvate transaminase (SGPT) - Gamma glutamyl transferase (γ-GT) - Alkaline phosphatase - Total bilirubin - Albumin	x	x	x	x	x	x	x	x	x	x	x	x
- Glycosylated haemoglobin - High density lipoprotein (HDL) - Low density Lipoprotein (LDL) - Cholesterol - Triglyceride	x								x		x	

Reviewer's Comment: The protocol specified procedures for Study 12-03, including but not limited to routine clinical testing for Study 12-03, are acceptable.

7.2.5 Metabolic, Clearance, and Interaction Workup

The active ingredient in TacXL is the same as in Prograf® (tacrolimus), with which routine in vitro and in vivo assessments have been previously addressed. Since tacrolimus is metabolized mainly by CYP3A enzymes, drugs or substances known to inhibit these enzymes may increase tacrolimus whole blood concentrations. Drugs known to induce CYP3A enzymes may decrease tacrolimus whole blood concentrations. Please see the Clinical Pharmacology Review in DARRTS for more information.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The potential hazards of tacrolimus and of similar drugs in the class of immunosuppressants are addressed in Section 2.4, Important Safety Issues with Consideration to Related Drugs, and in Section 7.3.4, Significant Adverse Events, of this review.

7.3 Major Safety Results

7.3.1 Deaths

7.3.1.1 Deaths in Study 158

A total of 10 deaths in the Tac group, 2 deaths in the TacXL group and 6 deaths in the cyclosporine group were observed up to one year after transplantation. The table below adapted from Table 40 in the Clinical Review of NDA 50-811 summarizes deaths up to one-year post-transplantation with comments regarding potential causes of death, related to immunosuppression.

Table 45: Study 158 Summary of Patient Deaths

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

00712001	55	CYC	55	Probable pulmonary embolus	

Patient base: Full analysis set; all randomized patients who received at least one dose of study drug. Patient Number 10222007 (CYC/MMF) died on day 19 but was never administered study drug. This patient is not included in the full analysis set and, therefore, is not included in this table. After day 365, two patients died (Patient Numbers 01812009 [CYC/MMF] and 07502001 [Tac/MMF]) and are included in this table but were not included in any efficacy analyses.
† Last dose of randomized study drug. Source: Study 158 Report Appendices 14.4.4.1 and 14.4.4.2.

Reviewer's Comments: The imbalance in deaths at 12 months after transplantation among patients receiving Tac/MMF compared to those receiving cyclosporine/MMF, appears to be driven by cases attributed to hazards of immunosuppression, based on the assessment of the primary cause of deaths in the case report forms and patient narratives. Although the attribution of cause of death in kidney transplant recipients is notoriously difficult, there appears to be a discernible pattern of deaths due to hazards of immunosuppression in the Tac group compared to the TacXL and cyclosporine group. One cannot exclude that increased exposure to mycophenolic acid (MPA) in patients treated with Tac and MMF could have contributed to a degree of immunosuppression greater than that observed in those treated with cyclosporine and MMF, given that cyclosporine inhibits the enterohepatic recirculation of MPA, and tacrolimus does not.

Although, subjects randomized to TacXL were exposed to similar whole blood trough concentrations of tacrolimus, compared to the Tac group, as well as similar doses of MMF, no imbalance with respect to mortality is observed compared to the cyclosporine group.

In subject 00292003, randomized to TacXL one cannot exclude the role of gastroenteritis, a known hazard of MMF, which as we will see below was observed more frequently in the tacrolimus groups, in the events that could have contributed to the cardiac and respiratory arrest (potentially related to electrolyte and fluid abnormalities resulting from the gastroenteritis).

7.3.1.2 Deaths in Study 12-03

As described in section 6.1.4.2 of this review a total of 18 subjects died during the 12 month study period in Study 12-03, 8 in the Tac group and 10 in the TacXL group. Of the 18 patients, six patients died during the 12-months post-transplant and twelve patients died following discontinuation from the study (See Table 46 below adapted from Applicant's Table 25).

Table 46: Study 12-03 Cause of Death during 12 Months Post-Transplant

Patient number	Cause of death MedDRA preferred term (investigator term)	Relationship to study drug†	Day of death	Days since last dose

Tac				
H1006	PCP pneumonia	No assessment¥	360‡	245
H1405	Cardiac arrest (cardiac arrest)	Unlikely	5	1
H2415	Multi organ dysfunction	No assessment¥	337‡	254
H2506	Unknown§	No assessment	127‡	125
H2702	Rectocolic adenocarcinoma	Possible	350	0
H4705	Sudden death§	No assessment	163‡	158
H7501	Multiple tumor disease	No assessment	182‡	54
H8203	Cardiac arrest§	No assessment	84‡	73
TacXL				
H1706	Uremia due to graft failure§	No assessment	136‡	79
H2507	Pulmonary adenocarcinoma with hepatic metastasis	No assessment¥	209‡	145
H3702	Septic shock (septic shock [bacterial])	Unlikely	5	0
H4714	Sudden death	No assessment¥	193‡	101
H5410	Interstitial pneumonitis	Possible	352‡	27
	Normocytic, normochronic anemia	Unlikely	352‡	
H5710	Septic shock (septic shock)	Definitely not	9‡	1
H6203	Acute pulmonary edema (acute pulmonary edema)	Unlikely	2	0
H6801	Heart infarction	Unlikely	322	1
H7102	Septic shock	Probable	180‡	126
H8404	Viral pneumonia	Probable	322	22

Modified Full Analysis Set
PCP = Pneumocystis carinii pneumonia
† Investigator assessed; ‡ Patient died after withdrawal from study; § Investigator term; ¥ No assessment done because death of patient occurred after final visit of 12-month period.
Source: Applicant's Study 12-03 Report Appendices 15.4.5.6 and 15.4.6.8

There was no discernible pattern of causes of death during the study an following withdrawal. The number of deaths reported during the study was comparable across treatment groups.

It is further noted that a total of four causes of deaths (for one patient, two causes of death were indicated) were considered by the investigator (blinded to treatment assignment) to have a relationship to study drug. Two deaths (septic shock and viral pneumonia) were considered as probable related to TacXL. These deaths are described by the Applicant below:

Patient H7102 (septic shock)

Patient H7102 died on Day 180 (i.e. 126 days after study drug discontinuation and withdrawal from the study) due to septic shock following severe bacterial sepsis on Day 54 caused by a pathogen not further specified. The study drug was discontinued and the patient was treated with ciprofloxacin from Day 47 to Day 57, cefotaxime from Day 57 to Day 61, and gentamicin on Day 61. The event was ongoing at the time of

withdrawal from the study on Day 61. In addition, the patient suffered from moderate angina pectoris (Day 9 to 11), severe myocardial ischemia (Day 39 and ongoing on time of withdrawal), severe cardiac arrest, and graft dysfunction (Day 50). The patient suffered graft loss on Day 125 due to ongoing dialysis.

Patient H8404 (viral pneumonia)

Patient H8404 died on Day 322 (i.e 22 days after study drug discontinuation and withdrawal from the study) due to pneumonia viral. On Day 301, the patient developed a severe pneumonia viral. The study medication was discontinued and the patient treated with ceftazidime and clarithromycin (Day 302 to 322), amikacin (Day 303 to 304), fluconazole, and ganciclovir (Day 303 to 322). The patient also had graft loss on this day due to ongoing dialysis.

In addition, there were two more deaths in the Tac group during the extension period (days of death 552 and 564), due to lower respiratory tract infection (bacterial) for one patient and invasive *aspergillus fumigatus* for the second patient.

> *Reviewer's Comment: The MedDRA preferred terms for stated cause of death are in general agreement with review of the patient narratives for deaths included in the appendix of the Applicant's study report. Recognizing that attribution of cause of deaths in renal transplantation patients is notoriously complex, the types of causes observed in this study are typical for solid organ transplantation and no particular pattern of difference was observed between treatment groups in Study 12-03. In particular, unlike Study 158, there were no greater number of deaths, or deaths due to apparent infectious causes (suggestive of overimmunosuppression) in the Tac group compared to the TacXL group in Study 12-03.*

7.3.2 Nonfatal Serious Adverse Events

7.3.2.1 Nonfatal Serious Adverse Events in Study 158

Nonfatal serious adverse events in Study 158 are represented below in Table 47 adapted from Table 41 in the FDA Clinical Review of NDA 50-811.

Table 47: Study 158 Summary of Treatment-Emergent Serious Adverse Events Not Resulting in Death Occurring ≥ 1% in Any Treatment Group

MedDRA (v. 6.1) System Organ Class Preferred Term	Treatment Group		
	Tac (n = 212)	TacXL (n = 214)	CYC (n = 212)
All Systems			
Any Adverse Event	109 (51.4%)	97 (45.3%)	110 (51.9%)
Infections and Infestations			
Cytomegalovirus Infection	12 (5.7%)	10 (4.7%)	11 (5.2%)

Urinary Tract Infection	7 (3.3%)	8 (3.7%)	11 (5.2%)
Human Polyomavirus Infection	4 (1.9%)	1 (0.5%)	1 (0.5%)
Urosepsis	4 (1.9%)	2 (0.9%)	2 (0.9%)
Pyelonephritis	3 (1.4%)	2 (0.9%)	2 (0.9%)
Sepsis	2 (0.9%)	3 (1.4%)	1 (0.5%)
Pneumonia	1 (0.5%)	1 (0.5%)	3 (1.4%)
Gastroenteritis	0	9 (4.2%)	1 (0.5%)
Gastrointestinal Disorders			
Diarrhea	9 (4.2%)	8 (3.7%)	3 (1.4%)
Nausea	4 (1.9%)	4 (1.9%)	2 (0.9%)
Vomiting	4 (1.9%)	5 (2.3%)	4 (1.9%)
Abdominal Pain	3 (1.4%)	1 (0.5%)	4 (1.9%)
Abdominal Strangulated Hernia	0	0	3 (1.4%)
Metabolism and Nutrition Disorders			
Dehydration	7 (3.3%)	7 (3.3%)	5 (2.4%)
Hyperglycemia	4 (1.9%)	5 (2.3%)	0
Diabetes Mellitus Inadequate Control	3 (1.4%)	1 (0.5%)	1 (0.5%)
Diabetes Mellitus	2 (0.9%)	5 (2.3%)	4 (1.9%)
Hyperkalemia	2 (0.9%)	5 (2.3%)	1 (0.5%)
Injury, Poisoning, and Procedural Complications			
Graft Dysfunction	4 (1.9%)	2 (0.9%)	2 (0.9%)
Therapeutic Agent Toxicity	4 (1.9%)	2 (0.9%)	1 (0.5%)
Investigations			
Blood Creatinine Increased	11 (5.2%)	8 (3.7%)	13 (6.1%)
Renal and Urinary Disorders			
Hydronephrosis	2 (0.9%)	1 (0.5%)	4 (1.9%)
Renal Failure Acute	2 (0.9%)	3 (1.4%)	3 (1.4%)
Hematuria	0	3 (1.4%)	4 (1.9%)
Vascular Disorders			
Deep Vein Thrombosis	5 (2.4%)	4 (1.9%)	2 (0.9%)
Hypotension	2 (0.9%)	4 (1.9%)	1 (0.5%)
Lymphocele	2 (0.9%)	1 (0.5%)	4 (1.9%)
Blood and Lymphatic System Disorders			
Anemia	3 (1.4%)	4 (1.9%)	1 (0.5%)
General Disorders and Administrative Site Condition			
Pyrexia	3 (1.4%)	2 (0.9%)	7 (3.3%)
Cheat Pain	2 (0.9%)	3 (1.4%)	0
Nervous System Disorders			
Convulsion	3 (1.4%)	1 (0.5%)	1 (0.5%)
Endocrine Disorder			
Hyperparathyroidism Tertiary	3 (1.4%)	0	0

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

Source: Applicant's Study Report Table 13.5.1.5 and Appendix 14.4.4.1.

The tables below, adapted from Tables 42-45 in the Clinical Review of NDA 50-811, compare the serious adverse events among TacXL, Tac and cyclosporine.

Table 48: Serious Adverse Events in Study 02-0-158: Higher in TacXL than Cyclosporine

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

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

Table 49: Serious Adverse Events in Study 02-0-158: Higher in Tac than Cyclosporine

MedDRA (v. 6.1) System Organ Class Preferred Term	**Tac (n=212)**	**CYC (n=212)**
Blood and Lymphatic System Disorders		
Anemia	3 (1.4%)	1 (0.5%)
Endocrine Disorders		

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

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

Table 50: Serious Adverse Events in Study 158: Higher in TacXL than Tac

MedDRA (v. 6.1) System Organ Class Preferred Term	**TacXL (n=214)**	**Tac (n=212)**
Blood and Lymphatic System Disorders		
Anemia	4 (1.9%)	3 (1.4%)
Gastrointestinal Disorders		
Vomiting	5 (2.3%)	4 (1.9%)
General Disorders and Administration Site Conditions		
Chest Pain	3 (1.4%)	2 (0.9%)
Infections and Infestations		
Gastroenteritis	9 (4.2%)	0

Urinary Tract Infection	8 (3.7%)	7 (3.3%)
Metabolism and Nutrition Disorders		
Hyperglycemia	5 (2.3%)	4 (1.9%)
Diabetes Mellitus	5 (2.3%)	2 (0.9%)
Hyperkalemia	5 (2.3%)	2 (0.9%)
Renal and Urinary Disorders		
Renal Failure Acute	3 (1.4%)	2 (0.9%)
Hematuria	3 (1.4%)	0
Vascular Disorders		
Hypotension	4 (1.9%)	2 (0.9%)

Full analysis set: all patients who received at least one dose of study drug. Within a MedDRA class, patients may have reported more than one adverse event. The sum of the terms by organ class may exceed 100%. Serious adverse events in this table occurred in ≥ 1% of patients in the MR4 arm and had an incidence greater than that in the Prograf arm.
Source: Study 02-0-158, Table 13.5.1.5, Table 9 Summary of Clinical Safety

Table 51: Serious Adverse Events in Study 158: Higher in Tac than TacXL

MedDRA (v. 6.1) System Organ Class Preferred Term	Tac (n=212)	TacXL (n=214)
Endocrine Disorders		
Hyperparathyroidism tertiary	3 (1.4%)	0
Gastrointestinal Disorders		
Diarrhea	9 (4.2%)	8 (3.7%)
Abdominal Pain	3 (1.4%)	1 (0.5%)
General Disorders and Administration Site Conditions		
Pyrexia	3 (1.4%)	2 (0.9%)
Infections and Infestations		
Cytomegalovirus Infection	12 (5.7%)	10 (4.7%)
Sepsis	4 (1.9%)	3 (1.4%)
Urosepsis	4 (1.9%)	2 (0.9%)
Human Polyomavirus Infection	4 (1.9%)	1 (0.5%)
Pyelonephritis	3 (1.4%)	2 (0.9%)
Strongyloidiasis	3 (1.4%)	0
Injury, Poisoning and Procedural Complications		
Graft Dysfunction	4 (1.9%)	2 (0.9%)
Therapeutic Agent Toxicity	4 (1.9%)†	2 (0.9%)‡
Investigations		
Blood Creatinine Increased	11 (5.2%)	8 (3.7%)
Metabolism and Nutrition Disorders		
Diabetes Mellitus Inadequate Control	3 (1.4%)	1 (0.5%)
Nervous System Disorders		
Convulsions	3 (1.4%)	1 (0.5%)
Respiratory, Thoracic and Mediastinal Disorders		

Pulmonary Embolism	3 (1.4%)	1 (0.5%)
Vascular Disorders		
Deep Vein Thrombosis	5 (2.4%)	4 (1.9%)

Full analysis set: all patients who received at least one dose of study drug. Within a MedDRA class, patients may have reported more than one adverse event. The sum of the terms by organ class may exceed 100%. Serious adverse events in this table occurred in ≥ 1% of patients in the Prograf arm and had an incidence greater than that in the MR4 arm.
† Includes the following Investigator descriptions: Prograf toxicity (2), tacrolimus toxicity (1), FK toxicity (1). ‡ Includes the following Investigator descriptions: tacrolimus toxicity (1), acute renal failure due to Prograf toxicity (1).
Source: Study 02-0-158, Table 13.5.1.5, Table 10 Summary of Clinical Safety

Reviewer's Comment: Events associated with diabetes were more common in the tacrolimus groups compared to the cyclosporine group, consistent with the labeled increased risk of new onset diabetes after transplantation and/or post-transplant diabetes mellitus, associated with the use of tacrolimus as described in the Prograf package insert.

It is further noted that serious adverse events of diarrhea and anemia (known potential hazards or MMF and MPA) were numerically greater in the TacXL and Tac arms compared to the cyclosporine arm. Although this may be interpreted as consistent with potentially higher exposure to MPA, since unlike cyclosporine, tacrolimus does not inhibit the enterohepatic recirculation of MPA, the overall differences are not very striking.

In addition, there were more events of gastroenteritis reported as infections in the TacXL group compared to the Tac or cyclosporine group.

7.3.2.2 Nonfatal Serious Adverse Events in Study 12-03

Nonfatal serious adverse events in Study 12-03 are represented below in Table 52 adapted from Table 26 in the Applicant's study report.

Table 52: Study 12-03 Incidence of Most Frequently Reported Serious Adverse Events Regardless of Relationship to Study Medication

MedDRA SOC MedDRA High Level Term *MedDRA Preferred Term*	**Tac (N=336) Patients (%)**	**TacXL (N=331) Patients (%)**
Infections and infestations	**64 (19.0)**	**79 (23.9)**
Bacterial infections NEC	26 (7.7)	31 (9.4)
Urinary tract infection bacterial	18 (5.4)	17 (5.1)
Bacterial pyelonephritis†	3 (0.9)	12 (3.6)
Cytomegaloviral infections	13 (3.9)	15 (4.5)
Cytomegalovirus infection	11 (3.3)	14 (4.2)

Infections NEC	8 (2.4)	9 (2.7)
Lower respiratory tract and lung infections	2 (0.6)	8 (2.4)
Renal and urinary disorders	**58 (17.3)**	**51 (15.4)**
Renal vascular and ischaemic conditions	21 (6.3)	18 (5.4)
Renal tubular necrosis	11 (3.3)	9 (2.7)
Renal failure and impairment	16 (4.8)	7 (2.1)
Renal failure acute	7 (2.1)	3 (0.9)
Ureteric disorders NEC	11 (3.3)	8 (2.4)
Ureteric stenosis	10 (3.0)	4 (1.2)
Nephropathies and tubular disorders NEC	7 (2.1)	13 (3.9)
Nephropathy toxic	6 (1.8)	9 (2.7)
Injury, poisoning and procedural complications	**31 (9.2)**	**34 (10.3)**
Non-site specific procedural complications	26 (7.7)	21 (6.3)
Graft dysfunction	12 (3.6)	13 (3.9)
Investigations	**25 (7.4)**	**17 (5.1)**
Renal function analyses	24 (7.1)	16 (4.8)
Blood creatinine increased	21 (6.3)	13 (3.9)
Gastrointestinal disorders	**23 (6.8)**	**22 (6.6)**
Diarrhoea (excl. infective)	5 (1.5)	8 (2.4)
Diarrhoea	5 (1.5)	8 (2.4)
Vascular disorders	**19 (5.7)**	**18 (5.4)**
Metabolism and nutrition disorders	**15(4.5)**	**17 (5.1)**
Diabetes mellitus (incl. subtypes)	8 (2.4)	8 (2.4)
Respiratory, thoracic and mediastinal disorders	**11 (3.3)**	**9 (2.7)**
Cardiac disorders	**11 (3.3)**	**11 (3.3)**
Ischemic coronary artery disorders	**8 (2.4)**	**5 (1.5)**
Blood and lymphatic system disorders	**7 (2.1)**	**10 (3.0)**

Full Analysis Set
Adverse events coded using MedDRA 6.1; Most frequently reported defined as incidence rate of at least 2% in either treatment group
† p=0.019 (Fisher's exact test)
MedDRA = Medical Dictionary for Drug Regulatory affairs; SOC = System Organ Class; NEC = Not elsewhere classified
Source: Study 12-03 Table 13.6.1.4

The incidence of the most frequently reported serious adverse events regardless of relationship to study medication appears generally comparable between TacXL and Tac. It is noted that bacterial pyelonephritis were more commonly reported as serious adverse events in the TacXL group compared to the Tac group (p=0.019 by Fisher's exact test). Bacterial pyelonephritis was reported in three patients in the Tac group and twelve patients in the TacXL group. Bacterial pyelonephritis of five patients (one in Tac and four in the TacXL group) was considered related to study medication; there was no statistical significant difference.

In addition, five hemorrhages were recorded in the study (TacXL group), four of which were hematoma and none were considered related to study medication, representing an

incidence <2% in the TacXL group (therefore not included in the table above), higher than in the Tac group (p=0.030 by Fisher's exact test).

> *Reviewer's Comment: Such a difference with respect to incidence of pyelonephritis reported as an adverse event was not observed in Study 158. The clinical significance of this finding is uncertain.*

The Applicant has also presented a tabulation of the incidence of most frequently reported serious adverse events assessed by the investigator (mostly blinded to treatment assessment in Study 12-03) as being causally-related to study medication, and no statistically significant differences were observed between Tac and TacXL (See Table 27 in the Applicant's study report).

7.3.3 Dropouts and/or Discontinuations

7.3.3.1 Dropouts and Discontinuations in Study 158

The table below adapted from Table 47 in the clinical review of NDA 50-811 summarizes the overall profile of dropouts/discontinuation from study medication, where adverse events remained the leading reason for discontinutations.

Table 53: Study 158 Summary of Subject Dispositions

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

> *Reviewer's Comment: Although fewer subjects randomized to TacXL discontinued from study medication compared to the other groups, comparisons across treatment groups, discontinuation from randomized treatment should be interpreted with caution in this open-label study, all the more that patients randomized to TacXL were allowed to receive TacXL for up to 3 years after transplantation, while those who discontinued cyclosporine would return to local*

standard of care, which was represented by tacrolimus+MMF as the preferred regimen in the US during the period of Study 158's conduct.

Table 54 below, adapted from Table 48 in the clinical review of NDA 50-811 summarizes the treatment emergent serious adverse events that led to discontinuation from study medication.

Table 54: Study 158 Incidence of Treatment Emergent Serious Adverse Events that Led to Discontinuation

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

Any AE	1 (0.5%)	2 (0.9%)	3 (1.4%)
Subdural Hematoma	1 (0.5%)	0	0
Drug Toxicity	0	0	2 (0.9%)
Graft Dysfunction	0	0	1 (0.5%)
Incision Site Complication	0	1 (0.5%)	0
Therapeutic Agent Toxicity	0	1 (0.5%)	0
Investigations			
Any AE	1 (0.5%)	0	2 (0.9%)
Blood Creatinine Increased	1 (0.5%)	0	0
Urine Output Decreased	0	0	2 (0.9%)
Metabolism and Nutrition Disorders			
Any AE	1 (0.5%)	1 (0.5%)	0
Diabetes Mellitus	1 (0.5%)	0	0
Diabetes Mellitus Inadequate Control	0	1 (0.5%)	0
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polys)			
Any AE	1 (0.5%)	0	1 (0.5%)
Metastatic Renal Cell Carcinoma	1 (0.5%)	0	0
Lymphoproliferative Disorder	0	0	1 (0.5%)
Social Circumstances			
Any AE	1 (0.5%)	0	0
Murder	1 (0.5%)	0	0
Surgical and Medical Procedures			
Any AE	1 (0.5%)	0	0
Nephrectomy	1 (0.5%)	0	0
Musculoskeletal and Connective Tissue Disorders			
Any AE	0	1 (0.5%)	0
Arthralgia	0	1 (0.5%)	0
Nervous System Disorders			
Any AE	0	0	1 (0.5%)
Encephalitis	0	0	1 (0.5%)
Vascular Disorders			
Any AE	0	0	1 (0.5%)
Hypotension	0	0	1 (0.5)

Full Analysis Set: All Randomized subjects who received at least one dose of study medication.
Within a MedDRA system organ class, a patient may experience more than one adverse event. The sum of the terms may exceed
100%.

<u>Reviewer's Comment</u>: No discernible pattern of serious events leading to discontinuation of study medication could be identified across treatment groups.

7.3.3.2 Dropouts and Discontinuations in Study 12-03

Withdrawal due to an adverse event occurred in 13.0% of TacXL patients and 11.6% of Tac patients. Table 55 below, adapted from Table 28 in the Applicant's study report summarizes the adverse events that resulted in discontinuation from study medication.

Table 55: Study 12-03 Incidence of Most Frequently Reported Adverse Events Leading to Discontinuation, Regardless of Relationship to Study Medication

MedDRA SOC MedDRA High Level Term *MedDRA Preferred Term*	**Tac (N=336) Patients (%)**	**TacXL (N=331) Patients (%)**
Renal and urinary disorders	**10 (3.0)**	**9 (2.7)**
Renal vascular and ischaemic conditions	7 (2.1)	6 (1.8)
Renal artery thrombosis	2 (0.6)	2 (0.6)
Renal vein thrombosis	2 (0.6)	2 (0.6)
Injury, poisoning and procedural complications	**9 (2.7)**	**9 (2.7)**
Non-site specific procedural complications	9 (2.7)	8 (2.4)
Graft dysfunction	4 (1.2)	5 (1.5)
Graft thrombosis	3 (0.9)	1 (0.3)
Gastrointestinal disorders	**4 (1.2)**	**1 (0.3)**
Infection and infestations	**3 (0.9)**	**10 (3.0)**
Sepsis, bacteraemia and viraemia	0	3 (0.9)
Septic shock	0	2 (0.6)
Neoplasm benign, malignant and unspecified (incl. cysts and polyps)	**3 (0.9)**	**0**
Blood and lymphatic system disorders	**2 (0.6)**	**2 (0.6)**
Coagulopathies	0	2 (0.6)
Thrombotic microangiopathy	0	2 (0.6)
Cardiac disorders	**2 (0.6)**	**2 (0.6)**
Ischemic coronary artery disorders	2 (0.6)	1 (0.3)
Mycoardial infarction	2 (0.6)	1 (0.3)
Metabolism and nutrition disorders	**1 (0.3)**	**3 (0.9)**
Diabetes mellitus (incl. subtypes)	0	3 (0.9)
Vascular disorders	**1 (0.3)**	**2 (0.6)**
Skin and subcutaneous tissue disorders	**2 (0.6)**	**0**

Full Analysis Set
Adverse events coded using MedDRA 6.1; Most frequently reported defined as incidence rate of at least 0.6%1% in either treatment group
There were no differences in incidence between FK506 and MR4 associated with a p-value < 0.05 (Fisher's exact test)
MedDRA = Medical Dictionary for Drug Regulatory affairs; SOC = System Organ Class
Source: Applicant's Study 12-03 Report Table 13.6.1.7

There were no differences in the incidence of the most frequently reported adverse events leading to discontinuation from the study between TacXL and Tac associated with a p-value < 0.05 (Fisher's exact test).

> *Reviewer's Comment: Overall, in the open label Study 158 or the double blind Study 12-03 there were no significant differences in the incidence of reported adverse events leading to discontinuation from study medication. The increased incidence of discontinuation from cyclosporine in Study 158, compared to the tacrolimus groups, needs to be interpreted with caution, given the differences in apparent incentives related to continuation or discontinuation of study drug.*

7.3.4 Significant Adverse Events

Organ transplant recipients experience many adverse events that would be considered significant adverse events according to ICH definition because of the nature of the surgical procedure and the level of systemic immunosuppression. Therefore, the tables of serious adverse events that did not lead to death (see tables above in Section 7.3.2 above) adequately characterize the types of risks that would be seen with the use of tacrolimus and tacrolimus extended release.

Adverse events of interest due to their know association with the use of tacrolimus and other systemic immunosuppressants including mycophenolate mofetil were evaluated in Study 158 and Study 12-03. These include infections, renal function disorders, glucose metabolism disorders, neurologic disorders, hypertension and neoplasms.

7.3.4.1 Infections

Treatment emergent infections in Study 158 are summarized in the Applicant's Table 49 copied below (Table 56 in this review):

Table 56: Study 158 Treatment Emergent Infections

Table 49: Summary of Treatment-Emergent Bacterial, Viral, or Fungal Infections Occurring ≥ 1% in Any Treatment Group

MedDRA (v. 6.1) Preferred Term	Treatment Group		
	Prograf/MMF (n = 212)	MR4/MMF (n = 214)	Neoral/MMF (n = 212)
All Groups			
Any Infection	146 (68.9%)	148 (69.2%)	123 (58.0%)
Pathogen Class Unspecified			
Any Pathogen Class Unspecified Adverse Event	110 (51.9%)	111 (51.9%)	92 (43.4%)
Urinary Tract Infection	54 (25.5%)	34 (15.9%)	47 (22.2%)
Upper Respiratory Tract Infection	24 (11.3%)	27 (12.6%)	29 (13.7%)
Nasopharyngitis	9 (4.2%)	8 (3.7%)	9 (4.2%)
Sinusitis	7 (3.3%)	15 (7.0%)*	5 (2.4%)
Bronchitis	6 (2.8%)	7 (3.3%)	3 (1.4%)
Wound Infection	5 (2.4%)	3 (1.4%)	1 (0.5%)
Cellulitis	4 (1.9%)	3 (1.4%)	6 (2.8%)
Pneumonia	4 (1.9%)	4 (1.9%)	5 (2.4%)
Sepsis	4 (1.9%)	4 (1.9%)	1 (0.5%)
Skin Infection	4 (1.9%)	0	0
Urosepsis	4 (1.9%)	2 (0.9%)	3 (1.4%)
Abscess	3 (1.4%)	0	1 (0.5%)
Bacteraemia	3 (1.4%)	1 (0.5%)	0
Otitis Media	3 (1.4%)	1 (0.5%)	0
Postoperative Infection	3 (1.4%)	2 (0.9%)	4 (1.9%)
Pyelonephritis	3 (1.4%)	3 (1.4%)	4 (1.9%)
Furuncle	2 (0.9%)	3 (1.4%)	1 (0.5%)
Bacteriuria	1 (0.5%)	3 (1.4%)	1 (0.5%)
Gastroenteritis	1 (0.5%)	14 (6.5%)*	4 (1.9%)
Pharyngitis	1 (0.5%)	2 (0.9%)	3 (1.4%)
Asymptomatic Bacteriuria	0	3 (1.4%)	1 (0.5%)
Respiratory Tract Infection	0	3 (1.4%)	0
Viral Infections			
Any Viral Infection Adverse Event	56 (26.4%)	50 (23.4%)	45 (21.2%)
Cytomegalovirus Infection	17 (8.0%)	15 (7.0%)	16 (7.5%)
Human Polyomavirus Infection	9 (4.2%)	6 (2.8%)	5 (2.4%)
Herpes Simplex	8 (3.8%)	10 (4.7%)	5 (2.4%)
Cytomegalovirus Viraemia	6 (2.8%)	3 (1.4%)	3 (1.4%)
Herpes Zoster	6 (2.8%)	7 (3.3%)	8 (3.8%)
Influenza	6 (2.8%)	3 (1.4%)	4 (1.9%)
Gastroenteritis Viral	5 (2.4%)	1 (0.5%)	1 (0.5%)
Cytomegalovirus Gastritis	0	3 (1.4%)	2 (0.9%)

Table continued on next page.

MedDRA (v. 6.1) Preferred Term	Treatment Group		
	Prograf/MMF (n = 212)	MR4/MMF (n = 214)	Neoral/MMF (n = 212)
Fungal Infections			
Any Fungal Infection	28 (13.2%)	33 (15.4%)	32 (15.1%)
Oral Candidiasis	9 (4.2%)	15 (7.0%)	13 (6.1%)
Candidiasis	5 (2.4%)	1 (0.5%)	3 (1.4%)
Body Tinea	4 (1.9%)	1 (0.5%)	0
Fungal Infection	3 (1.4%)	6 (2.8%)	1 (0.5%)
Fungal Skin Infection	1 (0.5%)	2 (0.9%)	4 (1.9%)
Oesophageal Candidiasis	1 (0.5%)	3 (1.4%)	3 (1.4%)
Tinea Versicolour	1 (0.5%)	3 (1.4%)	7 (3.3%)
Bacterial Infections			
Any Bacterial Infection	25 (11.8%)	18 (8.4%)	17 (8.0%)
Urinary Tract Infection Bacterial	6 (2.8%)	1 (0.5%)	6 (2.8%)
Clostridium Colitis	3 (1.4%)	3 (1.4%)	1 (0.5%)
Escherichia Urinary Tract Infection	3 (1.4%)	4 (1.9%)	6 (2.8%)
Urinary Tract Infection Enterococcal	3 (1.4%)	3 (1.4%)	0
Urinary Tract Infection Pseudomonal	3 (1.4%)	0	0

Patient base: Full analysis set; all randomized patients who received at least one dose of study drug.
Within any infection group, patients may have experienced more than one infection-related adverse event of interest. The sum of the terms may exceed 100%.
Statistical significance determined using Fisher's exact test (2-tailed) versus Neoral/MMF.
* Statistical significance at 0.05.
MMF: Mycophenolate mofetil.
MR4: Tacrolimus modified-release formulation.
Source: Tables 13.5.2.1, 14.2.2.1 and 14.2.2.2.

Prograf= Tac , MR4=TacXL, Neoral=CYC

The overall incidence of infections was numerically greater in the Tac (146/212; 68.9%) and TacXL (148/214; 69.2%) treatment groups compared to the cyclosporine treatment group (123/212; (58.0%). The incidence of sinusitis was significantly greater in the TacXL (MR4/MMF) treatment group than the cyclosporine (Neoral/MMF) treatment group (p-value = 0.0368; Fisher's exact test; Applicant's Analysis). By the Applicant's analysis there was a significantly higher incidence of urinary tract infection and skin infection across the three treatment groups (p-value = 0.0467 and 0.0239, respectively; Fisher's exact test), with numerically more events occurring in the Tac (Prograf/MMF) treatment group (the incidence of skin infection was < 2%).

Gastroenteritis, reported as an infection was significantly more frequently reported in the TacXL (MR4/MMF) treatment group (14/214; 6.5%) compared to the Tac (Prograf/MMF) treatment group (1/212; 0.5%) and the cyclosporine treatment group (1/212; 0.5%), ($p<0.05$ by two tailed Fisher's exact test versus cyclosporine, by the Applicant's analysis).

In Study 12-03 the overall incidence of infections was comparable between the TacXL(68.9%) and FK506 (64.6%) groups. The most frequently reported infections were bacterial infections in both treatment groups, as summarized in Table 57 below, adapted from the Applicant's study report Table 29.

Table 57: Study 12-03 Overall Summary of Infection

	Tac (N=336)		**TacXL (N=331)**	
	Patients (%)	**Events**	**Patients (%)**	**Events**
Viral infections	81 (24.1)	101	106 (32.0)	140
Bacterial infections	162 (48.2)	331	162 (48.9)	299
Fungal infections	30 (8.9)	33	31 (9.4)	36
Protozoal infections	2 (0.6)	2	1 (0.3)	1
Unknown	65 (19.3)	84	61 (18.4)	81
Other	0	0	3 (0.9)	3
Total	**217 (64.6)**	**550†**	**228 (68.9)**	**560**

Full Analysis Set; Infection based on investigator assessment
† One adverse event (Patient H7602) is documented with two infection types; thus, the total number of events is smaller than the sum of all events
Source: Applicant Study 12-03 report Table 13.6.2.1.1

The incidence of infections in Study 12-03 (based on investigator assessment and across MedDRA System Organ Classes) is presented in Table 58 below, adapted from the Applicant's study report Table 30.

Table 58: Incidence of Infections

MedDRA High Level Term *MedDRA Preferred Term*	**Tac (N=336) Patients (%)**	**TacXL (N=331) Patients (%)**
Bacterial infections NEC	**123 (36.6)**	**105 (31.7)**
Urinary tract infections	102 (30.4)	86 (26.0)
Bacterial pyelonephritis	7 (2.1)	14 (4.2)
Pneumonia bacterial	9 (2.7)	8 (2.4)
Upper respiratory tract infection – pathogen class unspecified	**47 (14.0)**	**49 (14.8)**
Nasopharyngitis	31 (9.2)	28 (8.5)
Pharyngitis†	4 (1.2)	12 (3.6)
Upper respiratory tract infection	9 (2.7)	5 (1,5)
Infections NEC	**30 (8.9)**	**32 (9.7)**
Infection	5 (1.5)	7 (2.1)
Cytomegaloviral infections†	**21 (6.3)**	**36 (10.9)**
Cytomegalovirus infection†	19 (5.7)	33 (10.0)
Herpes viral infection	**22 (6.5)**	**30 (9.1)**
Herpes simplex	11 (3.3)	15 (4.5)

Herpes zoster	5 (1.5)	10 (3.0)
Abdominal and gastrointestinal infections	21 (6.3)	20 (6.0)
Diarrhoea infectious	14 (4.2)	8 (2.4)
Gastroenteritis†	3 (0.9)	11 (3.3)
Viral infections NEC	**15 (4.5)**	**21 (6.3)**
Lower respiratory tract and lung infections	**16 (4.8)**	**18 (5.4)**
Bronchitis	8 (2.4)	10 (3.0)
Escherichia infections	**15 (4.5)**	**14 (4.2)**
Escherichia urinary tract infections	**15 (4.5)**	**14 (4.2)**
Fungal infections NEC	**13 (3.9)**	**15 (4.5)**
Candida infections	**14 (4.2)**	**12 (3.6)**
Oral candidiasis	9 (2.7)	5 (1.5)
Urinary tract infections	**14 (4.2)**	**9 (2.7)**
Urinary tract infection	10 (3.0)	7 (2.1)
Sepsis, bacteraemia and viraemia	9 (2.7)	7 (2.1)
Skin structures and soft tissue infections	7 (2.1)	9 (2.7)
Influenza viral infection	8 (2.4)	5 (1.5)
Influenza	8 (2.4)	5 (1.5)
Polyomavirus infections †	**1 (0.3)**	**7 (2.1)**
Tinea infections †	**0**	**5 (1.5)**

Full Analysis Set
Adverse events coded using MedDRA 6.1; Infection based on investigator assessment and reported in ≥ 2% in either treatment group or events associated with an incidence difference with a p-value < 0.05
MedDRA = Medical Dictionary for Drug Regulatory Affairs; NEC = Not elsewhere classified
† p = < 0.05 (Fisher's exact test) Source: Table 13.6.2.1.2

The most frequently reported infections were bacterial infections, upper respiratory tract infections - pathogen class unspecific, infections NEC, cytomegalovirus infections, herpes virus infections, abdominal, and gastrointestinal infections.

Infections reported significantly more frequently in the TacXL treatment group compared to the Tac group, associated with a p-value <0.05 (Fisher's exact test), included pharyngitis, cytomegalovirus infections, gastroenteritis, polyomavirus infections, and tinea infections.

> *Reviewer's Comment: Although uncommon (rate < 5%) the observation of a significant increased occurrence of gastroenteritis reported as an infection in the TacXL treatment group compared to the Tac treatment group in both Study 158 and Study 12-03, must be interpreted as a truly significant finding, all the more that the rate of gastroenteritis reported as a serious adverse event was significantly greater in the TacXL treatment group (8/214; 4.2%) compared to the Tac or cyclosporine treatment groups in Study 158. These observations raise questions about the comparative effect of once a day dosing with tacrolimus extended release compared to twice daily dosing with immediate release tacrolimus on the gastrointestinal tract, including but not limited to the local microbiota and mucosal immune system.*

Significantly more polyomavirus infection, namely BK virus infection, was reported in the TacXL group (7/331; 2.1%) compared to the Tac group (1/336; 0.3%). Five patients had transient BK-viraemia and/or transient BK-viruria; two patients had ongoing BK-viraemia/BK-viruria – one of them with creatinine augmentation, and one patient had human polyomavirus infection.

> *Reviewer's Comment: It is noted by the Applicant that the incidence of BK-viremia/BK-viruria was not prospectively investigated in this study. BK and polyomavirus infections and their consequences have been extensively studied in the literature, and are well recognized as a consequence of immunosuppression following renal transplantation. Indeed, the incidences observed in this study are lower than that reported in the literature on prospective evaluation of BK virus in recipients of kidney transplants. Nevertheless, one cannot reliably exclude the potential association of a true increased risk of polyomavirus infection with the administration of TacXL compared to Tac, in combination with MMF.*

Significantly more cytomegalovirus infections were reported in the Tac XL group in Study 12-03 as further summarized in the table below, adapted from the Applicant's study report Table 32.

Table 59 Study 12-03 Incidence of Cytomegalovirus Infections

MedDRA High Level Term *MedDRA Preferred Term*	**Tac (N=336)**		**TacXL (N=331)**	
	Patients (%)	**Events**	**Patients (%)**	**Events**
Cytomegalovirus infections†	**21 (6.3)**	**24**	**36 (10.9)**	**39**
Cytomegalovirus infection‡	19 (5.7)	21	33 (10.0)	36
Cytomegalovirus gastritis	2 (0.6)	2	2 (0.6)	2
Cytomegalovirus urinary tract infection	1(0.3)	1	0(0.0)	0
Cytomegalovirus viremia	0(0.0)	0	1(0.3)	0

Full Analysis Set; Adverse events coded using MedDRA 6.1; Infection based on investigator assessment
† p=0.038 (MedDRA high level term); ‡ p=0.043 (MedDRA preferred term); (Fisher's exact test);
MedDRA = Medical Dictionary for Drug Regulatory Affairs
Source: Applicant's Study Report Table 13.6.2.1.3

Cytomegalovirus infections post transplantation were reported in 36 patients in the TacXL treatment group and 21 patients in the Tac group. Of the total 57 patients, 52 patients recovered, three patients had evidence of ongoing infection at the final examination (all in the Tac group) and one patient in each group recovered with residual effects.

Reviewer's Comment: CMV mismatch (CMV seropositive donor and CMV seropositive recipient) is an important risk factor for developing post-transplant CMV infection, although to a lesser extent in the setting of anti-CMV infection prophylaxis post transplantation, as was used in this study. It is noted that there was a higher proportion of CMV seronegative patients in the TacXL treatment group (54 or 17.1%) who received a kidney from a donor who was CMV seropositive, compared to the Tac treatment group (43 or 13.7%). Thus, the difference in rates of CMV infection across treatment groups should be interpreted with caution.

In Study 158, where CMV prophylaxis was also used in patients with CMV mismatch, no particular differences were observed between Tac and TacXL treatment groups with respect to CMV infection, CMV viremia, or CMV gastritis, reported as adverse events.

Note that the approved Prograf® package insert as well as the one proposed for Astagraf® contains wording in the WARNINGS AND PRECAUTIONS section regarding Polyomavirus infections and Cytomegalovirus infections, which is consistent with class labeling for this risk associated with the use of systemic immunosuppressive agents to prevent rejection in solid organ transplantation.

7.3.4.2 Renal Function

Select treatment-emergent renal adverse events reported in Study 158 are summarized in the Applicant's study report Table 44 reproduced below (Table 60 in this review):

Table 60: Study 158 Summary of Select Renal Treatment Emergent Adverse Events

Table 44: Summary of Select Renal Treatment-Emergent Adverse Events of Interest

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

Patient base: Full analysis set; all randomized patients who received at least one dose of study drug.
Patients may have experienced more than one renal adverse event of interest. The sum of the terms may exceed 100%.
Statistical significance determined using Fisher's exact test (2-tailed) versus Neoral/MMF.
* Statistical significance at 0.05.
MMF: Mycophenolate mofetil.
MR4: Tacrolimus modified-release formulation.
Source: Table 14.2.2.4.

Prograf= Tac , MR4=TacXL, Neoral=CYC

The overall incidence of select renal adverse events was comparable across the three treatment groups.

> *<u>Reviewer's Comment</u>: The Applicant notes a statistically significant higher incidence of nephropathy toxic reported as an adverse event (p-value = 0.037; Fisher's exact test) in the cyclosporine (Neoral/MMF) treatment group compared to the Tac (Prograf/MMF) treatment group, and a numerically greater incidence compared to the TacXL (MR4/MMF) treatment group. However, such a difference in rate for this event was not associated with a difference in rates of other measures of renal function adverse events. While it is noted in the Applicant's analysis of renal function as a secondary endpoint that renal function in Study 158, as measured by creatinine clearance was statistically significantly lower in the cyclosporine group, the analysis did not adjust for baseline renal function (one-month after transplantation), nor did their appear to be adequate provisions for the handling of missing data. Thus, this reviewer concludes that from a safety perspective there were no clinically significant differences with respect to renal function in Study 158 (See section 6.1.5.2.1 of this review). The pattern of renal treatment emergent adverse events in Study 158 was similar between the Tac and TacXL groups.*

The incidence of adverse events of renal function in the first 12 months post-transplant in Study 12-03 is summarized in the Table 61 below adapted from the Applicant's study report table 33.

Table 61: Study 12-03 Incidence of Adverse Events of Renal Function

MedDRA High Level Term	Tac (N=336) Patients (%)	TacXL (N=331) Patients (%)
Renal vascular and ischaemic conditions	52 (15.5)	45 (13.6)
Bladder and urethral symptoms	43 (12.8)	43 (13.0)
Renal failure and impairment	40 (11.9)	29 (8.8)
Urinary abnormalities	32 (9.5)	34 (10.3)
Nephropathies and tubular disorders NEC	20 (6.0)	31 (9.4)
Ureteric disorders NEC	14 (4.2)	9 (2.7)
Urinary tract signs and symptoms NEC	8 (2.4)	9 (2.7)
Renal obstructive disorders	5 (1.5)	6 (1.8)
Genital and urinary tract disorders NEC	6 (1.8)	4 (1.2)
Glomerulonephritis and nephrotic	5 (1.5)	4 (1.2)
Renal disorders NEC	3 (0.9)	3 (0.9)
Myoneurogenic bladder disorders	1 (0.3)	4 (1.2)
Bladder disorders NEC	2 (0.6)	2 (0.6)
Renal lithiasis	3 (0.9)	1 (0.3)
Structural and Obstructive urethral disorders	2 (0.6)	2 (0.6)
Nephritis NEC	1 (0.3)	2 (0.6)
Renal neoplasms	1 (0.3)	2 (0.6)
Renal structural abnormalities and trauma	2 (0.6)	1 (0.3)
Bladder reflux conditions	1 (0.3)	0
Urethral disorders	1 (0.3)	0

Full Analysis Set
Adverse events coded using MedDRA 6.1
There were no differences in incidence between FK506 and MR4 associated with a p-value < 0.05 (Fisher's exact test); NEC = Not elsewhere classified
MedDRA = Medical Dictionary for Drug Regulatory Affairs
Source: Study 12-03 Report Table 13.6.2.2.1

By the Applicant's analysis, there were no clinically relevant differences between TacXL and Tac in the incidence of adverse events of renal function and no differences associated with a p-value < 0.05 (Fisher's exact test).

> *<u>Reviewer's Comment</u>: Although quite a number or urologic adverse events are included in the Applicant's table above, it remains that renal failure and impairment reported as an adverse event was not uncommon but occurred at comparable rates across treatment groups in Study 12-03. Moreover, renal function assessed as a secondary efficacy endpoint, as measured by serum*

creatinine and creatinine clearance at 12 months after transplantation was also comparable across treatment groups in Study 12-03, which as one recalls was conducted in double blind fashion until the last subject had completed 24 weeks (See section 6.1.5.2.2 of this review).

7.3.4.3 Glucose Metabolism Disorders

Study 158

Measures of the composite endpoint of glucose intolerance in Study 158, defined as fasting plasma glucose ≥ 126 mg/dL, HbA1c ≥ 6%, insulin use ≥ 30 days, or oral hypoglycemic use, are summarized in Table 62 below, adapted from the Applicant's study report Table 48 and Table 53 of the clinical review of NDA 50-811.

Table 62: Study 158 Summary of Glucose Intolerance

Parameter	Treatment Group		
	Tac (n = 212)	TacXL (n = 214)	CYC (n = 212)
Days 0 through 30			
Glucose Intolerance –	89/150 (59.3%)	82/163 (50.3%)	78/152 (51.3%)
Fasting Plasma Glucose ≥ 126 mg/dL	88/150 (58.7%)	81/163 (49.7%)	78/152 (51.3%)
HbA1c ≥ 6%	0/150	0/163	0/152
nsulin Use ≥ 30 days	3/150 (2.0%)	1/163 (0.6%)	1/152 (0.7%)
Oral hypoglycemic Use	7/150 (4.7%)*	4/163 (2.5%)	1/152 (0.7%)
Any Time During Study			
Glucose Intolerance –	112/150 (74.7%)*	113/163 (69.3%)	93/152 (61.2%)
Fasting Plasma Glucose ≥ 126 mg/dL	96/150 (64.0%)*	92/163 (56.4%)	80/152 (52.6%)
HbA1c ≥ 6%	59/150 (39.3%)***	66/163 (40.5%)***	28/152 (18.4%)
nsulin Use ≥ 30 days	9/150 (6.0%)	9/163 (5.5%)	4/152 (2.6%)
Oral hypoglycemic Use	15/150 (10.0%)*	23/163 (14.1%)***	5/152 (3.3%)

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

During the first 30 days in Study 158 post transplantation measures of glucose intolerance were comparable across treatment groups except for more oral hypoglycemic use in the Tac treatment group compared to the cyclosporine group.

Analyses of the composite endpoint for glucose intolerance, expanded to include any time during the study showed a significantly higher (p-value = 0.0137) incidence of glucose intolerance (as a composite endpoint) in the Tac treatment group compared to the CYC treatment group. The incidence of fasting plasma glucose ≥ 126 mg/dL was also significantly higher (p-value = 0.0481) in the Tac treatment group compared to the CYC treatment group. Furthermore, both the Tac and TacXL treatment groups had a significantly higher incidence of HbA1c ≥ 6% (p-value < 0.0001 for both; Fisher's exact test by Applicant's analysis) and oral hypoglycemic use (p-value = 0.0212 for Tac versus CYC and p-value = 0.0006 for TacXL versus CYC; Fisher's exact test by Applicant's analysis) compared to the CYC treatment group. As noted by the Applicant, this did not appear to result in a significant difference in insulin use ≥ 30 days at any time during the study across the three treatment groups.

With respect to HbA1c, although approximately 40% among the Tac and TacXL treatment groups reported a value ≥ 6.0% at any time during the study, compared to 18% in the cyclosporine group, the Applicant did not report any clinically meaningful differences in mean HbA1c values across the three treatment groups, and mean HbA1C values were < 6.7% at most points observed in all three treatment groups (Source; Applicant's study report Table 14.3.8).

New onset diabetes, and post-transplant diabetes mellitus (PTDM defined as requiring the use of insulin for ≥ 30 days, in an individual without prior history of diabetes) is a potential hazard of tacrolimus use, as reflected in the approved Prograf®(tacrolimus) package insert. African Americans and Hispanics are at increased risk for PTDM. By the Applicant's analysis, within the TacXL treatment group, the incidence of glucose intolerance for at-risk blacks was higher than that for at-risk whites at any time over the first year post transplant (Source Applicant's Table 14.3.6.9.2.3).

Differences in glucose intolerance between Hispanics and non-Hispanics were not clinically significant and any trends in glucose intolerance among the three treatment groups were similar to those seen in the overall population [Source: Applicant's Tables 13.5.2.2 and 14.3.6.9.2.4].

With respect to measures of glucose intolerance reported as an adverse event in Study 158, within the full analysis set, numerically greater patients in the Tac (45/212; 21.2%) or TacXL (41/214; 19.2%) treatment groups experienced hyperglycemia (as an adverse event) than those in the cyclosporine (32/212; 15.1%) treatment group. In addition, the incidence of diabetes mellitus (as an adverse event) was significantly higher (p-value = 0.0161; Fisher's exact test by the Applicant's analysis) in the TacXL (30/214; 14.0%) and numerically lower in the Tac (24/212; 11.3%) than in the cyclosporine group (Source: Applicant's study report Tables 13.5.1.1 and 14.2.2.2).

Study 12-03

The incidence of glucose metabolism disorders reported as adverse events in Study 12-03, overall and in patients without pre-existing glucose metabolism disorders, is presented in Table 63 below, adapted from the Applicant's study report Table 34.

Table 63: Study 12-03 Incidence of Glucose Metabolism Disorder

Overall Incidence		
MedDRA High Level Term *MedDRA Preferred Term*	**Tac (N=336) Patients (%)**	**TacXL (N=331) Patients (%)**
Diabetes mellitus (incl subtypes)	69 (20.5)	68 (20.5)
Diabetes mellitus	25 (7.4)	32 (9.7)
Diabetes mellitus insulin-dependent	24 (7.1)	22 (6.6)
Diabetes mellitus non-insulin-dependent	21 (6.3)	16 (4.8)
Diabetes mellitus inadequate control	0	2 (0.6)
Hyperglycaemic conditions NEC	70 (20.8)	67 (20.2)
Hyperglycaemia	65 (19.3)	61 (18.4)
Glucose tolerance impaired	4 (1.2)	5 (1.5)
Hypoglycaemic conditions NEC	6 (1.8)	3 (0.9)
Hypoglycaemia	6 (1.8)	3 (0.9)
Incidence in Patients Without Pre-existing Glucose Metabolism		
MedDRA High Level Term *MedDRA Preferred Term*	**Tac (N=179) Patients (%)**	**TacXL (N=179) Patients (%)**
Diabetes mellitus (incl subtypes)	54 (18.1)	50 (17.6)
Diabetes mellitus	17 (5.7)	18 (6.3)
Diabetes mellitus insulin-dependent	18 (6.0)	19 (6.7)
Diabetes mellitus non-insulin-dependent	20 (6.7)	16 (5.6)
Hyperglycaemic conditions NEC	64 (21.5)	63 (22.2)
Hyperglycaemia	59 (19.8)	57 (20.1)
Glucose tolerance impaired	4 (1.3)	5 (1.8)
Impaired fasting gluciose	1 (0.3)	1 (0.4)
Hypoglycaemic conditions NEC	4 (1.3)	2 (0.7)
Hypoglycaemia	4 (1.3)	2 (0.7)

Full Analysis Set
Adverse events coded using MedDRA 6.1
There were no differences in incidence between FK506 and MR4 associated with a p-value < 0.05 (Fisher's exact test)
MedDRA = Medical Dictionary for Drug Regulatory Affairs
Source: Applicant's Study Report Table 13.6.2.4.2

No significant difference was observed across treatment groups with respect to these measures of glucose metabolism disorder reported as adverse events.

New Onset Diabetes after Transplantation

On March 8, 2013, the Division of Transplant and Ophthalmology Products requested That the Applicant provide additional presentation of data from Studies 02-0-158 and FG-506E-12-03 with respect to new onset diabetes mellitus after transplantation (NODAT). Responses to these requests were submitted on March 22, 2013, and are summarized below.

The original criteria for the definition of NODAT was based on the definition of diabetes mellitus based on the 2003 ADA/WHO guidelines regarding a single elevated fasting plasma glucose (FPG) ≥ 126 mg/dL [American Diabetes Association, 2011].[14] These were the definitions used in the report of Study 158, as summarized in the Table 64 below (Table 1 from the Applicant's Submission).

Table 64: NODAT (Using Study 02-0-158 Definition) 1 year after Transplantation in Kidney Transplant Recipients without Pre-existing Diabetes Mellitus (Study 02-0-158)

	Tac (n=212)	TacXL (n=214)	CYC (n=212)
NODAT	112/150 (74.7%)	113/163 (69.3%)	93/152 (61.2%)
FPG ≥ 126 mg/dL	96/150 (64.0%)	92/163 (56.4%)	80/152 (52.6%)
HbA1c ≥ 6%	59/150 (39.3%)	66/163 (40.5%)	28/152 (18.4%)
Insulin use ≥ 30 consecutive days	9/150 (6.0%)	9/163 (5.5%)	4/152 (2.6%)
Oral hypoglycemic use	15/150 (10.0%)	23/163 (14.1%)	5/152 (3.3%)

All randomized patients who received at least one dose of study drug.
FPG: fasting plasma glucose; MMF: mycophenolate mofetil; NODAT: new onset diabetes after transplant.
Patients with NODAT were defined as having one or more of the criteria listed individually in the table while on therapy. A patient was only counted once regardless of how many glucose intolerance criteria were met.
The sum of the terms may exceed 100%. The population (denominator) is the number of patients with no history of diabetes mellitus or posttransplant diabetes mellitus.
Source: Study 02-0-158 1-year CSR Table 13.5.2.2

Using the same composite definition of NODAT the Applicant has provided a similar table for Study 12-03 (See Table 65 below, adapted from Attachment 1, Table 1.1 in the Applicant's submission).

Table 65: NODAT (Using Study 02-0-158 Definition) 1 year after Transplantation in Kidney Transplant Recipients without Pre-existing Diabetes Mellitus (Study 12-03)

	Tac (n=336)	TacXL (n=331)
NODAT	236 / 327 (72.2%)	237 / 310 (76.5%)

[14] American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. January 2011;34(Suppl 1):S62-9.

FPG ≥ 126 mg/dL	194 / 327 (59.3%)	198 / 310 (63.9%)
HbA1c ≥ 6%	120 / 327 (36.7%)	112 / 310 (36.1%)
Insulin use ≥ 30 consecutive days	45 / 327 (13.8%)	44 / 310 (14.2%)
Oral hypoglycemic use	32 / 327 (9.8%)	31 / 310 (10.0%)

All randomized patients who received at least one dose of study drug.
FPG: fasting plasma glucose; MMF: mycophenolate mofetil; NODAT: new onset diabetes after transplant.
Patients with NODAT were defined as having one or more of the criteria listed individually in the table while on therapy. A patient was only counted once regardless of how many glucose intolerance criteria were met.
The sum of the terms may exceed 100%. The population (denominator) is the number of patients with no history of diabetes mellitus or posttransplant diabetes mellitus.

Increases in NODAT observed in de novo kidney transplantation result from a high frequency of elevated blood glucose levels in the early posttransplant period when large doses of corticosteroids are used, target calcineurin inhibitor trough concentrations are highest, and patients are stressed from the impact of the surgery. Thus, the Applicant has proposed the use of an updated definition of NODAT that may be more appropriate for describing the onset of clinically meaningful diabetes in the posttransplant population. The updated definition defines NODAT for at-risk patients as a composite endpoint consisting of any occurrence of one the following 4 parameters: (i) 2 posttransplant FPG levels ≥ 126 mg/dL ≥ 30 days apart, (ii) insulin therapy for ≥ 30 consecutive days, (iii) oral hypoglycemic agent use for ≥ 30 consecutive days, or (iv) HbA1c ≥ 6.5% on at least one occasion posttransplant [Yates et al, 2012; Kaposztas et al, 2010]. NODAT using the updated criteria is presented below for Study 158 and Study 12-03.[15] [16]

Table 66: Study 158 - NODAT (Using Updated Definition) 1 year after Transplantation in Kidney Transplant Recipients without Pre-existing Diabetes Mellitus

	Tac (n=212)	TacXL (n=214)	CYC (n=212)
Composite NODAT	53/151 (35.1%)	58/162 (35.8%)	27/152 (17.8%)
2 x FPG ≥ 126 mg/dL ≥ 30 days apart	35/151 (23.2%)	42/162 (25.9%)	18/152 (11.8%)
Insulin use for ≥ 30 consecutive days	12/151 (7.9%)	10/162 (6.2%)	6/152 (3.9%)
Oral hypoglycemic use for ≥ 30 consecutive days	13/151 (8.6%)	22/162 (13.6%)	4/152 (2.6%)
Other antidiabetic use for ≥ 30 consecutive days	0/151	0/162	0/152
HbA1c ≥ 6.5%	33/151 (21.9%)	31/162 (19.1%)	13/152 (8.6%)

All patients who received at least one dose of study drug.

[15] Yates CJ, Fourlanos S, Hjelmesæth J, Colman PG, Cohney SJ. New-onset diabetes after kidney transplantation – changes and challenges. Am J Transplant. 2012;12:820-8.
[16] Kaposztas Z, Gyurus E, Kahan BD. New-onset diabetes after renal transplantation: Diagnosis, incidence, risk factors, impact on outcomes, and novel implications. Transplant Proc. 2011;43:1375-94.

FPG: fasting plasma glucose; MMF: mycophenolate mofetil; NODAT: new onset diabetes after transplant. Patients with NODAT were defined as having one or more of the criteria listed individually in the table while on therapy. A patient was only counted once regardless of how many glucose intolerance criteria were met.
The sum of the terms may exceed 100%. The population (denominator) is the number of patients with no history of diabetes at baseline, no pre-transplant glucose > 200 mg/dL, no pre-transplant HbA1c > 6.5% and no extended antidiabetic medication use just before transplantation.
Source: ISS Table K6.1.1.1

Table 67: Study 12-03 - NODAT (Using Updated Definition) 1 year after Transplantation in Kidney Transplant Recipients without Pre-existing Diabetes Mellitus

	Tac (n=336)	TacXL (n=331)
Composite NODAT	90/ 299 (30.1%)	105/ 288 (36.5%)
2 x FPG ≥ 126 mg/dL ≥ 30 days apart	47/ 299 (15.7%)	51/ 288 (17.7%)
Insulin use for ≥ 30 consecutive days	29/ 299 (9.7%)	29/ 288 (10.1%)
Oral hypoglycemic use for ≥ 30 consecutive days	23/ 299 (7.7%)	20/ 288 (6.9%)
Other antidiabetic use for ≥ 30 consecutive days	0/ 299 (0.0%)	0/288
HbA1c ≥ 6.5%	39/ 299 (13.0%)	48/ 288 (16.7%)

All patients who received at least one dose of study drug.
FPG: fasting plasma glucose; MMF: mycophenolate mofetil; NODAT: new onset diabetes after transplant. Patients with NODAT were defined as having one or more of the criteria listed individually in the table while on therapy. A patient was only counted once regardless of how many glucose intolerance criteria were met.
The sum of the terms may exceed 100%. The population (denominator) is the number of patients with no history of diabetes at baseline, no pre-transplant glucose > 200 mg/dL, no pre-transplant HbA1c > 6.5% and no extended antidiabetic medication use just before transplantation.

> *Reviewer's Comment: Clinically significant NODAT was observed more frequently in the Tac and TacXL treatment groups compared to the cyclosporine treatment group in Study 158, as demonstrated most persuasively by the differences in proportion of subjects with HbA1c ≥ 6.5%. Although one should be cautious about the validity of cross study comparisons, all the more that Study 12-03 conducted outside the US did not included subpopulations considered at increased risk for NODAT (African Americans and Hispanic Americans), a similar pattern of clinically significant NODAT was observed in the Tac and TacXL treatment groups in Study 12-03.*

7.3.4.4 Neurologic Disorders

Neurologic disorders are a known hazard associated with the use of tacrolimus, and tacrolimus may cause a spectrum of neurotoxicities, particularly when used at high doses, as is reflected in the approved Prograf® packages insert.

The most common neurologic adverse events reported were, tremor, headaches, and paresthesias.

The most common neurologic adverse events reported in Study 158 are summarized in the Table below.

Table 68: Study 158 Incidence of Most Common Neurological Adverse Events

MedDRA (v. 6.1) System OrganClass Preferred Term	Tac (N=212) Patients (%)	TacXL (N=214) Patients (%)	CYC (N=212) Patients (%)
Tremor (excl. congenital)	73 (34.4)	75 (35)	42 (19.8)
Headaches NEC	51 (24.1)	46 (21)	52 (24.5)
Hypoesthesia	5 (2.4)	10 (4.7)	11 (5.2)
Paresthesias	3 (1.4)	12 (5.6)	13 (6.1)

Full Analysis Set: All randomized patients who received at least one dose of the study medication. Within a MedDRA system organ class, a patient may experience more than one adverse event. Adapted from Table 49 in the Clinical Review of NDA 50-811.

Table 69: Study 12-03 Incidence of Most Common Neurological Adverse Events

MedDRA High Level Term	Tac (N=336) Patients (%)	TacXL (N=331) Patients (%)
Tremor (excl. congenital)	58 (17.3)	58 (17.5)
Headaches NEC	33 (9.8)	40 (12.1)
Paresthesias and dysesthesias	16 (4.8)	19 (5.7)

Reviewer's Comment: Comparable rates of common neurologic adverse events, known to be associated with tacrolimus were observed across the Tac and TacXL treatment groups in Studies 158 and 12-03. The numerical differences in paresthesias, dysesthesias and hypoesthesia between Tac and TacXL groups are not clinically meaningful. It is noted that while there may have been an expectation that differences with respect to tacrolimus PK profile between once a day extended release tacrolimus compared to twice a day immediate release tacrolimus (lower Cmax for TacXL) might have translated into less tremor, the most common neurologic adverse effect, this expectation was not observed to be fulfilled in either Study 158 or Study 12-03. Thus, the use of extended release tacrolimus, did not convey any benefits with respect to this or any other known toxicity associated with the use of tacrolimus.

7.3.4.5 Hypertension

Hypertension is a common adverse event associated with the use of tacrolimus, as reflected in the approved Prograf package insert.

The incidence of hypertension disorders in the 12 months post-transplant for Study 158 and 12-03 is presented in the tables below.

Table 70: Study 158 Incidence of Hypertensive Disorders

MedDRA (v. 6.1) Preferred Term	Tac (N=212) Patients (%)	TacXL (N=214) Patients (%)	CYC (N=212) Patients (%)
Hypertension	68 (32.5)	70(32.7)	74 (34.9)
Hypertensive crisis	0	2 (0.6)	1(0.5)

Full Analysis Set
There were no differences in incidence between FK506 and MR4 associated with a p-value < 0.05 (Fisher's exact test)
MedDRA = Medical Dictionary for Drug Regulatory Affairs; NEC = Not elsewhere classified
Source: Study 158 CSR Table 14.2.2.4

Table 71: Study 12-03 Incidence of Hypertensive Disorders

MedDRA (v. 6.1) Preferred Term	Tac (N=336) Patients (%)	TacXL (N=331) Patients (%)
Hypertension	76 (22.6)	80 (24.2)
Hypertensive crisis	4 (1.2)	2 (0.6)

Full Analysis Set
There were no differences in incidence between FK506 and MR4 associated with a p-value < 0.05 (Fisher's exact test)
MedDRA = Medical Dictionary for Drug Regulatory Affairs; NEC = Not elsewhere classified
Source: Study 12-03 12 month CSR Table 13.6.2.6.1

There were no differences across treatment groups with respect to hypertension reported as a treatment emergent adverse event.

An analysis of the use of antihypertensive medication in study 158 was included in the clinical review of NDA 50-811 and is summarized in the table below, adapted from Table 61 of that review.

Table 72: Antihypertensive Drug Use in Study 158

	Tac (n = 212)	TacXL (n = 214)	CYC (n = 212)
Baseline Use	169/212 (79.7%)	165/214 (77.1%)	167/212 (78.8%)
During course of Study	202/212 (95.3%)	218/214 (97.2%)	203/212 (95.8%)
Taking 1 drug	21/212	25/214	20/212

Taking 2 drugs	42/212	44/214	60/212
Taking > 2 drugs	139/212	139/214	123/212

Source: Study 158 CSR Table 13.3.4.3

Hypertension and use of antihypertensive medication was very common across all treatment groups, involving almost 80% of the patients at baseline, and 95-97% during the course of the Study.

> *Reviewer's Comment: Hypertension requiring treatment is a manageable necessity associated with the type of immunosuppression needed to provide adequate protection against rejection.*

7.3.5 Submission Specific Primary Safety Concerns

On February 6, 2013 Astellas requested that NDA 204096 [Original 2 – Liver (Males)] for tacrolimus XL capsules be withdrawn without prejudice to refilling, and this request was acknowledged by the Agency in a letter dated May 14, 2013. (See memo to NDA file, dated May 13, 2013) Nevertheless, outstanding safety concerns remain from the earlier review of NDA 50-815 for tacrolimus extended release capsules in the indication of prevention of rejection in recipients of liver transplantation. Specifically, in a phase 3 randomized controlled trial, was female recipients in the TacXL arm had a significantly higher mortality rate at 12 months compared to females in the Tac arm. At 12 months, the incidence of death in TacXL females was 18.4% (14/76) compared to 7.8% (5/64) in Tac females (p=0.026, test for interaction using the Breslow Day test). The corresponding mortality rates in male subjects were 6.8% (11/161) and 10.6% (18/170) for TacXL and Tac respectively. (See Clinical and Statistical Reviews of ND 50-815 from 2008 in DARRTS)

Although a gender-related difference in outcome has not been observed in recipients of renal transplantation in Study 158 or Study 12-03 (See Section 6.1.7.1.1 of this review, as well as the Statistical Review of NDA 204096 in DARRTS), the concern of potential increased risk of death in female recipients of liver transplantation treated with TacXL needs to be addressed in labeling in the boxed WARNING and in the WARNINGS AND PRECAUTIONS section of the package insert. (See Section 9.2 Labeling Recommendations in this review)

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

7.4.1.1 Common Adverse Events in Study 158

In the clinical review of NDA 50-811 a 5% cutoff was chosen to display commonly occurring adverse events, resulting in approximately 10 subjects (out of 212 subjects

per arm) experiencing the adverse event. This higher rate was chosen because the sample size was only 212 per arm and transplant patients generally experience numerous adverse events post-transplantation because of the surgical procedure and the long duration of the clinical study. The table below adapted from Table 49 in the clinical review of NDA 50-811 summarizes the common adverse events occurring with an incidence >5% (Prograf=Tac; MR4=TacXL; Neoral=cyclosporine).

Table 73: Study 158 Summary of Common Adverse Events > 5%

MedDRA (v. 6.1) System OrganClass Preferred Term	Prograf N=212 (%)	MR4 N=214 (%)	Neoral N=212 (%)	p-value
All Systems				
Any AE	212	214	210	0.2201
Gastrointestinal Disorders				
Any AE	190 (89.6)	188 (87.9)	185 (87.3)	0.7523
Diarrhea	94 (44.3)	97 (45.3)	54 (25.5)	<0.0001
Nausea	82 (38.7)	90 (42.1)	99 (46.7)	0.2563
Constipation	76 (35.8)	89 (41.6)	87 (41)	0.4073
Vomiting	54 (25.5)	56 (26.2)	52 (24.5)	0.9341
Dyspepsia	38 (17.9)	32 (15.0)	32 (15.1)	0.6559
Abdominal Pain	27 (12.7)	29 (13.6)	38 (17.9)	0.2824
Flatulence	22 (10.4)	15 (7.0)	16 (7.5)	0.4150
Abd Pain Upper	21 (9.9)	16 (7.5)	18 (8.5)	0.6649
Abdominal Distention	16 (7.5)	11 (5.1)	18 (8.5)	0.3530
Loose Stools	15 (7.1)	11 (5.1)	4 (1.9)	0.0317
GERD	5 (2.4)	10 (4.7)	13 (6.1)	0.1342
Hemorrhoids	5 (2.4)	12 (5.6)	6 (2.8)	0.1688
Injury, Poisoning and Procedural Complications				
Any AE	163 (76.9)	148 (69.2)	156 (73.6)	0.1987
Post Procedural Pain	61 (28.8)	63 (29.4)	58 (27.4)	0.8923
Incision Site Complication	60 (27.8)	44 (20.6)	49 (23.1)	0.1670
Graft Dysfunction	50 (23.6)	39 (18.2)	37 (17.5)	0.2304
Complications of Transplant Surgery	15 (7.1)	7 (3.3)	13 (6.1)	0.1881
Therapeutic Agent Toxicity	12 (5.7)	7 (3.3)	10 (4.7)	0.4791
Post Procedural Discharge	7 (3.3)	11 (5.1)	13 (6.1)	0.3925
Metabolism and Nutrition Disorders				
Any AE	162 (76.4)	170 (79.4)	170 (80.2)	0.6158
Hypomagnesemia	60 (28.3)	55 (25.7)	47 (22.2)	0.3519
Hypophosphatemia	59 (27.8)	51 (23.8)	45 (21.2)	0.2820
Hyperkalemia	54 (25.5)	47 (22.0)	41 (19.3)	0.3141
Hyperglycemia	45 (21.2)	41 (19.2)	32 (15.1)	0.2580
Hyperlipidemia	37 (17.5)	35 (16.4)	52 (24.5)	0.0749

Hypokalemia	34 (16.0)	34 (15.9)	37 (17.5)	0.9106
Diabetes Mellitus	24 (11.3)	30 (14.0)	14 (6.6)	0.0362
Dehydration	20 (9.4)	16 (7.5)	9 (4.2)	0.0979
Hypocalcemia	18 (8.5)	18 (8.4)	28 (13.2)	0.1875
Fluid Overload	17 (8.0)	10 (4.7)	12 (5.7)	0.3587
Metabolic Acidosis	14 (6.6)	17 (7.9)	13 (6.1)	0.7866
Hypercholesterolemia	10 (4.7)	8 (3.7)	16 (7.5)	0.1895
Dyslipidemia	4 (1.9%)	12 (5.6)	6 (2.8)	0.1179
Infections and Infestations				
Any AE	146 (68.9)	148 (69.3)	123 (58.0)	0.0252
Urinary Tract Infection	54 (25.5)	34 (15.9)	47 (22.2)	0.0467
MedDRA (v. 6.1) System OrganClass Preferred Term (continued)	**Prograf N=212 (%)**	**MR4 N=214 (%)**	**Neoral N=212 (%)**	**p-value**
Upper Respiratory Tract Infection	24 (11.3)	27 (12.6)	29 (13.7)	0.7635
Cytomegalovirus Infection	17 (8.0)	15 (7.0)	16 (7.5)	0.9125
Oral Candidiasis	9 (4.2)	15 (7.0)	13 (6.1)	0.4951
Sinusitis	7 (3.3)	15 (7.0)	5 (2.4)	0.0537
Gastroenteritis	1 (0.5)	14 (6.5)	4 (1.9)	0.0007
General Disorders and Administration Site Conditions				
Any AE	139 (65.6)	139 (65.0)	145 (68.4)	0.7319
Edema Peripheral	74 (34.9)	76 (35.5)	97 (45.8)	0.0383
Edema	28 (13.2)	19 (8.9)	25 (11.8)	0.3425
Pyrexia	25 (11.8)	24 (11.2)	35 (16.5)	0.2275
Asthenia	23 (10.8)	17 (7.9)	23 (10.8)	0.4860
Fatigue	23 (10.8)	34 (15.9)	26 (12.3)	0.2981
Chest Pain	17 (8.0)	22 (10.3)	12 (5.7)	0.2234
Pain	11 (5.2)	14 (6.5)	15 (7.1)	0.7378
Anasarca	8 (3.8)	12 (5.6)	5 (2.4)	0.2358
Nervous System Disorders				
Any AE	134 (63.2)	135 (63.1)	117 (55.2)	0.1577
Tremor	73 (34.4)	75 (35)	42 (19.8)	0.0004
Headache	51 (24.1)	46 (21)	52 (24.5)	0.7386
Dizziness	27 (12.7)	21 (9.8)	24 (11.3)	0.6371
Hypoesthesia	5 (2.4)	10 (4.7)	11 (5.2)	0.2865
Paresthesia	3 (1.4)	12 (5.6)	13 (6.1)	0.0227
Blood and Lymphatic System Disorder				
Any AE	105 (49.5)	109 (50.9)	97 (45.3)	0.4674
Anemia	64 (30.2)	72 (33.6)	59 (27.8)	0.4341
Leukopenia	33 (15.6)	35 (16.4)	25 (11.8)	0.3624
Polycythemia	13 (6.1)	12 (5.6)	9 (4.2)	0.7024
Leukocytosis	4 (1.9)	12 (5.6)	9 (4.2)	0.1144
Vascular Disorders				
Any AE	105 (49.5)	109 (50.9)	111 (52.4)	0.8430
Hypertension	68 (32.1)	64 (29.9)	74 (34.9)	0.5406
Hypotension	18 (8.5)	23 (10.7)	20 (9.4)	0.7323
Orthostatic Hypotension	10 (4.7)	15 (7.0)	5 (2.4)	0.0807

Musculoskeletal and Connective Tissue Disorders				
Any AE	103 (48.6)	110 (51.4)	115 (54.2)	0.5289
Back Pain	27 (12.7)	32 (15.0)	30 (14.2)	0.8070
Pain in Extremity	27 (12.7)	27 (12.6)	26 (12.3)	1.0000
Arthralgia	26 (12.3)	27 (12.6)	28 (13.2)	0.9659
Muscle Cramp	17 (8.0)	20 (9.3)	23 (10.8)	0.6074
Osteopenia	12 (5.7)	13 (6.1)	13 (6.1)	1.0000
Respiratory, Thoracic and Mediastinal Disorders				
Any AE	93 (43.9)	91 (42.5)	86 (40.6)	0.7921
Cough	27 (12.7)	16 (7.5)	21 (9.9)	0.2041
MedDRA (v. 6.1) System OrganClass Preferred Term (continued)	**Prograf N=212 (%)**	**MR4 N=214 (%)**	**Neoral N=212 (%)**	**p-value**
Dyspnea	24 (11.3)	29 (13.6)	28 (13.2)	0.7836
Pharyngolaryngeal Pain	15 (7.1)	17 (7.9)	11 (5.2)	0.5425
Dyspnea Exertional	12 (5.7)	10 (4.7)	8 (3.8)	0.6541
Skin and Subcutaneous Tissue Disorders				
Any AE	92 (43.4)	98 (45.8)	78 (36.8)	0.1468
Pruritus	22 (10.4)	28 (13.1)	16 (7.5)	0.1791
Alopecia	15 (7.1)	14 (6.5)	4 (1.9)	0.0217
Acne	13 (6.1)	18 (8.4)	22 (10.4)	0.2954
Rash	11 (5.2)	11 (5.1)	5 (5.2)	0.2335
Psychiatric Disorders				
Any AE	89 (42.0)	87 (40.7)	77 (36.3)	0.4569
Insomnia	64 (30.2)	55 (25.7)	45 (21.2)	0.1073
Anxiety	24 (11.3)	27 (12.6)	22 (10.4)	0.7663
Depression	13 (6.1)	12 (5.6)	11 (5.2)	0.9317
Renal and Urinary Disorders				
Any AE	81 (38.2)	79 (36.9)	106 (50.0)	0.0111
Dysuria	23 (10.8)	15 (7.0)	20 (9.4)	0.3630
Hematuria	18 (8.5)	19 (8.9)	23 (23)	0.6871
Proteinuria	5 (2.4)	14 (6.5)	11 (5.2)	0.1006
Cardiac Disorders				
Any AE	39 (18.4)	37 (17.3)	38 (17.9)	0.9570
Tachycardia	12 (5.7)	11 (5.1)	10 (4.7)	0.9264
Reproductive System and Breast Disorders				
Any AE	34 (16.0)	33 (15.4)	37 (17.5)	0.8599
Eye Disorders				
Any AE	25 (11.8)	30 (14.0)	24 (11.3)	0.6924
Endocrine Disorders				
Any AE	15 (7.1)	30 (4.2)	24 (12.3)	0.0084
Hirsutism	0 (0.0)	0 (0.0)	18 (8.5)	<0.0001
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)				
Any AE	13 (6.1)	9 (4.2)	12 (5.7)	0.6684

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

Reviewer's Comment: Although subjects in the Prograf and MR4 arms decreased their doses of MMF to a mean dose of approximately 1500 mg/day, these subjects still experienced significantly more adverse events associated with MMF than subjects in the Neoral arm, including diarrhea and loose stools. As a correlate dehydration and orthostatic hypotension were also more common in the Tac and TacXL treatment groups compared to the cyclosporine treatment group. This is interpreted by this reviewer as a reflection of increased mycophenolic acid exposure in tacrolimus treated subjects compared to the cyclosporine treated subjects (despite similar starting doses of 2g MMF per day, as specified in the CellCept package insert for use with cyclosporine in renal transplantation) related to the inhibition of enterohepatic recirculation of MPA with cyclosporine and the absence of such inhibition with tacrolimus.

Subjects in the TacXL treatment group experienced significantly more gastroenteritis compared with the subjects in Tac treatment group. Although the Applicant proposes that the higher gastroenteritis is due to the MMF, both arms had comparable exposures of MMF. The difference may have been due to a higher diagnosis rate in the TacXL arm compared with the Tac arm. In order for and event to be categorized as gastroenteritis, the subject needed a positive culture or laboratory test documenting an infectious agent; therefore, differences could exist if there were potential biases with respect to the investigation for an infectious etiology. Note to the reader of this comment, a similar difference with respect to gastroenteritis reported as adverse events was observed between TacXL and Tac patients in Study 12-03 which provided a double-blind comparison between the two formulations in the context of lower MMF dosing.

TacXL versus cyclosporine

In Study 158 there were no significant differences between the TAcXL and the cyclosporine arms among study subjects ≥ 65 years. Study subjects 16 to 64 years of age in the TacXL arm compared with those in the cyclosporine arm had a significantly ($p \leq 0.05$, Fisher's exact test) higher incidence of:

- diarrhea (46.3% versus 24.5%)
- tremor (34.7% versus 19.8%)
- diabetes mellitus (13.2% versus 6.3%)
- chest pain (11.6% versus 5.2%)
- sinusitis (7.4% versus 2.6%)
- gastroenteritis (7.4% versus 1.6%)
- alopecia (6.8% versus 2.1%)

- blood phosphorous decreased (5.8% versus 1.6%)
- pruritus generalized (2.6% versus 0)
- dysphagia (2.6% versus 0)

and a lower incidence of:

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

Tac versus cyclosporine

Study subjects ≥ 65 years in the Tac arm had a significantly (p≤ 0.05, Fisher's exact test) higher incidence of hyperglycemia compared with those in the cyclosporine group (34.8% versus 5.0%).

Study subjects 16 to 64 years of age in the Tac arm compared with those in the cyclosporine arm had a significantly (p≤ 0.05, Fisher's exact test) higher incidence of:

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

and a lower incidence of

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

TacXL versus Tac

The safety profile of TacXL was similar to Tac. TacXL had a significantly higher incidence of lower abdominal pain, gastroenteritis, and paresthesias whereas the Tac arm had significantly more urinary tract infections.

Table 74: Study 158 Significantly Different Adverse Events between Tac and TacXL

MedDRA (v. 6.1) System OrganClass Preferred Term	Tac (n=212)	TacXL (n=214)	p-value
Lower abdominal pain	2 (0.9%)	10 (4.7%)	0.0359
Urinary Tract Infections	54 (25.5%)	34 (15.9%)	0.0166

Gastroenteritis	1 (0.5%)	14 (6.5%)	0.0008
Paresthesias	3 (1.4%)	12 (5.6%)	0.0320

Source: Study 158 CSR Table 14.2.2.3; p-value using the Fisher's exact test.

Most of the episodes of paresthesias were mild to moderate in intensity. Two subjects (Numbers 00111003 and 00711008) had their dose of MR4 reduced as a result of paresthesias and did not report this event again. One subject (Number 00161013) permanently discontinued therapy and one subject (Number 00812002), who experienced paresthesias twice, had a dose reduction of TacXL after the first event then crossed over to cyclosporine/MMF treatment after the second event.
[Source: Study 158 CSR Appendices 14.4.2.3 and 14.4.4.1].

The Applicant has proposed the following table to describe common adverse events in Study 158 occurring in ≥ 15% of TacXL treated patients though one year.

Table 75 : Applicant's Proposed Listing of Common Adverse Events (≥ 15% of TacXL)

(b) (4)

(b) (4)

[redacted]

Reviewer's Comment: Using a cut-off of ≥ 15% is consistent with other product labeling in this class. Although it appears to minimize significant differences in events that occurred at lesser rates, including paresthesias and gastroenteritis reported as an infection, such information can be provided in the subsections addressing specific categories of adverse events in section 5 WARNINGS AND PRECAUTIONS of the package insert as deemed necessary.

7.4.1.2 Common Adverse Events in Study 12-03

The incidence of the most frequently reported adverse events defined as incidence rate of at least 10% in either treatment group regardless of relationship to study medication is presented in the table below adapted from the Applicant's CSR Table 23.

Table 76: Study 12-03 Incidence of Most Frequently (≥ 10% in any group) Reported Adverse Events Regardless of Relationship to Study Medication

MedDRA SOC MedDRA High Level Term *MedDRA Preferred Term*	**Tac (N=336) Patients (%)**	**TacXL (N=331) Patients (%)**
Metabolism and nutrition disorders	**231 (68.8)**	**236 (71.3)**
Potassium imbalance	79 (23.5)	91 (27.5)
Hyperkalaemia	49 (14.6)	50 (15.1)
Hypokalaemia	36 (10.7)	48 (14.5)
Diabetes mellitus (incl. subtypes)	69 (20.5)	68 (20.5)
Hyperglycaemic conditions NEC	70 (20.8)	67 (20.2)
Hyperglycaemia	65 (19.35)	61 (18.4)
Infections and infestations	**216 (64.3)**	**228 (68.9)**
Bacterial Infections	123 (36.6)	105 (31.7)
Urinary tract infection bacterial	102 (30.4)	86 (26.0)
Upper respiratory tract infections – pathogen class unspecified	47 (14.0)	49 (14.8)
Pharyngitis†	4 (1.2)	12 (3.6)
Cytomegaloviral infections †	21 (6.3)	36 (10.9)
Cytomegaloviral infection †	19 (5.7)	33 (10.0)
Abdominal and gastrointestinal infections	21 (6.3)	21 (6.3)
Gastroenteritis †	3 (0.9)	11 (3.3)
Polyomavirus infections †	1 (0.3)	7 (2.1)
Tinea infections †	0	5 (1.5)
Gastrointestinal disorders	**223 (66.4)**	**203 (61.3)**
Diarrhoea (excl. infective)	103 (30.7)	88 (26.6)
Diarrhoea	103 (30.7)	88 (26.6)
Nausea and vomiting symptoms	79 (23.5)	81 (24.5)
Nausea	42 (12.5)	51 (15.4)

Vomiting	43 (12.8)	42 (12.7)
Gastrointestinal atonic and hypomotility disorders NEC	64 (19.0)	47 (14.2)
Constipation	60 (17.9)	45 (13.6)
Gastrointestinal and abdominal pains (excl. oral and throat)	47 (14.0)	49 (14.8)
Abdominal pain	28 (8.3)	39 (11.8)
Gastrointestinal disorders NEC †	3 (0.9)	11 (3.3)
Renal and urinary disorders	**160 (47.6)**	**156 (47.1)**
Renal vascular and ischaemic conditions	52 (15.5)	45 (13.6)
Renal tubular necrosis	38 (11.3)	35 (10.6)
Bladder and urethral symptoms	43 (12.8)	43 (13.0)
Renal failure and impairment	40 (11.9)	29 (8.8)
Urinary abnormalities	32 (9.5)	34 (10.3)
Blood and lymphatic system disorders	**146 (43.5)**	**167 (50.5)**
Anaemias NEC	88 (26.2)	105 (31.7)
Anaemia	87 (25.9)	102 (30.8)
Leukopenias NEC	39 (11.6)	53 (16.0)
Leukopenia	37 (11.0)	51 (15.4)
Anaemias due to chronic disorders †	2 (0.6)	9 (2.7)
Nephrogenic anaemia †	2 (0.6)	9 (2.7)
Injury, poisoning and procedural complications	**150 (44.6)**	**140 (42.3)**
Non-site specific procedural complications	121 (36.0)	111 (33.5)
Graft dysfunction	56 (16.7)	57 (17.2)
Urinary tract procedural complications †	1 (0.3)	7 (2.1)
Urinary anastomotic leak †	0	6 (1.8)
Vascular disorders	**123 (36.6)**	**135 (40.8)**
Vascular hypertensive disorders NEC	76 (22.6)	80 (24.2)
Hypertension	76 (22.6)	80 (24.2)
Haemorrhages NEC †	10 (3.0)	22 (6.6)
Haematoma †	5 (1.5)	14 (4.2)
Investigations	**130 (38.7)**	**114 (34.4)**
Renal function analyses	66 (19.6)	57 (17.2)
Blood creatinine increased	63 (18.8)	54 (16.3)
Liver function analyses	47 (14.0)	35 (10.6)
General disorders and administration site conditions	**119 (35.4)**	**110 (33.2)**
Oedema NEC	68 (20.2)	54 (16.3)
Oedema peripheral	48 (14.3)	38 (11.5)
Pain and discomfort NEC	41 (12.2)	38 (11.5)
Nervous system disorders	**102 (30.4)**	**108 (32.6)**
Tremor (excl. congenital)	58 (17.3)	58 (17.5)
Tremor	58 (17.3)	58 (17.5)
Headaches NEC	33 (9.8)	40 (12.1)
Headache	33 (9.8)	39 (11.8)
Musculoskeletal and connective tissue disorders	**73 (21.7)**	**79 (23.9)**
Musculoskeletal and connective tissue signs and symptoms NEC	43 (12.8)	40 (12.1)
Joint related signs and symptoms †	17 (5.1)	30 (9.1)
Athralgia †	13 (3.9)	29 (8.8)
Respiratory, thoracic and mediastinal disorders	**83 (24.7)**	**70 (21.1)**
Psychiatric disorders	**71 (21.1)**	**64 (19.3)**
Disturbances in initiating and maintaining sleep	34 (10.1)	29 (8.8)
Insomnia	34 (10.1)	29 (8.8)
Skin and subcutaneous tissue disorders	**68 (20.2)**	**57 (17.2)**

Apocrine and eccrine gland disorders †	10 (3.0)	1 (0.3)
Night sweats †	9 (2.7)	0
Cardiac disorders	**44 (13.1)**	**42 (12.7)**
Reproductive system and breast disorders	**36 (10.7)**	**39 (11.8)**
Testicular and epididymal disorders	4 (1.2)	8 (2.4)
Testicular disorder †	0	5 (1.5)
Menstruation and uterine bleeding NEC	3 (0.9)	7 (2.1)
Dysmenorrhoea †	0	5 (1.5)

Full Analysis Set
Adverse events coded using MedDRA 6.1. Most frequently reported defined as incidence rate of ≥ 10% in either treatment group together with events with an incidence difference associated with a p-value < 0.05
MedDRA = Medical Dictionary for Drug Regulatory affairs; NEC = Not Elsewhere Classified; SOC = System Organ Class
† p = < 0.05 (Fisher's exact test)
Source: Study 12-03 12 month CSR Table 13.6.1.2

The table below summarizes adverse events with a difference in incidence between Tac XL and Tac associated with a p-value < 0.05 (Fisher's exact test).

Table 77: Study 12-03 Notable Differences in Adverse Events (p-value <0.05)

MedDRA (v. 6.1) System OrganClass Preferred Term	Tac XL N=331 Patients (%)	Tac N=336 Patients (%)
Pharyngitis	12 (3.6)	4 (1.2)
CMV infections	36 (10.9)	21 (6.3)
Tinea infections	5 (1.5)	0
Gastroenteritis	11 (3.3)	3 (0.9)
Polyomavirus infections	5 (1.5)	0
Gastrointestinal disorders NEC	11 (3.3)	3 (0.9)
Anemias due to chronic disorders *Nephrogenic anemia*	9 (2.7) 9 (2.7)	2 (0.6) 2 (0.6)
Urinary tract procedural complications *Urinary anastomotic leak*	7 (2.1) 6 (1.6 (1.8)	1 (0.3) 0
Hemorrhages NEC *Hematoma*	22 (6.6) 14 (4.2)	10 (3.0) 5 (1.5)
Joint related signs and symptoms *Arthralgia*	30 (9.1) 29 (8.8)	17 (5.1) 13 (3.9)
Testicular disorder	5 (1.5)	0
Dysmenorrhea	5 (1.5)	0
Apocrine and eccrine gland disorders *Night sweats*	1 (0.3) 0	10 (3.0) 5 (1.5)

Reviewer's Comment: Notable differences in gastroenteritis, pharyngitis, CMV infections, and polyomavirus infections are addressed in Section 7.3.4.1 of this review.

Reviewer's Comment: Overall, there appears to be a pattern of lower frequency of common adverse events in Study 12-03 compared to Study 158, which may reflect the differences in study design including blinding (open label in Study 158, double blind to week 24 in Study 12-03), and active control comparator (cyclosporine in Study 158, tacrolimus in Study 12-03). The difference in frequency of reporting of common adverse events may also reflect that Study 158 was largely a US study (80% of the subjects) conducted under an IND, while study 12-03 was conceived and conducted a non-US post-marketing study. Thus, tables describing common adverse events in labeling should not pool data from these two studies.

7.4.2 Laboratory Findings

Routine laboratory measurements for hematology and biochemistry were taken throughout Study 158, and a summary of select laboratory parameters of interest are presented in the table below.

Table 78: Study 158 Summary of Select Laboratory Parameters of Interest

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

Source: Table 13.6.5 Study 158 Report

Glucose laboratory data from both Study 158 and 12-03 were addressed as a safety measure in section 7.3.4.3 of this review on glucose metabolism disorders. Renal function data from both Study 158 and Study 12-03 were addressed as secondary endpoints in Section 6.1.5.2 of this review.

In Study 12-03 as well, routine laboratory measurements for hematology and biochemistry were taken throughout the study. Clinical laboratory data are summarized in the Applicant's Tables 13.6.3.1 (SI units) and 13.6.3.2 (US units). Values outside the

reference range and clinically relevant values outside the reference range were flagged on the listings.

In Study 12-03 all clinically relevant findings in the laboratory variables assessed were to be reported as adverse events and discussed in Section 9.1.1 of the Applicant's 12-month Study Report, and addressed in Section 7.4.1 of this review, while events of interest are addressed in Section 7.3.4 of this review. Renal function, as assessed by serum creatinine and creatinine clearance, is also discussed in Section 8.1.7 of the Applicant's 12-month Study Report and in Section 6.1.5.2.2 of this review.

There were no clinically relevant differences in any hematology or biochemistry parameters between TacXL and Tac during the study.

7.4.3 Vital Signs

Vital signs were monitored in all of the clinical studies reviewed in this submission. No clinically significant differences in the mean values for pulse rate, temperature, blood pressure, and weight were found across treatment groups.

Hypertension, which is a known hazard of the use of tacrolimus was addressed as an adverse event of interest in section 7.3.5.5 of this review.

7.4.4 Electrocardiograms (ECGs)

ECG information was collected in clinical trials and reviewed. No specific clinical QT safety studies were included in this submission.

ECG's were performed as part of the routine baseline and follow-up. No unusual trends were noted on the results of the ECG of study subjects. Because these subjects have a complicated medical history, there were abnormalities noted in a number of the ECGs, but no trends suggestive of an ECG abnormality associated with the any of the study arms. Although, tacrolimus has not been knownto be cardiotoxic or cause ECG abnormalities, recent labeling supplement regarding QT prolongation has been submitted to the NDAs for Prograf® (tacrolimus). That submission is currently under review. Conclusions of that review should also be applied to this NDA for tacrolimus extended release capsules.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were included in this application. This NDA is for a modified-release version of a known product, tacrolimus.

7.4.6 Immunogenicity

Immunogenicity is not applicable for orally administered tacrolimus extended release capsules.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Please see the Clinical Pharmacology Review in DARRTS for detailed information.

Although renal function impairment, tremors, infections, hypertension, glucose metabolism disorders including NODAT, are considered drug-related adverse events associated with the use of tacrolimus, exploration of dose dependency performed by the Applicant and the FDA did not yield conclusive results. These exploratory evaluations were limited by the range of tacrolimus exposures resulting from the use of target concentrations and therapeutic drug monitoring to guide tacrolimus dosing in the larger clinical trials.

Based on FDA analysis of the relationship between tacrolimus trough concentrations and adverse events of special interest, there were no significant differences in the mean tacrolimus trough concentration-time profiles of patients in Study 12-03 with and without CMV infections or bacterial pyelonephritis.

Because the incidence of gastroenteritis was significantly higher in TacXL patients than in Prograf patients in both Studies 12-03 and 158, the relationship of whole blood tacrolimus exposures with this adverse event was explored. Based on FDA review of the observed tacrolimus trough concentration profiles of gastroenteritis cases, a clear and consistent relationship with high tacrolimus trough concentrations was not found. As mentioned above in Section 7.3.51 of this review increased incidence of gastroenteritis in the TacXL patients could have been influenced by factors (e.g., differences in formulation, dosing frequency) that altered the local environment in the gut thereby increasing the susceptibility to infections caused by intestinal microflora.

7.5.2 Time Dependency for Adverse Events

No specific analyses of time to onset of adverse events, duration of event and the extent to which the adverse event resolves were included in this submission.

7.5.3 Drug-Demographic Interactions

Although Black and Hispanic kidney transplant patients are described as being at increased risk for new onset diabetes after transplantation (NODAT) in the Prograf

Label, based on findings from earlier clinical studies, now significant differences were noted with respect to NODAT among Blacks in Study 158, and the number of Black patients in Study 12-03 was too small to make meaningful comparisons.

7.5.4 Drug-Disease Interactions

Not applicable.

7.5.5 Drug-Drug Interactions

The approved Prograf® package insert includes a comprehensive section on drug interactions which should apply to tacrolimus extended release capsules, and are included in the Applicant's proposed package insert for tacrolimus extended release capsules.

7.6 Additional Safety Evaluations

Not applicable.

7.6.1 Human Carcinogenicity

The carcinogenicity of this product is the same as for Prograf. As an immunosuppressant, it places patients at increased risk of malignancies related to the degree and duration of immunosuppression such as lymphomas and skin malignancies [See class labeling in the boxed WARNING].

7.6.2 Human Reproduction and Pregnancy Data

No new human reproduction and pregnancy data was included in this NDA submission. What is included in the approved Prograf package insert with respect to pregnancy, and nursing mothers should also apply to tacrolimus extended release capsules.

7.6.3 Pediatrics and Assessment of Effects on Growth

No assessment of effect on growth was conducted because most of the studies involved adults. In the one pediatric conversion study, the length of the study was too short to assess growth. Furthermore, pediatric transplant patients are often on other drugs that may affect growth (such as corticosteroids), making it extremely difficult to attribute growth difficulties to tacrolimus. However, there are no known growth effects based on the experience with Prograf, which has been used in pediatric transplant patients for more than 18 years.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or

new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

The Applicant has requested a waiver for the requirement of pediatric studies in patients 0 to < 5 years and a deferral for children aged 5 to 16 years.

The Applicant's rationale for partial waiver in pediatric kidney transplant recipients aged 0 to < 5 years of age is based on the claim that studies to investigate the use of TacXL for the proposed indication of prophylaxis or organ rejection in kidney transplant recipients within this age group are highly impractical because the number of pediatric patients is so small (Section 505B(a)(4)(B)(i) of the Act).

The Applicant has further noted that based on the 2010 annual data report of the Scientific Registry of Transplant Recipients (SRTR), over the three year period from 2007 to 2009, there were only seven (7) pediatric kidney transplant patients ages younger than one (1) year and only 478 pediatric kidney transplant patients ages between one (1) to five (5) years old in the United States. By contrast, there were 2,050 kidney transplant patients ages between six (6) to 17 years old in the United States.

> *Reviewer's Comment: While a study in liver transplant recipients less than 1 year of age would indeed be highly impractical, pharmacokinetic information using an age appropriate pediatric formulation of could still be obtained in children 1 year and older. Thus, in consultation with the Pediatric Research Committee (PeRC) it is recommended that required pediatric study under PREA be waived in patients birth to less than 1 year, and deferred for patients 1 to less than 5 years of age in order to develop a pediatric formulation. Wording to that effect should be included regulatory correspondence to the Applicant.*

The Applicant has requested deferral of pediatric studies required under PREA and proposed a pediatric plan for TacXL in pediatric kidney transplant recipients from 5 to 16 years of age. The reasons for the deferral request are that adult studies have been completed and are ready for approval, as well as that a pediatric plan has been included in this NDA submission which includes an ongoing pharmacokinetic study in 10 stable pediatric transplant recipients aged 5 to 16 years of age, Study PMR-EC-1206: A Phase II, Open-Label, Multi-Center Study to Compare the Pharmacokinetics of Tacrolimus in Stable Pediatric Allograft Recipients Converted from a Prograf® Based Immunosuppressive Regimen to a Tacrolimus Prolonged Release, Advagraf® Based Immunosuppressive Regimen, Including a Long-Term Follow-Up.

> *Reviewer's Comment: After consultation with the PeRC, is it recommended that the requirements for pediatric studies under PREA be deferred for children aged 5 to 16 years or age. Wording to that effect should be included in the regulatory*

correspondence to the Applicant. The expected due date for completion and reporting of Study PMR-EC-1206 is May 31, 2014.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The overdose experience would be based on the experience with Prograf®. Reference should be made to the Overdose section in the Prograf® package insert.

Postmarketing cases of overdose with tacrolimus have been reported. Acute overdosages of up to 30 times the intended dose have been reported with Prograf. Some of these cases were symptomatic with adverse reactions consistent with those already recognized as potential hazards of tacrolimus, including nervous system disorders (tremor, confusional state, balance disorders, encephalopathy, and somnolence), abnormal renal function, hypertension, gastrointestinal disturbances (nausea, vomiting, and diarrhea), and infections. While most cases can resolve without sequelae after prompt decrease of tacrolimus, and medical management of the associated adverse events, fatal outcomes can occur.

Tacrolimus is not a drug with abuse potential. Tacrolimus is intended for chronic use. If tacrolimus is discontinued in a renal transplant recipient who is transitioned to another form of systemic immunosuppressive regimen, withdrawal symptoms or rebound in the form of unexpected rejection episodes are not expected.

7.7 Additional Submissions / Safety Issues

Not applicable.

8 Postmarket Experience

Tacrolimus extended release capsules have been approved in 69 countries including Japan (Gracepto®), countries in Europe (Advagraf®) and Canada (Advagraf®).

Marketing Errors Reported in Europe

Following marketing approval of Advagraf in Europe, medication errors have been reported including incorrect frequency of dosing (i.e., once daily Prograf dosing and twice daily Advagraf dosing); inadvertent, unintentional or unsupervised substitution of one formulation for the other; and coadministration of the 2 formulations. Detailed analyses done to date by the Applicant indicate that these errors can be classified as errors in prescribing (by physicians), dispensing (by pharmacist) and administration (by physician, nurse or patient).

Detailed analyses of the circumstances of error and potential root causes have been performed by the Applicant. As of 30 September 2011, Advagraf/Prograf medication

errors have been reported from 14 of the 43 countries where Advagraf is launched, including 10 of 26 European Economic Area (EEA) countries and 4 of 17 non-EEA countries. The vast majority of reports originated in the UK (78/120 cases). A particular feature of the local prescribing and dispensing systems in the UK is the use of International Nonproprietary Names (INN, e.g., tacrolimus) without specification of immediate-release or extended-release formulation, which can lead to erroneous prescribing and/or dispensing of the intended formulation. Other frequent reasons for error included confusion between the 2 formulations, the misimpression that the formulations are interchangeable and errors related to pharmacy computer software programs.

For additional information on the issue of medication errors, please see the review from the Division of Medical Error Prevention & Analysis (DMEPA) review in DARRTS.

9 Appendices

9.1 Literature Review/References

Not applicable.

9.2 Labeling Recommendations

As of the writing of this review a final package insert has not been agreed to. A draft label including recommendations and comments was sent to the Applicant on June 14, 2013.

These include recommendations for some of the clinical portions of the label.

The boxed WARNING should reflect the information on malignancies and serious infections included in the Prograf®(tacrolimus) label, that are considered class labeling for immunosuppressants in solid organ transplantation.

In addition, the boxed WARNING should also address the specific concern with respect to increased risk of death in female recipients of liver transplantation treated with TacXL (See Section 7.3.5 of this review). The following wording should be proposed:

Mortality in Liver Transplantation

- **Increased mortality in female transplant recipients was observed in a clinical trial of liver transplantation. Use in liver transplantation is not recommended *[see Warnings and Precautions (5.3)]*.**

Section 5 WARNINGS AND PRECAUTIONS should be based on what is included in the corresponding section of the package insert for Prograf (tacrolimus) capsules, and in addition address the concerns specific to TacXL.

A serious concern remains the potential increased risk of death in female recipients of liver transplantation treated with TacXL which should be addressed in Section 5 of the package insert with the following wording:

> **5.4 Liver Transplant Recipients**
>
> In a clinical trial of 571 liver transplant recipients randomized 1:1 to TRADENAME XL or Prograf, mortality at 12 months in female patients treated with TRADENAME XL was 10% higher compared to female patients treated with Prograf. Use of TRADENAME XL in liver transplantation is not recommended *[see Boxed Warning].*

An additional potential concern is that tacrolimus-XL is not interchangeable or substitutable with tacrolimus immediate release. Thus, to Section 5 is needed the addition of a subsection on Medication Errors. The following wording has been proposed by the Agency:

> **5.5 Medication Errors**
>
> TRADENAME XL extended release capsules are not interchangeable or substitutable with tacrolimus immediate release capsules. Medication and dispensing errors, including inadvertent or unintentional substitution between Prograf (twice daily immediate-release) and TRADENAME XL (once daily extended-release) tacrolimus formulations have been observed in postmarketing surveillance of TRADENAME XL in countries where it is approved and marketed. This has led to serious adverse events, including graft rejection, or other adverse reactions, which could be a consequence of either under- or over-exposure to tacrolimus. [*see How Supplied (16)*]
> Note that TRADENAME XL is supplied in short, square bottles and blisters; Prograf is supplied in tall, round bottles and blisters. TRADENAME XL and Prograf are further differentiated by different color schemes.

The subsection 6.1 Clinical Studies Experience in Section 6 ADVERSE REACTIONS, should include information from Study 158 (Study1 – With Basiliximab Induction) and Study 12-03 (Study 2 – Without Induction).

Information on selected significant adverse reactions observed during Studies 1 and 2 should also be summarized in Section 6.1 and include information on New Onset Diabetes after Transplant (NODAT), Infections, and Glomerular Filtration Rate.

A Table summarizing the incidence of adverse reactions that occurred in ≥15% of TRADENAME XL treated patients compared to control through one year of treatment in Studies 1 and 2 should be included, without pooling the numbers from the two studies, which are too disparate with respect to basiliximab induction use, blinding, concomitant MMF use, tacrolimus exposure, and study population, as noted above in this review.

Section 7 DRUG INTERACTIONS should also be based on the corresponding section included in the package insert for Prograf (tacrolimus) capsules. Given data that has been submitted on the effect of ethanol on dissolution of the extended release capsules (See CMC Review in DARRTS) addition of a subsection is needed on Alcohol with wording as described below:

> Consumption of alcohol while taking TRADENAME XL may increase the rate of release of tacrolimus and/or adversely alter the pharmacokinetic properties and the effectiveness and safety of TRADENAME XL. Therefore, alcoholic beverages should not be consumed with TRADENAME XL [*see Dosage and Administration (2.5)*]

Section 8 USE IN SPECIFIC POPULATIONS should also be based on the corresponding section in the Prograf package insert. With respect to the subsection on Pediatric use the following wording is recommended:

> The safety and efficacy of TRADENAME XL in pediatric kidney transplant patients < 16 years of age has not been established.

Section 10 OVERDODAGE should also be based on the corresponding section in the package insert for Prograf (tacrolimus) capsules as well as postmarketing information from the use of TacXL in the counties it has been marketed in, if applicable. The list of adverse reactions observed in symptomatic cases of overdosage should include those associated with overdosage of TacXL and/or Progaf. This needs to be comprehensive enough to inform the practitioner what signs and symptoms may be associated with overdosing, and what major organ systems may be involved. Although the Applicant has proposed to state in this section that “Most cases resolved without sequelae. One of these reported cases was fatal”, the exact number of cases that resolved without sequelae should be given to provide context to define “most”, and the number of fatal cases should be clarified.

Section 14 CLINICAL STUDIES should include under subsection 14.1 Prophylaxis of Organ Rejection in Kidney Transplant a description of both Study 1 – Induction with Basiliximab (Study 158) and Study 2 – No Induction (Study 12-03). Subsections on Tacrolimus Dosing, and MMF Dosing should be included prior to a subsection on Efficacy Results.

Section 17 PATIENT COUNSELING INFORMATION should also be based on that provided in the Prograf package insert, and include all parts that are relevant to tacrolimus. To this should be added, under the subsection Administration, wording addressing: the potential for medication error; the effect of alcohol on dissolution; and particular precautions regarding what to do if a dose is missed. Wording to that effect should be proposed as described below, in addition to wording based on what is used for Prograf:

Advise patients to

- Not switch between TRADENAME XL and tacrolimus immediate release oral products without supervision of a physician. If the appearance of this medicine is not the same as usual, or if dosage instructions have changed, speak to your doctor or pharmacist as soon as possible to make sure that you have the right medicine.
- Not take TAC-XL with alcoholic beverages [see Dosage and Administration 2.5)].
- Take a missed dose of TRADENAME XL as soon as the patient remembers but not more than 14 hours after the scheduled time (i.e. for a missed 8AM dose, take by 10PM). Beyond the 14 hour timeframe, the patient should wait until the usual scheduled time the following morning to take the next scheduled dose. Do not take 2 doses at the same time.

9.3 Advisory Committee Meeting

Not advisory committee meeting was held to discuss this application.

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/s/

MARC W CAVAILLE COLL
06/19/2013

JOETTE M MEYER
06/19/2013