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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	July 11, 2013
From	Joette M. Meyer, PharmD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 204096
Applicant	Astellas Pharma US, Inc.
Date of Submission	September 20, 2012
PDUFA Goal Date	July 21, 2013
Proprietary Name / Established (USAN) names	Astagraf XL Tacrolimus extended-release capsules
Dosage forms / Strength	0.5, 1, and 5 mg oral capsules
Proposed Indication(s)	Prophylaxis of organ rejection in adult patients receiving kidney transplants with concomitant use of mycophenolate mofetil (MMF) and adrenal corticosteroids [1]
Recommended:	Approval, pending resolution of CMC issues (see Section 3)

1. Introduction

Astagraf XL is a once daily extended-release formulation of tacrolimus (tacrolimus XL) that has been studied in kidney, liver, and heart transplant patients. At the time of NDA submission, it was approved in 69 other countries, including Canada, Europe and Japan. Prograf® (tacrolimus oral capsules) is an immediate-release oral formulation of tacrolimus dosed twice daily, which was approved by the FDA in on April 8, 1994 for use in kidney transplant patients. Tacrolimus oral capsules are also available generically.

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. The Agency administratively split the NDA into three separate NDAs for each indication: NDA 50-811 (kidney), NDA 50-815 (liver) and NDA 50-816 (heart). Study 02-0-158 (referred to hereafter as Study 158) was included in the kidney submission as an adequate and well controlled trial to support safety and efficacy.

On January 19, 2007, the Agency issued an approvable letter for the kidney and liver indications and a non-approvable letter for the heart indication. See Clinical Review for NDA 204096, Section 2.5 (Summary of Presubmission Regulatory Activity Related to Submission)

[1] The FDA indication recommended for approval has been modified to: prophylaxis of organ rejection in patients receiving a kidney transplant with mycophenolate mofetil (MMF) and corticosteroids, with or without basiliximab induction

by Marc Cavaillé-Coll, MD, PhD, for the list of deficiencies related to the kidney indication found in the January 19, 2007 approvable letter. These deficiencies were related to pharmacokinetic (PK) differences between Prograf and tacrolimus XL, such that a safe and effective initial dose could not be identified and an unfavorable safety profile of tacrolimus XL compared to Prograf in Study 158. The sponsor was advised to provide additional PK data to support an initial dose of tacrolimus XL and to submit an additional clinical trial comparing tacrolimus XL to Prograf. It was noted that the ongoing trial Study FG-506E-12-03 (hereafter referred to as Study 12-03) could provide the additional data needed to support the safety and efficacy of tacrolimus XL.

On September 12, 2007 the sponsor submitted a complete response to the January 19, 2007 approvable letter for NDA 50-811 (kidney indication). The submission contained results from the PK substudy of Study 12-03, as well as some limited information on safety and efficacy in this population. This submission addressed the deficiency related to determination of an initial dose of tacrolimus XL but did not address the clinical deficiency. In addition, while reviewing NDA 50-815 (liver indication), the Division found that there was a gender-related difference in the 12-month mortality between the tacrolimus XL and Prograf treatment groups, such that women treated with tacrolimus XL had a higher mortality rate than women treated with Prograf. A gender difference was also found in the onset of post-transplant diabetes mellitus (PTDM). The Division became concerned that the gender-related difference in mortality and PTDM between the tacrolimus XL and Prograf treatment groups observed in liver transplant patients may also exist in kidney transplant patients.

According to the Division Director's April 30, 2008 review for NDA 50-815:

> … The results of Study FG-11-03 demonstrate that Advagraf is non-inferior to Prograf, based on the gender analyses conducted by the Division, the excess mortality in women receiving Advagraf treatment compared to Prograf poses a safety issue. Specifically, the incidence of death in female *de novo* liver transplant recipients at 12-months post-transplantation in the Advagraf arm was 18.4% (14/76) compared to 7.8% (5/64) in the female recipients in the Prograf arm. The corresponding mortality rates in male patients were 6.8% (11/161) in the Advagraf arm and 10.6% (18/170) in the Prograf arm of the study (p=0.026, test for interaction using the Breslow Day test).
>
> The number of deaths in females receiving Advagraf was higher than the number of deaths in females receiving Prograf during both the blinded portion of Study FG-11-03 (first 24 weeks) and the unblinded follow-up portion of the study (6-12 months). The causes of deaths in women receiving Advagraf were primarily related to immune and infectious causes.
>
> We also noted higher numbers of cardiac-related deaths and post-transplant diabetes mellitus in females receiving Advagraf compared to females receiving Prograf, and a higher number of deaths in females liver transplant recipients of a male donor liver in females on Advagraf compared to females on Prograf, raising further safety concerns…

(b) (4)

. See Clinical Review for NDA 204096, Section 2.5 (Summary of Presubmission Regulatory Activity Related to Submission) by Marc Cavaillé-Coll, MD, PhD, for the list of deficiencies related to the kidney indication found in the March 13, 2008 approvable letter for NDA 50-811. One of the options

offered to address the deficiencies was for the sponsor to submit the full study report for Study 12-03.

(b) (4) On September 29, 2009, a meeting was held to discuss the proposed data to support submission of a new NDA for the kidney indication, containing the complete results for Study 12-03.

A pre-NDA meeting was held January 31, 2012 to discuss the submission of an NDA for tacrolimus XL for the following indications:

- Prophylaxis of organ rejection in adults (> 18 years old) receiving allogeneic kidney transplants.
- Prophylaxis of organ rejection in men (> 18 years old) receiving allogeneic liver transplants.

The NDA was submitted on September 20, 2103 and was filed on December 4, 2012. The review classification was determined to be Standard. On December 14, 2013 the sponsor was notified that for administrative purposes the NDA was administratively split into:

- NDA 204096/Original 1 - Prophylaxis of organ rejection in adult patients receiving kidney transplants.
- NDA 204096/Original 2 - Prophylaxis of organ rejection in adult male patients receiving liver transplants

On February 6, 2013 the sponsor requested that NDA 204096 [Original 2 – Liver (Males)] for tacrolimus XL capsules be withdrawn without prejudice to refiling.

Therefore, this review focuses on the data submitted to support the kidney indication. However, the data from the liver indication has implications for product labeling. See Section 12.

2. Background

The FDA has approved eight drugs/biologics for the indication of "prophylaxis of organ rejection" in patients receiving a kidney transplant. See the Appendix for a table summarizing these drugs/biologics, treatment regimens and design characteristics of studies which supported FDA approval. Of note, azathioprine (Imuran®) is not included in the table and was approved by the FDA in 1968 for the indication of "as an adjunct for the prevention of rejection in renal homotransplantations." No randomized, controlled trials were conducted to support the NDA. Instead, approval was based on experience in over 16,000 transplants that showed a 5-year patient survival of 35% to 55%.[2]

[2] Imuran® package insert: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/016324s034s035lbl.pdf

3. CMC/Device

The following summary was abstracted from the complete CMC review by Mark R. Seggel, PhD, dated June 14, 2013 in DARRTS.

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	COMMENTS
EES	Overall recommendation of ACCEPTABLE	As per Office of Compliance EES Summary Report, May 29, 2013
ONDQA Biopharmaceutics	*PMC under negotiation*	Discussed below
OSE / DMEPA	Proprietary name acceptable *Other labeling issues pending resolution*	See Section 12 of CDTL review for details
Environmental Assessment	Categorical exclusion acceptable	As per CMC review
Product Quality Microbiology	Acceptable	As per review by Erika Pfeiler, December 7, 2012

Source: Adapted from table on page 9 of CMC review; 6/14/13

Recommendation and Conclusion on Approvability
Tacrolimus drug substance chemistry, manufacturing and controls is incorporated into this New Drug Application by reference to Astellas' approved NDA 50-708 (Prograf (tacrolimus) capsules), and to their associated Type II DMF 16833. There are no outstanding drug substance CMC issues.

In general, sufficient information to assure the identity, strength, purity, and quality and bioavailability of the drug product, Astagraf XL (tacrolimus extended-release capsules), is provided in this NDA. However, evolving concerns about the potential for (b) (4) of amorphous tacrolimus in the (b) (4) formulation and in the drug product, and interest in enhancing the utility of proposed regulatory dissolution test method and acceptance criteria have necessitated the development of post-marketing commitments to address these issues. As of the date of this review, the post-marketing commitments are not finalized.

An overall recommendation of "Acceptable" was issued by the Office of Compliance.

Recommendations regarding the labeling (package insert, container and carton labels) have been made. Negotiations of all aspects of the labeling are underway at this time.

Therefore, from the CMC and Biopharmaceutics perspectives, this NDA is not recommended for approval. Final agreement must be reached on the post-marketing commitments and the labeling issues must be resolved before a recommendation for approval can be made.

Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Post-Marketing Commitments to (1) further characterize the potential for (b) (4) of amorphous tacrolimus in the (b) (4) and in the finished capsules, (2) optimize the dissolution test method with respect to detection of (b) (4) of the amorphous drug in the drug product, to (3) develop suitably discriminating dissolution test acceptance criteria are currently under negotiation.

4. Nonclinical Pharmacology/Toxicology

The following summary was abstracted from the complete pharmacology/toxicology review by Aaron M. Ruhland, PhD, dated June 12, 2013 in DARRTS. Of note, for purposes of this review, tacrolimus XL is referred to as Tac-XL.

The applicant did not submit any new nonclinical studies to support the nonclinical safety of Tac-XL. The applicant relies on nonclinical studies conducted for the approval of Prograf (NDAs 50-708 and 50-709 for capsule and injection, respectively) to support this extended release formulation. For details, refer to the Pharmacology review conducted by Lauren E. Black (dated 12-16-1993).

The applicant included an amendment to the study report for a nonclinical proof of concept study entitled "Comparison between the effects of bolus intramuscular administration and continuous infusion of FK506 on skin allograft rejection in rats (Report No. CRR980201). This study was reviewed by Dr. Shukal Bala (see Microbiology/Immunology review dated 5-10-2013) [discussed in Section 6 of this review (Microbiology/Immunology) below].

Approvability: Approvable from a Pharmacology/Toxicology perspective.

Additional Non Clinical Recommendations

- The following comment should be communicated to the applicant:
    - In the labeling, please update Section 10, "Overdosage", to include safety margins related to the doses which produced lethality in the nonclinical studies. Information should be included regarding oral dosage forms in adults and non-adults. The margins should be based on body surface area conversions of the doses which caused lethality in the acute nonclinical studies.
    - In the labeling, please update Section 13.1 "Carcinogenicity" to include safety margins related to doses which produced lymphoma in the nonclinical dermal studies of Protopic®. The safety margin should be based on exposure comparisons (preferably AUC) of patients administered Astagraf XL (at 0.2 mg/kg) and the exposures observed in the nonclinical dermal study.

Other changes to the labeling are recommended (see FDA redline version of Section 1.3.3). These changes were incorporated into the draft labeling sent to the applicant [on Friday,

June 14, 2013].

5. Clinical Pharmacology/Pharmacometrics

The following summary was abstracted from the complete clinical pharmacology review by Gerlie Gieser PhD/Jee Eun Lee PhD dated June 13, 2013 in DARRTS. Of note, for purposes of this review, tacrolimus XL is referred to as TAC-XL.

To support the approval of the kidney indication of NDA 204096, 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), all these studies were also previously reviewed under NDA 50-811 by Dr. Seong Jang (Clinical Pharmacology reviewer) [see reviews dated January 19, 2007 and March 6, 2008 in DARRTS].

Summary of Important Clinical Pharmacology Findings

Exposures to tacrolimus and concomitant immunosuppressive drugs in Phase 3 Studies 12-03 and 158:

The first table below compares Studies 12-03 and 158 in terms of the actual initial TAC-XL doses, the observed tacrolimus trough concentrations, and the actual doses of concomitantly administered immunosuppressive drugs. For comparison, the second table below shows the protocol specified doses of the immunosuppressive drugs and the target tacrolimus trough concentrations in these two primary Phase 3 studies. The TAC-XL starting doses and the observed tacrolimus trough concentrations were slightly higher in Study 12-03 than in Study 158 (first table below). However, in Study 158, the TAC-XL based dosing regimen also consisted of basiliximab (antibody induction agent), and compared to Study 12-03, Study 158 used higher cumulative doses of concomitant MMF and oral corticosteroids. Note that at the time of the Pre-NDA Meeting on 28 February 2012, the FDA and the sponsor agreed that the actual starting doses of TAC-XL and the observed tacrolimus trough concentration ranges should be described in the labeling, assuming the efficacy and the safety of the evaluated TAC-XL dosing regimens were acceptable.

TAC-XL Based Immunosuppressive Regimens Evaluated in De Novo Kidney Transplant Patients in Phase 3 Study 12-03 and Phase 3 Study 158 (actual drug doses and observed concentrations)

	Study 12-03	Study 158
Initial TAC-XL dose (actual mean on day)	Pre-operative (day 0): 0.15 mg/kg[a] as one dose within 12 h prior to reperfusion; AM on empty stomach Post-operative (day 1): 0.2 mg/kg not < 4 hours after the pre-operative dose or > 12 h after reperfusion; AM on empty stomach	0.14 mg/kg [b] prior to or within 48 hours of reperfusion; AM
Tacrolimus trough concentration range (10^{th} – 90^{th} percentile)[c]	Days 1-60: 6-20 ng/mL Month 3 to 12: 6-14 ng/mL	Days 1-60: 5-17 ng/mL Month 3 to 12: 4-12 ng/mL
MMF daily dose (actual mean)	Days 1-14: 2 g/day thereafter: 1 g/day	Days 1-60: 2 g/day Month 3-12: 1.5 g/day
Basiliximab induction (i.v.)	not allowed	20 mg i.v.on day 0 and a second 20 mg dose between days 3 to5
Methylprednisolone i.v. bolus dose (median)	Peri-operative (day 0): 625 mg Day 1 post-reperfusion: 150 mg	Day 0: 625 mg
Oral corticosteroid dose (median prednisone equivalent, mg/day)	Days 2-14: 20 Days 15-28: 15 Days 29-42: 10 Days 43-84: 5 Days 85 -365: 5	Day 1: 250 Days 2-14: 50 Days 15-30: 20 Days 31-60: 15 Days 61-90: 10 Days 91-365: 10

[a] median 0.1 mg/kg, [b] median 0.15 mg/kg, [c] observed in 80% of the patients
Source: Table 1 in Clinical Pharmacology review for NDA 204096, 6/13/13

TAC-XL Based Dosing Regimens Evaluated in De Novo Kidney Transplant Patients in Phase 3 Study 12-03 and Phase 3 Study 158 (protocol specified)

	Study 12-03	Study 158
Initial TAC-XL dose	Pre-operative (day 0): 0.1 mg/kg as one dose within 12 h prior to reperfusion; AM on empty stomach Post-operative (day 1): 0.2 mg/kg not < 4 hours after the pre-operative dose or > 12 h after reperfusion; AM on empty stomach	0.15 – 0.2 mg/kg prior to or within 48 hours of reperfusion; AM
Target tacrolimus trough concentration range (ng/mL)	up to Day 28: 10 –15 ng/mL Days 29 -168: 5-15 ng/mL thereafter 5-10 ng/mL	Days 0 to 90: 7 -16 ng/mL thereafter 5-15 ng/mL
MMF daily dose (BID dosing)	2 g/day until Day 14, then 1 g/day	2 g/day (up to 3 g/day allowed for African-Americans). Dose equivalent changes in dosing intervals (TID, QID) allowed for tolerability concerns.
Basiliximab induction (i.v.)	not allowed	20 mg i.v.on day 0 and a second 20 mg dose between days 3 to5
Methylprednisolone i.v. bolus dose	Peri-operative (day 0): ≤ 1000 mg Day 1 post-reperfusion: 125 mg	Day 0: 500 to 1000 mg
Oral corticosteroid dose (prednisone equivalent, mg/day)	Days 2-14: 20 Days 15-28: 15 Days 29-42: 10 Days 43-84: 5 Days 85 -365: 0 to 5	Day 1: 200 By Day 14: 20 to 30 By Month 1: 10 to 20 By Month 2: 10 to 15 By Month 3 to 12: 5 to 10

Source: Table 1A in Clinical Pharmacology review for NDA 204096; 6/13/13

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

General Clinical Pharmacology and Biopharmaceutics of TAC-XL:

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 TAC-XL as single doses in a crossover fashion.

Diurnal Variation in PK. In healthy subjects, evening dosing of TAC-XL resulted in a 35% lower $AUC_{0\text{-}inf}$ compared to morning dosing. *TAC-XL 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 TAC-XL 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 TAC-XL 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 TAC-XL was administered 1.5 hours after consumption of the meal, and by 10% when administered 1 hour prior to the meal. *To achieve maximum possible tacrolimus exposure, TAC-XL should be taken on an empty stomach, preferably at least 1 hour before breakfast or at least 2 hours after breakfast.*

In healthy subjects, the *nasogastric* administration of TAC-XL as an aqueous suspension prepared from the capsule contents resulted in a 30% higher tacrolimus Cmax, a shorter Tmax (by 1 hour), and a 17% lower AUC_{inf} than that following oral administration of the intact TAC-XL capsules. The *oral* administration of the same aqueous suspension resulted in a comparable $AUCi_{nf}$, a 28% higher Cmax, and a shorter Tmax (by 1.5 hours) than that following oral administration of the intact TAC-XL capsules. *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. In vitro dissolution testing in 40% ethanol at pH 1.2 resulted in accelerated dissolution (i.e., dose-dumping) of tacrolimus from TAC-XL 0.5 mg and 5 mg capsules. No in vivo follow on studies had been conducted. *TAC-XL should not be taken with alcoholic beverages.*

Relative Bioavailability. In terms of systemic exposure to tacrolimus, the Day 1 and steady-state tacrolimus AUC_{0-24} for TAC-XL 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.

Drug-Drug Interactions. In healthy subjects, coadministration of a 4 mg dose of TAC-XL 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 TAC-XL with *rifampin* (600 mg/day) for 12 days decreased the mean AUC_{inf} and C_{max} of tacrolimus by 56% and 46%, respectively. *Adjustment of TAC-XL doses and frequent monitoring of tacrolimus trough concentrations are recommended when coadministering TAC-XL with strong CYP3A inhibitors and strong CYP3A inducers.*

Correlation of C_{trough} to AUC_{0-24}. For TAC-XL, 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).

Management of Missed Dose. Based on simulations, taking a missed TAC-XL 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.

Exposure-Efficacy Relationships:
Based on the findings of the PK substudy of Study 12-03, the administration of equivalent daily doses of TAC-XL once daily and Prograf twice daily to de novo kidney transplant patients on Day 1 post-transplant resulted in tacrolimus C_{24} and AUC_{0-24} that were approximately 20-25% lower in TAC-XL patients than in Prograf patients. Additionally, in the main trial of Study 12-03, the observed mean and median tacrolimus trough concentrations were numerically lower in TAC-XL patients than in Prograf patients during the first 14 days of the clinical trial. Based on the sponsor's analysis, there was no significant difference between TAC-XL patients with acute rejection and those without acute rejection, in terms of the mean-tacrolimus trough concentration time profiles during the first 14 days.

Exposure-Safety Relationships:
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 TAC-XL 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. According to the FDA Medical reviewer, the increased incidence of gastroenteritis in the TAC-XL 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.

From a Clinical Pharmacology perspective, NDA 204096 is recommended for approval provided satisfactory agreement is reached with the sponsor regarding the recommended changes to the labeling [These changes were incorporated into the draft labeling sent to the applicant on Friday, June 14, 2013].

6. Clinical Microbiology/Immunology

The following summary was abstracted from the complete microbiology/immunology review by Shukal Bala, PhD dated May 10, 2013 in DARRTS.

In this submission, the applicant included a study report (Report no. CRR980201) comparing the activity of bolus intramuscular administration and continuous intravenous infusion of tacrolimus on skin allograft rejection in rats. The study is summarized in the review.

This NDA should be approved with respect to Immunology/Microbiology.

Comments:
• The labeling proposed by the applicant is same as that for immediate-release capsules of tacrolimus (Prograf®).
• No changes are recommended in section 12.1 "Mechanism of action"

CDTL Comment: The wording regarding (b) (4) *is misleading, as per OPDP comment regarding Section 12.1 of the package insert (see review by Christine Corser, PharmD, dated June 7, 2013 in DARRTS). The information was removed from the version of the package insert that was sent to the sponsor on June 14, 2013.*

7. Clinical/Statistical- Efficacy

The following summary was abstracted from the complete statistical review by Joy Mele, PhD dated June 4, 2013 in DARRTS and the clinical review by Marc Cavaillé-Coll, MD, PhD dated June 19, 2013 in DARRTS. Of note, for purposes of this review, tacrolimus XL is referred to as Tac-XL. Also, the clinical pharmacology reviewer created several of the tables included on tacrolimus exposure and MMF dosing.

***De novo* Trials**
The efficacy and safety of tacrolimus XL in *de novo* kidney transplantation was assessed in two randomized, multicenter, active-controlled 12-month trials (Study 158 and Study 12-03), as discussed in more detail below. A third trial, PMR-EC-12-10, was a 24-week randomized, open-label trial of three tacrolimus XL-containing arms compared to a Prograf control arm, which was also reviewed by the Statistical Reviewer as a supportive trial, but will not be discussed further in this review.

Study 158 -- Induction with Basiliximab
Study 158 was a randomized, open-label, non-inferiority trial of tacrolimus XL (N=214) compared to Prograf (tacrolimus immediate release) (N=212) and Neoral (cyclosporine USP, modified) (N=212), of 12 months duration conducted primarily in the US (about 80% of patients) with additional sites in Canada and Brazil. Patients were stratified by donor type (living or deceased) and transplant history (primary or re-transplant). All patients received basiliximab induction and concomitant treatment with MMF (1 gm twice daily) and corticosteroids. The primary endpoint was efficacy failure at one year where a failure is defined as death, graft loss, or biopsy confirmed acute rejection (BCAR). Patients missing endpoint data, i.e. lost to follow-up, were counted as failures in the primary analysis. A non-inferiority margin of 10% was pre-specified for the comparison of each tacrolimus arm to Neoral (cyclosporine; CsA) for the primary endpoint. Serum creatinine and creatinine clearance were named as secondary efficacy endpoints.

CDTL comment: The trial was designed for a primary comparison of the tacrolimus XL and Neoral arms, as at the time the study was designed Prograf was not approved for use with MMF. The statistical reviewer in 2007 concluded M1 was about 13% for the comparison between tacrolimus XL and CsA; therefore a 10% margin could be justified for this comparison, but a margin between the tacrolimus XL and Prograf arms could not be justified. Prograf/MMF was approved in 2009 and this regimen is now considered to be standard of care. Therefore in the current submission the primary comparison for efficacy (and safety) was between tacrolimus XL and Prograf. The current statistical reviewer concluded that an M1 for this comparison is about 30%. Assuming at least 50% retention of effect, the non-inferiority margin would be 15% or less.

Treatment groups were balanced with respect to baseline demographics. Most transplant recipients were white (about 75%) and male (about 64%). Blacks made up approximately 30% of the population. About half of donors were deceased. Almost all patients had no previous history of previous transplantation. The mean age was 48 years (range 17 to 77 years)

CDTL Comment: Study 158 was included in the original NDA for 50-811 for the kidney indication and the clinical review of that application was authored by Hui-Hsing Wong, MD, JD, dated January 19, 2007 in DARRTS. The statistical reviewer was LaRee Tracy, MA, and the statistical review for NDA 50-811 is dated January 12, 2007 in DARRTS.

Study 12-03 -- No Induction

Study 12-03 was a randomized double-blind, double dummy (until the last patient had completed 24 weeks on study treatment) non-inferiority trial of tacrolimus XL (N=331) compared to Prograf (N=336), of 12 months duration conducted entirely outside the US (Europe, North and South America, Africa, and Australia). Patients with a high immunologic 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 immunologic reasons were excluded, as were recipients of donor kidneys with cold ischemia time > 30 hours, or donor kidney's from a non-heart beating donor. All patients received concomitant treatment with MMF (1 gm twice daily for the first 14 days, then reduced to 0.5 mg twice daily) and corticosteroids without induction. The primary endpoint for this study was the event rate of biopsy-confirmed acute rejection (BCAR) by local assessment at Week 24; a non-inferiority margin of 10% was pre-specified, but not justified. The incidence of BCAR at Month 12 was a secondary endpoint. Serum creatinine and creatinine clearance were also secondary efficacy endpoints.

CDTL Comment: As requested by FDA, the sponsor has calculated the efficacy failure rate at 1 year for Study 12-03 consistent with that in 158 (i.e., death, graft loss, BCAR as assessed by local review or lost to follow-up).

The statistical reviewer concludes that in Study 12-03 M1 for the BCAR endpoint can be estimated at about 28%. Assuming at least 50% retention of effect, the non-inferiority margin would be 14% or less.

This patient population is similar to the one in Study 158 with the exception of more deceased donor organs (73%) and a lower representation of Blacks (approximately 5%). The mean age was 46 years (range 19 to 69 years).

Tacrolimus Dosing – Studies 158 and 12-03

The following table summarizes the protocol dosing in Studies 158 and 12-03 for tacrolimus XL, Prograf, and Neoral (Study 158 only).

Summary of Immunosuppressant Dosing Regimens in Studies 158 and 12-03

Study Number	Induction Regimen	Tacrolimus			MMF	Corticosteroids
		Pre-dose	Initial Dose	Target Trough level		
Study 158						
Tac-XL	basiliximab Day 0: 20 mg Day 3, 4 or 5: 20 mg	NONE	0.15-0.2 mg/kg Per day	Days 0-90: 7-16 ng/ml Days >90: 5–15 ng/ml	Post-op 1 g BID [Blacks could get 1.5 g BID]	Methylprednisolone Day 0: iv bolus 500-1000 mg Day 1: oral 200 mg iPrednisone mg/d Days 2-14: 20-30 Days 15-30: 10-20 Days 31-60: 10-15 Mos 3-12: 5-10
Prograf		NONE	0.075-0.1 mg/kg BID			
CsA		NONE	4-5 mg/kg BID	Days 0-90: 125-400 ng/ml Days >90: 100-300 ng/ml		
Study 12-03						
Tac-XL	--	0.1 mg/kg	0.2 mg/kg Per day	Days 0-28: 10–15 ng/ml Days 29-168 5–15 ng/ml Days >168: 5–10 ng/ml	Pre-op 1g BID Post-op Days 1-14 1g BID Days>14 0.5 g BID	Methylprednisolone iv bolus: Day 0: ≤ 1000 mg Day 1: 125 mg iPrednisone mg/d Days 2-14: 20 Days 15-28: 15 Days 29-42: 10 Days 43-84: 5 Days >84: ≤ 5 withdrawal for selected subjects
Prograf	--	0.1 mg/kg	0.1 mg/kg BID			

Source: Adapted by statistical reviewer from Table 1 in Module 2.7.3 Kidney Transplantation, Summary of Clinical Efficacy, NDA 204096; statistical review of NDA 204096; 6/4/13

In Study 158, the actual tacrolimus starting dose (given any time up to day 2 post-transplant) of tacrolimus XL was higher than Prograf (0.15 mg/kg versus 0.1 mg/kg). In Study 12-03, the actual tacrolimus doses on day 0 (0.1 mg/kg/day pre-operative) and day 1 (0.2 mg/kg/day post-operative) were comparable between the tacrolimus XL and Prograf arms. Thereafter, to achieve comparable mean tacrolimus trough concentrations (C_{24}), higher total mean daily doses of tacrolimus XL were required for tacrolimus XL than Prograf (on average, by 15% in Study 158 and by 25% in Study 12-03).

In Study 158, African-American patients required higher tacrolimus XL doses to attain similar trough concentrations as Caucasian patients.

Tacrolimus XL Doses and Mean Whole Blood Trough Concentrations in African-American and Caucasian Kidney Transplant Patients in Study 158

Time After Transplant	Caucasian Patients n=160		African-American Patients n=41	
	Dose (mg/kg)	Mean Trough Concentration (ng/mL)	Dose (mg/kg)	Mean Trough Concentration (ng/mL)
Day 7	0.14	10.65	0.14	7.78
Month 1	0.14	11.11	0.17	10.92
Month 6	0.10	7.95	0.13	8.42
Month 12	0.09	7.53	0.12	7.33

Source: Adapted by clinical pharmacology reviewer from Table 2 in Sponsor's proposed package insert (August 2012 version), NDA 204096

Observed tacrolimus whole blood trough concentrations measured at protocol specified time points for tacrolimus XL in Study 158 and Study 12-03 are shown in the table below. In Study 1, the protocol-specified target tacrolimus whole blood trough concentrations (C_{trough}) were 7-16 ng/mL for the first three months and 5-15 ng/mL thereafter. Approximately 80% of tacrolimus XL patients maintained tacrolimus whole trough blood concentrations between 5 to 17 ng/mL during months 1 through 2 and, then, between 4 to 12 ng/mL from months 3 through 12. In Study 2, the protocol-specified target tacrolimus whole blood trough concentrations (C_{trough}) were 10-15 ng/mL during the first month, 5-15 ng/mL from Month 2 to Month 6, and 5-15 ng/mL thereafter. Approximately 80% of tacrolimus XL patients maintained tacrolimus whole trough blood concentrations between 6 to 20 ng/ml during months 1 through 2 and, then between 6 to 14 ng/mL from months 3 through 12.

Observed Tacrolimus Whole Blood Trough Concentrations for Tacrolimus XL Kidney Transplant Patients Evaluated in Studies 158 and 12-03

Scheduled Visit	Median (P10-P90[a]) tacrolimus whole blood trough concentrations (ng/mL)	
	Study 1	Study 2
Day 3	9.6 (4.9 – 20.2)	13.8 (6.5 – 25.5)
Day 7	9.1 (4.4 – 16.8)	10.1 (5.5 – 17.3)
Day 14	10.0 (5.7 – 16.9)	10.8 (6.7 – 17.9)
Month 1	10.5 (5.6 – 17.1)	12.0 (7.5 – 17.6)
Month 2	9.4 (6.1 – 14.2)	11.1 (6.6 – 17.3)
Month 6	7.7 (4.4 – 11.5)	9.2 (5.7 – 13.5)
Month 12	7.2 (3.8 – 10.4)	8.0 (5.1 – 13.8)

a) 10 to 90th Percentile: range of C_{trough} that excludes lowest 10% and highest 10% of C_{trough}

Source: Adapted by clinical pharmacology reviewer from Table 14 in Sponsor's proposed package insert (August 2012 version), NDA 204096

MMF Dosing – Studies 158 and 12-03

In Study 158, patients in each group started MMF at 1 gram twice daily. The MMF dose was reduced to less than 2 grams per day by month 12 in 56% of patients in the tacrolimus XL

group as shown in the table below. Approximately 57% of the MMF dose reductions were because of adverse reactions in the tacrolimus XL group.

In Study 12-03, patients in each group received MMF at 1 gram twice daily starting pre-operatively. In majority of the patients, the MMF dose was reduced to 0.5 grams twice daily starting after day 14, as per the protocol, as shown in the table below.

Distribution of TacrolimusXL/MMF Patients (%) Based on Time-Averaged MMF Dose[a]

	Study 158			Study 12-03		
	Time-averaged MMF dose [a]			Time-averaged MMF dose [a]		
Time period (Days)	Less than 2.0 (g/day)	2.0 (g/day)	Greater than 2.0 (g/day)	Less than 2.0 (g/day)	2.0 (g/day)	Greater than 2.0 (g/day)
1-30	30%	64%	6%	82%	17%	0%
1-90	42%	52%	7%	93%	7%	0%
1-180	52%	44%	4%	94%	6%	0%
1-365	56%	41%	3%	95%	5%	0%

a) Time-averaged MMF dose = (total MMF dose)/(duration of treatment). A time-averaged MMF dose of 2.0 grams per day means that the MMF dose was not reduced in those patients during the time period.

Source: Adapted by clinical pharmacology reviewer from Table 15 in Sponsor's proposed package insert (August 2012 version), NDA 204096

Efficacy Results – Studies 158 and 12-03

In Study 158, the efficacy failure rate including patients who developed biopsy-confirmed acute rejection (BCAR), graft failure, death, and/or lost to follow-up at 12 months, as well as the rates of the individual events, is shown in the table below for the intent to treat (ITT) population. The Month 12 results show that tacrolimus XL is comparable to both Prograf and Neoral/cyclosporine (CsA) with upper bounds of the confidence intervals of 6% or less; within a non-inferiority boundary of 10%. Looking at the event rates by type of failure, most of the events are rejections, as would be expected and there are no notable differences between tacrolimus XL and Prograf.

Efficacy Failure Rates at Month 12 in Study 158 in the ITT Population (efficacy failure defined as BCAR, death, graft loss, or lost-to-follow-up)[1]

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

1 Results based on applicant's study report and FDA statistical review dated 1/12/2007
2 Negative values favor Tac-XL
3 Graft loss includes all patients with a graft loss; 1 Tac-XL patient and 3 Prograf patients died after a recorded graft loss.
4 According to the study report, graft loss includes deaths, graft failures (permanent dialysis or retransplant) and LTFU
Source: Adapted from Table 3.1.4 in the statistical review of NDA 204096; 6/4/13

CDTL Comment: The imbalance in deaths between the Prograf arm (N=9) and the tacrolimus XL (N= 3) and CsA arms (N=5) was discussed in the 2007 clinical and statistical reviews for NDA 50-811, as well as in the current clinical review. The clinical reviewers believe many of the deaths in the Prograf arm are as result of over immunosuppression based on the assessment of the primary cause of deaths in the case report forms and patient narratives. One explanation is that the MMF dosing was too aggressive when used with tacrolimus. The Symphony-ELiTE study, which was used to support the approval of the Prograf/MMF regimen used lower doses of MMF and lower trough concentrations of tacrolimus and did not show an imbalance in deaths compared to a cyclosporine-containing comparator arm. In the current submission, Study 12-03 which also used lower doses of MMF (although higher to comparable exposure to tacrolimus, due to the lack of an induction agent) than in Study 158, also did not show an imbalance in deaths between the treatment tacrolimus XL (N=10) and Prograf (N=8) arms. See table below.

In Study 12-03, the efficacy failure rate including patients who developed biopsy-confirmed acute rejection (BCAR), graft failure, death, and/or lost to follow-up at 12 months, as well as the rates of the individual events, is shown in the table below for the ITT population.

The efficacy failure results show about a 5% higher rate of failures for tacrolimus XL than Prograf. The upper bound for the confidence interval on the treatment difference was about 11%; this is one percent higher than the 10% margin proposed by the applicant. However, the estimate is below an M1 of 30% and a non-inferiority margin of 15%, based on conserving 50% of the treatment effect over placebo.

Efficacy Failure Rates in Study 12-03 at Months 12 and 24 in the ITT population (efficacy failure defined as BCAR, death, graft loss, or lost-to-follow-up)

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

[1]Negative values favor Tac-XL
[2]Results based on applicant's Kaplan-Meier analyses which produced KM estimates and difference in estimates
[3]Computed by statistical reviewer.
[4]The applicant reported 68 BCARs in Table 21 of their study report, however, dataset EFF recorded 67 BCARs. Additional data was requested from the applicant to explain the discrepancy. One additional patient was identified (H8204) as having a BCAR but not included as such in the submitted data; however, the patient was recorded as an efficacy failure.
Source: Adapted from Table 3.2.6 in the statistical review of NDA 204096; 6/4/13

Efficacy Analysis by Age/Race/Sex/Geographic Region

The statistical reviewer compared tacrolimus XL to Prograf in Studies 158 and 12-03 for the efficacy failure endpoint of BCAR, graft loss, death or lost-to-follow-up in the above mentioned subgroups. None of the subgroup analyses analysis showed a significant risk difference, although some subgroups were limited by small patient numbers.

Because of the FDA concern regarding a significant interaction for sex by treatment seen for deaths in a study for liver transplant patients, this reviewer looked at the deaths by sex for Studies 158 and 12-03. There was no significant interaction seen in kidney transplant patients. For females, fewer deaths were seen in patients receiving tacrolimus XL than Prograf in each of the two studies. Also comparable rates of new onset diabetes after transplant (NODAT) were seen for the two treatment groups with no evidence of a treatment difference by sex, as suggested in the liver transplant Study 11-03.

CDTL Comment: See the statistical review of Study 11-03 (by LaRee Tracy, MA; NDA 50-811 dated January 12, 2007 in DARRTS) for details regarding the significant treatment by sex interaction seen for mortality for the liver indication.

Efficacy Summary/Conclusions for *De Novo* Trials

The following efficacy conclusions and recommendations were obtained from the complete statistical review by Joy Mele, PhD dated June 4, 2013 in DARRTS Of note, for purposes of this review, tacrolimus XL is referred to as Tac-XL.

Statistical Conclusions and Recommendations

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

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

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

The following efficacy summary was obtained from the complete clinical review by Marc Cavaillé-Coll, MD, PhD dated June 19, 2013 in DARRTS. Of note, for purposes of this review, tacrolimus XL is referred to as TacXL.

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.

Conversion Trials

The sponsor also submitted three single arm, short term (≤ 12 weeks) conversion trials (i.e., patients ≥ 6 months post-transplant on a stable immunosuppressive regimen) summarized in the table below.

Summary of Phase 2 Conversion Trials in Kidney Transplantation

Study	Key Design Features/Endpoints
02-0-131	Single arm, open-label Converted from Prograf to Tacrolimus XL Primary endpoint 5 wk PK parameters, also BPAR/GL/D/LTFU @ 1 yr 6 year patient/graft survival
FG-506E-12-02	Single arm, open-label Converted from Prograf to Tacrolimus XL Primary endpoint 8 wk PK parameters, also BPAR/GL/D/LTFU @ 1 yr 5 year patient/graft survival
FJ-506E-KT01	Single arm, open-label Converted from Prograf to Tacrolimus XL Primary endpoint 2 wk PK parameters, also BPAR @ 12 weeks

Efficacy Summary/Conclusions for Conversion Trials

These conversion trials were primarily PK trials and were single arm and not randomized (i.e., patients on Prograf were converted to tacrolimus XL, but there was not a control arm of patients continuing on Prograf for comparison. Furthermore, they were not designed to collect long-term information on BPAR, after participation in the short-term PK portion of these studies. (b) (4) However, the review team did not consider these to be adequate

and well controlled trials (b) (4)

8. Safety

The following safety summary was obtained from the complete clinical review by Marc Cavaillé-Coll, MD, PhD dated June 19, 2013 in DARRTS. Of note, for purposes of this review, tacrolimus XL is referred to as TacXL and immediate release tacrolimus as Prograf or Tac.

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. In addition, these two studies used different regimens of concomitant immunosuppression with MMF.

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.

Adverse events of interest were evaluated in the clinical trials and should be reflected in labeling.

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 ($p < 0.5$).

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.

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.

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. 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.

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

The safety profile of tacrolimus XL is comparable to Prograf and is characterized by adverse events consistent with the calcineurin-inhibitor (CNI) class of drugs: infections, malignancies, glucose metabolism disorders, nephrotoxicity, neurotoxicity, hyperkalemia, and hypertension. MMF, which is used concurrently in the treatment regimen with tacrolimus XL is also associated with infections, malignancies, as well as adverse reactions related to gastrointestinal toxicity and bone marrow suppression.

Overall, in Studies 158 and 12-03, the safety profile of tacrolimus XL was comparable to that of Prograf. The rate of discontinuations due to adverse reactions, common adverse reactions, and selected CNI-related adverse reactions related to new onset diabetes after transplant (NODAT), infections, and renal function are discussed in more detail below.

The following safety summary was obtained from the Adverse Reactions, Clinical Studies Experience (Section 6.1) of the revised draft package insert submitted by the sponsor on June 28, 2013. This version reflects incorporation of the division's edits/comments/request for information sent to the sponsor on June 14, 2013. Of note, Study 158 is referred to as Study 1 and Study 12-03 is referred to as Study 2. This version does not reflect final, agreed upon labeling.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In addition, the clinical trials were not designed to establish comparative differences across study arms with regards to the adverse reactions discussed below.

The data described below reflect exposure to ASTAGRAF XL in 545 renal transplant recipients exposed to ASTAGRAF XL for periods up to two years [*see Clinical Studies (14)*].

The most frequent diseases leading to transplantation were glomerulonephritis, polycystic kidney disease nephrosclerosis/hypertensive nephropathy, and diabetic nephropathy in both studies.

Study 1: With Basiliximab Induction
The proportion of patients who discontinued treatment due to adverse reactions was 9% in the ASTAGRAF XL arm and 11% in the Prograf control arm through 12 months of treatment. The most common adverse reactions leading to discontinuation in ASTAGRAF XL-treated patients were related to infections or renal/urinary disorders. The most common (≥ 30%) adverse reactions observed in the ASTAGRAF XL group were: diarrhea, constipation, nausea, peripheral edema, tremor and anemia.

Study 2: Without Induction
The proportion of patients who discontinued treatment due to adverse reactions was 13% in the ASTAGRAF XL arm and 11% in the Prograf control arm through 12 months of treatment. The most common adverse reactions leading to discontinuation in ASTAGRAF XL-treated patients were related to infections, graft dysfunction, renal vascular/ischemic conditions and diabetes. The most common (≥30%) adverse reaction observed in the ASTAGRAF XL group was anemia.

Information on selected significant adverse reactions observed during Studies 1 and 2 are summarized below.

New Onset Diabetes After Transplant (NODAT)
New onset diabetes after transplantation (defined by the composite occurrence of ≥ 2 fasting plasma glucose values that were > 126 mg/dL at ≥ 30 days apart, insulin use for ≥ 30 consecutive days, oral hypoglycemic use for ≥ 30 consecutive days, oral hypoglycemic use for ≥ 30 consecutive days, and/or HbA_{1C} ≥ 6.5%) is summarized in Table 2 below for Study 1 and Study 2 through one year post-transplant.

Table 2. Composite NODAT through 1 year post transplant in Studies 1 and 2

	Study 1		Study 2	
	ASTAGRAF XL n (%) (N=162)	Prograf n (%) (N=151)	ASTAGRAF XL n (%) (N=288)	Prograf n (%) (N=299)
Composite NODAT	58 (36)	53 (35)	105 (37)	90 (30)
≥ 2 Fasting Plasma Glucose Values ≥ 126 mg/dL ≥ 30 days apart	42 (26)	35 (23)	51 (18)	47 (16)
Insulin use ≥ 30 consecutive days	10 (6)	12 (8)	29 (10)	29 (10)
Oral hypoglycemic use ≥ 30 consecutive days	22 (14)	13 (9)	20 (7)	23 (8)
HbA_{1C} ≥ 6.5%	31 (19)	33 (22)	48 (17)	39 (13)

Infections
Adverse reactions of infectious etiology were reported based on clinical assessment by physicians. The causative organisms for these reactions are identified when provided by the physician. The overall number of infections, serious infections, and select infections with identified etiology reported in patients treated with ASTAGRAF XL or the control in Studies 1 and 2 are shown in Table 3.

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	23 (11)	9 (4)	27 (8)	26 (8)

Glomerular Filtration Rate
The estimated mean glomerular filtration rates, using the Modification of Diet in Renal Disease (MDRD) formula, by treatment group at Month 12 in the ITT population in Studies 1 and 2 are shown in Table 4.

Table 4. Estimated Glomerular Filtration Rate (mL/min/1.73m^2) by MDRD Formula at 12 Months Post-Transplant*

	Study 1		Study 2	
	ASTAGRAF XL (n=201)	Prograf (n=202)	ASTAGRAF XL (n=287)	Prograf (n=300)
Month 1 Baseline Mean (SD)	56 (20)	56 (21)	51 (19)	52 (20)
Month 12 LOCF*				
Mean (Standard deviation)	58 (21)	56 (23)	52 (20)	55 (19)
Median (Min-Max)	56 (0, 177)	57 (0, 120)	54 (0, 116)	54 (0, 134)
Mean Difference XL-Prograf**	**+2.3 (-1.2, +5.8)**		**-1.8 (-4.6, +0.8)**	

*Subject's last observation carried forward for missing data at Month 1; patients who died, lost the graft or were lost to follow-up are imputed as zeroes
**Tacrolimus XL-Prograf treatment mean difference results of analysis of covariance model with Month 1 Baseline as a covariate.

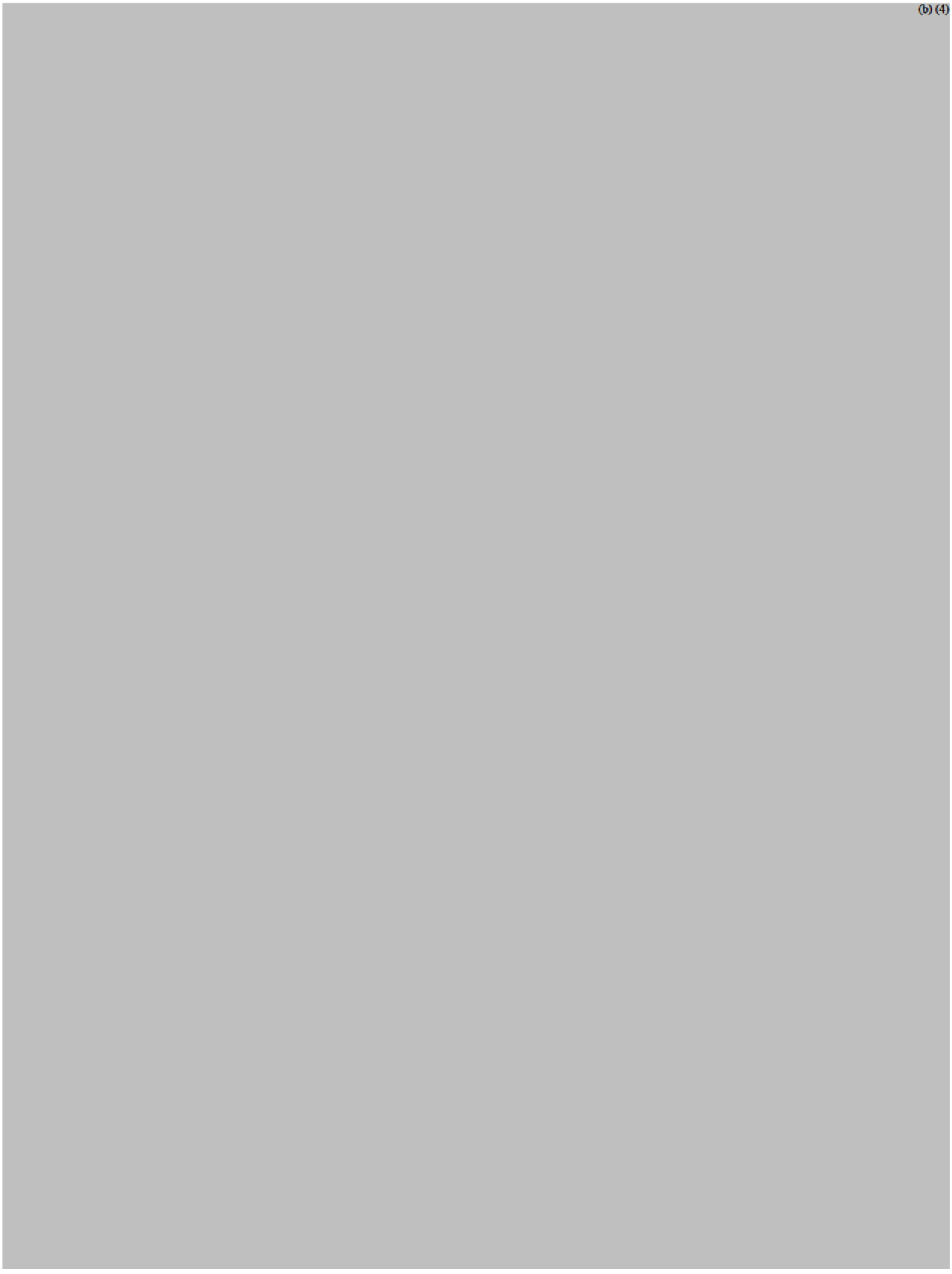
The incidence of adverse reactions that occurred in ≥ 15% of ASTAGRAF XL treated patients compared to control through one year of treatment in Studies 1 and 2 are shown in Table 5.

Table 5. (b) (4) Adverse Events Occurring in ≥ 15% of ASTAGRAF XL-Treated Patients Through One year Post Transplant in Studies 1 or 2*

	Study 1		Study 2	
Adverse Reactions	ASTAGRAF XL n (%) (N=214)	PROGRAF n (%) (N=212)	ASTAGRAF XL n (%) (N=331)	PROGRAF n (%) (N=336)
Anemia	70 (33)	61 (29)	103 (31)	87 (26)
Blood Creatinine Increased	40 (19)	49 (23)	54 (16)	63 (19)
Constipation	85 (40)	68 (32)	45 (14)	60 (18)
Diarrhea	96 (45)	94 (44)	88 (27)	103 (31)
Edema Peripheral	76 (36)	73 (34)	38 (12)	49 (15)
Fatigue	34 (16)	22 (10)	7 (2)	6 (2)
Graft Dysfunction	29 (14)	45 (21)	57 (17)	56 (17)
Headache	46 (22)	50 (24)	39 (12)	33 (10)
Hyperglycemia	34 (16)	39 (18)	61 (18)	65 (19)
Hyperkalemia	43 (20)	49 (23)	50 (15)	49 (15)
Hyperlipidemia	35 (16)	36 (17)	23 (7)	28 (8)
Hypertension	59 (28)	63 (30)	80 (24)	76 (23)
Hypomagnesemia	52 (24)	57 (27)	9 (3)	12 (4)
Hypophosphatemia	50 (23)	59 (28)	15 (5)	22 (7)
Insomnia	52 (24)	60 (28)	29 (9)	34 (10)
Leukopenia	35 (16)	33 (16)	51 (15)	37 (11)
Nausea	76 (36)	75 (35)	51 (15)	42 (13)
Tremor	75 (35)	73 (34)	58 (18)	58 (17)
Urinary Tract Infection	34 (16)	53 (25)	7 (2)	10 (3)
Urinary Tract Infection Bacterial	1 (1)	6 (3)	86 (26)	102 (30)
Vomiting	53 (25)	53 (25)	42 (13)	43 (13)

* Studies 1 and 2 were not designed to support comparative claims for ASTAGRAF XL for the adverse reactions reported in this table.

Less Frequently Reported Adverse Reactions (b) (4) <15%) by System Organ Class
The following adverse reactions were also reported in clinical studies of kidney transplant recipients who were treated with ASTAGRAF XL.


(b) (4)

(b) (4)

9. Advisory Committee Meeting

No Advisory Committee Meeting was held.

10. Pediatrics

The sponsor requested 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.

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 [3] 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 currently conducting a pharmacokinetic study in 10 stable pediatric kidney

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

transplant recipients aged 5 to 16 years of age.[4] The primary objective is 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.

The Division agreed with the sponsor's request. See Clinical Review by Joette M. Meyer, PharmD dated June 20, 2013 in DARRTS.

The Pediatric Research Committee (PeRC) met to discuss the sponsor's request on May 22, 2013 and 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
- 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

CDTL Comment: On July 3, 2013 the PeRC held an additional discussion to obtain clarification on whether, under PREA, the sponsor must develop a pediatric formulation for patients 1 to less than 5 years of age for the specific product being approved (i.e., Astagraf XL) or whether the pediatric formulation could be one that contains the active ingredient but a different formulation (e.g., Prograf, immediate release tacrolimus).

In an email from July 2, 2013, Sonal Vaid, attorney for the Office of the Commissioner, stated (b) (5) [redacted]

Formal confirmation of this information from PeRC, as well as specific wording for the action letter, is pending at the time of this review.

[4] 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

11. Other Relevant Regulatory Issues

Medication Errors

The following summary was abstracted from the complete Label, Labeling and Packaging review by Jung Lee, RPh, Division of Medication Error Prevention and Analysis in DARRTS dated June 17, 2013. Of note, for purposes of this review, tacrolimus XL is referred to as TAC-ER.

Medication errors involving confusion between TAC-ER and Prograf (tacrolimus immediate-release) capsules were reported in the United Kingdom and other parts of Europe as a result of similarities with product characteristics. Both products contain the same active ingredient (tacrolimus), share an overlapping dosage form (capsule), route of administration (oral), strengths (0.5 mg, 1 mg, 5 mg), similar indications for use, similar prescribers, as well as a similar patient population.

As a result of the confusion between these two products in the international market, particularly in the United Kingdom, where the majority of the reports originated, risk mitigation strategies were implemented in the European Union (EU) in late 2008 and early 2009 including the issuance of a Dear Healthcare Professional Letter, modifications to the package inserts for both tacrolimus and Prograf, as well as additional labeling of TAC-ER's outer packaging emphasizing the once-daily dosing regimen. The risk mitigation strategies focused on resolving the knowledge deficit among practitioners concerning the difference between the extended-release and immediate release formulations, highlighting the differences in dosing regimens, and including a warning in the package insert that medication errors have occurred involving inadvertent, unintentional or unsupervised substitution of immediate-release or extended-release tacrolimus formulations.

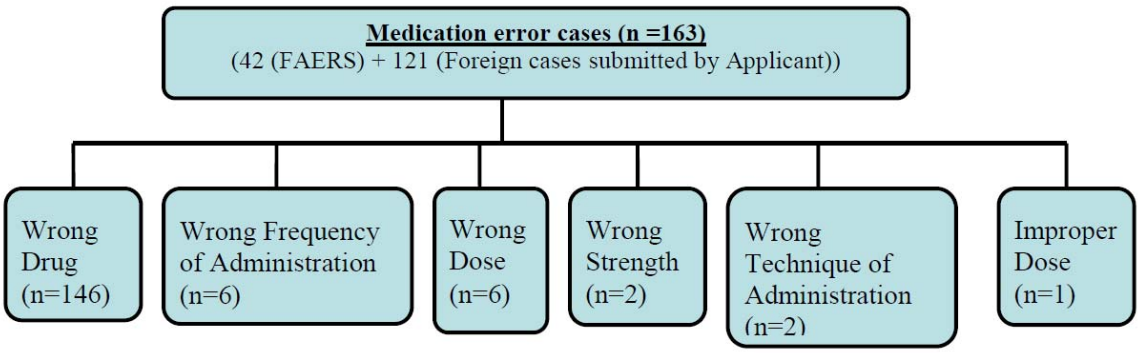
DMEPA communicated comments regarding labels and labeling to the sponsor in 2008, the majority of which were addressed in the current NDA submission.

As part of the current review, DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for TAC-ER medication error reports (N=313 reports identified). In addition, they reviewed the 152 foreign post marketing medication error report narratives provided by the sponsor in their submission dated August 6, 2012 under IND 64148. Of the total 456 cases identified, 302 were excluded leaving 163 cases for review (42 from FAERS and 121 foreign). They also reviewed the TAC-ER labels, package insert labeling, and the Dear Healthcare Provider, Dear Pharmacist, and Dear Professional Society Letters, in addition to the sample bottles for TAC-ER and Prograf.

As noted in the figure below, the majority of reported errors were due to of wrong drug (146 cases): 107 cases were due to wrong dispensing and 39 cases due to wrong prescribing in which TAC-ER and Prograf were confused and one drug inadvertently prescribed and/or

dispensed for the other. These wrong dispensing and prescribing errors resulted in overdose, underdose, graft rejection, as well as other adverse events.

Figure 1: TAC-ER medication errors (n = 163) categorized by type of error



Source: Figure 1, Label, Labeling and Packaging review by Jung Lee, RPh, Division of Medication Error Prevention and Analysis in DARRTS dated June 17, 2013.

The 53 of the erroneous prescribing and/or dispensing of the unintended formulation reports originated in the United Kingdom where prescribing is done primarily with the use of International Nonproprietary Names (INN) (tacrolimus) instead of by proprietary names[5] whereby the specific formulation (immediate-release or extended-release) was not specified. In the Risk Management Plan submitted by the sponsor in the NDA, their analysis of the potential root cause for these medication errors was attributed to a lack of education and awareness, poor communication between healthcare professionals and patient, prescribing by INN, ambiguity of the prescribing, ordering and dispensing computer system, price differences, and also due to possible similarities in the outer packaging of TAC-ER and Prograf.

The sponsor proposes to implement medication error risk mitigation strategies similar to the strategies implemented in the EU for tacrolimus extended-release in the US to help mitigate the confusion between the immediate-release Reference Listed Drug (Prograf) and extended-release formulations. The risk mitigation strategies proposed by the sponsor for the US market to differentiate the two formulations include the following:

1. A unique proprietary name with the modifier 'XL'
2. Different shape and size bottles
3. Different cap colors
4. Different capsule colors, capsule size, capsule imprints
5. A communication plan which includes a Dear Healthcare Providers, Dear Pharmacists, and Dear Professional Societies Letters to inform them of the risk of medication errors
6. A warning statement in the Warnings and Precautions section of the insert labeling for TAC-ER regarding medication errors reported with unintentional substitution of Prograf with TAC-ER.

[5] http://www.gabionline.net/layout/set/print/Country-Focus/United-Kingdom/Policies-and-Legislation

The sponsor also proposed to differentiate the extended-release formulation from the immediate-release formulations by adding the statement "extended-release" to the label, adding the dosing frequency statement "Once-Daily" on the principal display panel of the container labels and carton labeling.

CDTL Comment: The review division, 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. Astellas was notified of that the medication error issue should be handled outside of a REMS on January 30th, 2013. On February 19, 2013, Astellas resubmitted the medication error information to the NDA as a separate document (Medication Error Minimization Strategy).

Overall, DMEPA concluded, efforts to differentiate TAC-ER from all tacrolimus immediate-release capsules through risk mitigation strategies that include the use of different color schemes, different bottle shapes and sizes, and different capsule sizes and colors may likely mitigate some errors, particularly with the brand Prograf. However, since the majority of prescriptions dispensed are generics and these strategies are focused on differentiating TAC-ER from the Prograf, all medication errors cannot be expected to be mitigated with these strategies alone. In conjunction with the aforementioned strategies, ensuring the prominence of other features of the label and labeling, such as ensuring the statement "extended-release" is presented with equal prominence with the active ingredient, "tacrolimus" and including the dosing frequency statement "Once-Daily" for the extended-release formulation on the container labels and carton labeling, as well as highlighting the difference in formulations through the use of the modifier 'XL' in the unique proprietary name may further assist in mitigating the confusion between TAC-ER, the RLD Prograf, and other generic immediate-release capsule formulations.

CDTL Comment: DMEPA also noted several comments in their review regarding the sponsor's proposed container labels and carton labeling and healthcare letters which were communicated to the sponsor on June 21, 2013.

Medication Error Risk Management Strategy

The sponsor is also proposing to monitor adverse event information related to medication errors post-marketing by implementing a pharmacovigilance plan and communication plan, outside of a REMS.

The following summary was obtained from the sponsor's June 25, 2013 submission which summarizes their medication error risk management strategy.

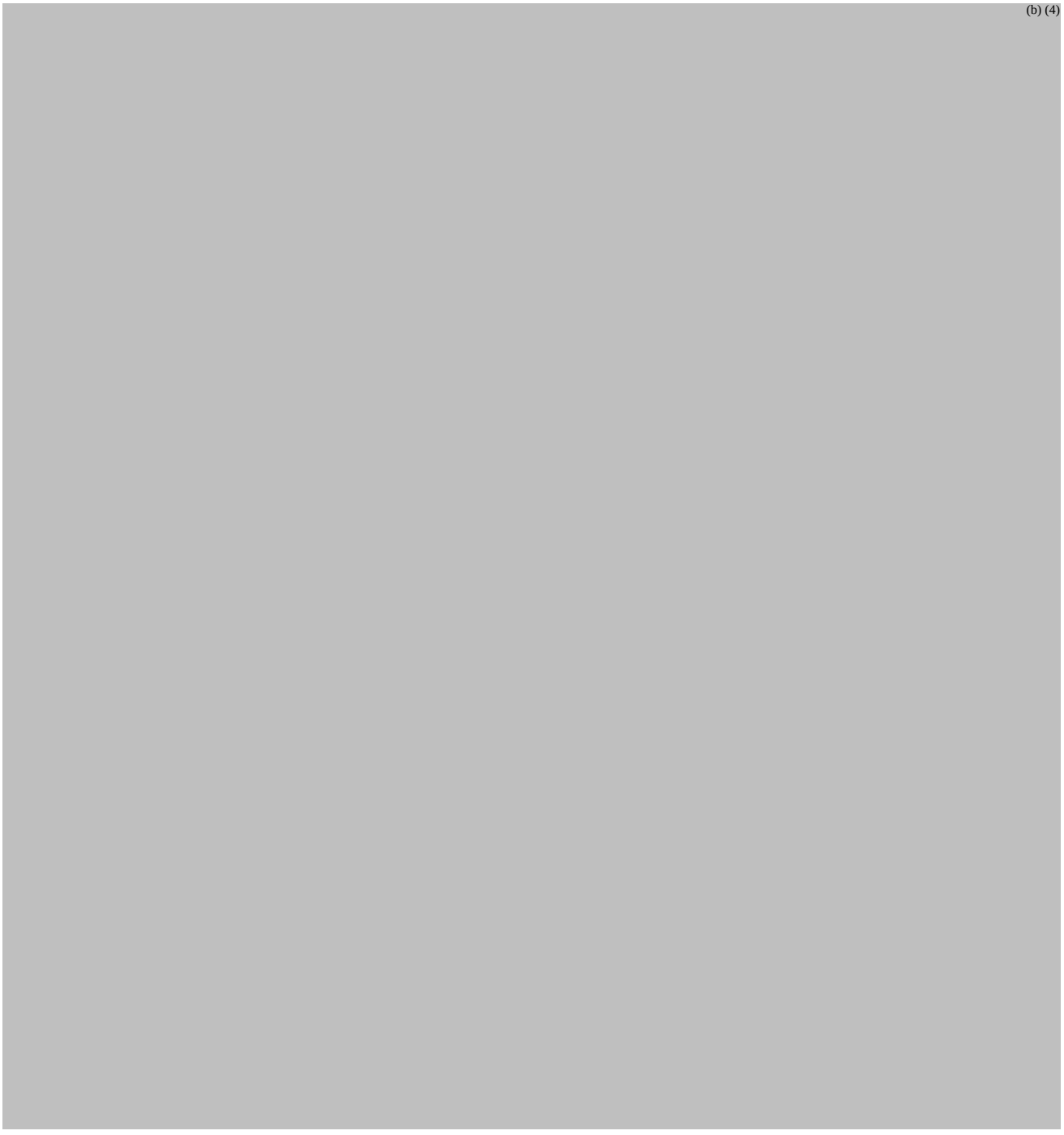
Pharmacovigilance Plan
A pharmacovigilance plan to enhance monitoring and capture of adverse event information related to medication errors will consist of the following:

- Targeted Data Questionnaire for medication error reports to standardize accurate and complete data collection to increase the reliability of causality assessments.

- Aggregate review of all medication error cases that will be included in each Periodic Adverse Drug Experience Report (PADER) and Periodic Safety Update Report (PSUR).

Communication Plan
A communication plan is targeted to inform patients, HCPs, pharmacists, and members of professional societies regarding the potential risk of medication errors due to unintentional substitution between approved tacrolimus formulations (once-daily extended-release and twice-daily immediate-release versions). The Communication Plan will encompass the elements below:

(b) (4)



(b) (4)

CDTL Comment: The Division, in consultation with DMEPA and OPDP, provided suggestions for the sponsor on the wording for the following letters: Dear Health Care Provider Letter, Dear Pharmacist Letter, and Dear Professional Society Letter which were sent to the sponsor on July 11, 2013.

DSI Audits

The following sites for Studies 158 and 12-03 were audited by DSI and were found to be acceptable (all received "Voluntary Action Indicated" recommendations).

Investigator Site Name, Address	Protocol ID#	Number of Subjects Enrolled/Audited	Outcome
Helio Tedesco Silva, Jr., M.D. Hospital do Rim e Hipertensao Fundacao Oswaldo Ramos Rua Borges Lagoa 960 Sao Paulo, SP 04038-002 Brazil	02-0-158	42/20	VAI
Bernhard Kraemer, M.D. Klinik und Poliklinik fuer Innere Medizin II Franz-Josef-Strauß-Allee 11 Regensburg 93042 Germany	FG-506E-12-03	34/34	VAI
Lars Backman, M.D., Ph.D. Director of Transplant Surgery Akademiska Sjukhuset Uppsala, Sweden	FG-506E-12-03	22/7	VAI
Harold Yang, MD, PhD Pinnacle Health 205 South Front Street Harrisburg, PA 17105-8700	02-0-158	36/12	VAI

As noted in the inspectional summaries by Kassa Ayalew, MD from the Office of Scientific Investigations, Division of Good Clinical Practice Compliance dated June 30, 2013 in DARRTS: the studies appear to have been conducted adequately. Although regulatory violations were noted at the sites, it is unlikely, based on the nature of the violations, that they significantly affect overall reliability of safety and efficacy data from the site(s).

The overall recommendation from OSI is that the data generated by the sites inspected are considered reliable and may be used in support of the indication.

12. Labeling

Proprietary name

The proposed proprietary name, Astagraf XL, is the fifth name submitted for this product. The previous names reviewed include:

1. Prograf MR (OSE review # 06-0114, dated April 20, 2006)
2. Prograf XL (OSE review # 2006-143, dated September 7, 2006)
3. Advagraf (OSE review # 2007-2052, dated March 22, 2007 and OSE review #2012-1212 and #2012-2549 dated November 19, 2012)
4. Graceptor XL (OSE review # 2013-127, dated April 4, 2013).

On April 9, 2013, the Applicant submitted the Request for Proprietary Name Review for the proposed proprietary name Astagraf XL under NDA 204096. It was found to be acceptable from both a promotional and safety perspective and the sponsor was notified May 31, 2013. See proprietary name review by Jung Lee, RPh, Division of Medication Error Prevention and Analysis in DARRTS dated May 31, 2013.

Labeling (Package Insert and Medication Guide)

The Division sent a proposed revised version of the package insert (PI) and Medication Guide to the sponsor, after consultation with OPDP and the patient labeling group from the Division of Medical Policy Programs (DMPP), on June 14 and 17, 2013, respectively. See consult reviews in DARRTS by Christine Corser, PharmD of OPDP dated June 7, 2013 and Shawna Hutchins, MPH, BSN, RN of DMPP dated June 6, 2013.

The sponsor addressed the requested revisions in a submission dated June 28, 2013. However, this version does not reflect final, agreed upon wording. The following is a summary by the CDTL of only the key items and sections in the PI and rationale for their inclusion. The Medication Guide will not be discussed, but follows the key points found in the Full Prescribing Information of the PI. Much of the information is similar to what can be found in the approved PI for Prograf (and generics).

BOXED WARNING

- Consistent with Prograf warnings related to malignancies and serious infections
- An additional warning added about mortality with Astagraf XL seen in female liver transplant recipients (in Study 11-03, NDA 50-815):

  > Increased mortality in female transplant recipients was observed in a clinical trial of liver transplantation. Use in liver transplantation is not recommended

INDICATIONS AND USAGE

- Indication written to encompass use with or without an induction agent as seen in Study 158 and Study 12-03, respectively.

- Limitations of use mention avoiding simultaneous use with cyclosporine (same as Prograf) and adds a new limitation to address the potential for medication errors:
  ASTAGRAF XL extended- release capsules are not interchangeable or substitutable with tacrolimus immediate- release capsules.

DOSAGE AND ADMINISTRATION

- Contains subsections on dosing in adult kidney transplant patients, as well as those with renal or hepatic impairment, administration instructions, and therapeutic drug monitoring.
  - Dosage regimens used in both Studies 158 and 12-03 are included
  - Statement added to avoid use with alcoholic beverages (as per Clinical Pharmacology review)
  - Recommendation for taking a missed dose up to 14 hours after the scheduled time (as per Clinical Pharmacology review)
  - Section on therapeutic drug monitoring the same as Prograf PI

CDTL Comment: The sponsor has proposed including information on (b) (4) *This statement will be deleted,* (b) (4)

WARNINGS AND PRECAUTIONS

- Many sections are consistent with those found in Prograf. Two new sections on the risk of mortality in female liver transplant recipients and the risk of medication errors were added:

5.1 Management of Immunosuppression
5.2 Lymphoma and Other Malignancies5.3 Serious Infections
5.4 Liver Transplant Recipients
In a clinical trial of 571 liver transplant recipients randomized 1:1 to ASTAGRAF XL or Prograf, mortality at 12 months was 10% higher among the 76 female patients treated with ASTAGRAF XL compared to the 64 female patients treated with Prograf. Use of ASTAGRAF XL in liver transplantation is not recommended [see *Boxed Warning*].
5.5 Medication Errors
ASTAGRAF XL extended- release capsules are not interchangeable or substitutable with tacrolimus immediate- release capsules. Medication and dispensing errors, including inadvertent or unintentional substitution between twice daily immediate-release and ASTAGRAF XL (once daily extended-release) tacrolimus formulations have been observed in postmarketing surveillance of ASTAGRAF 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 ASTAGRAF XL is supplied in short, square bottles and blisters, and contains the statement "ONCE DAILY" on its label.
5.6 Polyoma Virus Infections
5.7 Cytomegalovirus (CMV) Infections
5.8 New Onset Diabetes after Transplant
5.9 Nephrotoxicity
5.10 Neurotoxicity
5.11 Hyperkalemia

5.12 Hypertension
5.13 Use with Sirolimus
5.14 Use with CYP3A Inhibitors and Inducers Including Those That Prolong QT
5.15 Immunizations
5.16 Pure Red Cell Aplasia

ADVERSE REACTIONS

- Serious and otherwise important adverse reactions (ARs) found in WARNINGS AND PRECAUTIONS are bulleted

- Subection on "Clinical Studies Experience" can be found in Section 8 of this review and contains safety information from Studies 158 and 12-03 with regard to NODAT, Infections, Glomerular Filtration Rate (GFR) and common (≥15%) and less common (<15%) ARs.

CDTL Comment: Only results from the Astagraf XL and Prograf arms of Studies 158 and 12-03 are included in the Clinical Studies subsection. The Neoral arm from Study 158 was not felt to be needed for comparison and may appear to give a competitive safety advantage to Astagraf XL.

The GFR results were placed in Adverse Reactions section of the PI instead of Clinical Studies, as done for Zortress (everolimus) and Nulojix (belatacept), because GFR was prespecified as one of many secondary endpoints in the trial, unlike the other two products where is was given more importance as an outcome measure.

- Post-marketing experiences includes ARs reported with Prograf

DRUG INTERACTIONS

- Consistent with Prograf, with the exception of addition of information on effect of alcohol on the rate of release of tacrolimus from the Astagraf XL capsule:

7.3 Alcohol
Consumption of alcohol while taking ASTAGRAF XL may increase the rate of release of tacrolimus and/or adversely alter the pharmacokinetic properties and the effectiveness and safety of ASTAGRAF XL. Therefore, alcoholic beverages should not be consumed with ASTAGRAF XL [see *Dosage and Administration (2.5)*].

CDTL Comment: The sponsor wishes to (b) (4) [redacted] *. However,* (b) (4) [redacted] *is not acceptable to the Division* (b) (4) [redacted] *Therefore, the above subection has been revised from what the sponsor submitted to what the Division considers acceptable, i.e., patients on Astagraf XL should not consume alcohol at all.*

USE IN SPECIFIC POPULATIONS

- The subsections on Pregnancy, Nursing Mothers, Renal Impairment and Hepatic Impairment is consistent with Prograf.
- The Pediatric Use subsection notes that Astagraf XL has not been studied in pediatric patients less than 16 years of age.
- The Geriatric Use subsection includes the numbers of patients in Studies 158 and 12-03 aged 65 years of age and older (b) (4) and is consistent with 21 CFR 201.57.

CDTL comment: Upon review of the limited number of geriatric patients studied, the Division will replace the wording in this subsection with the wording in the regulations for situations where there are insufficient numbers of patients:
Clinical studies of (name of drug) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

- A Race subsection has been added:
  8.8 Race
  The data from ASTAGRAF XL administration in (b) (4) kidney transplant patients indicate that African-American patients may require higher doses to attain comparable trough concentrations compared to Caucasian patients [*see Dosage and Administration (2.1), Clinical Pharmacology (12.3), Clinical Studies (14)*].

OVERDOSAGE

- Symptoms associated with overdose of either Astagraf XL or Prograf have been added.
- Safety margins related to oral and IV doses which produced lethality in nonclinical acute toxicity studies are included.

CLINICAL PHARMACOLOGY

- Wording regarding the (b) (4) was removed from the Mechanism of Action subsection as is was felt to be misleading by OPDP, (b) (4)
- The Pharmacokinetics subsection contains PK information obtained following administration of Astagraf XL and details on drug-drug interaction studies conducted with immediate release tacrolimus (also found in the Prograf PI).

CLINICAL STUDIES

- Studies 158 and 12-03 are described, in terms of the design and patient population, tacrolimus exposure and MMF dosing, and efficacy results for the endpoint of efficacy failure (BPAR, graft loss, death, and lost to follow-up) as well as the individual components of the endpoint separately. The treatment difference for

efficacy failure and associated 95% confidence interval for each trial were also included. The Neoral arm of Study 158 is not discussed.

- A table of tacrolimus doses and mean trough concentrations in African-American compared to Caucasian kidney transplant recipients was also included, similar to a table found in the Prograf PI in Dosage and Administration.

HOW SUPPLIED/STORAGE AND HANDLING

- Information was added to alter the prescriber to the differences between Astagraf XL and Prograf in order to prevent medication errors:

  ASTAGRAF XL is supplied in short, square bottles and blisters; statement 'ONCE DAILY' on its label.

  ASTAGRAF XL and tacrolimus immediate- release capsules are further differentiated by different color schemes.

PATIENT COUNSELING INFORMATION

- Contains a subsection on which advises physicians to talk to patients about the lack of interchangeability between Astagraf XL and tacrolimus immediate release products, that Astagraf XL should not be taken with alcoholic beverages and that a missed dose may be taken within 14 hours of the scheduled time.
- Discusses the following risks, as described elsewhere in the PI, similar to Prograf:

Development of Lymphoma and Other Malignancies
Increased Risk of Infection
New Onset Diabetes After Transplant
Nephrotoxicity
Neurotoxicity
Hyperkalemia
Hypertension
Drug Interactions
Pregnant Women and Nursing Mothers
Immunizations

Capsule Colors, Bottle Shape and Colors, and Trade Dress

CDTL Comment: On June 26, 2013 the Division requested a teleconference with the sponsor to discuss the color schemes of the capsules, the bottles and the bottle caps and labels for Astagraf XL (all strengths) using Prograf bottles, bottle caps, and trade dress (all strengths) for comparison. The Division noted that the proposed (b) (4)

(b) (4)

Major issues that were discussed, resolved, or not resolved at the time of completion of the CDTL review.

At the time of the CDTL review, the CMC group is continuing to work with the sponsor on the wording for the post-marketing commitments and labeling issues. An addendum to the CMC review is expected to be completed soon.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

All disciplines, with the exception of CMC (pending finalization of post-marketing commitments and labeling issues),agree that tacrolimus XL (Astragraf XL) should be approved for the indication of prophylaxis of organ rejection in patients receiving a kidney transplant with mycophenolate mofetil (MMF) and corticosteroids, with or without basiliximab induction. The CDTL concurs with an approval recommendation, pending resolution of the CMC issues.

Risk Benefit Assessment

The following risk benefit assessment was obtained from the complete clinical review by Marc Cavaillé-Coll, MD, PhD dated June 19, 2013 in DARRTS. Of note, for purposes of this review, tacrolimus XL is referred to as Astagraf XL or TacXL and immediate release tacrolimus as Prograf or Tac.

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.

CDTL Comment: I agree that tacrolimus XL (Astagraf XL) was shown to be non-inferior to immediate release tacrolimus (Prograf) for the endpoint of efficacy failure, defined as biopsy confirmed (or proven) acute rejection, death, graft loss or loss to follow-up in Studies 158 and 12-03. Due to unresolved safety issues with Study 158 (as noted previously in the January 19, 2007 and March 13, 2008 approvable letters for NDA 50-811), Study 12-03 was also reviewed in the current NDA for efficacy and safety. Study 12-03 was designed without an induction agent and compared initially higher exposure to tacrolimus with reduced doses of MMF after day 14 in both arms compared to the regimen used in Study 158. Overall, the safety profile of tacrolimus XL was similar to immediate release tacrolimus. There was no significant interaction for sex by treatment for death or NODAT, as seen previously with tacrolimus XL compared to immediate release tacrolimus in liver transplant patients (Study 11-03, NDA 50-815). According to DMEPA, the risk mitigation strategies of different color schemes, bottle shapes and sizes, capsule sizes and colors may mitigate some medication/dispensing errors. Other strategies (formatting, type size on the bottle and carton container labels and choice of proprietary name) will also assist in mitigation of errors. Finally, the sponsor will send dear health care provider, pharmacist, and professional society letters to raise awareness of the potential for medication/dispensing errors.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

Astellas 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:

1. 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).
2. 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).

On February 6, 2013 Astellas requested that NDA 204096 [Original 2 – Liver (Males)] for tacrolimus XL capsules be withdrawn without prejudice to refiling.

As noted above, the Division in consultation with DRISK and DMEPA determined that the medication error issue should be handled outside of a REMS. On February 19, 2013, Astellas resubmitted the medication error information to the NDA as a separate document (*Medication Error Minimization Strategy*). On April 18, 2013 Astellas requested that the REMS for NDA 204096 be withdrawn.

Since the liver indication has been withdrawn and the medication errors are being managed independent of a REMS, both of the proposed goals of the REMS are no longer relevant and the DRISK and the Division agreed that the REMS can be withdrawn. A letter acknowledging the withdrawal of the liver indication and REMS was issued May 14, 2013. See also review by Suzanne Robottom, PharmD, DRISK, dated May 23, 2013 in DARRTS.

DRAFT Recommendations for other Postmarketing Requirements and Commitments

CDTL Comment: The CMC group has been in discussions with the sponsor to finalize the CMC post-marketing commitments (PMCs), as noted above. Draft PMCs received from the sponsor on July 9, 2013 are included below. It should be noted that the CMC group has not reviewed this submission at the time of this review. An addendum to the CMC review will be entered in DARRTS once the PMCs are final.

PMC No. 1 - Optimize the dissolution method with respect to detection of (b) (4) by evaluating the dissolution profiles of 0.5 mg and 5 mg capsules containing (b) (4) under different test conditions· (medium with 0.0%, 0.05% and 0.1% added sodium lauryl sulfate (SLS), at paddle speeds of 50, 75 and 100 rpm).

a. Final protocol by September 21, 2013
b. Interim report by March 21, 2014
c. Completed study by September 21, 2014
d. Final report by November 21, 2014

PMC No.2- Optimize the acceptance criteria for the regulatory dissolution test method by analyzing the dissolution profile data of all the strength of your product at release and on stability, obtained by collecting data at two-hour intervals until a minimum of (b) (4) of tacrolimus is released, as well as at the 24 hour time point. Based on these results, propose the revised acceptance criteria for the dissolution test of your product.

a. Final protocol by September 21, 2013
b. Interim report by March 21, 2014
c. Completed study by September 21, 2014
d. Final report by November 21, 2014

PMC No.3- Evaluate the relationship between [redacted] (b) (4) and dissolution rate under stressed conditions and under long term stability.

a. Final protocol by September 21, 2013
b. Interim report by January 21, 2014
c. Completed study by September 21, 2014
d. Final report by November 21, 2014

PMC No.4- Characterize the [redacted] (b) (4) in order to confirm the proposed shelf life [redacted] (b) (4) using a validated and appropriately discriminating direct measurement (e.g., ss-NMR, NIR) of [redacted] (b) (4) and using the optimized discriminating dissolution test. Evaluate stressed and aged samples. Compare the [redacted] (b) (4) prior to introduction into manufacture of capsules, to the [redacted] (b) (4) of the resulting capsules.

a. Final protocol by September 21, 2013
b. Interim report by January 21, 2014
c. Completed study by September 21, 2014
d. Final report by November 21, 2014

Recommended Comments to Applicant

None.

APPENDIX

Summary of FDA Approvals of Immunosuppressants (last three decades)

(See footnote at the end of table for definition of abbreviations used in the table)

Drug NDA/BLA (Year Approved)	***De novo* or Conversion Population (Location) Study Name or No. [No. Enrolled]**	**Design (arms, comparator, duration)**	**Endpoints and Timing of Endpoints**	**Type and Duration of Blinding**	**TDM vs. Fixed Dosing and Other Comments**
Sandimmune® soft gelatin capsules (cyclosporine capsules, USP), Sandimmune® oral solution (cyclosporine oral solution, USP), and Sandimmune® injection (cyclosporine injection, USP)[6] NDA 050-573 Injection NDA 050-574 Oral Solution NDA 050-625 Oral Capsule **(1983)**	*De novo* (Minnesota) [n=98]	Randomized 12-month CsA + CS (n=47) compared to ALG + AZA + CS (n=51)	12 month primary endpoint of graft survival	Open label	Fixed dose No Clinical Studies section in PI; therefore data not discussed
	De novo (Pittsburgh) [n=41]	Randomized 12-month CsA + CS (n=21) compared to AZA + CS (n=20)	12 month primary endpoint of graft survival	Open label	Fixed dose No Clinical Studies section in PI; therefore data not discussed
	De novo (Canada) [n=209]	Randomized 12-month CsA + CS (n=103) compared to AZA + CS (n=106)	12 month primary endpoint of patient/graft survival	Open label	Started as fixed dose, continued with TDM No Clinical Studies section in PI; therefore data not discussed
Neoral® soft gelatin capsules (cyclosporine capsules, USP) MODIFIED and Neoral® oral solution (cyclosporine oral	Conversion (OLM102) [n=466]	Randomized 12-week with 9 month extension (12 months) Patients on Sandimmune were	12 month primary endpoint of safety and tolerability of Neoral in patients switched from	Double blind (12 months)	TDM No Clinical Studies section in PI; therefore data not discussed

[6] Sandimmnue® Drug Approval Package

Drug NDA/BLA (Year Approved)	*De novo* or Conversion Population (Location) Study Name or No. [No. Enrolled]	Design (arms, comparator, duration)	Endpoints and Timing of Endpoints	Type and Duration of Blinding	TDM vs. Fixed Dosing and Other Comments
		randomized 4:1 to be converted to Neoral (n=373) or remain on Sandimmune (n=93) for 12 months	Sandimmune on a 1:1 dose ratio		
solution, USP) MODIFIED[7] NDA 050-715 Oral Capsule NDA 050-716 Oral Solution **(1995)**	*De novo* (location not specified) Study N103 [n=101]	1:1 Randomized 12-week PK/PD study	Not specified	Double blind (12 weeks)	TDM No Clinical Studies section in PI; therefore data not discussed
	De novo (Europe) Study OLM103 [n=86]	1:1 Randomized 12-weeks with extension up to 12 months Neoral in comparison to Sandimmune, no specific regimen	Safety and tolerability of Neoral in comparison to Sandimmune	Double blind (12 weeks)	TDM No Clinical Studies section in PI; therefore data not discussed
CellCept® (mycophenolate mofetil capsules)[8] NDA 050-722 Oral Capsule **(1995)**	*De novo* (US) [n=499]	Randomized 12 month, 3 arm ALG + CsA + MMF (2g/d) + CS (n=167) and ALG + CsA + MMF (3g/d) + CS (n=166) compared to ALG + CsA + AZA + CS (n=166)	6 month primary endpoint of treatment failure (BPAR, GL, Death, early termination) (Patient and graft survival at 1 year also reviewed)	Double blind (6 months)	Fixed dose (TDM for CsA) Discussed in Clinical Studies section of PI
	De novo (Europe/Canada/Australia)	Randomized 12 month, 3	6 month primary	Double blind	Fixed dose (TDM for

[7] Neoral® Drug Approval Package
[8] CellCept® package insert: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/050722s028,050723s027,050758s026,050759s033lbl.pdf

Drug NDA/BLA (Year Approved)	*De novo* or Conversion Population (Location) Study Name or No. [No. Enrolled]	Design (arms, comparator, duration)	Endpoints and Timing of Endpoints	Type and Duration of Blinding	TDM vs. Fixed Dosing and Other Comments
	[n=503]	arm CsA + MMF (2g/d) + CS (n=173) and CsA + MMF (3g/d) + CS (n=166) compared to CsA + AZA + CS (n=166)	endpoint of treatment failure (BPAR, GL, Death, early termination) (Patient and graft survival at 1 year also reviewed)	(6 months)	CsA) Discussed in Clinical Studies section of PI
	De novo (Europe) [n=491]	Randomized 12 month, 3 arm CsA + MMF (2g/d) + CS (n=165) and CsA + MMF (3g/d) + CS (n=160) compared to CsA + CS. (n=166)	6 month primary endpoint of treatment failure (BPAR, GL, Death, early termination) (Patient and graft survival at 1 year also reviewed)	Double blind (6 months)	Fixed dose (TDM for CsA) Discussed in Clinical Studies section of PI
Prograf® (tacrolimus) capsules and Prograf® (tacrolimus) injection[9] NDA 050-708/S-008 Oral Capsule NDA 050-709/S-006 Injection **(1997; Kidney indication)**	*De novo* (US) [n=412]	Randomized 12-month TAC + AZA + CS (n=205) compared to CsA + AZA + CS (n=207) Both arms received ALG induction	12 month primary endpoint of patient and graft survival	Open label	TDM
	De novo (Europe) [n=545]	Randomized 12-month TAC + AZA + CS (n=270) compared to CsA + AZA + CS (n=275) ALG induction in some patients	12 month primary endpoint of patient/graft survival	Open label	Due to inspection issues not included in Clinical Studies section of PI[10]

[9] Prograf® package insert: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/050708s041,050709s034lbl.pdf
[10] Prograf® Supplemental Drug Approval Package (1997)

Drug NDA/BLA (Year Approved)	*De novo* or Conversion Population (Location) Study Name or No. [No. Enrolled]	Design (arms, comparator, duration)	Endpoints and Timing of Endpoints	Type and Duration of Blinding	TDM vs. Fixed Dosing and Other Comments
Rapamune® (sirolimus) oral solution[11] NDA 21-083 Oral Solution **(1999)**	*De novo* (US) Study 301/"Study 1" in the PI ([n=719]	Randomized 24 month, 3 arm CsA + SIR (2mg) + CS (n=284) and CsA + SIR (5mg) + CS (n=274) Compared to CsA + AZA + CS (n=161)	6 month primary endpoint of efficacy failure (BPAR, GL or death) Patient and graft survival at 1 year were co-primary endpoints	Double blind (12 months?)	Fixed dose (TDM for CsA) Discussed in Clinical Studies section of PI
	De novo (Global) Study 302/"Study 2" in the PI [n=576]	Randomized 36 month, 3 arm CsA + SIR (2mg) + CS (n=227) and CsA + SIR(5mg) + CS (n=219) compared to CsA + Placebo + CS (n=130)	6 month primary endpoint of efficacy failure (BPAR, GL or death) Patient and graft survival at 1 year were co-primary endpoints	Double blind (12 months?)	Fixed dose (TDM for CsA) Discussed in Clinical Studies section of PI
Rapamune® (sirolimus) tablets[12] NDA 21-110 Oral Tablet **(2000)**	*De novo* (Global) Study 309 [n=576]	Randomized 36 month CsA + SIR (tablet) + CS (n=239) Compared to CsA + SIR (solution) + CS (n=238)	3 month primary endpoint of efficacy failure (BPAR, GL or death) Patient and graft survival at 1 year were co-primary endpoints	Open label	TDM Not mentioned in detail current version of Clinical Studies section of PI (discussed as "Study 3" prior to 2008 version)[13]
Rapamune®	*De novo*	Randomized	12 month	Open	TDM

[11] Rapamune® package insert:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021083s053,021110s067lbl.pdf
[12] Rapamune® package insert:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021083s053,021110s067lbl.pdf
[13] Rapamune® package insert (original version, dated 8/25/00):
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21110_Rapamune_prntlbl.pdf
[14] Rapamune® package insert:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021083s053,021110s067lbl.pdf

Drug NDA/BLA (Year Approved)	*De novo* or Conversion Population (Location) Study Name or No. [No. Enrolled]	Design (arms, comparator, duration)	Endpoints and Timing of Endpoints	Type and Duration of Blinding	TDM vs. Fixed Dosing and Other Comments
(sirolimus) tablets[14] NDA 21-110/S-003 Oral Tablet **(2003)**	(Global, Non US) Study 310/ "Study 3" in the PI [n=430]	36 month, CsA (withdrawal) + SIR + CS (n=215) Compared to CsA + SIR + CS (n=215)	primary endpoint of graft survival	label	Discussed in Clinical Studies section of current PI
	De novo (US) Study 212/ "Study 4" in the PI [n=224]	Single arm, 12 month, CsA + SIR + CS Antibody induction per local practice	12 month primary endpoint of efficacy failure (BPAR, GL, death and renal function)	Open label	TDM Discussed in Clinical Studies section of current PI
Myfortic® (mycophenolic acid) delayed-release tablets[15] NDA 050-791 **(2004)**	*De novo* (Global) [n=423]	CsA + MPA + CS (n=213) Compared to CsA + MMF + CS (n=210) (41% of patients received antibody induction)	6 and 12 month primary endpoint of treatment failure (BPAR, GL, death or LTFU)	Double blind (12 months)	Fixed dose (TDM for CsA) Discussed in Clinical Studies section of current PI
	Conversion (Global) [n=322]	CsA + MPA + CS(optional) (n=159) CsA + MMF + CS(optional) (n=163)	6 and 12 month primary endpoint of treatment failure (GL, death or LTFU)	Double blind (12 months)	Fixed dose (TDM for CsA) Discussed in Clinical Studies section of current PI
Rapamune® (sirolimus) oral solution and tablets[16] NDA 21-110/S-043 Oral Tablet	Conversion (Global) Convert Trial/"Study 5" in the PI [n=576] (Tablet)	SIR + MMF/AZA + CS (n=496) Compared to CNI + MMF/AZA + CS (n=245)	12 month primary endpoint of calculated GFR	Open label	TDM Discussed in Clinical Studies section of current PI

[15] Myfortic® package insert: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/050791s012lbl.pdf
[16] Rapamune® package insert: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021083s053,021110s067lbl.pdf

Drug NDA/BLA (Year Approved)	***De novo* or Conversion Population (Location) Study Name or No. [No. Enrolled]**	**Design (arms, comparator, duration)**	**Endpoints and Timing of Endpoints**	**Type and Duration of Blinding**	**TDM vs. Fixed Dosing and Other Comments**
NDA 21-083/S-033 Oral Solution **(2008)**					
Prograf® (tacrolimus) capsules and Prograf® (tacrolimus) injection[17] NDA 50-708/S-027 Oral Capsule NDA 50-709/S-021 Injection **(2009)**	*De novo* (Global, Non US) "Study 1" in the PI (n=1589)	Randomized 12 month Dac + TAC + MMF + CS (n=401) Std.CsA + MMF + CS (n=390) Dac + Red.CsA + MMF + CS (n=399) Dac + SIR + MMF + CS (n=399)	12 month primary endpoint of BPAR, GL, death or LTFU	Open label	TDM Discussed in Clinical Studies section of current PI
	De novo (Global) "Study 2" in the PI [n=424]	Bas + TAC + MMF + CS (n=212) Bas + CsA + MMF + CS (n=212) Bas + TAC-XL + MMF + CS (n=214)	12 month primary endpoint of BPAR, GL, death or LTFU	Open label	TDM Discussed in Clinical Studies section of current PI
Zortress® (everolimus) tablets[18] NDA 21-560 Oral Tablet **(2010)**	*De novo* (Global, non US) [n=588]	Randomized 36 month, CsA + EVE (1.5mg) + CS (n=194) and CsA + EVE (3mg) + CS (n=198) Compared to GL, death or	6 month primary endpoint of efficacy failure (BPAR, GL, death or LTFU)	Double blind (12 months)	Fixed dose (TDM for CsA) fixed dose regimen shown to be unsafe[19]

[17] Prograf® package insert: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/050708s041,050709s034lbl.pdf
[18] Zortress® package insert: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021560s006lbl.pdf
[19] Zortress® Drug Approval Package from 2010 discusses the Approvable letter from 2004 and the fixed dose studies B201 and B251: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/021560s000_zortress_toc.cfm

Drug NDA/BLA (Year Approved)	*De novo* or Conversion Population (Location) Study Name or No. [No. Enrolled]	Design (arms, comparator, duration)	Endpoints and Timing of Endpoints	Type and Duration of Blinding	TDM vs. Fixed Dosing and Other Comments
		CsA + MMF + CS (n=196)	LTFU at 1 year were co-primary endpoints		Discussed in Boxed Warning and Warnings and Precautions section of current PI
	De novo (Global, including US) [n=583]	Randomized 36 month, CsA + EVE (1.5mg) + CS (n=193) and CsA + EVE (3mg) + CS (n=194) Compared to CsA + MMF + CS (n=196)	6 month primary endpoint of efficacy failure (BPAR, GL, death or LTFU) GL, death or LTFU at 1 year were co-primary endpoints	Double blind (12 months)	Fixed dose (TDM for CsA) fixed dose regimen shown to be unsafe[20] Discussed in Boxed Warning and Warnings and Precautions section of current PI
	De novo (Global) [n=554]	Red. CsA + EVE + CS (n=277) Compared to Std. CsA + MPA + CS (n=277) Basiliximab induction in both arms	12 month primary endpoint of efficacy failure (BPAR, GL, death or LTFU)	Open label	TDM for both everolimus and CsA Discussed in Clinical Studies section of current PI
Nulojix® (belatacept) for injection[21] **BLA 125288** **(2011)**	*De novo* (Global) "Study 1" in the PI [n=666]	Randomized 36 month Bela (MI) + MMF + CS (n=219) Bela (LI) + MMF + CS (n=218)	12 month primary endpoint of efficacy failure (BPAR, GL, death or LTFU)	Open label	Belatacept fixed dose, TDM for CsA Discussed in Clinical Studies

[20] Zortress® Drug Approval Package from 2010 discusses the Approvable letter from 2004 and the fixed dose studies B201 and B251: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/021560s000_zortress_toc.cfm
[21] Nulojix® package insert: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125288s030lbl.pdf

Drug NDA/BLA (Year Approved)	*De novo* or Conversion Population (Location) Study Name or No. [No. Enrolled]	Design (arms, comparator, duration)	Endpoints and Timing of Endpoints	Type and Duration of Blinding	TDM vs. Fixed Dosing and Other Comments
		(n=226) Compared to CsA + MMF + CS (n=221) Basiliximab induction in all arms			section of current PI
	De novo (Global) "Study 2" in the PI [n=543]	Randomized 36 month Bela (MI) + MMF + CS (n=184) Bela (LI)+MMF + CS (n=175) CsA + MMF + CS (n=184) Basiliximab induction in all arms	12 month primary endpoint of efficacy failure (BPAR, GL, death or LTFU)	Open label	Belatacept fixed dose, TDM for CsA Discussed in Clinical Studies section of current PI

ALG: antilymphocyte globulin; AZA: azathioprine; Bas: basiliximab; Bela: belatacept; BPAR: biopsy proven acute rejection; CS: corticosteroids; CsA: cyclosporine; Dac: daclizumab; D: death; EVE: everolimus; eGFR: estimated glomerular filtration rate; GL: graft loss; LI: lower intensity; LTFU: loss to follow-up; MI: moderate intensity; MMF: mycophenolate mofetil; MPA: mycophenolic acid; NI: non-inferiority; PD: pharmacodynamics; PI: package insert; PK: pharmacokinetics; SIR: sirolimus; Reduced: reduced dose; Standard: standard dose; TAC: tacrolimus

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/s/

JOETTE M MEYER
07/11/2013