CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204096Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	See electronic stamp date
From	Renata Albrecht, MD Division of Transplant and Ophthalmology Products
Subject	Division Director Summary Review
NDA Number	NDA 204096
Related IND	IND 64148
Related NDA	NDA 50-811 (withdrawn)
Review type	Standard
Applicant Name	Astellas Pharma US Inc.
Date of Submission **Date of Receipt**	September 21, 2012 September 21, 2012
PDUFA Goal Date	July 21, 2013
Proprietary Name / **Established (USAN) Name**	Astagraf XL Tacrolimus extended-release capsule
Dosage Forms/ Strength	0.5, 1 and 5 mg oral capsules
Therapeutic Class **Proposed Indication**	Calcineurin inhibitor Prophylaxis of organ rejection in kidney transplant recipients
Action	*Approval*

Material Reviewed/Consulted	**Names of discipline reviewers**
Medical Officer Review	Marc Cavaille Coll, Joette Meyer 6/19/2013
CDTL Review Pediatric documents	Joette Meyer 7/11/2013 Joette Meyer 7/12/2013 (2)
Administrative Review	Ozlem Belen 5/13/2013
Statistical Review	Joy Mele, Karen Higgins 6/4/2013, 7/17/2013
Pharmacology/Toxicology Review	Aaron Ruhland, Lori Kotch 6/12/2013, 7/15/2013
Clinical Pharmacology Review	Gerlie Gieser, Jee Lee, Yaning Wang, Phil Colangelo 6/13/2013
ONDQA CMC Review	Mark Seggel, Tapash Ghosh, Rapti Madurawe 6/14/2013 Mark Seggel, Angelica Dorantes, Rapti Madurawe 7/12/2013
Product quality microbiology	Erika Pfeiler, Bryan Riley 12/7/2012
Immunology Review	Shukal Bala, Renata Albrecht 5/10/2013, 7/17/2013
OC/Facilities Inspection	Acceptable (see CMC review)
OSI/DGCPC	Kassa Ayalew, Susan Thompson 6/10/2013
OSE/DMEPA Proprietary Name Review and Letter	Jung Lee, Jamie Wilkins Parker, Carol Holquist 5/30/2013 Carol Holquist 5/30/2013
OSE/DMEPA Label, Labeling and Packaging Review	Jung Lee, Jamie Wilkins Parker 6/17/2013
OPDP/DPDP Review	Christine Corser 6/7/2013
DHCP Letter Recommendations	Christine Corser 7/2/2013
OMP/DMPP MedGuide Review	Shawna Hutchins, Melissa Hulett, LaShawn Griffiths 6/6/2013
OSE/OMEPRM/DRISK	Suzanne Robottom, Claudia Manzo 5/23/2013
Pediatric Review Committee	May 22, 2013
Project Manager	Hyun Son, Jackie Smith
CPMS	Judit Milstein, Diana Willard

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader
ONDQA=Office of New Drug Quality Assessment
OSI/DGCPC=Office of Scientific Investigations/Division of Good Clinical Practice Compliance (formerly Division of Scientific Investigation (DSI)
OSE=Office of Surveillance and Epidemiology
OMEPARM=Office of Medication Error Prevention and Risk Management
DMEPA=Division of Medication Error Prevention and Analysis
OPDP/DPDP=Office of Prescription Drug Promotion/Division of Professional Drug Promotion; formerly, DDMAC=Division of Drug Marketing, Advertising and Communication
CPMS=Chief Project Management Staff
OMP=Office of Medical Policy, DMPP=Division of Medical Policy Programs
DRISK=Division of Risk Management

1. Summary and Recommendations

Tacrolimus is a calcineurin inhibitor. It was approved in 1994 under the trade name Prograf, and is currently indicated for prophylaxis of organ rejection in liver, kidney and heart transplant recipients. Prograf is an immediate release formulation and is given twice daily. Astellas has now developed an extended release formulation which is dosed once-daily, and will be marketed under the trade name Astagraf XL; the name has been found to be acceptable by DMEPA.

The applicant submitted two Phase 3 controlled clinical trials both of which demonstrated that Astagraf XL[1] was non-inferior to Prograf on the endpoint of biopsy-proven acute rejection (BPAR), when used with mycophenolate mofetil and corticosteroids, in a regimen with or without basiliximab induction. The application is being approved for the following use:

> **1 INDICATIONS AND USAGE:**
>
> **1.1 Prophylaxis of Organ Rejection in Kidney Transplant**
>
> ASTAGRAF XL is indicated for the prophylaxis of organ rejection in patients receiving a kidney transplant. It is recommended that ASTAGRAF XL be used concomitantly with mycophenolate mofetil (MMF) and corticosteroids, with or without basiliximab induction [*see Clinical Studies (14)*]. Therapeutic drug monitoring is recommended for all patients receiving ASTAGRAF XL [*see Dosage and Administration (2.5)*].
>
> **1.2 Limitations of Use**
>
> - ASTAGRAF XL extended-release capsules are not interchangeable or substitutable with tacrolimus immediate-release capsules.
> - ASTAGRAF XL should not be used simultaneously with cyclosporine.

The starting doses recommended are reflected in following table to be included in labeling, and doses are adjusted based on target trough concentrations.

Table 1. Recommended Initial Oral Dose and Observed Whole Blood Trough Concentrations in Kidney Transplant Patients

Treatment Regimen	Oral Dose	Observed Whole Blood Trough Concentrations[a]
With basiliximab induction	0.15 mg/kg/day	Day 1 to 60: 5-17 ng/mL Month 3 to12: 4-12 ng/mL
Without induction	Pre-operative: 0.1 mg/kg/day Post-operative: 0.2 mg/kg/day	Day 1 to 60: 6-20 ng/mL Month 3 to 12: 6-14 ng/mL

a)10th - 90th percentile; see also Clinical Studies (14) for description of immunosuppressive regimens.

[1] Other names used for this product during development: MR, MR4, FK506E, Prograf XL, Advagraf.

Additional information on use in African-American patients, patients with renal impairment, or hepatic impairment, administration instructions and therapeutic drug monitoring (TDM) is also included. Three strengths of Astagraf XL capsules will be marketed: of 0.5 mg, 1 mg and 5 mg.

The overall safety profile for Astagraf XL was not significantly different from Prograf in the Phase 3 studies. Common adverse reactions seen in more than 30% of patients included diarrhea, constipation, nausea, peripheral edema, tremor and anemia. Gastroenteritis (NOS) was the one adverse reaction found to be more common in the Astagraf XL arm in both trials, although cases reported as bacterial or viral gastroenteritis were comparable between the arms. Warnings regarding adverse reactions including malignancies, serious infections, new onset diabetes after transplant, nephrotoxicity, neurotoxicity, hyperkalemia, hypertension, are included in labeling, along with information on various drug interactions. This includes information that when Astagraf XL (or immediate release tacrolimus) is coadministered with mycophenolate products, exposure to MPA is higher than with cyclosporine coadministration because cyclosporine interrupts the enterohepatic recirculation of MPA while tacrolimus does not. Clinicians should monitor for MPA associated adverse events and reduce the dose of concomitantly administered mycophenolic acid products, if needed.

Two additional issues were raised by this application

- Higher mortality in female liver transplant recipients:
  Astagraf XL was evaluated in a clinical trial of 471 liver transplant recipients randomized to Astagraf XL or Prograf. Mortality at 12 months was 10% higher among the 76 female patients (18%) treated with ASTAGRAF XL compared to the 64 female patients (8%) treated with Prograf. Therefore, the labeling notes that use of Astagraf XL in liver transplantation is not recommended

- Medication Errors during dispensing and administration:
  The extended release formulation has been marketed under the name Advagraf in Europe since 2007 and as Graceptor in Japan. The product is currently approved for the prophylaxis of organ rejection in kidney and other organ transplant patients in 69 countries. During the initial marketing, medication errors were reported when the products were inadvertently interchanged during dispensing or when patients took the wrong drug/dose. The information regarding these events was reviewed in detail by DMEPA, the corrective measured implemented in Europe examined, and multiple strategies to minimize medication errors introduced, including distinct shape and sizes of bottles, different colors for capsules (see Section 3, CMC), a warning in the product labeling, and plans to issue letters to health care providers informing them of the difference in the formulations and presentations.

  The labeling informs that 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. 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. Information in Section 16, How

Supplied, includes a description of the capsules, bottles and caps, and notes the statement "ONCE DAILY" is included on the product label.

Facility inspections are acceptable, clinical site inspections recommend the data are considered reliable, labeling has been finalized, and four PMCs have been agreed-to by the applicant.

All review disciplines have recommended that the application be approved and labeling is acceptable. The application will be issued an *Approval* letter.

1.1 Deficiencies

None

1.2 Post-Marketing Studies:

See section 13.3

1.3 Other Issues

Tacrolimus is an old antibiotic. The immediate release formulation of tacrolimus was approved in 1994. After repeal of Section 507 of the Act in 1997, old antibiotics still did not qualify for exclusivity. However, in 2008, new drug applications for old antibiotics could request exclusivity for new uses. Astellas has submitted documentation requesting exclusivity; this information will be attached to the Exclusivity Summary document.

2. Background

Kidney transplantation is the generally-preferred treatment for end-stage kidney disease. The other available management is dialysis, however, studies have shown that survival after kidney transplantation is improved compared to survival while on dialysis. Because the transplanted kidney is an allograft, patients need to receive chronic immunosuppressive treatment (drugs or biologics) to prevent the recipient's immune system from rejecting the kidney. At present, there is no treatment that can reliably induce a recipient's tolerance for the allograft; therefore, patients with kidney transplants need chronic immunosuppression.

There are a number of approved immunosuppressants available, including calcineurin inhibitors (cyclosporine or tacrolimus), mammalian target-of-rapamycin inhibitors (sirolimus or everolimus), azathioprine, mycophenolate mofetil, mycophenolic acid, therapeutic proteins, antibodies, and corticosteroids.

Astagraf XL is the extended release formulation of Prograf. Development of Astagraf XL was under IND 64148. The applicant's initial development involved pharmacokinetic studies, expecting to show that Astagraf XL had equivalent bioavailability to Prograf. However, as summarized in the Clinical Pharmacology Reviews, the products were not equivalent during initial treatment, and higher mg:mg doses were needed with Astagraf XL than Prograf. Therefore a complete clinical program including Phase 3 studies was needed.

2.1 Application History

The initial application for Astagraf XL was under NDA 50-811. However, because the results of the PK studies failed to show equivalence, the applicant was issued an approvable letter to conduct a controlled trial. The clinical trial that was submitted consisted of Study 20-0-158 (158), but the information was considered insufficient to support approval, so the results of Study 12-03, which was ongoing at that time in Europe as a PMC requested by the European regulatory agency, were requested. The applicant withdrew NDA 50-811, and related NDA 50-815 (liver) and NDA 50-816 (heart) to reevaluate their development plans. The tacrolimus extended-release product was accepted in Europe under the trade name Advagraf. When the product was initially marketed, medication errors due to confusion between Prograf and Advagraf were reported, and mainly attributed to pharmacy electronic ordering systems that did not specify the formulation to be dispensed.

The pre NDA meeting for the present application was held January 31, 2012 and a separate meeting to discuss CMC was held February 14, 2012. Both the kidney and the liver indications were discussed. The applicant was asked to provide a summary of the medication errors reported in Europe and the steps taken to address them, as well as results of any new clinical studies in liver transplant recipients.

NDA 204096 was submitted with two indications. As summarized in the acknowledgment letter to the NDA, the applicant withdrew the liver indication in males only and the REMS. The Division has planned to discuss the precedent of granting an indication for one-gender only at an Advisory Committee.

Therefore, only the indication for prophylaxis of organ rejection in kidney transplant recipients is reviewed for this action. Study 158, a three arm trial, was reviewed previously under NDA 50-708 and NDA 50-709 to determine whether it would support labeling for Prograf with MMF. In this application, it is used to evaluate the efficacy of tacrolimus extended release capsules. A second new study, FG-506E-12-03 (12-03), is also submitted.

3. CMC/Product Quality Microbiology

For complete details, see the reviews by the product quality reviewers. The following summary is excerpted from these reviews:

The CMC reviewer concluded that, in general, sufficient information to assure the identity, strength, purity, and quality and bioavailability of the drug product, Astagraf XL (tacrolimus extended-release capsules), was provided in this NDA. The Office of Compliance issued an overall recommendation of Acceptable on May 29, 2013. Labeling is acceptable and agreement was reached on four post-marketing commitments (See Section 13.3)

Tacrolimus (FK506) is a macrolide (macrolactam) antibiotic produced by the bacterium *Streptomyces tsukubaensis*. Manufacturing and controls is incorporated into by reference to Astellas' approved NDA 50-708 (Prograf (tacrolimus) capsules), and to their associated Type II DMF 16833.

(b

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

The proportions of inactive ingredients and tacrolimus are the same across all three product strengths, the only differences being the amount filled into each capsule and the capsule size.

Astagraf XL Capsules are a non-sterile product for oral administration. Results from microbial limits testing of all clinical and primary stability batches met acceptance criteria

The same formulation was used for all clinical samples (single-dose biopharmaceutics studies, repeated-dose biopharmaceutics studies, phase 2 and phase 3 studies), primary stability batches and proposed commercial production batches.

The product has a 36-month expiration dating period when stored in the original blister/blister pouch or bottle at 25°C (excursions to 15-30°C permitted).

To address the inadvertent substitution and medication errors first reported when the product was marketed in Europe, Astellas has developed a distinct bottle shape and distinct bottle cap colors for the Astagraf XL products. The Prograf bottles are column shaped and taller and narrower than the square-shaped Astagraf XL bottles. The differential color scheme is summarized below.

Prograf presentations and Astagraf XL presentations

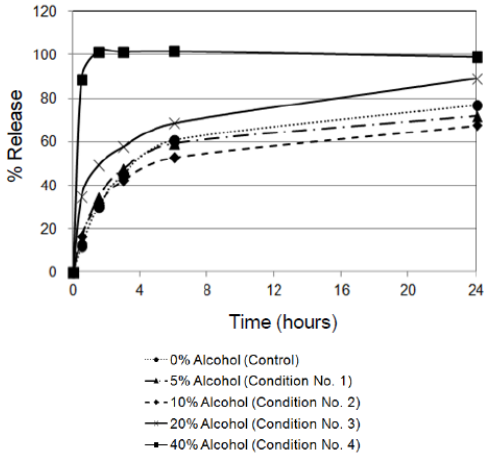
Product/ Strength	**Capsule**		**Bottle Cap**		**Trade Dress**
	Capsule cap	**Capsule body**	**Inner bottle cap***	**Outer bottle cap**	
Prograf 0.5 mg	Yellow	Yellow	Yellow	Yellow	White field/ Green font
Prograf 1 mg	White	White	White	White	White field/ Blue font
Prograf 5 mg	Pink	Pink	Pink	Pink	White field/ Pink font
Astagraf XL 0.5 mg	Yellow	Orange	White	Brown	Brown field/ white font
Astagraf XL 1 mg	White	Orange	White	Blue	Blue field /white font
Astagraf XL 5 mg	Pink	Orange	White	Orange	Orange field/white font

*inner cap is tamper proof and forms the sleeve around the neck of the bottle

Figure 2 Visual Appearance of Advagraf and Prograf Capsules

Dose Dumping:
In vitro testing showed dose dumping in the presence of 40% alcohol (Graph below), thus labeling warns not to take capsules with alcohol.

Figure 1 Dissolution Profiles of Tacrolimus Extended-Release (FK506E, MR4) Capsules 0.5 mg with Different Concentrations of Alcohol



Source: CMC review page 33

Environmental Assessment:
The applicant's request for exemption from environmental assessment was considered acceptable (21 CFR 25.31(b)).

(b) (4) **(withdrawn)**

(b) (4)

(b) (4)

Post Marketing Commitments (PMCs):
CMC noted evolving concerns about the potential for (b) (4) of amorphous tacrolimus in the (b) (4) formulation and in the drug product, and an interest in enhancing the utility of proposed regulatory dissolution test method and acceptance criteria. Astellas agreed to address these issues via four PMCs (See Section 13.3).

Comments:
The Product Quality reviewers recommend approval of the application from the CMC Biopharmaceutics and Microbiology sterility perspectives.

4. Nonclinical Pharmacology/Toxicology

For detailed information, see Pharmacology/Toxicology (P/T) Reviews.

Astellas relies on the nonclinical studies previously conducted to support the approval of Prograf. No new toxicology studies were submitted. The Pharmacology/Toxicology Reviewer provided labeling recommendations to reflect changes in the safety margins which result from changes in the recommended dosing regimen and clinical pharmacokinetics associated with the extended release dosage form. These have been incorporated in the package insert.

Comment: The application is recommended for approval by Pharmacology/Toxicology and labeling revisions have been finalized.

5. Clinical Pharmacology/Biopharmaceutics

For complete information, see the Clinical Pharmacology review.

The application contained 22 studies with clinical pharmacology or tacrolimus dose and concentration information from de novo kidney transplant patients, stable kidney transplant patients and healthy subjects; many had been reviewed under NDA 50-811.

The following table presents the doses used and trough concentrations achieved in Studies 158 and 12-03.

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: Clinical Pharmacology Review, page 3

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: Clinical Pharmacology Review, page 3

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.

There is diurnal variation with AUC lower in the evening, thus morning dose is recommended. High fat meals reduce AUC. Nasogastric administration of a suspension prepared from capsule contents resulted in 20% higher Cmax, shorter Tmax and lower AUC; the stability of the suspension was not evaluated. In vitro dissolution testing in 40% ethanol at pH 1.2 caused dose-dumping. Coadministration with ketoconazole increased AUC and Cmax, coadministration with rifampin reduced both parameters. This information is included in labeling.

Comment: From a Clinical Pharmacology perspective, NDA 204-096 is recommended for approval and labeling has been finalized..

6. Clinical Microbiology/Immunology

For detailed information, see Immunology Reviews.

The reviewer noted that a nonclinical study showed no significant differences in median skin allograft survival times between rats administered tacrolimus by daily intramuscular bolus injections (profile representative of immediate release formulation) and those receiving continuous intravenous infusion (sustained-release profile somewhat representative of the extended-release formulation). Labeling revisions to the Mechanism of Action section recommended by OPDP were made.

Comment:
The reviewer recommends approval from the immunology perspective; labeling is finalized.

7. Clinical/Statistical-Efficacy

For complete details regarding the study design and outcome of the clinical studies, see Clinical and Statistical Reviews. The summary below is excerpted from these reviews:

7.1 Phase 3 clinical trials

The applicant submitted two Phase 3 trials of 12-month duration (Table below) and another trial of 6-month duration which is not included in this summary. Study 02-0-158 is abbreviated as Study 158 and Study FG-506E-12-03 is abbreviated as 12-03 in the reviews.

Summary of Phase 3 trials using Tacrolimus XL in kidney transplantations

Study	Design	Treatment Duration	Tac-XL Astagraf XL	Prograf	Comments
02-0-158	Phase 3 multicenter, randomized, third arm of cyclosporine, plus MMF and corticosteroids, with basiliximab induction	Open-label (OL) 1 year Month 12 efficacy failure defined as death, graft failure, biopsy-confirmed acute rejection, or lost to follow-up	N=226 Initial dose of 0.15 to 0.2 mg/kg once daily (OD)	N=219 Initial dose of 0.075 to 0.1 mg/kg twice daily (BID)	FDA reviewed in full in 2007. Stat reviewer concluded that Tac-XL was effective compared to cyclosporine but more data was needed to assess dosing & safety.
FG-506E-12-03	Phase 3 multicenter, randomized 1:1 to once a day or twice a day tacrolimus plus MMF and corticosteroids, no induction therapy	Double Blind (a) 24 wks OL 28 wks Week 24 biopsy-proven acute rejection Month 12 efficacy failure was a 2nd endpoint	N=346 Initial dose of 0.2 mg/kg OD	N=353 Initial dose of 0.1 mg/kg BID	Statistical review of PK substudy in 2008

Source: Statistical Review, page 6.
(a) The patient treatment assignments remained blinded for 12 months for 96 percent of the patients participating in the trial. Patients were enrolled from January 14, 2004 to December 20, 2005. The trial was unblinded July 28, 2006. [Source: Addendum to Statistical Review, page 2-3]

Patients in Study 158 received induction with basiliximab, MMF and corticosteroids. Target trough concentrations for tacrolimus were 7-16 ng/mL for the first 90 days, 5-15 ng/mL thereafter. The patients in Study 12-03 received no induction, MMF and corticosteroids. Target troughs were 10-15 ng/mL for the first 28 days, then 5-15 ng/mL until day 168 and 5-10 ng/mL thereafter. These targets were achieved in about 80% of patients; the labeling includes a table showing achieved troughs over the course of the 12 month trial. Labeling also includes a summary of actual MMF doses used during the same time.

Efficacy failure results for Studies 158 and 12-03

	Study 158		Study 12-03	
	Tac-XL (n=214)	Prograf (n=212)	Tac-XL (n=331)	Prograf (n=336)
Efficacy Failure	30 (14%)	32 (15%)	93 (28%)	78 (23%)
Death	3 (1%)	9 (4%)	10 (3%)	8 (2%)
Graft Loss	5 (2%)	9 (4%)	28 (9%)	24 (7%)
BCAR	22 (10%)	16 (8%)	68 (21%)	54 (16%)
Lost-to-FU	3 (1%)	4 (2%)	4 (1%)	7 (2%)
Tac-XL-Prograf (CI)	-1% (-8%, +6%)		+4.9% (-2%, +11.5%)	

*Source: Statistical Review, page 4.

The primary endpoint was efficacy failure endpoint (BPAR, death, graft loss or lost to follow-up), assessed at Month 12 in both trials. The most common reason for efficacy failure was acute rejection, and most of these events occurred in the first month after transplant. The analysis showed that the upper limit of the confidence interval was +6% for Study 158 and

+ 11.5% for Study 12-03, therefore more than 50% of the treatment effect (M1 = 30%) was preserved and the results show tacrolimus extended release (Astagraf XL) is non-inferior to tacrolimus immediate release (Prograf).

A third study #1210 was a four arms study that enrolled over 1200 patients but only followed patients for 24 weeks. The results are included in the statistical review.

7.2 Non-Inferiority Margin

The statistical reviewer independently calculated the contribution of tacrolimus to the immunosuppressive regimen in these trials, and determined the M1 is about 30% based on the published literature. Results of published studies suggest a rejection rate for Prograf 0.1 mg BID + Induction+MMF+CCS of 14% (95% CI of 12%, 17%) and a rejection rate for the putative placebo, Induction+MMF+CCS, of 55% (95% CI 47%, 63%). Details are provided in the Statistical Review, Appendix 7.1.

7.3 Other Trials

As noted earlier, the original application proposed an indication for prophylaxis of organ rejection in male liver transplant recipient which was later withdrawn, as well as a proposal to including information (b) (4) in labeling. (b) (4)

section of labeling.

Comment: The clinical and statistical reviewers recommend approval, concluding that the benefits of treatment with Astagraf XL outweigh the risks and labeling has been finalized.

8. Safety

The details on the safety evaluation are included in the Clinical, Statistical and consultative reviews.

Safety data for 545 Astagraf XL treated patients was evaluated.

In Study 158, 9% of Astagraf XL treated kidney transplant recipients and 11% Prograf-treated recipients discontinued treatment due to adverse reactions. 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.

In Study 12-03 13% of Astagraf XL treated kidney transplant recipients and 11% Prograf-treated recipients discontinued treatment due to adverse reactions. 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.

Overall, there were no significant differences in the adverse reactions between the two products. Information on warnings and precautions and adverse reactions is comparable to what is seen with tacrolimus immediate release capsules.

Two new warnings are regarding the higher mortality reported in liver study in female liver transplant recipients; thus use in liver transplant is not recommended. In addition, there is information that Astagraf XL and Prograf are not interchangeable. More detailed information is provided on NODAT, seen in approximately one-third of the patients in the studies, infections reported in over 60% of patients.

Gastroenteritis was reported more often in the Astagraf XL arm than the Prograf arm in both studies (see table below). The clinical reviewer noted this raises questions about the comparative effect of once a day dosing with tacrolimus extended release compared to twice daily dosing with immediate release tacrolimus on the gastrointestinal tract, including but not limited to the local microbiota and mucosal immune system. Nine patients in Study 158 were reported as having serious gastroenteritis on Astagraf XL, zero on Prograf. In study 12-03, these numbers were 1 and 0, respectively. In the two studies combined, there were 24 reports of gastroenteritis (NOS) in the Astagraf XL arms and 4 in the Prograf arms. Cases classified as bacterial gastroenteritis were reported in 3 and 2 patients, respectively and cases classified as viral were reported in 5 and 4 patients, respectively.[2] The duration ranged from 1 day to 3 days in most patients. In 4 patients, the range was from 1 month to 12 months.

Overall Infections and Select Infections by Treatment Group in Phase 3 Studies through 12 Months Post-Transplant

	Study 1		Study 2	
	ASTAGRAF XL n (%) (N=214)	Prograf n (%) (N=212)	ASTAGRAF XL n (%) (N=331)	Prograf n (%) (N=336)
All Infections	148 (69)	146 (69)	228 (69)	216 (64)
Serious Infections	48 (22)	49 (23)	79 (24)	64 (19)
Bacterial Infections	18 (8)	25 (12)	125 (38)	137 (41)
Respiratory Infections	73 (34)	65 (31)	75 (23)	74 (22)
Cytomegalovirus Infections	21 (10)	24 (11)	38 (12)	21 (6)
Polyomavirus Infections	6 (3)	10 (5)	7 (2)	1 (0)
Gastroenteritis	16 (7)	6 (3)	16 (5)	8 (2)

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

Glomerular filtration rate in the Astagraf XL arm showed a mean difference of approximately +2 mL/min/1.73m^2 in Study 158 and - 2 mL/min/1.73m^2 in Study 12-03.

[2] Source, NDA 204096, amendment submitted July 17, received July 18, 2013.

Adverse Events Occurring in ≥ 15% of ASTAGRAF XL-Treated Kidney Transplant Patients Through One year Post Transplant in Studies 1 or 2[a]

	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)
Constipation	85 (40)	68 (32)	45 (14)	60 (18)
Diarrhea	96 (45)	94 (44)	88 (27)	103 (31)
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)
Increased Blood Creatinine	40 (19)	49 (23)	54 (16)	63 (19)
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)
Peripheral Edema	76 (36)	73 (34)	38 (12)	49 (15)
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

In addition to Study 158 and Study 12-03, a third study, Study 1210, was submitted in the application but only evaluated patients for 24 weeks. The safety information from this study was reviewed and included in the Statistical Review (page 28). The yellow highlights are for 5% or more difference between arms, the blue highlights are for between study differences. None of the differences in the adverse events were statistically significantly different.

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

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

Source: Statistical Review page 28

The reviewers noted that 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.

8.1 Subgroup analysis

The statistical reviewer examined outcome by subgroups and noted no significant differences. Because of a higher rate of deaths in females in the liver study of tacrolimus extended-release, the statistician looked at outcome by gender and found no significant interaction in either study (158 or 12-03) of kidney transplant recipients. For females, fewer deaths were seen on Astagraf XL than Prograf in each of the two studies.

Comment:
The adverse reactions were reviewed. The reviewers concluded that the benefits outweigh the risks and recommend approval of the application. The adverse reaction findings and class labeling will be included in the warnings, precautions and adverse reactions section of labeling, as appropriate.

8.2 Medication Errors

Medication errors involving confusion between tacrolimus extended-release capsules and tacrolimus immediate-release capsules have been reported as a result of similarities with their

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 Advagraf's and Prograf's package inserts, as well as additional labeling of Advagraf'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.

The following additional measures were taken: different shape and size of bottles, different bottle cap colors, different capsule colors size and imprints, compared to the Prograf product. Following these risk mitigation strategies, including ordering using the complete name, tacrolimus extended-release capsules, has led to decline in medication error reports.

Table 1 Advagraf Bottle Presentations

Strength	Advagraf Bottles		Prograf Bottles	
	Color Scheme	Shape	Color Scheme	Shape
0.5 mg	brown	short, square plastic bottles	yellow	tall, round plastic bottles
1 mg	blue		white	
5 mg	orange		pink	

In the US, Astellas is implementing a similar plan, by having different proprietary names, and different shapes for bottles, and colors (See Section 3, CMC for details).

The approved product labeling includes warnings about potential for medication error and importance of checking the appearance of the prescription when dispensed and asking the pharmacist of HCP if they have any question. The labels display "once daily" under the strength to remind prescribers and patients of the regimen.

Astellas plans to issue Dear Healthcare Provider, Dear Pharmacist, and Dear Professional Society Letters. Draft letters have been provided in the application and recommendations regarding the content from the review team sent to Astellas. It is anticipated that the letters and/or the Astagraf XL web site will display color images of the bottles, blister packs and capsules so that health care providers, pharmacists and patients can check for presentation and appearance.

Of note IMS report shows that in 2012, approximately (b) (4) of patients receiving a dispensed prescription for oral tacrolimus received the generic formulation compared to approximately (b) (4) who received the brand name.

9. Advisory Committee Meeting

The review of the kidney transplant indication did not raise new scientific issues that needed input from the Advisory Committee.

10. Pediatrics

The application is a new formulation of an approved chemical entity. PREA requires all applications for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment unless the applicant has obtained a waiver or deferral.

The applicant requested a waiver of pediatric studies in 0-1 year old and 1-5 year old patients because there are too few patients (less than (b) (4) in the 0-1 age group and less than (b) (4) in the 1-5 year age group yearly). Pediatric studies in children over 5 to 16 years of age were deferred and the applicant is conducting a conversion study in this age group in Europe.

At the May 22, 2013 Pediatric Review Committee (PeRC) meeting, the recommendation was made that studies in the 1-5 year old group should be deferred so Astellas could develop a pediatric formulation. In response to the Division's question whether this could be either the extended-release (XR) or immediate release (IR) tacrolimus, Sonal Vaid in consultation with Kim Dettelbach of Office of Chief Counsel advised (July 2, 2013) that

The sponsor requested a waiver based on the fact that the necessary studies are impossible or highly impracticable. [The Division] asked whether the sponsor could be required to develop a pediatric formulation of tacrolimus either using the XR or IR formulation. My preliminary take was that we (b) (5)

There was also discussion at PeRC that if Prograf contained pediatric information for the kidney transplant recipients, it may be possible to consider waiving Astagraf XL if it would not be used in a substantial number of patients (i.e., 50,000) and would not provide a meaningful therapeutic benefit.

In summary, the recommendations from PeRC were:
•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

11. Other Relevant Regulatory Issues

11.1 Compliance Inspection - Facilities

The Office of Compliance issued an EES summary report with an overall recommendation of Acceptable on May 29, 2013, as summarized in the CMC review.

11.2 Office of Scientific Investigation (OSI) Audits

OSI inspected 4 study sites. The final classification for all clinical investigator inspections was Voluntary Action Indicated (VAI). OSI recommended the data generated may be used in support of the application.

11.3 Debarment Certification

Astellas certified that they did not and will not use in any capacity the service of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in the connection of this application.

11.4 Financial Disclosure

The medical officer notes that the applicant provided disclosure of financial arrangements with 2 clinical investigators who participated in Study 158 and concluded that these arrangements did not impact the clinical study results.

11.5 Other Regulatory Issues

Exclusivity Determination: Tacrolimus is an old antibiotic first approved in 1994. After repeat of Section 507 of the Act, old antibiotics still did not qualify for exclusivity. Astellas, in their submissions dated September 21, 2012 and July 2 (received July 3), 2013 is requesting exclusivity. In their documentation, then note that in 2008, section 505(v) was added to the FDCA to help incentivize development of antibiotics. This section states that if the drug that is the subject of the NDA contains an antibiotic drug that was the subject of an application approved by FDA under 507, such an antibiotic is eligible for 3 year exclusivity under section 505(c) or 505(j) as long as the condition of use is different from any condition of use for which Prograf was approved and as long as the NDA satisfies requirements under 505(c)(3)(E)(iii).

They go on to state that Prograf is administered twice a day, and Astagraf XL (tacrolimus extended-release capsules) are intended to be dosed once daily. Astellas believes this represents a "new condition of use," and provides the following discussion:

FDA has not specifically defined the phrase "condition of use" for purposes of determining whether a particular change to an already approved drug product would qualify for three-year exclusivity. The FDA has, however, identified certain types of product changes that would normally warrant three-year exclusivity, including "changes in dosing regimen." Further, FDA has stated that conditions of use "include, among other things, indications and dosage instructions…." (describing the information that an ANDA must include to show that the conditions of use for which the applicant is seeking approval have been previously approved for the reference listed drug).

The Division will prepare an Exclusivity Summary for this application and include the information submitted by the applicant as an attachment to the Summary.

12. Labeling

The package insert, MedGuide and carton and container labeling were reviewed as applicable by the Division, DMEPA, OPDP/DPDP, OMP/DMPP and labeling recommendations were

discussed. Finals carton and container labels were submitted July 2, (received July 3) 2013, PI and MedGuide were submitted on July 17, (received July 18) 2013.

- **Package insert (PI):** The PI is written in PLR format. Labeling recommendations from reviewers have been incorporated.

- **Medication Guide:** Revisions recommended from various reviewers including OMP and OPDP have been incorporated.

- **Carton and Container Labels**: The labels have been reviewed by the Division, CMC and DMEPA and agreement reached.

- **Proprietary Name**: The proposed proprietary names Prograf MR, Prograf XL, Advagraf and Graceptor XL were rejected. The trade name Astagraf XL was considered acceptable from a promotional and safety perspective on May 31, 2013 and a letter to Astellas accepting the name Astagraf XL was signed by Dr. Holquist on the same day.

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action

The NDA will be issued an *Approval* letter given that two large controlled Phase 3 trials showed the product is safe and effective for the prophylaxis of organ transplant in kidney transplant recipients. All disciplines recommend approval, the facilities are acceptable and investigator site inspections recommend the clinical trial data are reliable. Labeling has been finalized.

13.2 Risk Benefit Assessment

End-stage kidney disease is a life-threatening condition with limited treatment options: dialysis or kidney transplantation. Long-term outcome and survival has been shown to be greater after transplantation than dialysis. The recipients of the kidney allograft need to receive immunosuppressants to prevent the recipient's immune system from rejecting the allograft. There are a number of immunosuppressants available. Because transplant recipients are generally on multiple drugs including immunosuppressants and drugs for managing other medical conditions, Astellas developed a once-daily formulation of tacrolimus as an extended release capsule.

Managing transplant patients is a balance in terms of providing sufficient immunosuppression to keep the recipient from rejecting the organ, but adjusting doses and immunosuppressants to minimize toxicity. The increased survival, reduced graft loss and reduced rates of acute rejection achieved with these products, is weighed against the toxicity associated with their use. The goal of management is achieve adequate immunosuppression and to minimize the toxicity through dose reduction, changing drugs, or treating the toxicity (e.g., infection, hypertension, NODAT, etc.).

The efficacy of the extended release capsule was evaluated in two Phase 3 studies using somewhat different regimens. Each of these studies showed the extended-release capsules to

be non-inferior to the immediate release capsules of tacrolimus. For the evaluation of adverse events, there were no significant differences reported, with the exception of gastroenteritis which was reported more commonly in the Astagraf arm than the Prograf arm in both studies (Study 158: 7% vs. 3%; Study 12-03: 2% vs. 5%).

Dosing of Astagraf XL, like Prograf and several of the other immunosuppressants, is based on TDM. For this application, as for other products that are dosed using TDM, the labeling includes information not only on the recommended starting dosing and target trough concentrations over time, but also provides information on the actual doses and/or trough concentrations used in the clinical trials.

Overall, the reviewers concluded that the benefits of Astagraf XL outweigh its risk in the prophylaxis of organ rejection in kidney transplant recipients; Astagraf XL represents another treatment option.

13.3 Recommendation for other Postmarketing Requirements and Commitments

Astellas has agreed to the following four post-marketing commitments:

2061-3 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%, .05% and 0.1 % added sodium lauryl sulfate (SLS), at paddle speeds of 50, 75 and 100 rpm).

The timetable you submitted on July 9, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2013
Interim report:	03/2014
Study Completion:	09/2014
Final Report Submission:	11/2014

2061-4 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.

The timetable you submitted on July 9, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2013
Interim report:	03/2014
Study Completion:	09/2014
Final Report Submission:	11/2014

2061-5 Evaluate the relationship between (b) (4) (b) (4) and dissolution rate under stressed conditions and under long term stability.

The timetable you submitted on July 9, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2013
Interim report:	01/2014
Study Completion:	09/2014
Final Report Submission:	11/2014

2061-6 Characterize the [redacted] (b) (4) in order to onfirm 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.

The timetable you submitted on July 9, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2013
Interim report:	01/2014
Study Completion:	09/2014
Final Report Submission:	11/2014

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

/s/

RENATA ALBRECHT
07/19/2013