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APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 204-096	Submission Date(s): 09/21/2012
Drug	Tacrolimus extended-release oral capsules (TAC-XL)
Trade Name	Astagraf XL®
Clinical Pharmacology	Gerlie Gieser, Ph.D.
Clinical Pharmacology Team Leader	Philip M. Colangelo, Pharm.D., Ph.D.
Pharmacometrics Reviewer	Jee Eun Lee, Ph.D.
Pharmacometrics Team Leader	Yaning Wang, Ph.D.
OCP Division	DCP4
OND Division	DTOP
Sponsor	Astellas
Submission Type; Code	NDA
Formulation; Strength(s)	oral extended-release capsules: 0.5 mg, 1 mg, and 5 mg
Indication	Prophylaxis of organ rejection in patients receiving allogeneic kidney transplantation
Dosage and Administration	(b) (4) [redacted]

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1. Executive Summary

Tacrolimus immediate release capsules (Prograf®) is a twice-a-day (BID) oral capsule formulation marketed by Astellas. Prograf® was first approved by FDA in 1994 for the prophylaxis of organ rejection in liver transplant patients, and eventually in 1997 for kidney transplant patients and in 2006 for heart transplant patients. Tacrolimus-extended release capsules (TAC-XL) were developed by Astellas as a once-a-day (QD) oral capsule formulation of tacrolimus. On 21 September 2012, the sponsor submitted NDA 204-096 to seek approval of TAC-XL extended release oral capsules for the prophylaxis of allograft rejection in male/female kidney transplant patients and in male liver transplant patients but later withdrew the liver indication from the NDA. TAC-XL is currently approved for the prophylaxis of organ rejection in kidney and other organ transplant patients in 69 countries including Japan, Canada and European countries.

To provide evidence of the efficacy and safety of TAC-XL for the prophylaxis of acute rejection in adult kidney transplant patients, the sponsor submitted the findings of two primary Phase 3 clinical trials in de novo kidney transplant patients (Study 20-158 and Study FG-506E-12-03) and one supportive 6-month Phase 3 clinical trial in de novo kidney transplant patients [PMR-EC-1210 (OSAKA)]. Also submitted were three PK studies in stable kidney transplant patients (≥ 6 months post-transplant) converted from Prograf® BID to TAC-XL QD. The FDA Statistical review (see Statistical review by Joy Mele, Ph.D for further details) revealed that TAC-XL once daily demonstrated non-inferiority to Prograf twice daily in all three clinical trials, based on efficacy failure [a composite endpoint of locally biopsied confirmed acute rejection (LBPAR), death, graft loss or lost-to-follow-up]. The treatment differences were comparable among the three trials, even when subgrouping by gender, race, age, or geographic region. Based on the FDA Medical review (see Medical review by Marc Cavaille-Coll, MD, Ph.D for further details), TAC-XL and Prograf had comparable safety with the exception of gastroenteritis (a type of infection) which was statistically significantly more common in the TAC-XL group compared to the Prograf group in both Study 158 and Study 12-03. It was determined by the FDA review team that the TAC-XL based immunosuppressive regimens evaluated in both Studies 12-03 and 158 represented acceptable dosing regimens for the prophylaxis of kidney rejection in adult kidney transplant patients.

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

1.1. Summary of Important Clinical Pharmacology Findings

<u>Exposures to tacrolimus and concomitant immunosuppressive drugs in Phase 3 Studies 12-03 and 158:</u>
Table 1 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, Table 1A 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 (Table 1). 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

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be described in the labeling, assuming the efficacy and the safety of the evaluated TAC-XL dosing regimens were acceptable.

Table 1. 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

Table 1A. 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,	Days 2-14: 20	Day 1: 200 By Day 14: 20 to 30

mg/day)	Days 15-28: 15 Days 29-42: 10 Days 43-84: 5 Days 85 -365: 0 to 5	By Month 1: 10 to 20 By Month 2: 10 to 15 By Month 3 to 12: 5 to 10

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 $AUC_{0\text{-}24}$ 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 ($\geq$ 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.

1.2. Recommendations

From a Clinical Pharmacology perspective, NDA 204-096 is recommended for approval provided satisfactory agreement is reached with the sponsor regarding the recommended changes to the labeling.

1.3. Phase 4 Commitments

Pediatric PK studies
The FDA Pediatric Review Committee (PeRC) has the following recommendations regarding the PREA requirements for TAC-XL:

- The sponsor's proposal to conduct a PK study [PMR-EC-1206] in stable organ transplant patients 5 to <16 years old who could swallow the intact TAC-XL capsule is acceptable.
- The sponsor should conduct a PK study in younger pediatric transplant patients (1 to < 5 years old) using an age-appropriate oral formulation of immediate release tacrolimus.

- The sponsor's proposal to waive the research study requirement in pediatric transplant patients <1 year old is acceptable.

At the time of the writing of this review, the PeRC recommendation in the second bullet will not be imposed upon the sponsor as a Post Marketing Requirement / Commitment (PMR / PMC). The use of immediate release tacrolimus and TAC-XL in pediatric organ transplant patients will be addressed by the Division of Transplant and Ophthalmology Products at a later time.

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Gerlie Gieser, Ph.D.
Clinical Pharmacology Reviewer
DCP4/OCP/OTS

_____.
Jee Eun Lee, Ph.D.
Pharmacometrics Reviewer
OCP/OTS

Concurrence _____.
Yaning Wang, Ph.D.
Pharmacometrics Team Leader
OCP/OTS

_____.
Phil Colangelo, Pharm.D., Ph.D.
Clinical Pharmacology Team Leader
DCP4/OCP/OTS

2. Question Based Review

2.1. General Attributes of the Drug and the Drug Product

2.1.1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of TAC-XL?

The original NDA of TAC-XL (tacrolimus extended release capsules) for the prophylaxis of organ rejection in patients receiving allogeneic kidney, liver and heart transplantation was previously submitted on 19 December 2005 (NDA 50-811). In January 2007, FDA sent the sponsor approvable letters for the kidney and liver indications and a non-approvable letter for the heart indication, citing lack of sufficient data to support safe and effective use of TAC-XL. (b) (4)

On 21 September 2012, the original NDA of TAC-XL was resubmitted with the sponsor seeking approval of the product for the prophylaxis of organ rejection in male/female patients receiving allogeneic kidney transplant and in male patients receiving liver transplant (NDA 204-096). On 06 February 2012, the sponsor withdrew the liver indication from the NDA.

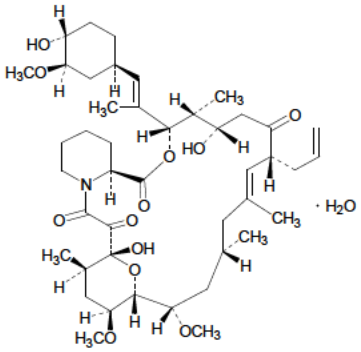
Note that the majority of the Clinical Pharmacology studies were previously reviewed by Dr. Seong Jang at the time of the original NDA submissions for the kidney, liver and heart transplant indications (prior to September 2013). For completeness and ease of reference, his clinical pharmacology findings and recommendations pertaining to the kidney indication are incorporated in the current NDA review.

2.1.2. What are the highlights of the chemistry and physicochemical properties of the drug substance and the formulation of the drug product as they related to clinical pharmacology and biopharmaceutics review?

TAC-XL are hard-gelatin capsules containing the equivalent of 0.5 mg, 1 mg or 5 mg of anhydrous tacrolimus. Like Prograf® immediate release oral capsules, TAC-XL contains the following inactive ingredients: (b) (4) Both the active and inactive ingredients are directly proportional across all capsule strengths.

Tacrolimus is the active ingredient in TAC-XL. Tacrolimus is a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*. Chemically, tacrolimus is designated as [3*S*-[3*R**[*E*(1*S**,3*S**,4*S**)], 4*S**, 5*R**, 8*S**, 9*E*, 12*R**, 14*R**, 15*S**, 16*R**,18*S**,19*S**,26a*R**]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25, 26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12, 18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-*c*] [1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate.

The chemical structure of tacrolimus is:



Tacrolimus has an empirical formula of $C_{44}H_{69}NO_{12}\bullet H_2O$ and a formula weight of 822.03. Tacrolimus appears as white crystals or crystalline powder. It is practically insoluble in water, freely soluble in ethanol, and very soluble in methanol and chloroform. Ethylcellulose is also freely soluble in ethanol.

2.1.3. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Tacrolimus inhibits T-lymphocyte activation, although the exact mechanism of action is not known. Experimental evidence suggests that tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin inhibited. This effect may prevent the dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT), a nuclear component thought to initiate gene transcription for the formation of lymphokines (such as interleukin-2, gamma interferon). The net result is the inhibition of T-lymphocyte activation (i.e., immunosuppression).

The proposed indication of TAC-XL is for the prophylaxis of organ rejection in subjects receiving allogeneic kidney transplant.

2.1.4. What are the sponsor's proposed dosage(s) and route(s) of administration?

De novo kidney transplant patients:

When used with basiliximab induction, mycophenolate mofetil, and maintenance corticosteroids, the initial TAC-XL oral dosage recommendations for adult kidney transplant patients are presented in Table 2. The initial oral dose of TAC-XL should be administered prior to or within 48 hours of the completion of the transplant procedure, but may be delayed until renal function has recovered. Dosing should be titrated based on clinical assessments of rejection and tolerability, and to maintain trough concentration ranges as noted in Table 2. Frequent monitoring of tacrolimus trough levels is recommended in the early post-transplant period to ensure adequate drug exposure.

Table 2. Summary of Initial TAC-XL Dosage Recommendations and Observed Whole Blood Tacrolimus Trough Concentrations in De Novo Kidney Transplant Recipients

(b) (4)

TAC-XL should be taken in the morning consistently with or without food. TAC-XL should not be taken with grapefruit juice, and alcoholic beverages should be avoided. The capsules should not be chewed, split or crushed.

For patients unable to swallow the TAC-XL capsules, an extemporaneously compounded suspension prepared from the capsule contents can be given by nasogastric tube.
(Reviewer's Note: This alternative mode of TAC-XL administration will not be recommended in the package insert for the following reasons: (1) Nasogastric administration of TAC-XL results in a significant decrease in tacrolimus AUC compared to when taking the intact TAC-XL capsules. (2) Only a limited number (n=12) of de novo kidney transplant recipients in the two Phase 3 trials received their initial TAC-XL doses as an aqueous suspension administered via a nasogastric tube. (3) Stability studies on the extemporaneously compounded aqueous suspension had not been conducted.)

TAC-XL capsules are for oral administration. In patients unable to tolerate oral medications (usually during the first 2-3 days post-surgery), therapy should start with tacrolimus injection (e.g., Prograf®) as a continuous IV infusion. The first dose of TAC-XL oral capsules should be given 8-12 hours after discontinuing the IV infusion.

Stable Kidney Transplant Patients (≥ 6 months post-transplant):
(Reviewer's Note: (b) (4)

The Phase 2 studies conducted to compare the PK of tacrolimus in stable kidney transplant patients before and after conversion to TAC-XL were not considered by FDA to be adequate and well controlled clinical trials.)

Conversion from tacrolimus immediate release
For stable kidney transplant patients converted from tacrolimus immediate release (e.g., Prograf® capsules) to TAC-XL, a single daily morning dose of TAC-XL equivalent to the patient's previous stable total daily dose of tacrolimus immediate release on a 1:1 (mg:mg) basis should be given initially. Subsequent TAC-XL dosage should be titrated based on clinical assessments of rejection and tolerability, and to maintain whole blood trough concentrations similar to those prior to conversion. Following conversion, the whole blood tacrolimus trough concentrations should be monitored every 4-7 days until stable within the desired therapeutic range.

Conversion to or from cyclosporine
For stable kidney transplant patients (≥ 6 months post-transplant) converted to or from cyclosporine, TAC-XL or cyclosporine should be discontinued at least 24 hours before initiating the other. It is recommended that the first dose of the next drug be further delayed in the presence of elevated concentrations of the previous drug.

2.2. General Clinical Pharmacology

2.2.1. Based on pharmacokinetic parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The pharmacokinetics of tacrolimus after single oral administration of TAC-XL at 3 different dose levels (1.5 mg, 4 mg and 10 mg) by a crossover study design demonstrated dose-linearity in the dose range of 1.5 mg to 10 mg. There was no dose dependency in the frequency of adverse events among the 3 doses and single oral administration of TAC-XL capsule up to 10 mg was well tolerated in healthy Japanese adult males.

Figures 1A through 1D show the linear correlation between TAC-XL dose (mg and mg/kg) and the whole blood tacrolimus AUC_{0-24}, C_{max}, C_{24h} or C_{trough}, and elimination half-life ($t_{1/2}$). Note that the observed mean TAC-XL doses throughout the first 12 months in the primary Phase 3 clinical trials (Studies 158 and 12-03) did not usually exceed 0.2 mg/kg in de novo kidney transplant patients. Additionally, stable transplant patients (≥ 6 months post-transplant) upon 1 mg: 1mg total daily dose conversion from tacrolimus immediate release are expected to receive lower tacrolimus doses than de novo kidney transplant recipients. Thus, the range of mg/kg doses tested in this dose-proportionality/dose-linearity study is adequate to evaluate the correlation of TAC-XL doses and the tacrolimus PK parameters in kidney transplant patients.

As seen in Table 3 and Figures 1A through 1D, there is linearity in the PK of tacrolimus within the range of TAC-XL doses evaluated in this Phase 1 study of healthy subjects.

Table 3. PK parameters of TAC-XL capsules after single oral administration to healthy subjects

Dose		C_{max} (ng/mL)	C_{max}/D (ng/mL)	t_{max} (hr)	AUC_{0-24} (ng·hr/mL)	AUC_{0-120} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	$AUC_{0-\infty}/D$ (ng·hr/mL)	CL/F (mL/min)	MRT (hr)	$t_{1/2}$ (hr)	Vdz/F (L)
1.5 mg	N	16	16	16	16	16	16	16	16	16	16	16
	Mean	3.41	2.27	2.44	34.18	67.42	75.10	50.07	450.74	43.92	36.50	1240.00
	S.D.	1.51	1.01	1.59	13.49	30.23	33.88	22.59	360.93	9.80	7.83	486.07
	CV (%)	44.4	44.4	65.2	39.5	44.8	45.1	45.1	80.1	22.3	21.4	39.2
	Geomean	3.11	2.07	-	31.45	59.61	66.45	44.30	376.24	42.58	35.46	1155.55
4 mg	N	16	16	16	16	16	16	16	16	16	16	16
	Mean	9.02	2.26	2.44	95.42	187.70	205.91	51.48	383.79	43.56	36.76	1199.47
	S.D.	3.09	0.77	1.26	33.71	74.92	84.69	21.17	170.10	6.16	4.59	497.24
	CV (%)	34.3	34.3	51.8	35.3	39.9	41.1	41.1	44.3	14.1	12.5	41.5
	Geomean	8.56	2.14	-	89.85	173.58	189.51	47.38	351.79	43.15	36.49	1111.27
10 mg	N	16	16	16	16	16	16	16	16	16	16	16
	Mean	26.53	2.65	2.25	253.95	475.24	516.26	51.63	376.00	41.27	36.25	1169.42
	S.D.	7.99	0.80	0.86	86.86	179.41	196.66	19.66	158.85	5.07	3.13	467.27
	CV (%)	30.1	30.1	38.1	34.2	37.8	38.1	38.1	42.2	12.3	8.6	40.0
	Geomean	25.50	2.55	-	240.26	442.65	479.65	47.97	347.47	40.98	36.12	1086.87

-; not calcurated.
The geomean and geoCV(%) were calculated using non-zero data only.

Source: 1/19/2007 Clinical Pharmacology review of NDA 50-811, Table 26

Figure 1A.
Correlation between TAC-XL Dose (mg and mg/kg) and AUC_{0-24} in Healthy Subjects (Study FJ-506E-0002)

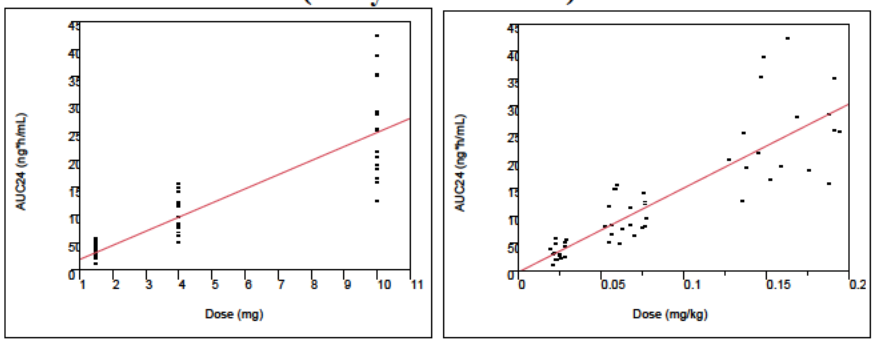


Figure 1B.
Correlation between TAC-XL Dose (mg and mg/kg) and C_{24} (C_{trough}) in Healthy Subjects (Study FJ-506E-0002)

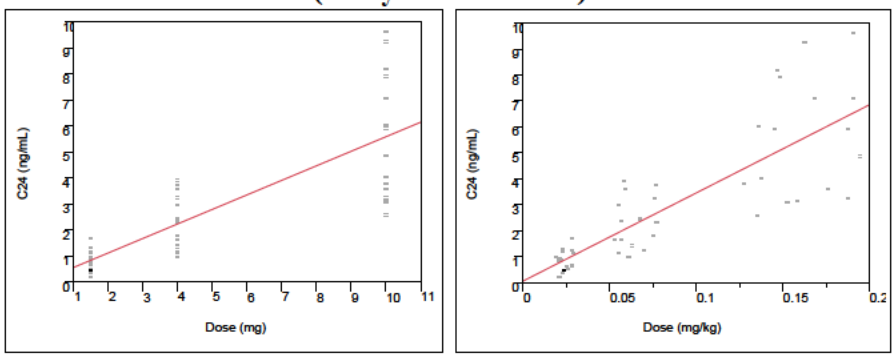


Figure 1C.
Correlation between TAC-XL Dose (mg and mg/kg) and C_{max} in Healthy Subjects (Study FJ-506E-0002)

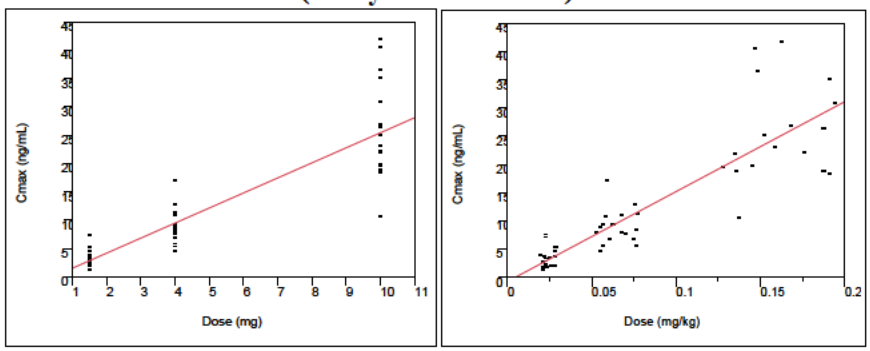
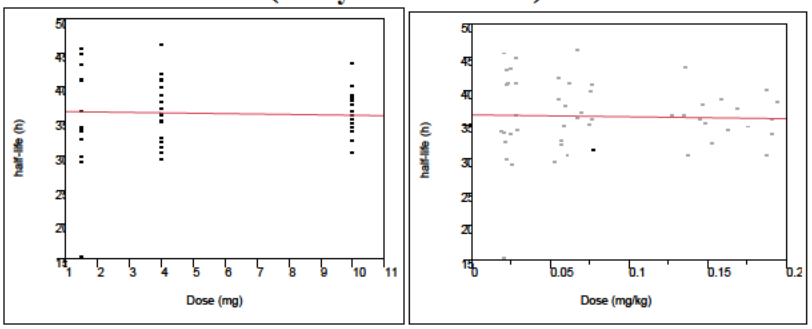


Figure 1D.
Correlation between TAC-XL Dose (mg and mg/kg) and $t_{1/2}$ in Healthy Subjects (Study FJ-506E-0002)



2.2.2. What are the design features of the Phase 3 clinical trials (in de novo kidney transplant patients) and the Phase 2 clinical studies (in stable kidney transplant patients) used to support dosing of TAC-XL?

De novo Kidney

Table 4 summarizes the study designs of the three Phase 3 trials in de novo kidney transplant patients (Studies 12-03, 158, and 1210) that were proposed to support approval of TAC-XL (known earlier as Advagraf®) in the prophylaxis of allograft rejection in kidney transplant patients; all three trials used Prograf (tacrolimus immediate release capsules) as the active comparator or reference formulation. Neoral® (cyclosporine) was also used as another active comparator in one of the three Phase 3 trial.

Table 4
Study Design of the Three Phase 3 Clinical Efficacy and Safety Studies in De Novo Kidney Transplant

Parameter	Study 02-0-158			Study FG-506E-12-03		Study PMR-EC-1210			
Design	Phase 3, multicenter, 1:1:1 randomized, open-label, comparative, 3-arm parallel group, noninferiority			Phase 3, multicenter, 1:1 randomized, double-blind, double-dummy, 2-arm parallel group, noninferiority		Phase 3b, multicenter, 1:1:1:1 randomized, open-label, comparative, 4-arm parallel group, noninferiority			
Advagraf and comparators FAS PPS	**Advagraf** (n = 214) (n = 211)	**Prograf** (n = 212) (n = 209)	**Neoral§§** (n = 212) (n = 209)	**Advagraf** (n = 331) (n = 280)	**Prograf** (n = 336) (n = 291)	**Advagraf** 0.2 mg/kg (n = 302) (n = 263)	**Prograf** 0.2 mg/kg (n = 309) (n = 237)	**Advagraf** 0.3 mg/kg (n = 304) (n = 246)	**Advagraf** 0.2 mg/kg + BAS (n = 283) (n = 230)
Timing of preoperative dose, if allowed	NA			Within 12 hours prior to reperfusion†		Within 12 hours prior to reperfusion and if possible within 3 hours prior to anesthesia†			
Protocol-defined initial preoperative CNI dose (po)	Not permitted			**Advagraf** 0.1 mg/kg	**Prograf** 0.1 mg/kg	**Advagraf** 0.1 mg/kg	**Prograf** 0.1 mg/kg	**Advagraf** 0.15 mg/kg	**Advagraf** 0.1 mg/kg
Timing of initial dose	Prior to or within 48 hours of completion of transplant procedure			Not < 4 hours after the preoperative dose or > 12 hours after reperfusion		Not < 4 hours after the preoperative dose or > 12 hours after reperfusion			
Antibody induction	Basiliximab 20 mg iv on day 0 and once between days 3 and 5			Not permitted		Not permitted			BAS 20 mg iv on day 0 and once on day 4
Protocol-defined initial postoperative dose per day	**Advagraf** 0.15 to 0.20 mg/kg po (AM)	**Prograf** 0.15 to 0.20 mg/kg (2 divided doses)		**Advagraf** 0.2 mg/kg po (AM)	**Prograf** 0.2 mg/kg po (2 divided doses)	**Advagraf** 0.2 mg/kg po (AM)	**Prograf** 0.2 mg/kg po (2 divided doses)	**Advagraf** 0.3 mg/kg po (AM)	**Advagraf** 0.2 mg/kg po (AM)
Actual mean dose on day 1‡	**Advagraf††** 0.14 mg/kg	**Prograf††** 0.11 mg/kg		**Advagraf‡‡** 0.20 mg/kg	**Prograf‡‡** 0.19 mg/kg	**Advagraf††** 0.16 mg/kg	**Prograf††** 0.16 mg/kg	**Advagraf††** 0.22 mg/kg	**Advagraf††** 0.17 mg/kg
Protocol-defined tacrolimus trough concentration	Days 0 to 90: 7 to 16 ng/mL Thereafter: 5 to 15 ng/mL			Up to day 28: 10 to 15 ng/mL Day 29 to day 168: 5 to 15 ng/mL Thereafter: 5 to 10 ng/mL		Days 0 to 14: 10 to 15 ng/mL Days 15 to 42: 5 to 12 ng/mL Days 43 to 168: 5 to 10 ng/mL			
Actual median tacrolimus trough concentration range (by month)	**Advagraf††** 0 to 2: 9 to 10 ng/mL 4 to 12: 7 to 8 ng/mL	**Prograf ††** 0 to 2: 9 to 11 ng/mL 4 to 12: 7 to 8 ng/mL		**Advagraf‡‡** 0 to 2: 10 to 14 ng/mL 3 to 12: 8 to 11 ng/mL	**Prograf‡‡** 0 to 2: 11 to 16 ng/mL 3 to 12: 8 to 10 ng/mL	**Advagraf‡‡** 0 to 2: 10 to 13 ng/mL 3 to 6: 8 to 9 ng/mL	**Prograf‡‡** 0 to 2: 8 to 16 ng/mL 3 to 6: 8 to 9 ng/mL	**Advagraf‡‡** 0 to 2: 10 to 18 ng/mL 3 to 6: 8 to 10 ng/mL	**Advagraf‡‡** 0 to 2: 9 to 12 ng/mL 3 to 6: 8 to 10 ng/mL
Protocol-defined MMF initial dose	2.0 g/day (2 divided doses) Black/African American patients could receive 3.0 g/day (2 divided doses).			Initial 14 days: 2 g/day (2 divided doses)		1 g preoperatively; 2 g/day (2 divided doses)			
Protocol-defined MMF reduction	Dose changes for adverse events if clinically indicated or withdrawal at the investigator's discretion			After day 14: 1 g/day		After day 14: 1 g/day			
Protocol-defined corticosteroid initial dose	Methylprednisolone (or equivalent) Day 0: 500 to 1000 mg iv Day 1: 200 mg po			Methylprednisolone (or equivalent) Day 0: Up to 1000 mg iv Day 1: 125 mg iv		Methylprednisolone (or equivalent) Day 0: up to 500 mg iv Day 1: 125 mg iv			Methylpred-nisolone (or equivalent) Day 0: up to 500 mg iv
Protocol-defined corticosteroid reduction schedule (po)	By day 14: 20 to 30 mg/d By month 1: 10 to 20 mg/d By month 2: 10 to 15 mg/d By month 3 to 12: 5 to 10 mg/d			Days 2 to 14: 20 mg/d Days 15 to 28: 15 mg/d Days 29 to 42: 10 mg/d Days 43 to 84: 5 mg/d Thereafter: 0 to 5 mg/d		Days 2 to 14: 20 mg/d Days 15 to 28: 15 mg/d Days 29 to 42: 10 mg/d Days 43 to 84: 5 mg/d Days 85 to 168: ≤ 5 mg/d			Days 1 to 168: 0 mg/d
Patient population Male Female Living donor Deceased donor White Black/African American	**Advagraf ††** 64.5% 35.5% 48.1% 51.9% 74.8% 19.2%	**Prograf ††** 64.2% 35.8% 50.0% 50.0% 71.7% 24.1%		**Advagraf ††** 61.6% 38.4% 26.9% 73.1% 83.7% 4.2%	**Prograf ††** 64.0% 36.0% 27.4% 72.6% 81.3% 5.7%	**Advagraf ††** 68.2% 31.8% 11.3% 88.7% 94.0% 4.6%	**Prograf ††** 68.3% 31.7% 13.3% 86.7% 95.8% 2.3%	**Advagraf ††** 67.1% 32.9% 10.9% 89.1% 95.7% 2.3%	**Advagraf ††** 65.4% 34.6% 12.7% 87.3% 93.6% 3.9%

Reference ID: 3323950

Protocol-defined primary analysis	Efficacy failure rate (BPAR, graft failure§, death or lost to follow-up¶) at 1 year	BPAR event rate within the first 24 weeks posttransplant	Efficacy failure (incidence and time to first graft loss, BPAR or graft dysfunction at week 24)
Protocol-defined primary analysis set for efficacy	Full analysis set (FAS)	Per Protocol Set (PPS)	Per Protocol Set (PPS)

All randomized patients who received at least one dose of study medication (Full Analysis Set); all patients from the Full Analysis Set with no major protocol violations (Per Protocol Set). Study FG-506E-12-03 also required patients to be enrolled prior to December 31, 2005 and receive a transplant to be included in the Per Protocol Set.

BAS: basiliximab; BPAR: biopsy-proven acute rejection; CNI: calcineurin inhibitor; CS: cyclosporine; FAS: full analysis set; MMF: mycophenolate mofetil; PPS: Per Protocol Set

†In Studies PMR-EC-1210 and FG-506E-12-03, recipients of a kidney from a living donor could be predosed with Advagraf or Prograf if the dosing did not occur > 72 hours prior to reperfusion and the dose did not exceed 0.2 mg/kg/day.

‡ Actual mean dose values for Study 02-0-158 are from day 3.

§ Graft failure is defined as a permanent return to dialysis (> 30 days) or retransplant.

¶ Lost to follow-up was defined as any patient who did not have at least 335 days of follow-up information.

†† These data are from the FAS.

‡‡ These data are from the PPS.

§§ Data for the Neoral treatment arm are not presented.

Note: Advagraf = TAC-XL

Source: Module 2.7.3 Kidney Transplantation, Table 1

The sponsor's proposed dosing regimen of TAC-XL in de novo kidney transplant patients was based on the actual tacrolimus starting dose and the observed tacrolimus trough concentrations achieved in Phase 3 Study 158, which showed that TAC-XL was non-inferior to Prograf® in terms of the efficacy failure rate (primary endpoint). Two other Phase 3 trials (Study 12-03 and Study 1210 (a.k.a. OSAKA) were proposed by the sponsor as supportive clinical trials. Note that the FDA Medical and the Statistical reviewers consider Study 12-03 (a double blind, double dummy trial) as the primary clinical trial. Based on the sponsor's analysis, in Study 12-03, TAC-XL is non-inferior to Prograf in both the Per-Protocol and the Full Analysis populations when adjusted for the imbalance in the number of patients at baseline with HLA DR mismatches, which is a known prognostic factor of acute rejections and poor long-term outcomes in kidney transplant patients.

Based on the findings of the FDA Statistical Reviewer, the non-inferiority of TAC-XL to Prograf was demonstrated in terms of efficacy failure, defined as the composite of biopsy proven acute rejection (BPAR), graft loss (GL), death (D), and loss-to-follow-up (LTFU), in all three Phase 3 clinical trials. Moreover, the safety analyses also showed no significant differences between the treatment groups when considering the collective results of the three trials.

Stable kidney (≥ 6 months post-transplant): conversion from Prograf (tacrolimus immediate release) to TAC-XL (tacrolimus extended release)

(b) (4)

The study designs of these Phase 2 conversion studies in stable kidney transplant patients are summarized below.

1. **Study 02-0-131(US Conversion Study)** was a phase 2, open-label, multicenter, single-sequence study of the pharmacokinetics of stable kidney transplant patients receiving Prograf-based immunosuppression at study entry. Patients received their stable commercial Prograf regimen during a 2-week screening period. On day 1, the patients continued to receive twice-daily Prograf as study medication. On day 8, the treatment was converted to once-daily TAC-XL (1:1 :: mg:mg on a total daily dose basis) for 4 weeks. Serial blood samples were collected for up to 24 hours for determination of tacrolimus pharmacokinetic profiles for Prograf on

days 1 and 7 and for TAC-XL on days 8, 14 and 21. The target tacrolimus C_{trough} was 5-20 ng/mL but lower concentrations were considered acceptable in the absence of clinical signs of lack of efficacy.

2. **Study FG-506E-12-02 (EU Conversion Study)** was a phase 2, open-label, multicenter, 4-period crossover replicate design study in stable, adult transplant patients (≥ 6 months post-transplant) receiving Prograf-based immunosuppression at study entry. Following a 2-week screening period, there were four 14-day treatment periods in which tacrolimus therapy was switched on a 1:1 :: mg:mg total daily dose basis between Prograf and TAC-XL. Four 24-hour pharmacokinetic profiles were performed on days 14 and 42 (Prograf) and days 28 and 56 (TAC-XL). The target tacrolimus C_{trough} was 5-15 ng/mL.

3. **Study FG-506E-KT01 (Japanese Conversion Study)** was a multicenter, open-label, phase 2 conversion study from Prograf capsules to TAC-XL capsules (1:1 :: mg:mg on a total daily dose) in stable Japanese kidney transplant patients. The treatment periods were 1 week for Prograf capsules and 12 weeks for TAC-XL. Serial whole blood samples were collected for 24 hours after administration of the last Prograf dose (day -1) and on day 7 of conversion to TAC-XL. The target tacrolimus C_{trough} was 5-15 ng/mL but lower concentrations were considered acceptable in the absence of clinical signs of lack of efficacy.

   For Year 1, the patient and graft survival rates of the stable kidney transplant patients converted from Prograf twice daily to TAC-XL once daily in the US conversion study (n=67) were 100% and 98.5%, respectively, and in the EU conversion study (n= 68) were 98.5% and 97%, respectively. For Year 5, the patient and graft survival rates in the US study were 95% and 86.9%, respectively, and in the EU study were 93.6% and 92.2%, respectively. During the pharmacokinetic study period, approximately 30% of patients in the US Study required dosage adjustment following conversion to TAC-XL. In the EU conversion study, 4.4% (3/68) required one or more dosage adjustments upon conversion to TAC-XL during the first treatment period; none of the 60 patients included in the PK subset (i.e., with 4 complete PK profiles) required dosage adjustment during the 56-day duration of the study. In both the US and EU studies, there were no patient deaths, graft losses, or occurrences of acute rejection during the pharmacokinetic treatment period. In both studies, all patients had stable renal function, except one patient in the US study who had human polyomavirus infection confirmed by kidney biopsy. In the Japanese conversion study (n=35), 14% of the patients required tacrolimus dose adjustment after conversion to TAC-XL and there were no deaths or graft loss during the 12-week study period.

Stable kidney transplant: conversion to and from cyclosporine

(b) (4)

Note that both tacrolimus and cyclosporine are calcineurin inhibitors; concomitant use could lead to additive or synergistic nephrotoxicity.

2.2.3 Were the observed whole blood trough concentrations (C_{trough}) of tacrolimus with TAC-XL once daily comparable to Prograf® twice daily in the Phase 3 clinical trials involving de novo kidney transplant patients? Were the C_{trough} achieved in these studies within the protocol-specified target ranges in these Phase 3 studies?

Yes, the whole blood tacrolimus trough concentrations of TAC-XL and Prograf were generally comparable in Studies 158 and 12-03 during the durations of these studies, except during the first 14 days when the median trough concentrations were lower for TAC-XL than Prograf by 0.4 to 2.9 ng/mL; the difference was greatest on day 1 and diminished with time (Figures 2 and 3, and Tables 5 and 7). Using the time periods (i.e., Days 1-60 and Months 3-12) in the sponsor's proposed TAC-XL package insert, the 10^{th}-90^{th} percentiles of tacrolimus trough concentrations achieved in TAC-XL patients in Study 158 and Study 12-03 were comparable to those achieved in Prograf patients (Tables 6 and 8).

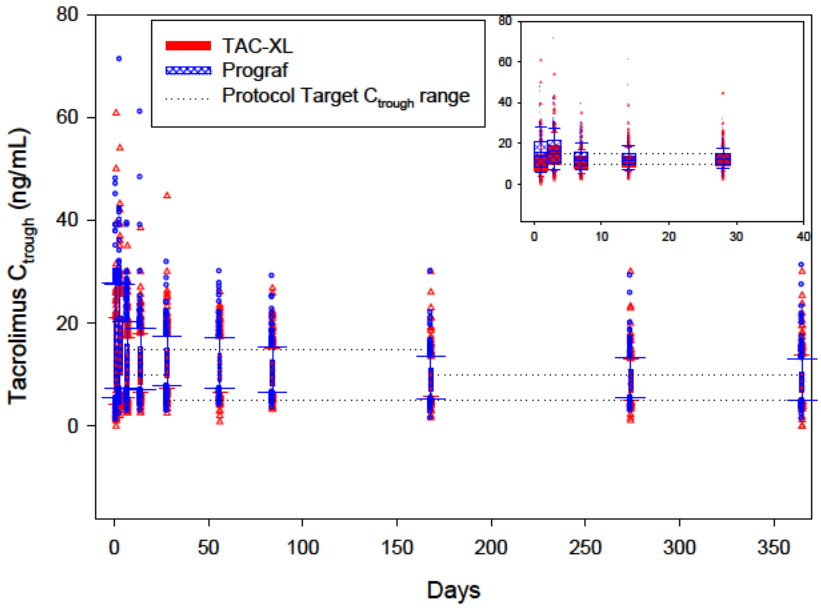
In general, tacrolimus trough concentrations in Study 12-03 and Study 158 were within protocol specified target ranges. In Study 12-03, the target C_{trough} ranges for both TAC-XL and Prograf were 10-15 ng/mL on Days 1 through 28, 5-15 ng/mL on Days 29 through 168 and 5-10 ng/mL thereafter. During the first 3 to 7 days of the trial, a greater proportion of TAC-XL and Prograf patients had their trough concentrations above the target range (10-15 ng/mL for the first 28 days in Study 12-03) than compared to later times.

In Study 158, the target C_{trough} ranges for both TAC-XL and Prograf were 7-16 ng/mL for Days 0 through 90, and 5-15 ng/mL thereafter. On Day 3, a numerically higher number of patients had their tacrolimus trough concentrations above the target range; at later time points, at least 50% of the patients had their tacrolimus trough concentrations closer to the lower limit of the target trough concentration ranges. In Study 158, the observed tacrolimus trough concentration means, medians and ranges were not significantly different, when excluding from the analyses those patients who cross-covered to another treatment arm. Furthermore, it is noted that the 10th to 90th percentile of the observed tacrolimus trough concentrations after Day 60 in Study 158 (4-12 ng/mL; Table 8) is comparable to the 10th to 90th percentile of the observed tacrolimus trough concentrations during the first 12 months of the ELiTE study (i.e., described as Study 1 in the current Prograf® US Package Insert).

The tacrolimus trough concentrations achieved in the TAC-XL and Prograf arms of the Phase 3b Study 1210 (OSAKA) were comparable to those achieved in the same treatment arms of the Phase 3 Study 12-03. The protocol specified starting pre-operative and post-operative doses of TAC-XL and Prograf (0.1 mg/kg and 0.2 mg/kg), as well as the concomitant immunosuppressive drugs evaluated in the 6-month open-label OSAKA study are the same as that evaluated in the >12-month double-blind, double-dummy Study 12-03.

Study 12-03

Figure 2. Box plots of Daily Tacrolimus Trough Concentrations in De Novo Kidney Transplant Patients in Study 12-03, by treatment



Legend: Box (25th to 75th percentile); whiskers (10th – 90th percentile)

Table 5. Median (10^{th} – 90^{th} percentile) Tacrolimus Trough Concentrations (ng/mL) in De Novo Kidney Transplant Patients in Study 12-03, by treatment

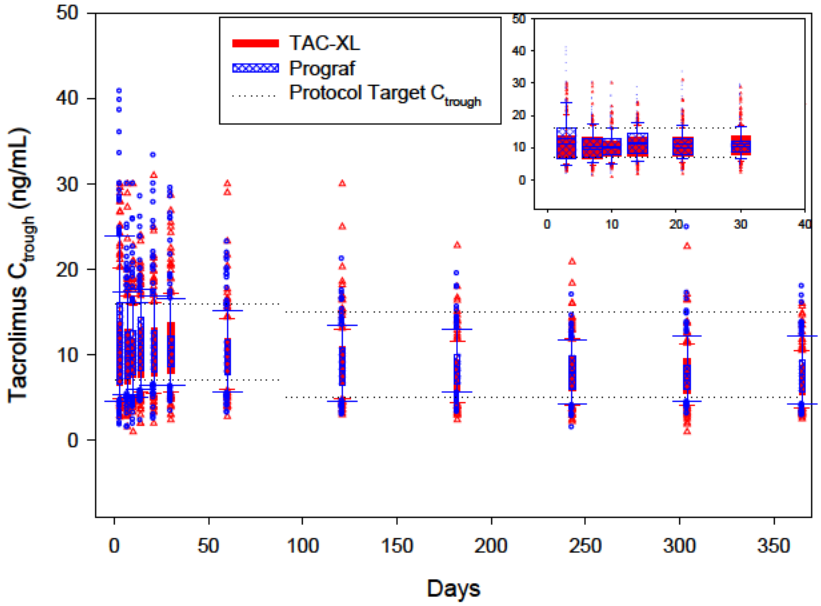
	n	TAC-XL	n	Prograf
DAY 1	296	10.0 (4.2-21.0)	314	13.9 (5.6-27.9)
DAY 3	317	13.8 (6.5-25.5)	332	15.3 (7.3-27.6)
DAY 7	316	10.1 (5.5-17.3)	326	12.0 (7.3-20.4)
DAY 14	305	10.8 (6.7-17.9)	317	12.0 (7.1-19.0)
MONTH 1	306	12.0 (7.5-17.6)	316	12.3 (7.9-17.4)
MONTH 2	289	11.1 (6.6-17.3)	305	11.2 (7.4-17.2)
MONTH 3	286	9.9 (6.6-15.2)	304	10.2 (6.7-15.5)
MONTH 6	273	9.2 (5.7-13.5)	296	8.6 (5.4-13.5)
MONTH 11	258	8.6 (5.0-13.0)	276	8.7 (5.6-13.4)
MONTH 12	279	8.0 (5.1-13.8)	285	8.3 (5.0-13.1)

Table 6. Tacrolimus Trough Concentrations of TAC-XL and Prograf in in De Novo Kidney Transplant Patients Study 12-03, by time period [Mean ± SD; Median (10^{th} – 90^{th} percentile)]

Time period	TAC-XL	Prograf
Days 1-60	12.2 ± 5.9 11.2 (6 - 20)	13.8 ± 6.6 12.5 (7 - 22)
Months 3-12	9.5 ± 3.9 9 (6 - 14)	9.6 ± 3.8 8.9 (6 - 14)

Study 158

Figure 3. Box plots of Daily Tacrolimus Trough Concentrations in in De Novo Kidney Transplant Patients in Study 158, by treatment



Legend: Box (25^{th} to 75^{th} percentile); whiskers (10^{th} – 90^{th} percentile)

Table 7. Median (10^{th} – 90^{th} percentile) Tacrolimus Trough Concentrations (ng/mL) in in De Novo Kidney Transplant Patients in Study 158, treatment

	n	TAC-XL	n	Prograf
DAY 3	181	9.6 (4.9 - 20.2)	170	11.2 (4.7 - 23.9)
DAY 7	166	9.1 (4.4 - 16.8)	151	9.7 (5.4 - 17.3)
DAY 10	160	9.4 (5.2 - 16.0)	144	9.8 (5.1 - 16.1)
DAY 14	162	10.0 (5.7 - 16.9)	151	11.2 (6.0 - 17.6)
DAY 21	177	9.9 (5.5 - 16.1)	160	9.9 (6.5 - 17.0)
MONTH 1	177	10.6 (5.7 - 17.1)	164	10.5 (6.5 - 16.6)
MONTH 2	176	9.4 (6.0 - 14.3)	164	9.2 (5.6 - 15.3)
MONTH 4	170	8.4 (4.8 - 13.1)	150	8.2 (4.6 - 13.5)
MONTH 6	165	7.7 (4.4 - 11.7)	147	8.0 (5.7 - 12.9)
MONTH 8	163	7.4 (4.1 - 11.9)	138	7.8 (4.3 - 11.8)
MONTH 10	156	7.1 (4.1 - 11.3)	138	7.1 (4.6 - 12.2)
MONTH 12	162	7.1 (3.8 - 10.5)	147	7.1 (4.3 - 12.2)

Table 8. Tacrolimus Trough Concentrations of TAC-XL and Prograf in De Novo Kidney Transplant Patients in Study 158, by time period [Mean ± SD; Median (10^{th} – 90^{th} percentile)]

Time period	TAC-XL	Prograf
Days 1-60	10.5 ± 4.8 9.7 (5 - 17)	11.1 ± 5.3 10.1 (6 - 17)
Months 3-12	8 ± 3.4 7.6 (4 - 12)	8.2 ± 3.1 7.7 (5 - 13)

2.2.4. Were the total daily tacrolimus doses of TAC-XL once daily comparable to Prograf® twice daily in Study 158 and Study 12-03?

In Study 12-03, the protocol specified initial pre-operative dose for both TAC-XL and Prograf was 0.1 mg/kg as one dose given within 12 hours prior to reperfusion; the initial post-operative tacrolimus daily dose (0.2 mg/kg/day) was to be administered at least 4 hours after the pre-operative dose but not more than 12 hours after reperfusion. In Study 158, the protocol specified starting dose was 0.15 to 0.2 mg/kg/day (given prior to or within the first 48 hours post-transplant). The mean ± SD daily doses of TAC-XL and Prograf in Study 12-03 are presented in Figure 4 and Table 9. The mean ± SD daily doses in Study 158 are presented in Figure 5 and Table 10.

In Study 12-03, the mean starting daily doses were comparable between TAC-XL and Prograf (i.e., approximately 0.15 mg/kg/day on Day 0 and 0.2 mg/kg/day on Day 1). In Study 158, the mean starting dose (given any time up to day 2 post-transplant) of TAC-XL was 40% higher than Prograf (0.14 mg/kg versus 0.1 mg/kg, as recommended in the Prograf USPI). Thereafter, to achieve comparable mean and median tacrolimus C_{trough}, higher total mean daily doses of tacrolimus were required with TAC-XL than Prograf (on average, by 25% in Study 12-03 and by 15% in Study 158).

Figure 4. Mean ± SD Daily Doses of TAC-XL and Prograf (mg/kg) in De Novo Kidney Transplant Patients in Study 12-03

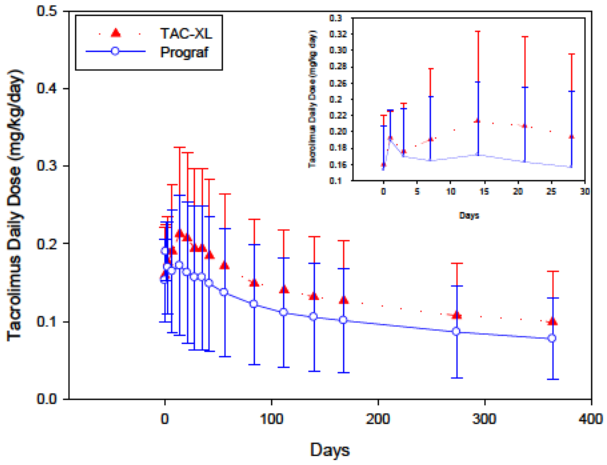


Table 9. Mean ± SD Daily Doses of TAC-XL and Prograf (mg/kg/day) in De Novo Kidney Transplant Patients in Study 12-03

Day	n	TAC-XL	n	Prograf
first dose◦	330	0.146 ±0.058	336	0.139 ± 0.051
0	328	0.160 ± 0.061	334	0.153 ± 0.054
1	321	0.193 ± 0.0326	329	0.190 ± 0.037
3	315	0.176 ± 0.059	324	0.170 ± 0.060
7	311	0.191 ± 0.087	318	0.164 ± 0.079
14	301	0.213 ± 0.111	311	0.172 ± 0.090
21	297	0.207 ± 0.110	307	0.163 ± 0.092
28	293	0.194 ± 0.102	305	0.157 ± 0.093
35	293	0.194± 0.102	305	0.157 ± 0.093
42	292	0.185 ± 0.098	303	0.149 ± 0.086
56	288	0.172 ± 0.094	302	0.137 ± 0.083
84	280	0.149 ± 0.083	299	0.122 ± 0.077
112	277	0.140 ± 0.078	298	0.111 ± 0.071
140	275	0.132 ± 0.078	293	0.105 ± 0.069
168	268	0.127 ± 0.077	292	0.101 ± 0.067
274	262	0.107 ± 0.068	281	0.086 ± 0.059
364	253	0.099 ± 0.065	266	0.078 ± 0.053

◦ about 80% patients received first dose on Day 0.

Figure 5. Mean ± SD Daily TAC-XL and Prograf Doses (mg/kg) in De Novo Kidney Transplant Patients in Study 158

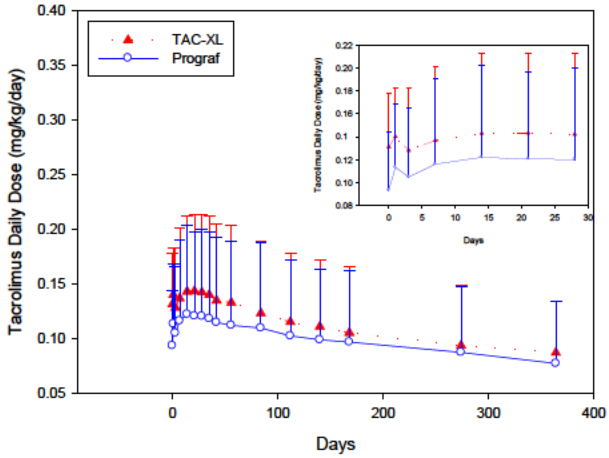


Table 10. Mean ± SD Daily TAC-XL and Prograf Doses (mg/kg/day) in De Novo Kidney Transplant Patients in Study 158

	n	TAC-XL	n	Prograf
first dose◦	189	0.141 ± 0.037	204	0.100 ± 0.037
0	35	0.131± 0.046	71	0.093± 0.050
1	136	0.140± 0.043	156	0.113± 0.055
3	188	0.128± 0.055	202	0.105± 0.060
7	188	0.137± 0.064	200	0.116± 0.074
14	184	0.143± 0.069	198	0.122± 0.081
21	184	0.143± 0.070	197	0.121± 0.076
28	180	0.142± 0.070	197	0.120± 0.080
35	179	0.140± 0.072	196	0.118± 0.080
42	176	0.135± 0.070	196	0.115± 0.078
56	175	0.133± 0.071	195	0.112± 0.077
84	174	0.123± 0.065	188	0.110± 0.078
112	172	0.115± 0.063	188	0.102± 0.069
140	171	0.111± 0.061	188	0.099± 0.065
168	171	0.105± 0.060	185	0.097± 0.066
274	169	0.094± 0.055	178	0.087± 0.060
364	92	0.087± 0.046	98	0.077± 0.056

◦patients received their first dose by day 2

2.2.5 Were mycophenolate mofetil (MMF) doses and mycophenolic acid (MPA) trough concentrations comparable between the Prograf®/MMF treatment group and TAC-XL/MMF treatment group in Study 158? Were the MMF doses comparable between the Prograf®/MMF treatment group and TAC-XL/MMF treatment group in Study 12-03? Was MMF dosing in these studies consistent with the protocol?

The mean and the median daily doses of MMF in Study 12-03 and Study 158, as well as the mean and median mycophenolate (MPA) trough concentrations were not substantially different between the TAC-XL/MMF and

Prograf®/MMF treatment groups. Thus, the comparison of the efficacy and safety profiles of tacrolimus between the two tacrolimus treatment groups does not appear to be confounded with potential differences in MMF doses and MPA trough concentrations between the two treatment arms.

Study 12-03

The protocol specified MMF doses were 2 grams daily (given as two divided doses) starting pre-operatively until Day 14, and 1 gram daily thereafter.

Table 11 compares the two treatment arms in terms of the daily doses of MMF, by time period. The mean and median daily doses of MMF over the given time periods were comparable between the TAC-XL/MMF group and the Prograf/MMF group. The percentage of patients with average daily MMF doses maintained at 2 grams per day, reduced to less than 2 grams per day, and increased to greater than 2 grams per day are provided per time period in Table 12. The distribution of patients receiving daily MMF doses <2, 2, and >2 grams per day during the first 1, 3, 6, and 12 months post-transplant was comparable between TAC-XL and Prograf. MMF administration as concomitant maintenance immunosuppressive therapy in this trial was consistent with the study protocol.

Study 158

The protocol specified starting dose of MMF was 2 grams daily (given as two divided doses); up to 3 grams daily was allowed for African-American patients. Dose-equivalent three times daily (tid), or four times daily (qid) dosing was permitted if tolerability was a concern. In Study 158, MPA trough concentrations were measured at Months 1, 6, and 12 but were not used as basis for MMF dose adjustments since target MPA concentration ranges were not identified.

Table 13 compares the three treatment arms in terms of the daily doses of concomitantly administered MMF, by time period. During the first 60 days, the mean and median daily MMF doses were comparable among the three treatment groups. During the next 9 months, the mean and median MMF daily doses of the two tacrolimus treatment arms (TAC-XL and Prograf) were comparable with each other and numerically lower than in the cyclosporine arm (Neoral). Table 14 compares the three treatment arms in terms of the percentage of patients with average daily MMF doses maintained at 2 grams per day, reduced to less than 2 grams per day, and increased to greater than 2 grams per day by time period. Using the time periods in the proposed TAC-XL package insert, the distribution of patients receiving daily MMF doses <2, 2, and >2 grams per day during the first 1, 3, 6, and 12 months post-transplant was comparable between TAC-XL and Prograf, with more patients reducing MMF daily doses to < 2g/day as time goes by. MMF administration as concomitant maintenance immunosuppressive therapy in this trial was consistent with the study protocol. Furthermore, based on the data presented in Table 14, MMF administration in Study 158 was comparable to MMF administration in the ELiTE Study (as shown in Table 19 of the current Prograf US Package Insert).

Table 11. Daily Mycophenolate Mofetil Doses (grams/day) co-administered with TAC-XL and Prograf over time period in De Novo Kidney Transplant Patients in Study 12-03, by treatment [Mean ± SD; Median (10^{th} – 90^{th} percentile)]

Time period	TAC-XL	Prograf
Days 1-14	1.9 ± 0.4 2 (1.5 - 2)	1.9 ± 0.3 2 (1.7 - 2)
Days 15-60	1.1 ± 0.3 1 (1 - 1.7)	1.1 ± 0.3 1 (1 - 1.6)
Months 3-12	1 ± 0.3 1 (0.7 - 1)	1 ± 0.3 1 (0.7 - 1)

Table 12. Distribution (%) of De Novo Kidney Transplant Patients by Average Daily Mycophenolate Mofetil Doses (grams/day) over time period in Study 12-03, by treatment

Time Period (Days)	TAC-XL			Prograf		
	< 2.0	2	> 2.0	< 2.0	2	> 2.0
1-30	82	17	0	87	13	0
1-90	93	7	0	96	4	0
1-180	94	6	0	96	4	0
1-365	95	5	0	97	3	0

Table 13. Daily Mycophenolate Mofetil Doses (grams/day) co-administered with TAC-XL and Prograf over time period in De Novo Kidney Transplant Patients in Study 158, by treatment [Mean ± SD; Median (10^{th} – 90^{th} percentile)]

Time period	TAC-XL	Prograf	Neoral
Days 1-60	1.9 ± 0.4 2 (1.4 – 2)	1.9 ± 0.4 2 (1.2 – 2)	2.0 ± 0.3 2 (1.6 – 2)
Months 3-12	1.6 ± 0.5 1.8 (0.8 – 2)	1.5 ± 0.6 1.7 (0.7 – 2)	1.8 ± 0.5 2 (1 – 2)

Table 14. Distribution (%) of De Novo Kidney Transplant Patients by Average Daily Mycophenolate Mofetil Doses (grams/day) over time period in Study 158, by treatment

Time Period (Days)	TAC-XL			Prograf			Neoral		
	< 2.0	2	> 2.0	< 2.0	2	> 2.0	< 2.0	2	> 2.0
1-30	29	65	5	24	70	6	17	74	8
1-90	42	53	5	39	54	6	17	65	9
1-180	52	45	3	50	43	7	36	55	9
1-365	58	40	2	60	36	4	42	50	8

Table 15 compares the observed MPA C_{trough} in the three treatment groups. At comparable or lower MMF doses, the two tacrolimus arms had numerically higher mean and median MPA C_{trough} compared to the cyclosporine arm. Unlike cyclosporine, tacrolimus is not known to interfere with the enterohepatic recycling of mycophenolic acid glucuronide (MPAG) to MPA (mycophenolic acid) so that the observation that decreased MMF doses are needed with time to achieve the same level of supplementary MPA–associated immunosuppression in tacrolimus patients than in cyclosporine patients is expected. These differences in MPA exposures could explain, at least in part, the observed higher incidence of MMF-associated adverse events (e.g., diarrhea and loose stools) in the TAC-XL and Prograf arms compared to the Neoral arm of Study 158. That the mean and median MPA C_{trough} values were comparable between the two tacrolimus treatment arms at all timepoints is consistent with the observation of numerically comparable rates of diarrhea and loose stools in TAC-XL and Prograf (47% versus 44%) in Study 158.

Table 15. Mycophenolate Trough Concentrations in De Novo Kidney Transplant Patients in Study 158, by treatment [Mean ± SD; Median (10^{th} – 90^{th} percentile)]

Time period	TAC-XL	Prograf	Neoral
Month 1	3.3 ± 2.2 2.8 (1 – 6.3)	3.8 ± 3.1 2.8 (1.1 – 8)	2.2 ± 2.1 1.5 (0.6 – 4.2)
Month 6	3.4 ± 2.5 2.8 (0.9 – 6.8)	3.4 ± 2.7 2.7 (1 – 6.7)	2.8 ± 3.1 1.8 (0.6 – 6)
Month 12	3.0 ± 2.5 2.5 (0.9 – 5.7)	3.1 ± 2.5 2.6 (0.8 – 6.6)	2.4 ± 2.4 1.6 (0.7 – 4.9)

2.2.6. Were the doses of maintenance corticosteroids comparable between the Prograf®/MMF/steroid treatment group and TAC-XL/MMF/steroid treatment group in Study 12-03 and Study 158? Were the doses used for corticosteroid taper in these studies consistent with the protocol?

The actual daily doses of corticosteroids in Study 12-03 and Study 158 are presented by time period in Table 16 and Table 17, respectively. In both Study 12-03 and Study 158, the mean and median daily corticosteroid doses were comparable between the TAC-XL group and the Prograf group throughout the first 12 months. After Day 0 (day of transplant), mean and median doses of concomitant corticosteroids were slightly higher in Study 158 than in Study 12-03.

Corticosteroid administration as maintenance therapy in these trials was generally consistent with the study protocol. In Study 12-03, methylprednisolone was to be given peri-operatively (on Day 0) as an intravenous (i.v.) bolus dose up to 1000 mg. A second i.v. bolus dose of 125 mg 1 day after reperfusion (Day 1). Thereafter oral prednisone (or equivalent) was administered on: Days 2 to 14, 20 mg/day; Days 15 to 28, 15 mg/day; Days 29 to 42, 10 mg/day; Days 43 to 84, 5 mg/day; thereafter, 0 to 5 mg/day. In Study 158, the initial intravenous bolus dose of methylprednisolone on Day 0 ranged from 500 to 1000 mg. Patients were to receive 200 mg methylprednisolone (or equivalent dose) orally on Day 1. Oral prednisone was then tapered according to the following schedule: by Day 14, 20 to 30 mg; by Month 1,10 to 20 mg; by Month 2, 10 to 15 mg; by Month 3 to 12, 5 to 10 mg.

Table 16. Daily Corticosteroid Doses (prednisone equivalent; mg/day) co-administered with TAC-XL and Prograf over time period in De Novo Kidney Transplant Patients in Study 12-03, by treatment [Mean ± SD; Median (10^{th} – 90^{th} percentile)]

Day	TAC-XL	Prograf
0	700 ± 338 625 (250 -1250)	679 ± 332 625 (250 - 1250)
1	157 ± 86 156 (125 - 156)	159 ± 95 156 (125 - 156)
2-14	20 ± 2 20 (20 - 20)	20 ± 2 20 (20 - 20)
15-28	16 ± 3 15 (15 - 20)	16 ± 3 15 (15 - 20)
29-42	12 ± 3 10 (10 - 15)	12 ± 3 10 (10 - 15)
43-84	7 ± 4 5 (5 - 10)	7 ± 4 5 (5 - 10)
85-365	5 ± 3 5 (2.5 - 7.5)	5 ± 2 5 (2.5 - 7.5)

Table 17. Daily Corticosteroid Doses (prednisone equivalent; mg/day) co-administered with TAC-XL and Prograf over time period in De Novo Kidney Transplant Patients in Study 158, by treatment [Mean ± SD; Median (10^{th} – 90^{th} percentile)]

DAY	TAC-XL	Neoral	Prograf
0	675 ± 248 625(625 - 1,250)	671 ± 246 625(569 -1,250)	654 ± 246 625(313 - 938)
1	253 ± 114 250(151 - 267)	250 ± 112 250(154 -267)	244 ± 95 250(159 - 267)
2-14	56 ± 41 45(30 - 95)	52 ± 33 43(30 -88)	53 ± 41 43(30 - 88)

15-30	25 ± 17 20(15 - 34)	27 ± 24 20(15 -33)	23 ± 14 20(15 - 30)
31-60	17 ± 9 16(10 - 23)	20 ± 24 16(10 -26)	18 ± 11 16(10 - 24)
61-90	12 ± 4 10(8 - 17)	15 ± 16 11(7 -21)	13 ± 12 10(8 - 19)
91-365	9 ± 4 8(5 - 11)	9 ± 6 8(5 -12)	9 ± 16 8(5 - 11)

2.2.7. Was basiliximab induction in Study 158 comparable between the Prograf and the TAC-XL treatment groups and consistent with the study protocol?

Yes. In Study 158, TAC-XL and Prograf patients received basiliximab 20 mg intravenously on day 0 (first dose could be administered before skin closure). A second dose was to be administered between days 3 to 5.

2.2.8. How do the tacrolimus exposure parameters (AUC_{0-24}, C_{trough} or C_{24}, and C_{max}) of TAC-XL extended release capsules administered once daily compare to that of Prograf immediate release capsules administered twice daily in healthy subjects, in de novo kidney transplant patients, and in stable kidney transplant patients?

Healthy subjects

In 24 healthy subjects who received TAC-XL and Prograf in a crossover fashion at total daily doses of 4 mg/day, the 90% confidence intervals of the TAC-XL:Prograf ratios of tacrolimus AUC_{0-24} on Day 1 and Day 10 (steady state), as well as that of tacrolimus C_{min} (or C_{24}) at steady state, but not on Day 1, were within the 80-125% bioequivalence (BE) acceptance criteria (Study FG04-25; Figure 6 and Tables 18 and 19). In these healthy subjects, the mean tacrolimus AUC_{0-24} of TAC-XL was not lower than Prograf on Day 1 and was lower by 7% on Day 10; the mean tacrolimus C_{24} of TAC-XL was lower than Prograf by 19% on Day 1 and by 13% on Day 10. As would be expected from an extended-release formulation with no dose-dumping characteristic under normal conditions of the gut, the C_{max} of TAC-XL was not higher than that of Prograf. On Day 1 and Day 10, the Cmax achieved with TAC-XL was lower than Prograf by about 40% and 30%, respectively.

Note that unlike the other relative bioavailability study (Study FG04-21) conducted in healthy subjects, Study FG04-25 used a tacrolimus dose (4 mg/day) that was reflective of the total tacrolimus dose received by stable kidney transplant patients; no other relative bioavailability studies used a higher tacrolimus dose that would be comparable to the total daily dose received by de novo kidney transplant patients.

Stable kidney transplant patients

In 60 stable kidney transplant patients who were converted to and from TAC-XL and Prograf on a 1mg:1mg tacrolimus total daily dose basis, the 90% confidence interval of the steady state tacrolimus AUC (TAC-XL:Prograf) ratios were within the 80-125% bioequivalence (BE) acceptance criteria (Study FG-506e-12-02-PK; Figure 7; Table 20). Although TAC-XL demonstrated bioequivalence with Prograf, the AUC_{0-24} and the C_{trough} of TAC-XL were still lower than Prograf by 7% and 9%, respectively. As would be expected from an extended-release formulation with no dose-dumping characteristic under normal conditions of the gut, the C_{max} of TAC-XL was not higher than that of Prograf. The steady state Cmax of TAC-XL was about 25% lower than Prograf.

Note that unlike the two other conversion studies (Studies 02-0-131 and KT-01) conducted in stable kidney transplant patients, Study 12-02-PK was designed to be a fully replicated four-way crossover study, and the total tacrolimus daily doses did not require adjustments in the 60 patients included in the PK Evaluable Set. Note that the majority (67/68) of the patients who participated in this PK study were enrolled in Study FG506-14-02 for

long-term follow-up. The remaining patients followed up after enrollment into the extension study were: 57 for 36 months, 56 for 48 months, and 21 for 66 months. At the end of the Study FG506-14-02, none of these patients experienced BPAR; a total of 5 patients experienced graft loss due to any of the following reasons: increased blood creatinine, cerebrovascular accident, malignant lung neoplasm, operative hemorrhage, and pulmonary embolism.

De novo kidney transplant patients

In 17 de novo kidney transplant patients who received TAC-XL (0.1 mg/kg pre-operatively on Day 0 and 0.2 mg/kg post-operatively on Day 1), the average tacrolimus AUC_{0-24} and C_{trough} on Day 1 were lower by 19% and 15%, respectively than in 17 patients who received Prograf at the same starting daily dose. By Day 3, TAC-XL patients had comparable mean dose-normalized AUC_{0-24} and C_{trough} values as the Prograf patients (PK substudy of Phase 3 Study 12-03; Figure 8; Tables 21 and 22). Surgery is known to alter gastric emptying time and intestinal transit time so it is possible that these factors may have contributed to the observed difference in tacrolimus AUC_{0-24} and C_{trough} between the modified release and the immediate release formulations of tacrolimus at immediate post-transplant days. At steady state (i.e., on Day 14), a comparable mean C_{trough} resulted in an approximately 20% higher dose-normalized AUC_{0-24} with TAC-XL than Prograf. As would be expected from an extended-release formulation with no dose-dumping characteristic under normal conditions of the gut, the C_{max} of TAC-XL was not substantially higher than that of Prograf. At comparable daily doses, the Cmax achieved with TAC-XL was about 15-20% lower on Day 1, 7% lower on Day 3, and about 20-30% higher on Day 14, compared to Prograf. (See section 2.2.10 of this NDA review for the discussion of the 12-month efficacy and safety outcomes in the de novo kidney transplant patients who participated in this PK substudy of Study 12-03.)

In Phase 2 Study 12-01, 34 de novo kidney transplant patients who received TAC-XL (0.2 mg/kg post-operatively on Day 1) had average tacrolimus AUC_{0-24} and C_{trough} on Day 1 that were lower by 35% and 18%, respectively, than the 34 patients who received Prograf (Figure 9, Tables 23 and 24). On Day 14, the average tacrolimus AUC_{0-24} and C_{trough} were comparable between TAC-XL and Prograf patients. However, on Day 42, the average tacrolimus AUC_{0-24} and C_{trough} were lower by 20% and 25%, respectively, than those patients who received Prograf. As would be expected from an extended-release formulation with no dose-dumping characteristic under normal conditions of the gut, the C_{max} (normalized by the daily dose) of TAC-XL was not higher than that of Prograf. At comparable tacrolimus daily doses, the Cmax achieved with TAC-XL was lower than Prograf by about 50% on Day 1, 6% on Day 14 and 25% on Day 42.

Figure 6. Whole Blood Tacrolimus concentration time profiles of TAC-XL (MR-4) and Prograf in Healthy Subjects, Day 1 and Day 10 (Study FG04-25)

Figure B: Geometric Mean Blood Concentrations of Tacrolimus on Day 1 (Linear Scale)

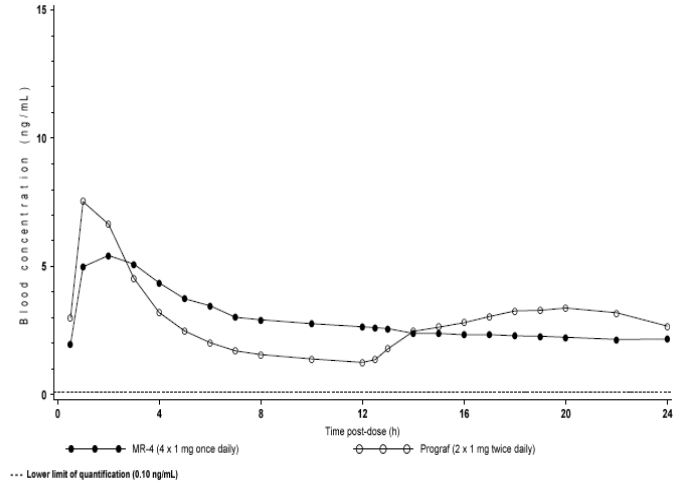


Figure C: Geometric Mean Blood Concentrations of Tacrolimus on Day 10 (0 to 24 h) (Linear Scale)

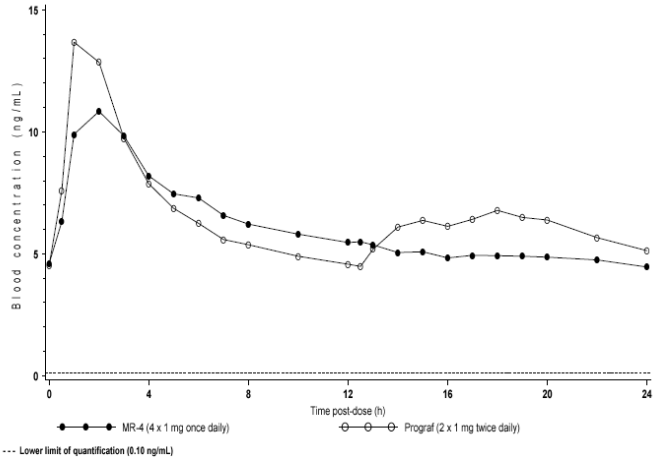


Table 18. PK Parameters of TAC-XL (MR-4) once daily and Prograf twice daily in Healthy Subjects (Study FG-506-04-25)

	4 x 1 mg once daily MR-4		2 x 1 mg twice daily Prograf®	
Parameter	Day 1 (N=24)	Day 10 (N=24)	Day 1 (N=24)	Day 10 (N=24)
AUC(0-24 h)* (ng.h/mL)	71.2 (30.4)	148 (32.9)	70.1 (36.1)	160 (34.6)
AUC(0-12 h)+ (ng.h/mL)	NA	NA	35.1 (40.2)	87.3 (36.2)
AUC(12-24 h)+ (ng.h/mL)	NA	NA	34.7 (35.2)	72.2 (33.4)
C_{max} (0-24 h) (ng/mL)	5.80 (36.3)	11.1 (31.6)	8.68 (40.0)	14.9 (32.7)
C_{max} (0-12 h) (ng/mL)	NA	NA	8.68 (40.0)	14.9 (32.7)
C_{max} (12-24 h) (ng/mL)	NA	NA	3.90 (30.6)	7.65 (26.8)
t_{max} (0-24 h)† (h)	2.00 (1.00-5.02)	2.00 (1.00-3.00)	1.00 (0.517-2.00)	1.00 (1.00-2.00)
t_{max} (0-12 h)† (h)	NA	NA	1.00 (0.517-2.00)	1.00 (1.00-2.00)
t_{max} (12-24 h)† (h)	NA	NA	7.00 (2.00-12.0)	5.00 (1.00-8.00)
C_{min}(24 h) (ng/mL)	2.17 (35.5)	4.46 (33.3)	2.67 (40.7)	5.13 (39.9)
$t_{½}$ (h)	NA	37.8 (8.78)	NA	37.6 (9.53)
RA_1	2.08 (28.3)		2.27 (21.0)	
RA_2	1.91 (36.7)		1.72 (29.4)	

Source: Final CSR, Table G; MR4=TAC-XL
Geometric mean (CV%) data are presented
† Median (min-max)
N = Number of subjects studied
NA = Not applicable
* AUC (0-τ) for TAC-XL, τ = 24 h
+AUC (0-τ) for Prograf∨, τ = 12 h

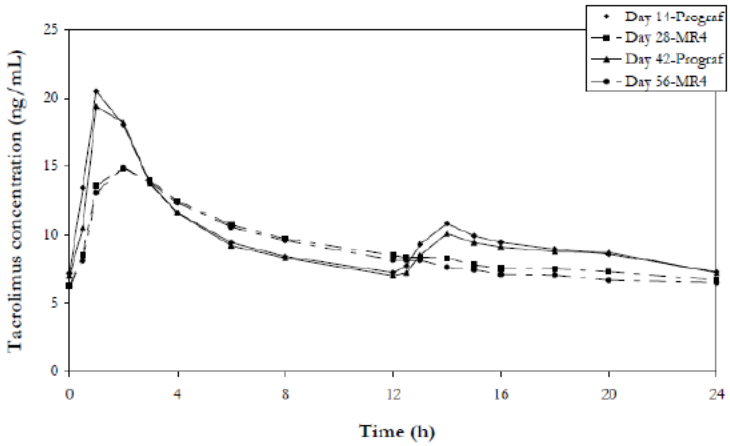
Table 19. Statistical Analysis of the Pharmacokinetic Parameters of Tacrolimus in Healthy Subjects (Study FG04-25)

Parameter	Dosing day	Ratio of geometric least squares means (A:B)	90% CI for the ratio lower	90% CI for the ratio upper
AUC(0-24 h)	1	1.02	0.91	1.13
	10	0.93	0.87	0.99
C_{max}(0-24 h)	1	0.67	0.59	0.75
	10	0.74	0.69	0.80
C_{min} (24 h)	1	0.81	0.72	0.92
	10	0.87	0.81	0.94
t_{max}(0-24 h)†	1	1.00	0.500	1.00
	10	0.500	0	0.500
t½	10	1.00	0.98	1.03

Source: Final CSR, Table H; MR4=TAC-XL
Treatment A = 4 x 1 mg once daily TAC-XL
Treatment B = 2 x 1 mg twice daily Prograf®
† Median difference and 90% CI for the difference presented

Reference ID: 3323950

Figure 7. Mean Whole Blood Concentrations of Tacrolimus Following Administration as Prograf and TAC-XL in stable kidney transplant patients (Study FG-506e-12-02-PK)



MR4 = TAC-XL
Source: FG-506E-12-02-PK Final Clinical Study Report, Figure 2

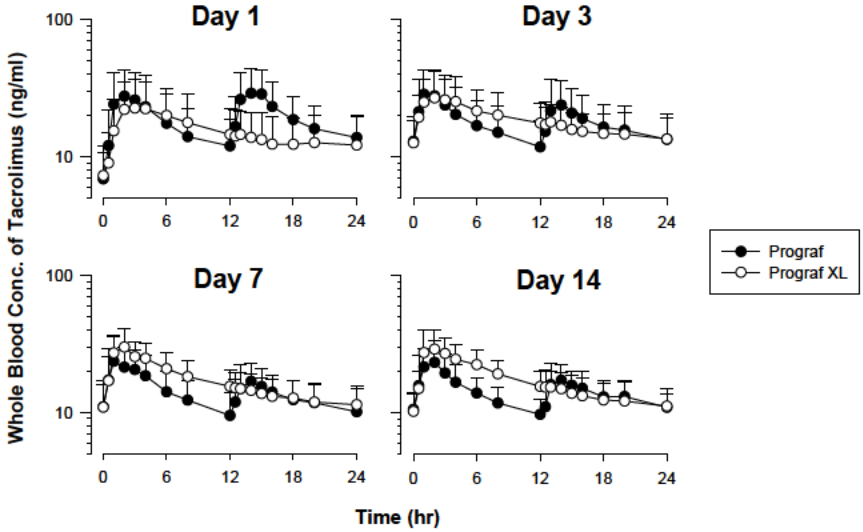
Table 20. Study FG-506e-12-02-PK (Stable kidney transplant patients)

Parameter	MR4	Prograf	Ratio (90% CI) MR4: Prograf
$AUC_{0\text{-}24}$ (ng.h/mL)	217.75	234.42	92.9% (89.8 to 96.0)
$ln(AUC_{0\text{-}24})$	210.57	227.30	92.6% (89.7 to 95.7)
C_{max} (ng/mL)	15.99	21.84	73.2% (67.7 to 78.7)
$ln(C_{max})$	15.26	20.47	74.6% (70.6 to 78.7)
C_{min} (ng/mL)	6.60	7.26	90.9% (87.3 to 94.6)
$ln(C_{min})$	6.36	7.03	90.5% (87.1 to 94.0)

Mean data from two steady state profiles presented
CI = Confidence interval; C_{min} = trough value determined using the whole blood tacrolimus concentration value at 24 hours on the day of profiling

MR4=TAC-XL
Source: FG-506E-12-02-PK Final Clinical Study Report, Table 8

Figure 8. Mean (±SD) whole blood concentration-time profiles of tacrolimus following administration as TAC-XL (n=17) or Prograf (n=17) in de novo kidney transplant patients on Day 1, Day 3, Day 7 or Day 14 (Phase 3 Study 12-03, PK substudy)



Prograf XL = TAC-XL
Source: 3/6/2008 Clinical Pharmacology review of NDA 50-811

Table 21. PK parameters of tacrolimus in De Novo Kidney Transplant Patients for TAC-XL (n=17) and Prograf (n=17) on Day 1, on Day 14 and at Week 6. PK Evaluable Set. Mean±SD [range] (Phase 3 Study 12-03, PK substudy)

	TAC-XL	Prograf	Ratio (90% CI) TAC-XL : Prograf
Day 1			
AUC_{0-24} (ng·hr/mL)	372±201	447±215	83 (56 to 110)
ln (AUC_{0-24})	332	397	84 (63 to 112)
C_{max} (ng/mL)	26.0±13.7	31.5±17.1	83 (54 to111)
ln (C_{max})	23.2	26.9	86 (63 to 119)
C_{24} (ng/mL)	12.1±7.24	13.8±6.3	88 (59 to 117)
ln (C_{24})	10.5	12.3	85 (63 to116)
Day 3			
AUC_{0-24} (ng·hr/mL)	437±175	428±206	102 (76 to 128)
ln (AUC_{0-24})	407	389	105 (82 to 133)
C_{max} (ng/mL)	31.0±13.9	33.4±15.1	93 (68 to 118)
ln (C_{max})	28.1	30.3	93 (71 to 121)
C_{24} (ng/mL)	13.5±5.62	13.4±7.06	101 (73 to 128)
ln (C_{24})	12.4	12.0	104 (79 to 136)
Day 7			
AUC_{0-24} (ng·hr/mL)	405±117	335±117	121 (101 to 141)
ln (AUC_{0-24})	388	319	122 (102 to 146)
C_{max} (ng/mL)	32.2±10.2	28.4±9.79	113 (93 to 133)
ln (C_{max})	30.8	26.9	114 (95 to 138)
C_{24} (ng/mL)	11.4±4.04	10.1±4.68	113 (88 to 138)
ln (C_{24})	10.6	9.30	114 (90 to 144)
Day 14			
AUC_{0-24} (ng·hr/mL)	412±109	340±87.8	121 (104 to 138)
ln (AUC_{0-24})	397	329	121 (102 to 142)
C_{max} (ng/mL)	32.7±9.03	27.1±11.6	121 (99 to 143)
ln (C_{max})	31.5	24.8	127 (103 to 157)
C_{24} (ng/mL)	11.2±3.93	11.0±2.78	102 (84 to 120)
ln (C_{24})	10.5	10.6	99 (82 to 120)

Mean total daily dose on Day 1: TAC-XL = 0.201 mg/kg; Prograf = 0.197 mg/kg
Mean total daily dose on Day 3: TAC-XL = 0.185 mg/kg; Prograf = 0.184 mg/kg
Mean total daily dose on Day 7: TAC-XL = 0.177 mg/kg; Prograf = 0.158 mg/kg
Mean total daily dose on Day 14: TAC-XL = 0.180 mg/kg; Prograf = 0.174 mg/kg
Source: 3/6/2008 Clinical Pharmacology review NDA 50-811

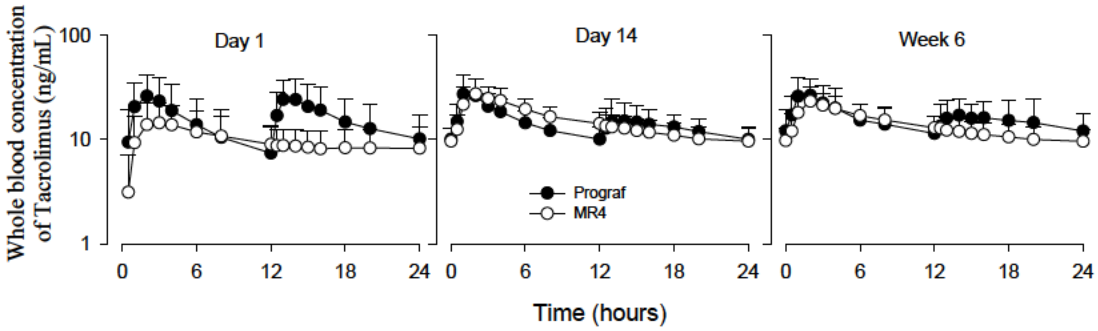
Reference ID: 3323950

Table 22. Dose-normalized PK parameters of tacrolimus in De Novo Kidney Transplant Patients for TAC-XL (n=17) and Prograf (n=17) on Day 1, on Day 3, on Day 7 and on Day 14. (Phase 3 Study 12-03, PK substudy)

	TAC-XL	Prograf	Ratio (90% CI) TAC-XL: Prograf
Day 1			
AUC_{0-24} (ng·hr/mL)	179.8	236.7	76.0% (52.4 to 99.5)
ln (AUC_{0-24})	168.0	207.7	80.9% (61.5 to 106.5)
Day 3			
AUC_{0-24} (ng·hr/mL)	256.3	237.7	107.8% (77.2 to 138.4)
ln (AUC_{0-24})	227.6	214.7	106% (80.4 to 139.9)
Day 7			
AUC_{0-24} (ng·hr/mL)	251.8	252.9	99.6% (61.5 to 137.7)
ln (AUC_{0-24})	228.5	212.8	107.4% (80.3 to 143.6)
Day 14			
AUC_{0-24} (ng·hr/mL)	257.1	212.8	120.8% (94.3 to 147.3)
ln (AUC_{0-24})	232.5	200.2	116.2% (90.9 to 148.5)

PK Evaluable Set
Data: dose-normalized to dose of 0.1 mg/kg/day
Natural log values transformed back to linear scale for presentation
Source: 3/6/2008 Clinical Pharmacology review of NDA 50-81

Figure 9. Mean whole blood concentration-time profiles of tacrolimus following administration as TAC-XL (n=34) or Prograf® (n=32) in De Novo Kidney Transplant Patients on Day 1, on Day 14 or at Week 6 (Study FG12-01)



Source: 3/6/2008 Clinical Pharmacology review of NDA 50-811

Table 23.PK parameters of tacrolimus in De Novo Kidney Transplant Patients for TAC-XL (n=34) and Prograf® (n=32) on Day 1, on Day 14 and at Week 6. PK Evaluable Set. Mean±SD [range] (Study FG12-01)

Day 1	TAC-XL	Prograf®	Ratio (90% CI) TAC-XL: Prograf®
AUC_{0-24} (ng·hr/mL)	232±102 [85.5-461]	361±215 [114-1144]	64.2% (45.2 to 83.1)
C_{max} (ng/mL)	18.2±7.63 [8.48-41.1]	34.2±13.9 [9.0-74.9]	53.4% (40.0 to 66.7)
C_{24} (ng/mL)	8.25±5.01 [1.85-23.6]	10.1±6.98 [2.34-3.4]	81.5% (56.9 to 106)
Day 14			
AUC_{0-24} (ng·hr/mL)	364±96.6 [173-543]	344±106 [154-580]	105.9% (93.8 to 118)
C_{max} (ng/mL)	29.9±9.6 [16.2-53.2]	31.7±12.6 [11.3-51.7]	94.1% (79.6 to 108.6)
C_{24} (ng/mL)	9.6±3.3 [3.73-15.9]	10.0±3.04 [4.31-15.7]	96.2% (83.3 to 109.1)
Week 6			
AUC_{0-24} (ng·hr/mL)	331±86.8 [172-608]	383±171 [216-1193]	86.6% (72.2 to 101.1)
C_{max} (ng/mL)	26.4±7.3 [11.2-41.6]	33±13 [15-74.4]	79.8% (66.8 to 92.9)
C_{24} (ng/mL)	9.6±2.93 [4.81-17.8]	12.1±5.91 [6.07-40.5]	79.6% (63.8 to 95.3)

Mean total daily dose on Day 1: TAC-XL = 0.189 mg/kg; Prograf® = 0.185 mg/kg
Mean total daily dose on Day 14: TAC-XL = 0.203 mg/kg; Prograf® = 0.190 mg/kg
Mean total daily dose at Week 6: TAC-XL = 0.175 mg/kg; Prograf® = 0.164 mg/kg
Source: 1/19/2007 Clinical Pharmacology review of NDA 50-811

Table 24. Dose-normalized PK parameters of tacrolimus in de novo kidney transplant patients for TAC-XL (n=34) and Prograf (n=32) on Day 1, on Day 14 and at Week 6 (Study FG12-01; PK Evaluable Set)

Day 1	TAC-XL	Prograf	Ratio (90% CI) TAC-XL: Prograf
AUC_{0-24} (ng·hr/mL)	122.27	196.34	62.3% (43.7 to 80.8)
ln (AUC_{0-24})	111.57	169.98	65.6% (53.6 to 80.4)
Day 14			
AUC_{0-24} (ng·hr/mL)	192.18	194.96	98.6% (82.5 to 114.6)
ln (AUC_{0-24})	177.80	181.49	98.0% (83.1 to 115.4)
Week 6			
AUC_{0-24} (ng·hr/mL)	215.58	260.71	82.7% (63.5 to 101.9)
ln (AUC_{0-24})	194.75	236.40	82.4% (68.8 to 98.7)

Data: dose-normalized to dose of 0.1 mg/kg
Natural log values transformed back to linear scale for presentation
Source: 1/19/2007 Clinical Pharmacology review of NDA 50-811

2.2.9. Is there a good correlation between tacrolimus *C_{trough} and AUC for TAC-XL and Prograf? Would targeting the same tacrolimus C_{trough} as Prograf in TAC-XL patients result in the same AUC_{0-24} as Prograf?

*Note: C_{trough} also referred to as either C_{24} or C_{min} in the discussion of this question.

In healthy subjects (Study F506-CL-0844), there was a good correlation between tacrolimus C_{24} and AUC_{0-24}; the correlation coefficients were 0.987 and 0.970 for TAC-XL and Prograf, respectively (Figure 10). Because the correlation lines of TAC-XL and Prograf diverge, targeting the same C_{trough} as Prograf in TAC-XL patients results in higher tacrolimus AUC than Prograf. At higher target tacrolimus C_{trough}, AUC in TAC-XL patients could be higher by as much as 20% than Prograf.

In stable kidney transplant patients (Study FG506E-12-02-PK), there was also a good correlation between tacrolimus C_{24} and AUC_{0-24}; the correlation coefficients were 0.88 and 0.82 for TAC-XL and Prograf, respectively

(Figure 11). There was no apparent divergence observed between the AUC_{24}-C_{24} correlation lines of TAC-XL and Prograf in these stable transplant patients who achieved tacrolimus C_{trough} not exceeding 15 ng/mL.

In the de novo kidney transplant patients included in the PK substudy of Phase 3 Study 12-03 (Study 12-03-PK), targeting the same C_{trough} or C_{24} as Prograf in TAC-XL patients resulted in lower tacrolimus AUC_{0-24} compared to Prograf on Day 1. On Day 3, the correlation between AUC_{0-24} and C_{24} was comparable between the TAC-XL group and the Prograf group in kidney transplant patients, so targeting the same C_{24} is expected to result in the same AUC_{0-24} (Figure 12). However, at steady state (i.e., on Day 7 and Day 14), the correlation between AUC_{0-24} and C_{24} was not comparable between the two treatment groups in Study 12-03-PK. The AUC_{0-24} tended to be higher in the TAC-XL group than that in the Prograf group at the same C_{trough}. Regardless of PK profiling day, the correlation coefficients between tacrolimus C_{24} and AUC_{0-24} in Study 12-03-PK were 0.873 and 0.922 for TAC-XL and Prograf, respectively. By contrast, in Phase 2 Study 12-01, the separation of the TAC-XL and Prograf AUC_{0-24} -C_{24} correlation lines was not observed at steady state (on Day 14 and Day 42; Figure 13).

Figure 10. Correlation Between AUC_{0-24} and C_{24} <u>in Healthy Subjects</u> Following Oral Doses of 4 mg TAC-XL Alone and Co-Administered With 400 mg Ketoconazole QD and for Two Doses of 2 mg Prograf® (12 Hours Apart) Alone and Co-Administered With 400 mg Ketoconazole QD (Study F506-CL-0844)

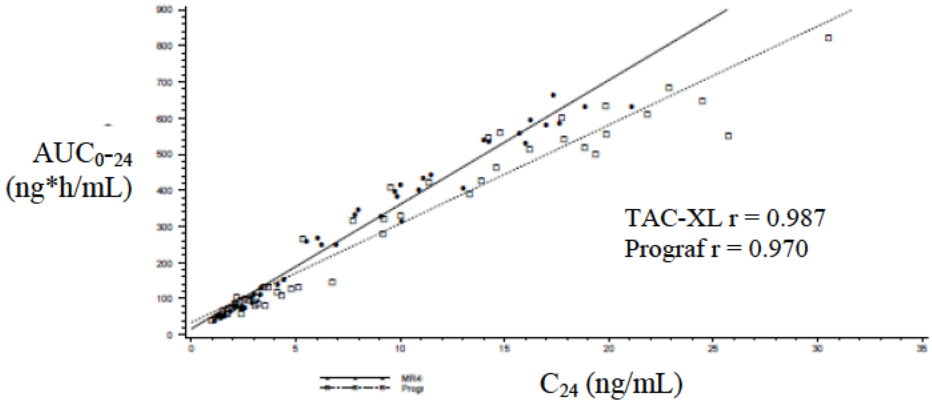


Figure Legend:
TAC-XL (MR4) = solid line with solid symbols
Prograf = dashed line with open symbols

Figure 11. Correlation between AUC_{0-24} and C_{min} <u>in stable kidney transplant patients</u> for tacrolimus administered as both Prograf and TAC-XL (Study FG506E-12-02-PK)

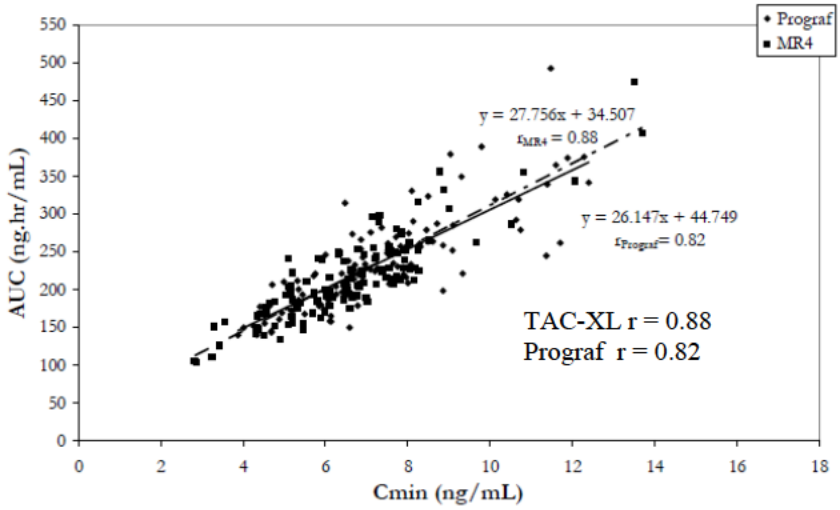
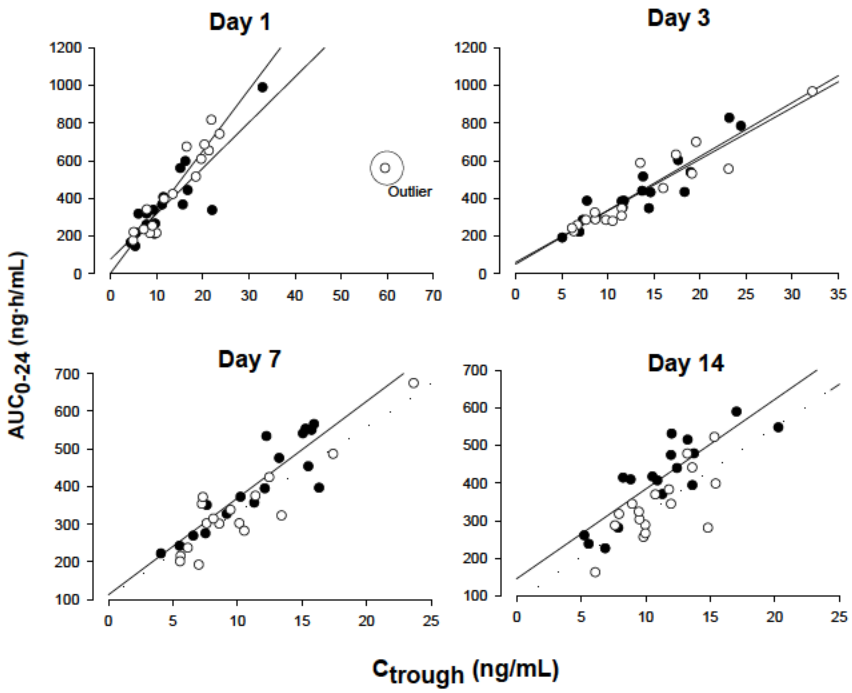
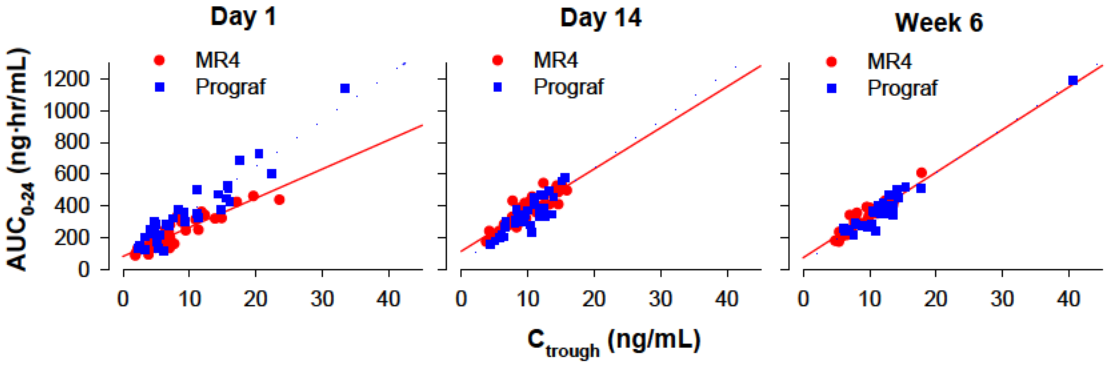


Figure 12. Correlation between AUC_{0-24} and C_{trough} for tacrolimus administered as TAC-XL (N=17; closed circles) and Prograf (N=17; open circles) in de novo kidney transplant patients (Study 12-03-PK)



Source: 3/6/2008 Clinical Pharmacology review of NDA 50-811

Figure 13. Correlation between AUC_{0-24} and C_{trough} (i.e., concentrations at 24 hr after the first dose of the day) for tacrolimus administered as TAC-XL (MR4; N=34) and Prograf® (N=32) in de novo kidney transplant patients (Study FG12-01)

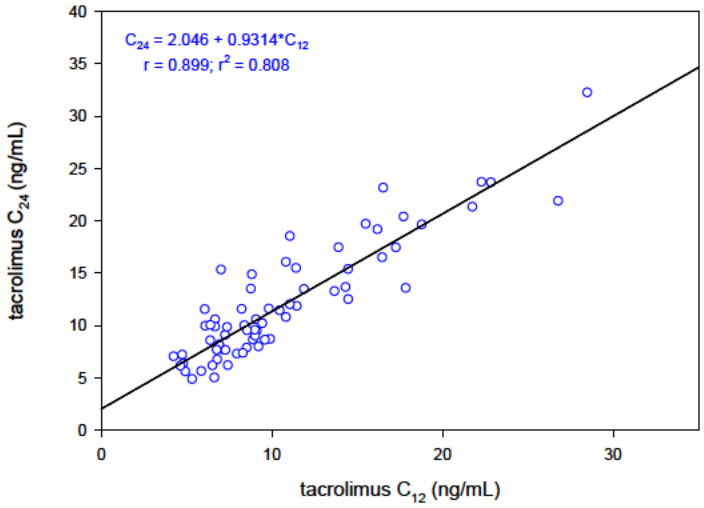


Source: 1/19/2007 Clinical Pharmacology review of NDA 50-811

Correlation between C_{12} and C_{24} of Prograf

Therapeutic drug monitoring of tacrolimus trough levels (C_{trough}) in Study 12-03 was accomplished using C_{12} for Prograf and C_{24} for TAC-XL. Figure 14 depicts the linear relationship between C_{12} and C_{24} of the Prograf patients included in the PK substudy (Study 12-03-PK). Based on the satisfactory correlation coefficient (r = 0.899) and the slope of the line (0.93), the use of C_{24} for the comparison of tacrolimus trough concentrations between TAC-XL and Prograf in the PK studies conducted to support this NDA is considered reasonable.

Figure 14. Correlation between C_{12} and C_{24} of Prograf in De Novo Kidney Transplant Patients (Study 12-03-PK)



2.2.10. For the de novo kidney transplant patients who participated in the PK substudy of Phase 3 Study 12-03, were the therapeutic outcomes (i.e., efficacy and safety) comparable between TAC-XL and Prograf? Was there any imbalance in baseline risk factors between the two treatment groups?

In the PK substudy of Phase 3 Study 12-03, the 24-hour tacrolimus whole blood concentration–time profiles were investigated in a subset of de novo kidney transplant patients (14 TAC-XL + 12 Prograf) with complete PK profiles on Days 1, 3, 7 and 14 (±3 days) after kidney transplantation. The results of this PK substudy showed that on Day 1, the systemic tacrolimus exposures, AUC_{0-24} and C_{trough} were lower by approximately 17% and 12%, respectively, for TAC-XL than for Prograf at comparable mean daily doses. On Day 14 (steady state), the AUC_{0-24} for TAC-XL was 21% higher than that for Prograf at comparable C_{trough} and mean daily doses.

Efficacy (12-03-PK)

The approximately 15-20% lower mean dose-normalized tacrolimus AUC_{0-24} and C_{trough} achieved with TAC-XL than Prograf on Day 1 did not appear to significa
ntly impact the 1-year therapeutic outcome for the patients who participated in the PK substudy (see Figure 15A for the PK subset; compare to Figure 15B, Kaplan-Meier plot for all ITT patients in the main trial). In the PK subset, the freedom from locally assessed biopsy proven acute rejection or BPAR (the primary endpoint) was comparable between TAC-XL and Prograf up to approximately day 100; the acute rejection episodes in the three cases (2 TAC-XL;1 Prograf) occurred on Days 6,7, and 99. At day 364, the proportion of TAC-XL patients free of BPAR (0.85) was not statistically significantly different from that of Prograf (0.92; log rank and Wilcoxon p values >0.65). It is important to note that as observed in the main trial, there was a higher percentage of TAC-XL patients than Prograf patients in the PK subset with HLA DR mismatches [7/13 (54%) versus 4/7 (36%)], a prognostic factor for acute rejection in kidney transplant patients. In fact, both BPAR cases in the TAC-XL arm had baseline HLA DR mismatch whereas the lone case in the Prograf arm did not. None of the patients included in the reviewer's PK analysis population died, experienced graft loss, or were lost to follow up during the 1-year study period.

Figure 15A. Kaplan-Meier plot of time to LBPAR in de novo kidney transplant patients (Study 12-03, PK subset)

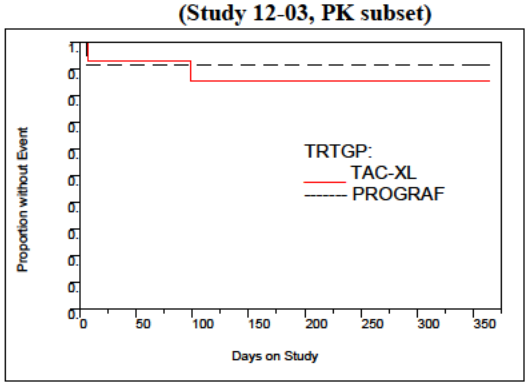
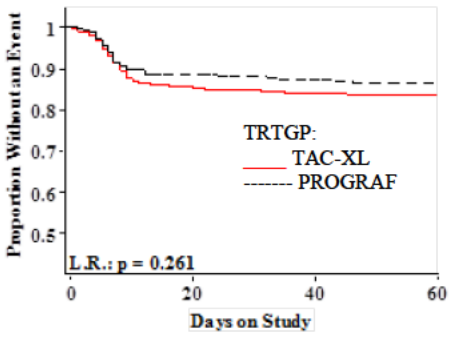


Figure 15B. Kaplan-Meier plot of time to LBPAR in de novo kidney transplant patients (Study 12-03, ITT population)



Source: Figure 3.3.2 of FDA Statistical Review (Joy Mele, PhD.)

Safety (12-03-PK)

The approximately 20% higher AUC at steady state achieved with TAC-XL at comparable mean daily doses and C_{trough} as Prograf did not appear to significantly influence the overall safety of TAC-XL compared to Prograf in this subset of patients. There was a comparable proportion of TAC-XL and Prograf patients with adverse events (93% vs. 92 %) and serious adverse events (50% vs. 50%), while the incidence of serious infections (29% vs. 17%) and malignancies (7% vs. 0%) were numerically higher in the TAC-XL group. (Note that in the main trial of Study 12-03, there was no statistically significant difference between TAC-XL and Prograf in terms of the proportion of patients with serious infections and infestations (24% vs. 19%) and malignancies (1.8% vs. 2.4%). None of the patients in the PK subset died. Likewise, in this subpopulation there were no cases of BK virus infections, sepsis, gastroenteritis, bacterial pyelonephritis and hemorrhages NEC (considered adverse events of special interest based on the safety findings in the 12-03 main trial). Of note, the lone TAC-XL patient (Patient H3826) in the PK subset who was reported to have experienced CMV infections (judged of possible relationship to study medication) from days 71-105 and days 127-240 had tacrolimus trough concentrations within protocol specified targets and not exceeding 15 ng/mL several weeks preceeding the adverse event, suggesting the potential lack of a temporal association between CMV infection and high tacrolimus exposures in this particular patient.

2.2.11. For the de novo kidney transplant patients who participated in the PK substudy of Phase 3 Study 12-03, is there a potential relationship between biopsy proven acute rejection (BPAR) and tacrolimus AUC_{0-24}, C_{trough} or C_{max} on Days 1, 3, 7, and 14?

The reviewer conducted an exploratory early exposure-response analysis to determine the relationship of tacrolimus AUC_{0-24h} and C_{trough} with efficacy failure, regardless of treatment assignment. Only those patients (14 TAC-XL and 12 Prograf) with a complete set of PK parameters on Days 1, 3, 7, and 14 were included in the analysis. None of these 26 tacrolimus-treated patients died, experienced graft loss or were lost to follow up; 2 TAC-XL patients (H3826, H8903) and 1 Prograf patient (H7103) experienced biopsy proven acute rejection on Days 99, 7, and 6, respectively. Of the 26 patients, Patient H8903 had the lowest time-averaged tacrolimus C_{trough} and the lowest time-averaged AUC_{0-24} over the first 7 days of the study. Table 25 compares the patients with and without acute rejection in terms of the mean ± SD and the median (10-90th percentile) tacrolimus C_{trough} and AUC_{0-24} by PK profiling day. The mean tacrolimus C_{trough} and AUC_{0-24} were consistently lower (on all study days) for the 3 patients with acute rejection than the 26 patients who did not experience acute rejection during the first year of the trial. With the exception of Day 1, the median tacrolimus C_{trough} and AUC_{0-24} were also lower for the patients who experienced acute rejection. In the three BPAR cases, the mean Cmax was numerically lower on

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Days 1, 3, 7 (but not Day 14); only the median Cmax was lower in the BPAR cases compared to those patients who did not experience BPAR, suggesting that Cmax is potentially a weaker tacrolimus exposure index of efficacy failure (i.e., BPAR). Based on the reviewer's logistic regression analysis, any observed trend of a higher probability of acute rejection with lower tacrolimus C_{trough} or AUC_{0-24} in these patients was not statistically significant (ANOVA p value >0.17).

The very low incidence of acute rejections (total n=3) in this subset of patients precludes a meaningful exposure-efficacy analysis by treatment group.

Table 25.

Tacrolimus AUC_{0-24}, C_{trough}, and C_{max} of de novo kidney transplant patients on PK profiling days in PK substudy, by acute-rejection status, regardless of treatment assignment [Mean ± SD; Median (10-90th percentile)]

Acute rejection status		C_{trough}, C_{24h}				AUC_{0-24}			
	n	Day 1	Day 3	Day 7	Day 14	Day 1	Day 3	Day 7	Day 14
YES	3*	9 ± 4.6 9.2 (4 – 13)	9.1 ± 2.5 8.7 (7 -12)	8.4 ± 4.2 6.6 (6 – 13)	10 ± 6.2 7.6 (5-17)	309 ± 132 339 (165 -423)	299 ± 83 288 (221-387)	316 ± 143 270 (201 –476)	380 ± 183 288 (261 –590)
NO	23	13.8 ± 11.5 9.6 (5 – 23)	12.5 ± 5.4 11.5 (6 - 22)	10.7 ± 3.8 10.1 (6 - 16)	11.8 ± 3.1 11.8 (8 - 15)	369 ± 183 319 (191 –685)	391 ± 156 347 (231 – 643)	365 ± 109 351 (224 – 547)	391 ± 92 399 (267 – 528)

Acute rejection status		C_{max}			
	n	Day 1	Day 3	Day 7	Day 14
YES	3*	22.7 ± 3.2 24.6 (19 - 25)	24.2 ± 5.3 27.2 (17- 28)	26.7 ± 5 27.6 (21- 32)	36.5 ± 14.7 36.4 (20 - 53)
NO	23	27 ± 16.5 22 (10 – 52)	29.1 ± 14.3 25.1 (15 –51)	30.4 ± 9.8 31.3 (18 –49)	30 ± 9.8 31.3 (18 – 49)

*Day of BPAR Event (n=3 patients): (Days 99, 6, 7)

2.2.12. For the de novo kidney transplant patients in the main trials, what are the characteristics of the exposure-response relationships (dose-response, concentration-response) for <u>efficacy</u>? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

Based on the assessment of the Pharmacometrics reviewer, time-averaged mean tacrolimus trough concentration (TAM, as used in the sponsor's analyses) is not an appropriate exposure measure for exploring the relationship between tacrolimus trough concentrations and efficacy (i.e., acute rejection), particularly because by study design, target tacrolimus trough concentration ranges decrease with time post-transplant. Specifically, average TAM is expected to be higher in patients who discontinued TAC-XL or Prograf therapy due to acute rejection, an event occurring mostly during the early post-transplant period. Furthermore, the lack of the actual time of sampling whole blood tacrolimus concentrations and the actual time of dosing for Study 12-03 precluded the development by the Pharmacometrics reviewer of a Population PK model necessary to estimate daily tacrolimus concentrations. Thus, given the therapeutic drug monitoring (TDM) or concentration-controlled design of Study 12-03 and the lack of reliable dosing times and sampling times to derive the exposures that can be used in a time-to-event analysis with time-dependent exposure, it was not possible to assess the exposure-response relationship

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for acute rejections because of the time-dependent nature of the exposure. See also Appendix 4.3 for the Pharmacometrics review.

See also Section 2.2.14 (Figure 18).

2.2.13. For the de novo kidney transplant patients in the main trials, what are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

Cytomegalovirus infections and bacterial pyelonephritis in Study 12-03:
Based on the analysis of the Pharmacometrics reviewer, there were no noticeable differences in mean concentrations of tacrolimus between patients with adverse events and patients without adverse events for cytomegalovirus infection and bacterial pyelonephritis (Figures 16 and 17.) Given the small number of patients with the relevant safety events and the TDM design, this observation should be interpreted with caution. See also Appendix 4.3 for the Pharmacometrics review.

Figure 16. Mean tacrolimus trough concentration profiles of de novo kidney transplant patients with and without cytomegalovirus infection following administration of TAC-XL (MR4) once daily or Prograf twice daily in Study 12-03

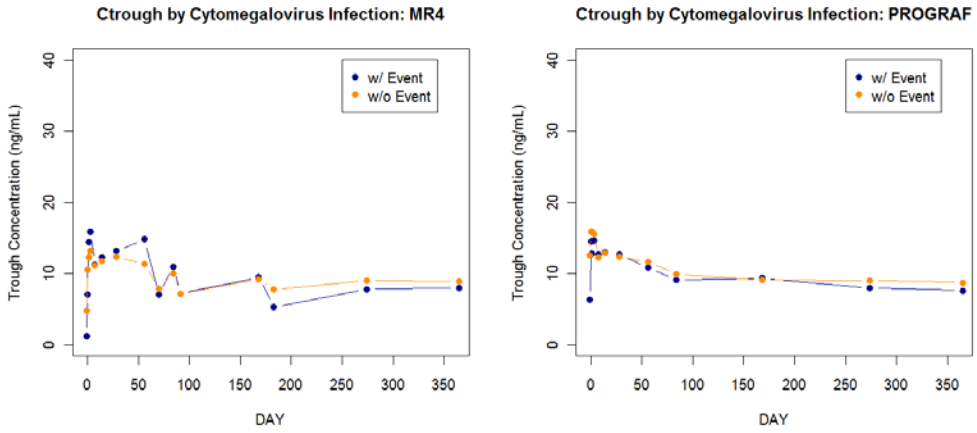
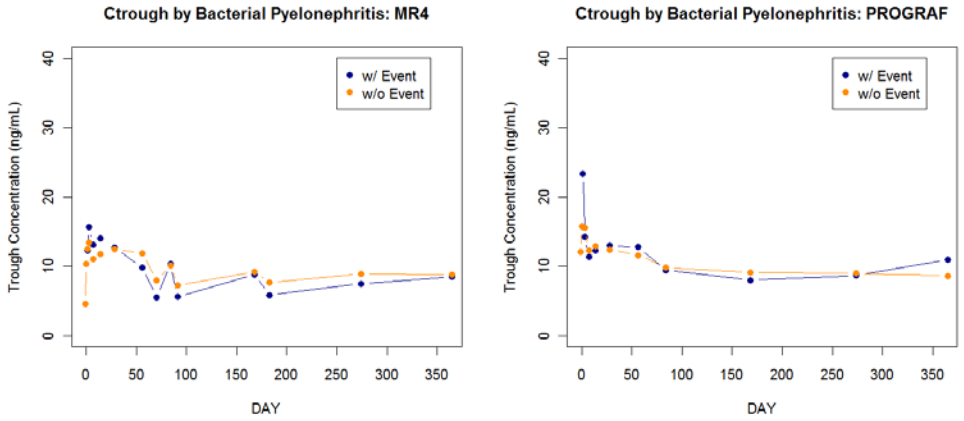


Figure 17. Mean tacrolimus trough concentration profiles of de novo kidney transplant patients with and without bacterial pyelonephritis following administration of TAC-XL (MR4) once daily or Prograf twice daily in Study 12-03



Gastroenteritis:
According to the FDA Medical reviewer (Dr. Marc Cavaille Coll), the rates of tacrolimus associated toxicities (e.g.., tremor, nephrotoxicity, hypertension, diabetes) that are known to be related to systemic (whole blood)

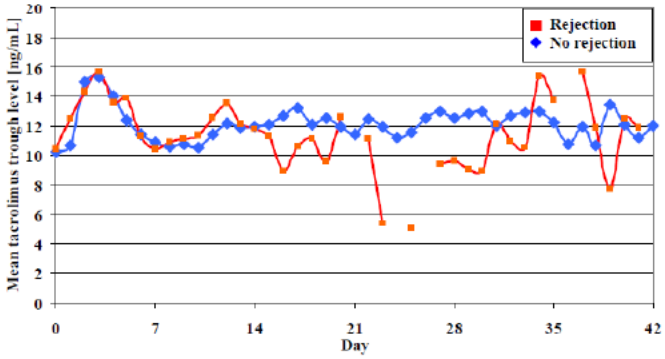
tacrolimus exposures were generally comparable between TAC-XL and Prograf. However, there was a statistically significant increased incidence ($p<0.05$, by Fisher exact test) of gastroenteritis reported as an infection in the TAC-XL arm compared to the Prograf arm in both Studies 158 and 12-03. As would be expected from an adverse event affecting mainly the gastrointestinal tract (the depot for orally administered extended release products like TAC-XL), such phenomenon could not be explained by differences in systemic tacrolimus exposures between the two arms. The higher rate of gastroenteritis in TAC-XL once daily extended release capsules compared to Prograf twice daily immediate release capsules could have been influenced by differences in formulation, dosing frequency, and perhaps the local tacrolimus exposures and the effect of such factors on gut microflora. Ethylcellulose ((b) (4) from the TAC-XL (b) (4)) is often added in oral formulations to enhance drug delivery or targeting to the colon. Based on the reviewer's exploratory exposure-safety analysis, there was no clear and consistent relationship between whole blood tacrolimus trough concentrations and the incidence of gastroenteritis in Study 158 and Study 12-03.

2.2.14. Based on any significant difference in tacrolimus exposures to Prograf, is a different initial dosage and/or drug concentration monitoring strategy from that evaluated in the Phase 3 trials appropriate for TAC-XL?

Initial Tacrolimus Exposure

In the 26 de novo kidney transplant patients included in the PK substudy of Study 12-03, both the arithmetic mean Day 1 tacrolimus AUC_{0-24} and C_{trough} in TAC-XL patients were lower than in Prograf patients, i.e., by approximately 20% and 15%, respectively. In Study 12-03 and Study 158, the median tacrolimus C_{trough} were numerically lower in TAC-XL patients than in Prograf patients during the first 14 days, and comparable thereafter. Based on the sponsor's analysis including all patients in the main trial (Study 12-03, Figure 18), the arithmetic mean tacrolimus C_{trough} were comparable during the first14 days in TAC-XL patients with BPAR and those without BPAR, suggesting that the lower early tacrolimus exposures with TAC-XL did not have a significant impact on the ability of TAC-XL to prevent acute rejections in kidney transplant recipients. Furthermore, that TAC-XL was non-inferior to Prograf in Study 158 in both the Per-Protocol (PP) and the Full Analysis Set (FAS) populations, as well as in Study 12-03 in the PP analysis (and the FAS analysis when adjusted for the higher rate of HLA DR mismatches in the TAC-XL arm) suggests that the lower early tacrolimus exposures in de novo kidney transplant patients did not have a statistically significant impact on the efficacy of TAC-XL. These lower tacrolimus trough concentrations during the first 14 days were likely compensated by the immunosuppressant effects of induction therapy consisting of high doses of corticosteroids administered at immediate post-transplant days (in Studies 12-03 and 158) and antibody induction (basiliximab in Study 158).

Figure 18. Whole blood tacrolimus trough concentration – time profiles of TAC-XL de novo kidney transplant patients with and without local biopsy-confirmed acute rejection at 24 weeks in (Study 12-03)



Source: Figure 4. Study 12-03 Clinical Study Report; Per Protocol Set

Note that based on the findings of the Phase 3b Study PMR-EC-1210 (OSAKA) which evaluated the 6-month efficacy and safety of TAC-XL with starting post-operative dose of 0.3 mg/kg, in addition to TAC-XL and Prograf with starting post-operative doses of 0.2 mg/kg, there was no additional therapeutic benefit to increasing the starting pre-operative dose of TAC-XL to 0.15 mg/kg on Day 0 and the starting post-operative dose to 0.3 mg/kg on Day 1.

Steady State Tacrolimus Exposure

In Study 12-03-PK, the tacrolimus AUC_{0-24} on Day 14 was 20% higher in TAC-XL patients than in Prograf patients, even though the tacrolimus C_{trough} were comparable between the two groups. Such phenomenon could be explained (at least in part) by the separation observed between the AUC_{0-24} -to-C_{24} correlation lines of TAC-XL and Prograf on Day 14 (Figure 12). Such separation in the correlation lines was not observed on Day 14 in the de novo transplant patients who participated in the Phase 2 Study 12-01 which employed (in addition to trough level monitoring) "limited" AUC monitoring on days 1, 3, 7, 11, 14 (and on other days, as clinically indicated) using immunoassays as an additional guide for adjustment of tacrolimus doses. The protocol specified targets were $AUC_{12} \geq 200$ ng*h/mL for Prograf and $AUC_{24} \geq 400$ ng*h/mL for TAC-XL. The time points for limited AUC monitoring include predose (0), 2, 4, 8, 12 h for Prograf, plus 24 h for TAC-XL. However, AUC monitoring (in addition to trough level monitoring) is not being recommended for use in TAC-XL patients at this time due to the following reasons: (1) AUC monitoring as implemented in Phase 2 Study 12-01 did not prove to be effective in determining a dose for TAC-XL that would result in comparable AUC and C_{trough} as Prograf at steady state (i.e., on Day 42), although it proved to be an effective technique in minimizing the disparity of the AUC-C_{trough} correlation lines of TAC-XL and Prograf, (2) The AUC monitoring technique used in the Phase 2 trial was not implemented in any of the Phase 3 trials. (3) In the Phase 3 trials, the same tacrolimus C_{trough} ranges were targeted for both the TAC-XL and Prograf patients, producing acceptable efficacy and safety results in all three Phase 3 trials. As per the Statistical review of Dr. Joy Mele, TAC-XL once daily demonstrated non-inferiority to Prograf twice daily in all three trials based on efficacy failure (the composite of locally biopsied confirmed acute rejection (LBPAR), death, graft loss or loss-to-follow-up. The treatment differences in efficacy failure events were comparable among the three trials, with no significant treatment by subgroup (gender, race, age, geographic region) differences observed. None of the tacrolimus-associated adverse events of interest showed a consistent trend in all three Phase 3 clinical trials. (4) AUC monitoring would involve additional costs, burden, time and patient inconvenience.

2.2.15. Based on the pharmacokinetic and the exposure-response findings, as well as the overall efficacy and safety findings in the Phase 3 clinical trials, what is (are) the recommended dosing regimen(s) of TAC-XL for the prophylaxis of acute rejection in de novo and stable kidney transplant patients?

A. TAC-XL Dose in De Novo Adult Kidney Transplant Patients

1. For use with MMF and corticosteroid taper :

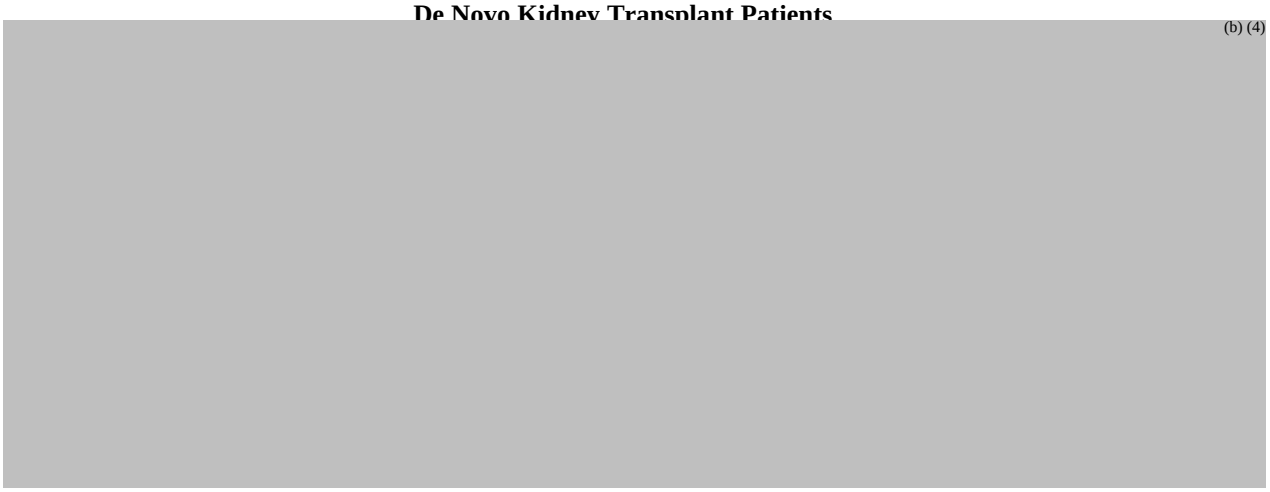
As evaluated in Phase 3 Study 12-03: One *pre-operative* oral dose of TAC-XL (0.1 mg/kg) should be given within 12 hours prior to reperfusion. The initial *post-operative* TAC-XL daily dose (0.2 mg/kg/day) should be administered in the morning at least 4 hours after the pre-operative dose but not more than 12 hours after reperfusion. Subsequent TAC-XL doses should be adjusted based on clinical signs of efficacy and toxicity, as well as to achieve tacrolimus C_{trough} similar to the observed ranges in Table 26. Note that although the calculated mean dose for both tacrolimus formulations on Day 0 (day of transplant) was 0.15 mg/kg, the median value was reflective of the protocol specified pre-operative doses of TAC-XL and Prograf (0.1 mg/kg). The calculated mean initial post-operative dose of TAC-XL and Prograf on Day 1 was 0.2 mg/kg. Thus, it is acceptable for the TAC-XL labeling to recommend initial pre-operative and post-operative doses of TAC-XL (when used with MMF and steroid taper) as specified in the protocol of Study 12-03.

2. For use with IL-2 receptor antagonist (e.g., basiliximab) for induction, corticosteroid taper, MMF:

As evaluated in Phase 3 Study 158: The initial oral TAC-XL dose [0.15 mg/kg/day (observed median value)] should be given in the morning (AM) prior to or within the first 48 hours after completion of transplant. Subsequent TAC-XL doses should be adjusted based on clinical signs of efficacy and toxicity, as well as to achieve tacrolimus C_{trough} similar to the observed ranges in Table 26. Note that the actual median initial dose of TAC-XL in the trial was 0.15 mg/kg (versus 0.1 mg/kg for Prograf). Thus, it is acceptable for the TAC-XL labeling to recommend the lower limit of the protocol-specified initial dose range of TAC-XL (when used with antibody induction, MMF and steroid taper) in Study 158.

Table 26.
Recommended Initial Oral Doses of TAC-XL and Observed Tacrolimus Trough Concentrations in De Novo Kidney Transplant Patients

(b) (4)



In the CLINICAL STUDIES section of the approved TAC-XL US Package Insert, a description of the protocol specified target C_{trough} ranges and the schedules of the concomitant immunosuppressive drugs (i.e., MMF, corticosteroids, basiliximab) used with TAC-XL in Study 12-03 and Study 158 could be included. Study 12-03:The target C_{trough} ranges for both TAC-XL and Prograf were 10-15 ng/mL on Days 1 through 28, 5-15 ng/mL on Days 29 through 168 and 5-10 ng/mL thereafter. Study 158: The target C_{trough} ranges for both TAC-XL and Prograf were 7-16 ng/mL for Days 0 through 90, and 5-15 ng/mL thereafter. See Sections 2.2.5 to 2.2.7 for the schedules of MMF, corticosteroids and basiliximab induction, as defined in the study protocols.

B. TAC-XL Dose in Stable Adult Kidney Transplant Patients (≥ 6 months post-transplant) Converted from Tacrolimus Immediate Release Formulation

Reviewer's Note: Based on the assessment of the FDA Medical and Statistical reviewers the Phase 2 PK studies conducted in stable kidney transplant patients were not adequate and well controlled clinical trials. As there will be no separate indication granted for conversion of kidney transplant patients to TAC-XL, the package insert will not describe a dosing regimen for this particular patient population. However, the PK parameters of tacrolimus in stable kidney transplant patients will be summarized in *Section 12.3 Pharmacokinetics*.

2.3. Intrinsic Factors

2.3.1. What is the effect of administering TAC-XL in the morning vs. evening?

In the clinical pharmacology study (Study 02-0-148) conducted to test the diurnal effect of absorption in healthy subjects, for both TAC-XL (MR4) and Prograf, the rate of absorption relative to the morning dose was slower and the extent of absorption was reduced following the evening dose (Table 27). A diurnal effect on the absorption of tacrolimus was observed. For TAC-XL, evening dosing reduced $AUC_{0\text{-}inf}$ by 35% relative to morning dosing. In accordance with the manner TAC-XL was administered in the Phase 3 trials, the recommended daily dose of TAC-XL should be given once daily in the morning (AM).

Table 27. Summary of PK parameters for TAC-XL (MR4) PM versus AM dosing in healthy subjects

Pharmacokinetic Parameter	Analysis of MR4 PM dose relative to MR4 AM dose			
	Test Mean† (PM dose)	Reference Mean† (AM dose)	Ratio‡ of Test Mean/ Reference Mean (%)	90% Confidence Interval§ (%)
C_{max} (ng/mL)	6.41	7.29	87.9	(60.0, 116)
lnC_{max}†† (ng/mL)	6.19	6.93	89.3	(77.5, 103)
$AUC_{0\text{-}t}$ (ng•hr/mL)	106	162	65.1	(48.5, 81.6)
$lnAUC_{0\text{-}t}$†† (ng•hr/mL)	96.7	153	63.3	(55.5, 72.1)
$AUC_{0\text{-}inf}$ (ng•hr/mL)	116	178	65.2	(48.8, 81.6)
$lnAUC_{0\text{-}inf}$†† (ng•hr/mL)	106	167	63.6	(55.8, 72.3)

Subject population base: Full analysis set; subjects randomized and who received at least one dose of study drug (for Treatment A, n = 24 and for Treatment B, n = 23).
C_{max}: Maximum observed concentration.
$AUC_{0\text{-}t}$: Area under the concentration time curve calculated from time 0 (predose) to the time of last measurable concentration (t).
$AUC_{0\text{-}inf}$: Area under the concentration time curve calculated from time 0 (predose) to infinity by extrapolation.
A validated LC/MS/MS method was used to determine whole blood tacrolimus concentrations. Whole blood tacrolimus concentrations below the LLOQ (0.1 ng/mL) were reported as <0.100ng/mL.
Treatment A: MR4 AM dose (MR4 reference treatment).
Treatment B: MR4 PM dose (MR4 test treatment).
†The least square means were calculated from an ANOVA model.
‡The ratio of pharmacokinetic parameter means for untransformed and natural log-transformed parameters were converted to percents.
§The 90% confidence interval for the ratio of parameter means of untransformed and natural log-transformed parameters. Bioequivalence was concluded if both 90% confidence intervals were contained within the range of 80% to 125%.
††The anti-logs of the natural log-transformed pharmacokinetic parameters are presented.
MR4=TAC-XL
Source: 1/19/2007 Clinical Pharmacology review of NDA 50-811, Table 25

2.3.2. Is the sponsor's proposal for management of a missed dose of TAC-XL appropriate?

Yes, based on the reviewer's simulation the sponsor's proposal of administering a TAC-XL dose in the evening (PM) preferably within 14 hours of missing the morning (AM) dose is not predicted to result in tacrolimus trough concentrations that are below the desirable lower limit (4 ng/mL) and/or above the desirable upper limit (20 ng/mL) of the target C_{trough} range (Figure 19, Table 28). If the 14 hour window is missed, the patient should wait to take the next regular AM dose of TAC-XL at which time the tacrolimus C_{trough} is predicted to be slightly below 4 ng/mL momentarily. The patient should not double the dose so C_{max} does not exceed 20 ng/mL. Note that in

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healthy subjects, PM dosing of TAC-XL resulted in a 35% lower tacrolimus AUC than that following AM dosing of TAC-XL as a result of the effect of diurnal variation on tacrolimus pharmacokinetics (Study 20-148), so doubling the dose the following morning is expected to result in a peak tacrolimus concentration that is significantly higher than that predicted for make-up doses taken in the evening. Note also that this simulation was done in stable kidney transplant patients who usually receive tacrolimus doses not exceeding 5 mg/day; whole blood tacrolimus concentrations are expected to be higher (by 2- to 3-fold) in de novo kidney transplant recipients because higher tacrolimus doses are provided to achieve higher target tacrolimus concentrations during the early post-transplant period.

Figure 19. Predicted whole blood tacrolimus concentration-time profiles for various scenarios to manage a missed AM dose of TAC-XL

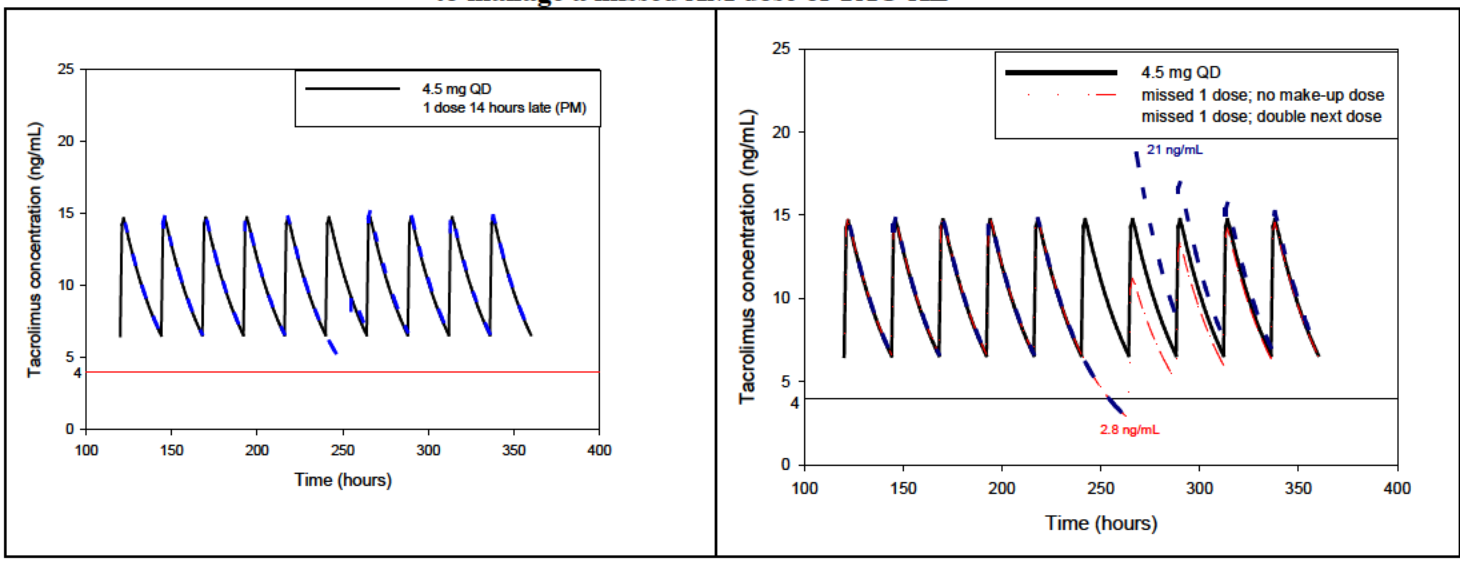


Table 28. Predicted tacrolimus parameters for various scenarios to manage a missed AM dose of TAC-XL

Simulation of 4.5 mg QD TAC-XL in stable kidney transplant patients (no missed doses): predicted Cmax,ss = 14.7 ng/mL predicted Cmin,ss = 6.6 ng/mL*	Predicted Time (h) tacrolimus concentrations are below 4 ng/mL after missed AM dose	Predicted Time (h) tacrolimus concentrations are above 20 ng/mL after next AM dose	Predicted Cmin (ng/mL) after missing AM dose (before next regular AM dose)	Predicted Cmax (ng/mL) after taking next regular AM dose
Missed AM dose (no make-up)	11	0	2.8	11.2
Missed 1 AM dose; double next regular AM dose	11	0	2.8	21.0
Take dose 4 h late (AM)	0	0	5.7	15.4
Take dose 14 h late (PM)	0	0	6.6	15.1
Take dose 16 h late (PM)	3	0	6.4	15.4

***compare to PK parameters obtained in Study 20-131: TAC-XL observed mean Cmax,ss =13.9 ng/mL; Cmin,ss = 6.1 ng/mL**

2.3.3. Do any specific populations of kidney transplant patients require a different TAC-XL starting dose and/or a different dosage adjustment strategy, as observed in Phase 3 clinical trials?

African Americans

In Study 158, approximately 20% were African Americans (Blacks); 75% were Caucasians (Whites). To achieve comparable mean whole blood tacrolimus trough concentrations, African American patients in Study 158 starting on day 14 for TAC-XL and starting on day 21 for Prograf, received mean tacrolimus daily doses that were on average higher by 30%, and 55%, respectively, than their Caucasian counterparts. Based on this observation, the TAC-XL labeling should state (as in Prograf labeling) that African American patients may require higher TAC-XL doses. In Study 12-03, there were not enough African Americans (< 6% of the patient population) to allow for a meaningful comparative analysis of tacrolimus exposures based on race.

In Study 158: The mean ± SD daily tacrolimus doses for the four treatment/race subgroups in Study 158 are presented in Figure 20 and Table 29. The mean ± SD whole blood tacrolimus trough concentrations in these patients are also presented in Figure 20. The mean starting/initial tacrolimus doses (i.e., until day 3) were not significantly different between African Americans and Caucasians for both the TAC-XL and Prograf groups to warrant a recommendation of different initial TAC-XL doses based on race. After day 3, African Americans received consistently higher TAC-XL and Prograf doses than Caucasians. These observations are consistent with the information in the Prograf® US Package Insert regarding the potential requirement for higher tacrolimus oral doses in African-American than Caucasian and Hispanic-American patients.

Figure 20. Mean ± SD Daily Tacrolimus Dose (mg/kg/day) and Tacrolimus Trough Concentrations in De Novo Kidney Transplant Patients in Study 158, by treatment/race

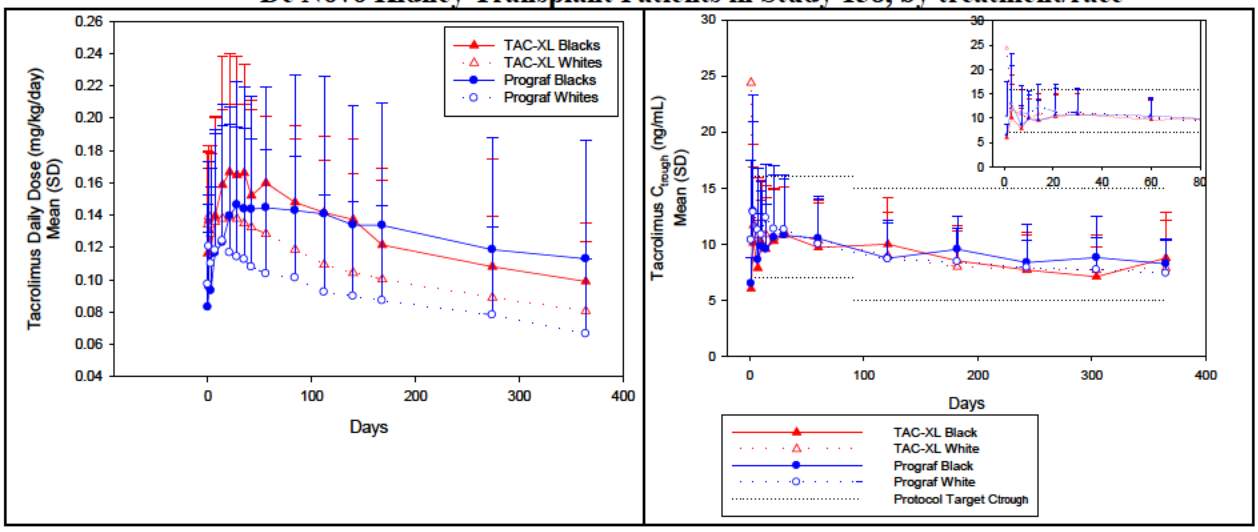


Table 29. Mean ± SD Daily Tacrolimus Dose (mg/kg/day) in De Novo Kidney Transplant Patients in Study 158, by treatment/race

DAYS	n	TAC-XL Blacks	n	TAC-XL Whites	n	PROGRAF Blacks	n	PROGRAF Whites
0	6	0.117 ± 0.052	29	0.134 ± 0.045	20	0.083 ± 0.047	49	0.097 ± 0.050
1	21	0.137 ± 0.042	108	0.139 ± 0.043	40	0.096 ± 0.057	110	0.121 ± 0.052
3	32	0.118 ± 0.060	144	0.129 ± 0.055	49	0.093 ± 0.064	145	0.110 ± 0.059
7	32	0.140 ± 0.062	144	0.136 ± 0.065	47	0.117 ± 0.074	145	0.118 ± 0.075
14	31	0.159 ± 0.079	141	0.138 ± 0.068	46	0.123 ± 0.072	144	0.124 ± 0.084
21	31	0.167 ± 0.073	141	0.139 ± 0.070	46	0.139 ± 0.068	143	0.117 ± 0.079
28	29	0.165 ± 0.074	139	0.138 ± 0.071	46	0.146 ± 0.076	143	0.114 ± 0.081
35	29	0.166 ± 0.068	138	0.135 ± 0.074	46	0.144 ± 0.075	142	0.113 ± 0.081
42	26	0.152 ± 0.059	138	0.133 ± 0.073	46	0.144 ± 0.070	142	0.108 ± 0.079
56	26	0.160 ± 0.059	138	0.129 ± 0.073	46	0.145 ± 0.075	141	0.104 ± 0.077
84	25	0.148 ± 0.048	138	0.119 ± 0.068	44	0.143 ± 0.084	136	0.101 ± 0.075
112	25	0.142 ± 0.047	136	0.109 ± 0.065	44	0.141 ± 0.085	136	0.092 ± 0.060
140	25	0.137 ± 0.050	135	0.104 ± 0.061	44	0.134 ± 0.074	136	0.090 ± 0.059
168	25	0.122 ± 0.047	135	0.100 ± 0.061	43	0.134 ± 0.076	134	0.087 ± 0.059
274	25	0.108 ± 0.067	133	0.089 ± 0.050	43	0.119 ± 0.069	127	0.078 ± 0.054
364	17	0.099 ± 0.036	72	0.081 ± 0.043	23	0.113 ± 0.073	70	0.067 ± 0.046

According to the US Package Insert (USPI) of Prograf® (tacrolimus immediate release oral capsules): In healthy subjects, there were no significant pharmacokinetic differences among the three ethnic groups (10 African-Americans, 12 Latino-Americans, 12 Caucasians) following a 4-hour IV infusion of 0.015 mg/kg. However, after a single oral administration of 5 mg, mean (±SD) tacrolimus C_{max} in African-Americans (23.6±12.1 ng/mL) was significantly lower than in Caucasians (40.2±12.6 ng/mL) ($p<0.01$). Mean $AUC_{0\text{-}inf}$ tended to be lower in African-Americans (203±115 ng·hr/mL) than Caucasians (344±186 ng·hr/mL). The mean (±SD) absolute oral bioavailability (F) in African-Americans (12±4.5%) and Latino-Americans (14±7.4%) was significantly lower than in Caucasians (19±5.8%, $p=0.011$). There was no significant difference in mean terminal $T_{1/2}$ among the three ethnic groups (range from approximately 25 to 30 hours). A retrospective comparison of African-American and Caucasian kidney transplant patients indicated that African-American patients required higher tacrolimus doses to attain similar trough concentrations.

Gender

In both Study 12-03 and Study 158, approximately one-third of the de novo kidney transplant patients were females (Figures 21 and 22). In both the TAC-XL and Prograf groups, comparable mean tacrolimus trough concentrations were achieved in females and males. For both TAC-XL and Prograf, there was no consistent trend and no significant differences observed in terms of the mean tacrolimus total daily doses (in mg) in females versus males.

Figure 21. Mean ± SD Daily Tacrolimus Dose (mg/day) and Tacrolimus Trough Concentrations in De Novo Kidney Transplant Patients in Study 12-03, by treatment/gender

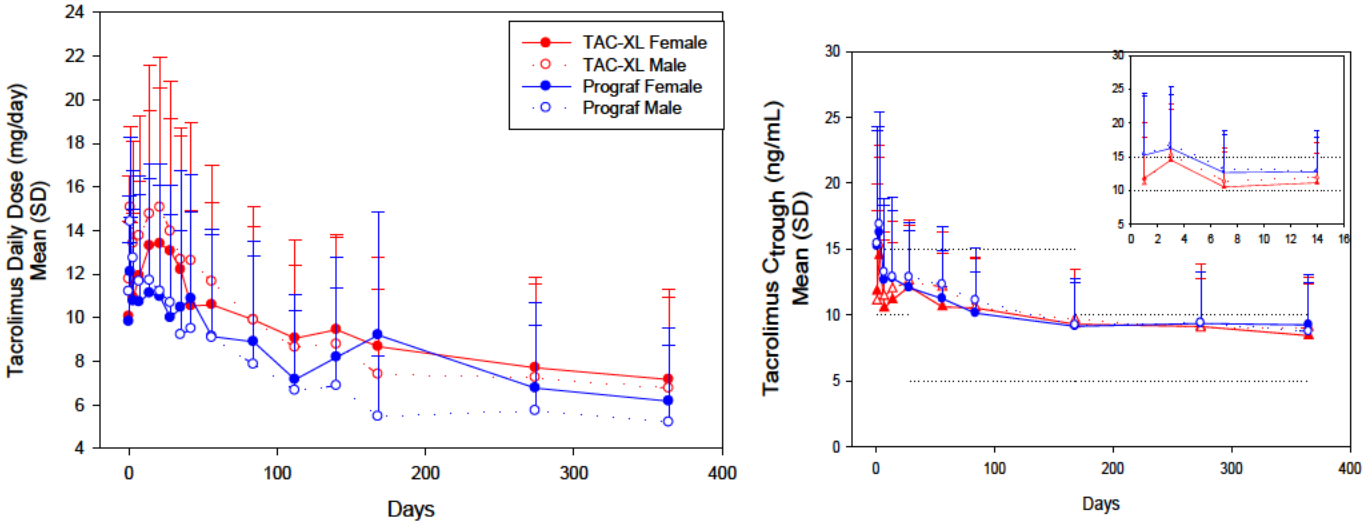
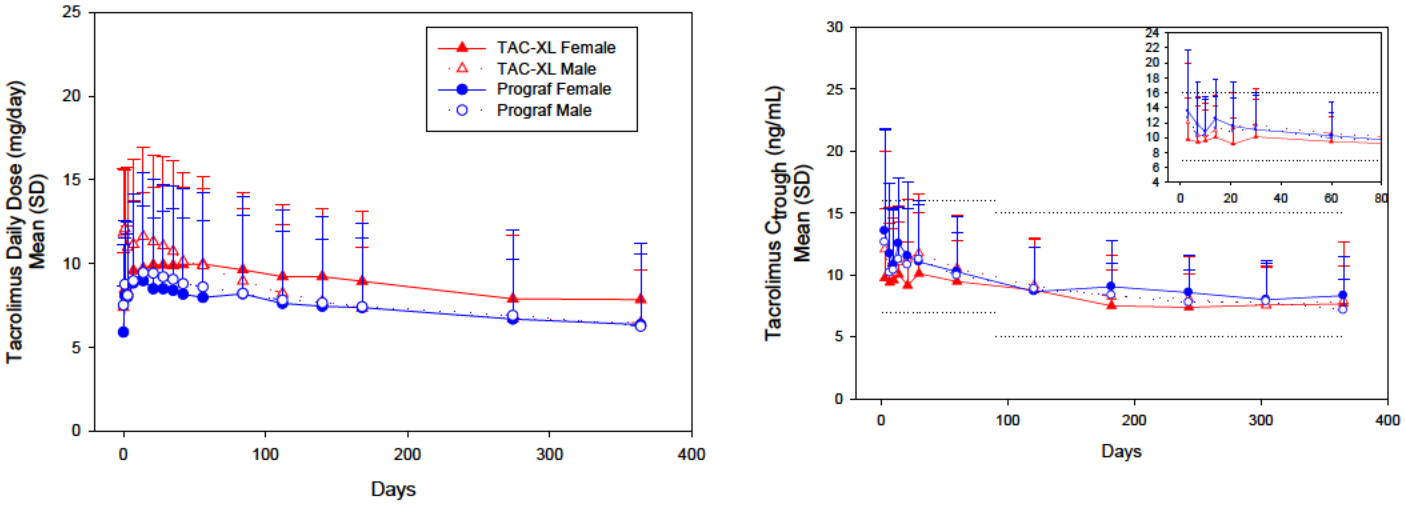


Figure 22. Mean ± SD Daily Tacrolimus Dose (mg/day) and Tacrolimus Trough Concentrations in De Novo Kidney Transplant Patients in Study 158, by treatment/gender



2.3.4. What is the dosage recommendation for patients with renal or hepatic impairment?

Renal Impairment

There was no renal impairment PK study conducted specifically for TAC-XL. As the elimination half-life of tacrolimus was not different between TAC-XL extended release and Prograf immediate release, and the elimination of tacrolimus is not expected to be different between extended release and immediate release formulations of tacrolimus, it is acceptable for TAC-XL to have a dosage recommendation for patients with renal impairment based on the information for PK in renal impairment in the Prograf USPI. The following statement or modification thereof may be suitable for the TAC-XL package insert:

In kidney transplant patients with post-operative oliguria, the initial dose of TAC-XL … may be delayed until renal function shows evidence of recovery.
The pharmacokinetics of tacrolimus in patients with renal impairment was similar to that in healthy subjects with normal renal function. However, due to its potential for nephrotoxicity, frequent monitoring of renal function is recommended; TAC-XL dosage should be reduced if indicated (see Warnings and Precautions, 5.9 Nephrotoxicity).

Hepatic Impairment
There was no hepatic impairment PK study conducted specifically for TAC-XL extended release capsules. As the elimination half-life of tacrolimus was not different between TAC-XL extended release and Prograf immediate release, and the elimination of tacrolimus is not expected to be different between extended release and immediate release formulations of tacrolimus, it is acceptable for TAC-XL to have the same dosage recommendation for patients with hepatic impairment as that for Prograf. The following statement (as excerpted from the Prograf USPI) is suitable for the TAC-XL package insert: *Due to the reduced clearance and prolonged half-life, patients with severe hepatic impairment (Child Pugh ≥ 10) may require lower doses of TAC-XL. Frequent monitoring of blood concentrations is warranted.*

2.3.5. What is the sponsor's proposed research plan for pediatric kidney transplant patients?

The sponsor is requesting a waiver for conducting studies under the Pediatric Research and Equity Act (PREA) in pediatric transplant patients 0 to <5 years old, and a deferral for pediatric patients 5 to <16 years old.
The waiver request for pediatric patients 0 to <5 years was based on the very low numbers of transplant patients in this age category. As per the FDA Pediatric Review Committee (PeRC) recommendation, the waiver request for children <1 year is acceptable but for pediatric patients 1 to <5 years who are usually not able to swallow the intact TAC-XL capsules, the sponsor should develop an age appropriate immediate release formulation, and to conduct a PK study using such formulation in this age group. The sponsor's deferral request for research studies in older pediatric patients (5 to <16 years) based on the pending approval of the TAC-XL extended release capsules for use in adult kidney transplant patients is acceptable. For the 5 to 16 year old pediatric patients, the sponsor is proposing to conduct Study PMR-EC-12-06, a Phase 2 study that will evaluate the PK, long term efficacy and safety of tacrolimus in stable kidney, liver, heart, lung or intestinal transplant patients following 1: 1 :: mg:mg total daily dose conversion from Prograf twice daily to TAC-XL once daily. A total of 24 kidney, 24 liver and 24 other organ transplant recipients will be enrolled (Table 30). The sponsor expects patient enrollment in this trial to be completed in May 2013 and the final study report to be submitted within one year of the last patient out. Only pediatric patients 5 to 16 years who are able to swallow the intact TAC-XL / Prograf capsules will be included. Overall, the sponsor's proposal to conduct Study PMR-EC-12-06 in stable (≥ 6 months post-transplant) pediatric patients rather than in de novo pediatric transplant patients is acceptable because there are early post-transplant patient intrinsic and extrinsic factors that could alter tacrolimus exposures and as such, confound the selection of appropriate doses in the various pediatric age subgroups. These factors include changes in gastrointestinal absorption during the first 1-2 weeks post-surgery, changes in the type and dosage of concomitant immunosuppressive drugs (e.g., corticosteroid taper) and other medications including but not limited to those used for prophylaxis of infections and for the treatment of acute rejections occurring mostly during the first 6 months post-transplant. In addition, the changes in the predefined target tacrolimus trough concentration ranges occurring during the first 6 months post-transplant could also complicate the determination of appropriate doses.

Table 30. Minimum number of patients in Proposed Pediatric Study PMR-EC-12-06

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

*Heart, lung, and intestinal transplantation
Source: Module 1.9.4. 1-9-4-proposed-pediatric-study-request.pdf

2.4. Extrinsic Factors

2.4.1. What is the effect of CYP3A inhibitors and CYP3A inducers on the tacrolimus pharmacokinetics of TAC-XL?

Frequent monitoring of whole blood tacrolimus concentrations and appropriate dosage adjustments are recommended when the concomitant administration of TAC-XL with drugs known to alter tacrolimus elimination are initiated or discontinued.

The sponsor performed the following two drug interaction studies with TAC-XL:
(i). Ketoconazole (strong CYP3A inhibitor)
In a study of 24 healthy male 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. Note that the magnitude of these increases were comparable to that observed when 2 doses of Prograf 12 hours apart were co-administered with ketoconazole for 9 days (8.2-fold and 3.5-fold, respectively).

(ii). Rifampin (strong CYP3A inducer)
In a study of 22 healthy male subjects, co-administration 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. Note that the magnitude of these decreases were comparable to that observed when 2 doses of Prograf 12 hours apart was co-administered with rifampin for 12 days (61% and 24%, respectively).

As both the metabolism/elimination of tacrolimus and the magnitude of metabolism-based drug interaction are not expected to be formulation dependent, the following drugs/dietary agents with metabolism-based interaction potential with tacrolimus (as mentioned in the Prograf package insert) should also be included in *Section 7. Drug Interactions* of the TAC-XL package insert: protease inhibitors (telaprevir, boceprevir, ritonavir), azole antifungal drugs (voriconazole, posaconazole, caspofungin, fluconazole, itraconazole, clotrimazole), calcium channel blockers (verapamil, diltiazem, nifedipine, nicardipine), antibacterials (erythromycin, clarithromycin, troleandomycin, chloramphenicol), grapefruit juice, antimycobacterial (rifadin), anticonvulsants (phenytoin,

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carbamazepine, phenobarbital), St. John's Wort, proton pump inhibitors (lansoprazole, omeprazole) in intermediate or poor CYP2C19 metabolizers, cimetidine, others (amiodarone, bromocriptine, nefazadone, metoclopramide, danazole, ethinyl estradiol, methylprednisolone). Note that for some of these drugs (e.g., caspofungin), the effect on tacrolimus AUC_{0-12} and C_{12} is described so if necessary to describe the detailed study findings in *12.3 Pharmacokinetics* it is appropriate to specify that the drug interaction study was done for tacrolimus immediate release formulation given twice daily (not TAC-XL).

2.4.2. What is the effect of absorption-altering drugs on the pharmacokinetics of tacrolimus following administration of TAC-XL?

Frequent monitoring of whole blood tacrolimus concentrations and appropriate dosage adjustments are recommended when the concomitant administration of TAC-XL with drugs known to alter tacrolimus absorption are initiated or discontinued. There were no drug interaction studies conducted specifically between TAC-XL and drugs that are known to alter gastric pH (e.g., antacids). Co-administration of Prograf with magnesium and/or aluminum hydroxide antacids was shown to increase the tacrolimus whole blood concentrations.

2.4.3. What is the effect of tacrolimus on the PK and/or PD of other drugs that are CYP3A substrates?

There are no clinical drug-drug interaction studies that have been conducted to systematically evaluate the potential of tacrolimus to alter the metabolism of other drugs that are also CYP3A substrates. At the current time, the available literature information does not provide compelling evidence to recommend conducting dedicated drug-drug interaction studies specifically with TAC-XL capsules.

2.4.4. Is the effect of TAC-XL on mycophenolic acid (MPA) exposures different from that of Prograf? cyclosporine?

In Phase 3 Study 158, at comparable mean doses of mycophenolate mofetil (MMF), the mean MPA trough concentrations in de novo kidney transplant patients receiving TAC-XL were comparable to Prograf but higher than Neoral (cyclosporine). Unlike cyclosporine, tacrolimus does not interfere with the enterohepatic recirculation of mycophenolic acid glucuronide (MPAG) to MPA. As recommended in the Prograf US package insert, TAC-XL patients should be monitored for MPA-associated adverse events; the dose of concomitantly administered mycophenolic acid products should be reduced, if needed.

2.5. General Biopharmaceutics

2.5.1. What is the effect of food on the bioavailability of TAC-XL and what dosing recommendations should be made regarding administration in relation to meals? In the primary Phase 3 clinical trial(s), when was TAC-XL administered relative to meals?

The presence of food affected the absorption of tacrolimus following administration of TAC-XL; the rate and extent of absorption is greatest under fasted conditions. In 24 healthy subjects, administration of TAC-XL immediately following a high fat meal (150 protein calories, 250 carbohydrate calories, and 500 to 600 fat calories) reduced C_{max}, AUC_{0-t}, and AUC_{0-inf} 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 (Study 01-0-123).

The timing of the meal also affected tacrolimus bioavailability. When TAC-XL was administered immediately after consumption of high-fat breakfast, tacrolimus AUC_{0-inf} was decreased approximately 25% relative to the fasted state. When TAC-XL was administered 1.5 hours after consumption of high-fat breakfast, tacrolimus

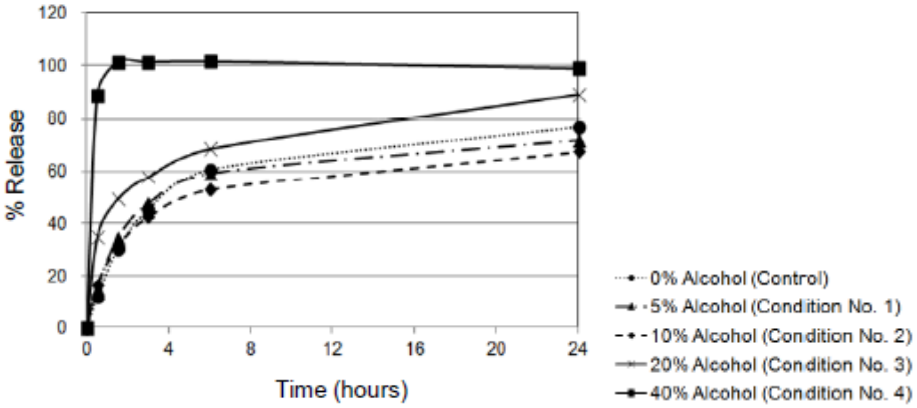
exposure was decreased approximately 35%. Administration of TAC-XL 1 hour prior to a high-fat breakfast reduced tacrolimus exposure by 10% (Study 02-0-153).

Based on the protocol of Phase 3 Study 12-03, the TAC-XL and Prograf doses were to be administered on an empty stomach or at least one hour before or 2-3 hours after a meal. For Study 158, the protocol did not specify the timing of TAC-XL dosing (and the Patient Case Report Forms did not capture the TAC-XL dosing time) relative to meals. Thus, to achieve maximal drug absorption, it is ideal that TAC-XL be taken on an empty stomach with fluid (preferably water) at least 1 hour before or at least 2-3 hours after a meal.

2.5.2. What is the effect of alcohol on the bioavailability of TAC-XL and what labeling recommendations should be made regarding administration in relation to alcohol consumption?

In *in vitro* dissolution studies, "dose-dumping" was observed with tacrolimus extended release (TAC-XL) 0.5 mg and 5 mg capsules in 40% alcohol at pH 1.2 (Figure 24 for 0.5 mg). Previously, in vitro dissolution studies in 20% ethanol at pH 4.5 were not able to detect dose dumping from 0.5 mg and 5 mg TAC-XL capsules. *In vivo* follow on studies have not been conducted. The TAC-XL package insert should warn against the concomitant administration of TAC-XL capsules with alcoholic beverages.

Figure 24.
Dissolution Profiles of Tacrolimus Extended-Release Capsules 0.5 mg with Different Concentrations of Alcohol



Source: Sponsor's Response to CMC information request (14 February 2013), Figure 1

2.5.3. For patients who are not able to swallow intact TAC-XL capsules immediately after transplant, what dosage of intravenous tacrolimus should be initially given?

According to the US Package Insert of Prograf® (tacrolimus immediate release oral capsules): The absolute bioavailability of oral tacrolimus is about 20% in adult and pediatric kidney transplant patients and healthy subjects. The recommended starting dose of tacrolimus injection is 0.03-0.05 mg/kg/day in kidney transplant patients as a continuous intravenous (IV) infusion. The tacrolimus injection should be discontinued as soon as the patient can tolerate the oral administration of the oral capsules. The first dose of oral therapy should be given 8-12 hours after discontinuing the IV infusion. Tacrolimus injection should be reserved for patients who are unable to take oral capsules. If signs or symptoms of anaphylaxis occur, the infusion should be stopped.

2.5.4. Is the nasogastric administration of TAC-XL as an aqueous suspension compounded from the capsule contents an acceptable alternative mode of administration in de novo kidney transplant patients who are not able to swallow intact capsules or are not able to receive oral medications immediately after surgery?

No. In Phase 3 Studies 158 and 12-03, a small number of de novo kidney transplant patients received tacrolimus as an extemporaneously compounded suspension of the TAC-XL capsules via a nasogastric tube (i.e., 1 patient and 11 patients, respectively). In healthy subjects, it had been shown that the nasogastric administration of TAC-XL as a suspension prepared from the capsule contents resulted in a 30% higher tacrolimus Cmax, a shorter Tmax (by 1 hour), and a 17-21% lower AUC than that following oral administration of the intact TAC-XL capsules (Study FG04-31). In view of the foregoing factors and the lack of stability data for the extemporaneously compounded suspension, the sponsor's proposal to (b) (4) is not acceptable.

In de novo kidney transplant patients who, due to their clinical condition are not able to swallow the intact capsules of TAC-XL during the first days post-surgery, the intravenous administration of appropriate doses of alternative commercially available products will be recommended in the TAC-XL package insert.

2.6. Analytical Section

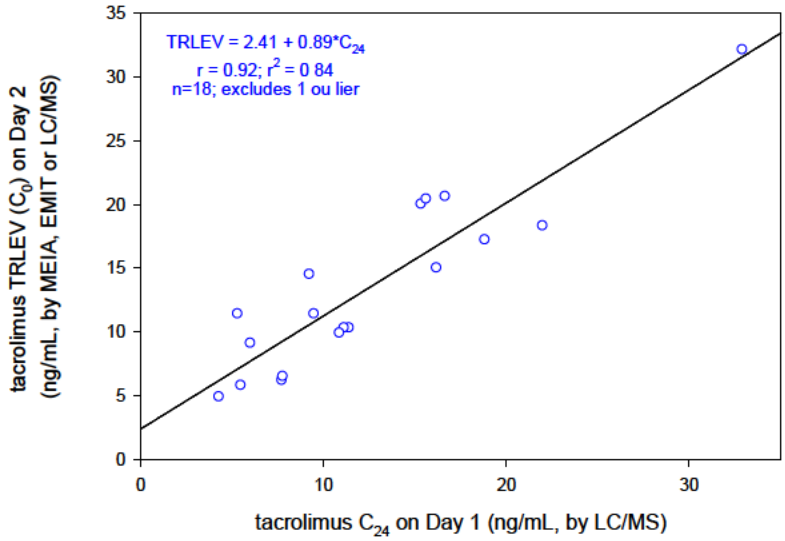
2.6.1. How are the active moieties identified and measured in whole blood in the clinical pharmacology and biopharmaceutics studies and the Phase 3 clinical trials?

In the clinical pharmacology studies and the PK substudies of the Phase 2 and 3 clinical trials that determined the pharmacokinetic parameters of tacrolimus from the whole blood concentrations of the drug, validated HPLC/MS/MS assays were used by the central bioanalytical laboratories. The linear range of these HPLC/MS/MS assays in the primary PK substudies was 0.059 -60.3 ng/mL for Study 12-03 in de novo kidney patients, and 0.030 – 60.2 ng/mL for Study 12-02 in stable kidney transplant patients.

In the Phase 2 and Phase 3 clinical trials involving kidney transplant patients, whole blood tacrolimus trough concentrations or levels (TRLEV) were also measured periodically to monitor the attainment of target tacrolimus trough concentrations in individual patients and to serve as guide for the adjustment of subsequent TAC-XL or Prograf doses; the assays used were specific to the clinical sites. The immunoassays of tacrolimus used for therapeutic drug monitoring in the clinical trials (EMIT®, MEIA®) have a linear range not exceeding 30 ng/mL so for whole blood samples with high tacrolimus concentrations, dilution of samples was necessary to achieve accurate measurements. Based on the sponsor's technical report, over 550 clinical sites voluntarily participated in the proficiency tests (for the different methods for therapeutic drug monitoring) that were conducted by the sponsor monthly from 2003 to 2005 (the years when the Phase 3 trials were conducted). Unlike LC/MS assays, immunoassays exhibit cross-reactivity with the tacrolimus metabolites (some of which are pharmacologically inactive). As expected, generally higher mean tacrolimus concentrations were reported for MEIA IMX than HPLC/MS/MS. The majority (73% in Study 158 and 65% in Study 12-03) of the samples for therapeutic drug monitoring in the Phase 3 clinical trials were assayed by the MEIA IMx immunoassay.

The reviewer's exploratory analysis suggests that there was a satisfactory correlation (r = 0.92) between the tacrolimus C_{24} on Day 1(assayed by HPLC/MS/MS) and the tacrolimus pre-dose concentration on Day 2 (TRLEV; assayed by EMIT, MEIA or LC/MS) in the de novo kidney transplant patients who received TAC-XL and who participated in the PK substudy of Phase 3 Study 12-03 (Figure 25). On Day 1, the correlation between AUC_{24} and C_{24} (r = 0.87; both obtained by HPLC/MS/MS) was slightly better than between AUC_{24} by LC/MS and TRLEV (r = 0.81; mainly by EMIT and MEIA immunoassays; Figure 26).

Figure 25.
Correlation between tacrolimus trough level (pre-dose on Day 2; by various assay methods) and C_{24} (24 hours after Day 1 dose; by LC/MS/MS) in adult de novo kidney transplant patients (Study 12-03-PK)



Pre-dose trough levels on Day 2 were measured by EMIT immunoassay (n=10), MEIA IMx (n=7) or LC/MS/MS (n=1).

Figure 26.
Correlation between tacrolimus trough level (pre-dose on Day 2; by various assay methods) and AUC_{0-24} for Day 1 in adult de novo kidney transplant patients (Study 12-03-PK)

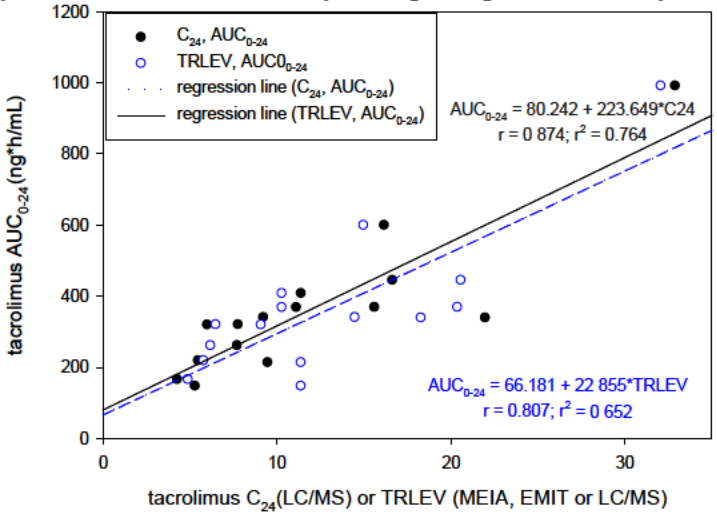


Table 32 summarizes the validation parameters for the HPLC/MS/MS assays used in the PK substudy of the Phase 3 Study 12-03 (de novo kidney) and the Phase 2 PK Study 12-02 (stable kidney conversion). Note that the other primary Phase 3 trial (Study 158) did not have a PK substudy. According to the sponsor, interference from concomitant medication was neither expected nor observed during the assay of the study samples. The very high specificity of the LC/MS/MS assay procedure precludes the detection of any compounds that do not possess the capability to produce the specific precursor ion followed by formation of the specific product ion produced and monitored in the mass spectrometer.

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Table 32.
Validation parameters of the HPLC/MS/MS assays used in Study 12-03-PK and Study 12-02-PK

	Study 12-03-PK (Phase 3 – de novo kidney)	Study 12-02-PK (Phase 2 – stable kidney conversion)
Bioanalytical ServiceLaboratory	(b) (4)	(b) (4)
Linear Range (ng/mL)	0.059 -60.3	0.030 – 60.2
Sensitivity (LLOQ; ng/mL)	0.059	0.030
Accuracy and Precision	CV bias within 20% at the LOQ and within 15% at the higher concentrations	(same as Study 12-03-PK)
Specificity	No interfering peaks at the retention time of tacrolimus and the internal standard	(same as Study 12-03-PK)
Matrix effect	In 10 different whole blood pools, CV of analyte peak area and internal standard peak area less than or equal to 8.5%	In 11 different whole blood pools, CV of analyte peak area and internal standard peak area less than or equal to 9.0%
Interference from analyte metabolites or concomitantly administered medications, including lithium heparinate	Interference not observed	(same as Study 12-03-PK)
Absolute Recovery (%) of Analyte from whole blood	Mean (CV) ~65% (10%) for low (1.85 ng/mL), medium (7.42 ng/mL), and high (29.7 ng/mL) tacrolimus concentrations and approximately 88% (14%) for internal standard Recovery of tacrolimus by precipitation and solid phase extraction (SPE) with acetonitrile and water	(same as Study 12-03-PK)
Freeze-thaw stability	Tacrolimus stable for at least three freeze-thaw cycles	(same as Study 12-03-PK)
On-bench stability	Tacrolimus stable in whole blood at room temperature for at least 20 hours at high (14.8 ng mL) and low (1.85 ng/mL) concentrations	(same as Study 12-03-PK)
On-instrument stability	Tacrolimus extracts stable on-instrument for at least 33 hours	(same as Study 12-03-PK)
Long-term stability in matrix at -20 ◦C	Tacrolimus stable in human whole blood when spiked at high (15.2 ng/mL) and low concentrations (1.89 ng/mL) for at least 169 days	(not in validation report)

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3. Detailed Labeling Recommendations (as of June 11, 2013)

The Clinical Pharmacology reviewer's deleted text is marked with a strikethrough; added text, with an underscore.

HIGHLIGHTS

(b) (4)

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4.2. Individual Study Reviews

The individual study reviews for the following studies are available upon request:

- **FG-506E-12-03 (Study 12-03) -** A Multicenter, 1:1 Randomized, Double Blind, Two Arm Parallel Group Study to Evaluate and Compare the Efficacy and Safety of Modified Release Tacrolimus TAC-XL Versus Tacrolimus Prograf in Combination with MMF (Cellcept®) and Steroids in Patients Undergoing Kidney Transplantation

- **020-158 (Study 158)** - A Phase III, randomized, open-label, comparative, multi-center study to assess the safety and efficacy of Prograf® (tacrolimus)/MMF, TAC-XL (modified release tacrolimus)/MMF, and Neoral® (cyclosporine)/MMF in de novo kidney transplant recipients

- **PMR-EC-1210 (OSAKA)** - A Multicenter, Four Arm, Randomized, Open Label Clinical Study Investigating Optimized Dosing in a Prograf®- and Advagraf®-Based Immunosuppressive Regimen in Kidney Transplant Subjects (OSAKA Study)

- **F506-CL-0844 (Study 0844) -** A Phase I, Four-Period Crossover Study to Investigate the Effect of Ketoconazole on the Pharmacokinetics of Oral Doses of Two Formulations in Healthy Male Subjects

- **F506-CL-0846 (Study 0846) -** A Phase I, Four-Period Crossover Study to Investigate the Effect of Rifampicin on the Pharmacokinetics of Oral Doses of Two Formulations in Healthy Male Subjects

- **FG506E-12-02-PK (Study 12-02-PK) -** A Phase II, Open-Label, Multi-Centre Study to Assess the Pharmacokinetics of Tacrolimus in Stable Kidney Transplant Patients Converted from a Prograf® Based Immunosuppression Regimen to a Tacrolimus Modified Release, FK506E (TAC-XL), Based Immunosuppression Regimen (TAC-XL PK KTx Replicate Conversion)

- **FJ-506E-KT01 (Study KT-01) -** A Phase II clinical study of a tacrolimus new oral formulation, FK506E (TAC-XL) capsules, in kidney transplant patients - Conversion study

4.3. Pharmacometrics Review

Submission	**NDA204096**
Submission Date	**September 21, 2012**
Generic Name	**Tacrolimus extended release**
Primary Reviewer	**Jee Eun Lee, Ph.D.**
Secondary Reviewer	**Yaning Wang, Ph.D.**
OCP Division	**DCP-4**
OND division	**OND/ DTOP**
Sponsor	**Astellas Pharmaceuticals, Inc.**
Formulation; Strength(s)	**Oral extended-release capsules: 0.5 mg, 1 mg, and 5 mg**
Indication	**Prevention of acute rejection in adult de novo kidney transplant patients (when used with MMF and steroids)**

1. SUMMARY OF FINDINGS

Key Review Questions

The purpose of this review is to address the following key questions.

Is there evidence of an exposure-response relationship for efficacy?

Given the therapeutic drug monitoring (TDM) design, it is impossible to assess the exposure-response relationship for efficacy because of the time-dependent nature of the exposure and the lack of reliable dosing time and sampling time to derive the exposure that can be used in a time-to-event analysis with time-dependent exposure. To minimize the impact of the trial design on the exposure-response analysis, the exposure within 28 days after the first dose was used in an exploratory exposure-response analysis. The results suggested that the lower (10 ng/mL) and upper (15 ng/mL) tacrolimus limits up to 28 Day were supported by the data.

Is there evidence of exposure-response relationship for safety?

There were no noticeable differences in mean concentrations of tacrolimus between patients with adverse events and patients without adverse events for cytomegalovirus infection and bacterial pyelonephritis. Given the small number of patients with the relevant safety events and the TDM design, this observation should be explained with caution.

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2. PERTINENT REGULATORY BACKGROUND

The immediate release formulation of tacrolimus (Prograf) was approved for the prophylaxis of organ rejection in liver transplantation in 1994, for the kidney transplantation in 1997 and for heart transplantation in 2006. The approved dosing regimens are summarized below.

Patient Population	Recommended Initial Oral Dosage (two divided doses every 12 hours)	Observed Whole Blood Trough Concentrations
Adult Kidney transplant		
In combination with azathioprine	0.2 mg/kg/day	month 1-3: 7-20 ng/mL month 4-12: 5-15 ng/mL
In combination with MMF/IL-2 receptor antagonist	0.1 mg/kg/day	month 1-12: 4-11 ng/mL
Adult Liver transplant	0.10-0.15 mg/kg/day	month 1-12: 5-20 ng/mL
Pediatric Liver transplant	0.15-0.20 mg/kg/day	month 1-12: 5-20 ng/mL
Adult Heart transplant	0.075 mg/kg/day	month 1-3: 10-20 ng/mL month ≥4: 5-15 ng/mL

(Source: approved labeling of Prograf)

The current submission is for an extended-release capsule formulation. This submission includes studies that were previously reviewed in 2007 and 2008. Complete responses were issued for the previous two reviews.

Previous Clinical Pharmacology review accepted the initial dose of 0.2 mg/kg/day for Tac XL. Exposure-response analyses for efficacy and safety (i.e., renal dysfunction, CMV and other infections, cardiac disorders, glucose intolerance) were recommended for Study 12-03 (Clinical Pharmacology review by Dr. Seong Jang in 2008). Additional exposure-response analysis to evaluate the effect of gender on efficacy and safety was also recommended.

3. REULTS OF SPONSOR'S ANALYSIS

Introduction

The sponsor's analyses were performed to assess the overall effect of treatment on the efficacy endpoints (i.e., efficacy failure and BPAR) while taking into account the differences in levels of tacrolimus exposure. The sponsor's analyses included three phase 3 studies (02-0-158, FG-605E-12-03 and PMR-EC-1210) and included data up to 12 months after the first dose.

Methods

Statistical comparisons were made for each pair of treatment groups using 2-sided tests at the 0.05 level of significance with no adjustments for multiplicity.

Based on the Cox regression for the time to first event, each efficacy endpoint was analyzed separately with treatment as a factor and tacrolimus trough concentration at the time of event as a time-dependent covariate. For each safety endpoint, 2 models were fitted, one including the interaction between treatment group and the tacrolimus concentration and another excluding the interaction term. If the interaction term was not significant at the 0.1 level, the results of the latter model were used for interpretation. If the interaction term was significant, the analyses were performed on each treatment group separately in order to determine the effect of exposure on each treatment group. Patients that did not have an event by the end of treatment-emergent period were censored at the end of the treatment emergent period. For the days without a tacrolimus trough concentration blood draw, the tacrolimus trough concentration was imputed using linear interpolation.

The time-averaged mean (TAM) tacrolimus concentration was calculated using area under the curve (AUC0-t) divided by total time (t). Area under the curve was calculated using interpolation to impute values between two trough concentrations. Trough concentrations prior to the first dose were assumed to be zero. Concentrations on days after the last available trough concentration were imputed to have the same value as the last available trough concentration through the last dose day. Using this method, the TAM was calculated for any time period when a patient is in the study (e.g., TAM for days 1-28, 1-90, etc.).

Additionally, a logistic regression was employed using treatment (Prograf and Advagraf) and the time-averaged mean concentration from first dose through time, t, as factors. Similar to the Cox regression analysis, 2 models were fitted for each efficacy endpoint; one including the interaction between treatment group and TAM and another excluding the interaction term. If the interaction term was not significant at the 0.1 level, the results of the latter model were used for interpretation; if it was significant, the analysis was repeated for each treatment group. Separate analyses were performed for each of the following values of t: day 28, day 90, and end of the study. If an event was observed prior to the set value of t, a patient's TAM was calculated only through the day of event.

In addition to the Cox and logistic regression analyses, the proportion of patients who experienced an event was summarized for each efficacy endpoint in two subgroups: below and above specified levels of TAM. The proportion of events was compared across treatment groups for each level of TAM using Fisher's exact test. Comparisons across TAM levels within each treatment group were also compared using Fisher's exact test. The same values of t used in the logistic regression analyses to compute TAM were used in these analyses. The specific levels of TAM used as cut points in these analyses were 4 ng/mL, 5 ng/mL, 6 ng/mL and 7 ng/mL. These cut points were based on previously agreed discussion with the agency. They are similar to the current approved trough concentrations for Prograf and reflect the observed tacrolimus trough concentration from Study 02-0-158.

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Results

Exposure-Response Analysis

The results of the Cox and logistic regression analyses in Studies 02-0-158, FG-506E-12-03 and PMR-EC-1210 are summarized in Tables 1, 2, and 3. The sponsor concluded that the results from the analyses for efficacy were generally consistent with expectation in that treatment differences were not substantially different when adjusting for levels of tacrolimus exposure or, in the case of treatment-by-level interaction, higher levels of tacrolimus exposure was associated with a lower hazard of an event (efficacy or BPAR). However, the results were indeed inconsistent and the higher levels of tacrolimus exposure were associated with a higher hazard of an event for Prograf, which is counter-intuitive. The use of time-averaged mean trough concentration for exposure-response analysis is likely to be accounted for these counter-intuitive results (See Reviewer's comments).

If the interaction of a model was not significant, the result of the statistical test comparing treatment groups (while adjusting for tacrolimus trough level) is indicated in the first column (labeled as "w/o INT") of each analysis as being statistically significant (SS) or not statistically significant (N) at the 0.05 level of significance. In this scenario, "- -" is placed in the second column (ADV, PGF) indicating there was no interaction between treatment group and tacrolimus trough level ($p \geq 0.10$) and therefore analysis on the effect of tacrolimus trough concentration on outcome was not performed for each treatment group.

If the interaction of a model was significant at a level of 0.10, then the effect of tacrolimus trough level for each treatment group is indicated in the second column (column labeled "ADV, PRG") as being either SS+, SS- or NS, based on a level of 0.05. A plus (+) sign after SS indicates the hazard ratio for that group was greater than 1.0 meaning that higher exposure is associated with a higher hazard of event in that treatment group. A minus (-) after SS indicates the hazard ratio for that treatment group was less than 1.0, meaning that higher exposure is associated with a lower hazard of event in that treatment group.

Table 1. Summary of Exposure-response Analyses for Efficacy Failure and BPAR in Study 02-0-158

Efficacy Parameter Population	Cox Regression Analyses		Logistic Regression Analyses					
			TAM Through Day 28		TAM Through Day 90		TAM Through Day 365	
	w/o INT (< 0.05) †	ADV, PGF (< 0.05) ‡	w/o INT (< 0.05) †	ADV, PGF (< 0.05) ‡	w/o INT (< 0.05) †	ADV, PGF (< 0.05) ‡	w/o INT (< 0.05) †	ADV, PGF (< 0.05) ‡
Efficacy failure								
Overall	NS	--	NS	--	NS	--	NS	--
Males	NS	--	NS	--	NS	--	NS	--
Females	NS	--	NS	--	--	NS, NS	NS	--
BPAR								
Overall	--	NS, SS-	NS	--	NS	--	NS	--
Males	--	NS, SS-	NS	--	NS	--	--	NS, NS
Females	NS	--	NS	--	NS	--	NS	--

† "--" indicates a statistically significant interaction (P < 0.10) between treatment group and tacrolimus trough level and therefore inferences on the overall treatment effect may not be appropriate. In this case, inferences about the effect of tacrolimus trough level on outcome is provided for each treatment group in the column "ADV, PRG.
‡ "--"indicates there was no interaction between treatment group and tacrolimus trough level (P ≥ 0.10) and therefore analysis on the effect of tacrolimus trough concentration on outcome was not performed for each treatment group.

(Source: Summary of Clinical Efficacy Table 32)

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Table 2. Summary of Exposure-response Analyses for Efficacy Failure and BPAR in Study FG-506E-12-03

Efficacy Parameter / Population	Cox Regression Analyses		Logistic Regression Analyses					
			TAM Through Day 28		TAM Through Day 90		TAM Through Day 365	
	w/o INT (< 0.05) †	ADV, PGF (< 0.05) ‡	w/o INT (< 0.05) †	ADV, PGF (< 0.05) ‡	w/o INT (< 0.05) †	ADV, PGF (< 0.05) ‡	w/o INT (< 0.05) †	ADV, PGF (< 0.05) ‡
Efficacy failure								
Overall	NS	--	NS	--	--	SS-, NS	--	NS, SS+
Males	NS	--	NS	--	--	SS-, NS	--	NS, SS+
Females	NS	--	NS	--	NS	--	NS	--
BPAR								
Overall	NS	--	NS	--	--	SS-, NS	--	NS, SS+
Males	NS	--	NS	--	--	SS-, NS	--	NS, SS+
Females	NS	--	NS	--	NS	--	NS	--

† "--" indicates a statistically significant interaction (P < 0.10) between treatment group and tacrolimus trough level and therefore inferences on the overall treatment effect may not be appropriate. In this case, inferences about the effect of tacrolimus trough level on outcome is provided for each treatment group in the column "ADV, PRG.
‡ "--"indicates there was no interaction between treatment group and tacrolimus trough level (P ≥ 0.10) and therefore analysis on the effect of tacrolimus trough concentration on outcome was not performed for each treatment group.

(Source: Summary of Clinical Efficacy Table 33)

Table 3. Summary of Exposure-response Analyses of Efficacy Failure and BPAR in Study PMR-EC-1210

Efficacy Parameter / Population	Cox Regression Analyses		Logistic Regression Analyses					
			TAM Through Day 28		TAM Through Day 90		TAM Through Week 24	
	w/o INT (< 0.05)†	ADV, PGF (< 0.05) ‡	w/o INT (< 0.05) †	ADV, PGF (< 0.05) ‡	w/o INT (< 0.05) †	ADV, PGF (< 0.05) ‡	w/o INT (< 0.05) †	ADV, PGF (< 0.05) ‡
Efficacy failure								
Overall	--	SS-, NS	--	SS-, NS	--	SS-, NS	--	NS, SS+
Males	NS	--	NS	--	NS	--	NS	--
Females	--	SS-, NS	--	SS-, NS	--	SS-, NS	--	SS-, SS+
BPAR								
Overall	--	SS-, NS	NS	--	NS	--	NS	--
Males	NS	--	NS	--	NS	--	NS	--
Females	NS	--	NS	--	NS	--	NS	--

† "--" indicates a statistically significant interaction (P < 0.10) between treatment group and tacrolimus trough level and therefore inferences on the overall treatment effect may not be appropriate. In this case, inferences about the effect of tacrolimus trough level on outcome is provided for each treatment group in the column "ADV, PRG.
‡ "--"indicates there was no interaction between treatment group and tacrolimus trough level (P ≥ 0.10) and therefore analysis on the effect of tacrolimus trough concentration on outcome was not performed for each treatment group.

Dose: Advagraf 0.2 mg/kg and Prograf 0.2 mg/kg

(Source: Summary of Clinical Efficacy Table 34)

Reviewer's comments: The use of time-averaged mean trough concentrations is an inappropriate exposure measure for the exposure-response analysis. The tacrolimus concentrations in patients tend to be higher at the earlier phase of the trial compared to those at the later phase when doses are adjusted to target a decreasing concentration range. Patients who had an event of acute rejection stopped treatment for alternative rescue therapy. As a result, data only included their earlier phase concentrations. Thus, by averaging trough concentrations, time-averaged mean (TAM) for those patients are likely to be higher than the TAM for patients who continued receiving treatment until a later event or no event at all. Therefore, the exposure-response analysis could produce a counter-intuitive result: higher concentration is associated with higher hazard of having an event of acute rejection. This problem is evident in the

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exposure-response analysis results for Prograf with TAM through Week 24 (the last column of the Tables 2 and 3) where higher hazard with higher exposure is indicated with SS+.

The figures in Figure 1 illustrate the problem associated with TAM with examples of two patients: patient H8208 who had acute rejection on Day 11 and patient H4015 who did not experience efficacy failure and was censored at the end of the study. Even though the TAM in patient H8208 was higher than that for patient H4015, it was because only higher concentrations of earlier phase of treatment are reflected in the TAM calculation due to the discontinuation of treatment in patient H8208. Thus, the relationship between the TAM and the response suggested that higher concentration of tacrolimus was associated with higher hazard of acute rejection.

Another caveat of the sponsor's analysis is the assumption of a linear relationship between tacrolimus exposure and the log-hazard or log-odds for the event. The reviewer's analyses suggested nonlinear relationships between tacrolimus exposure and the log-hazard for the event.

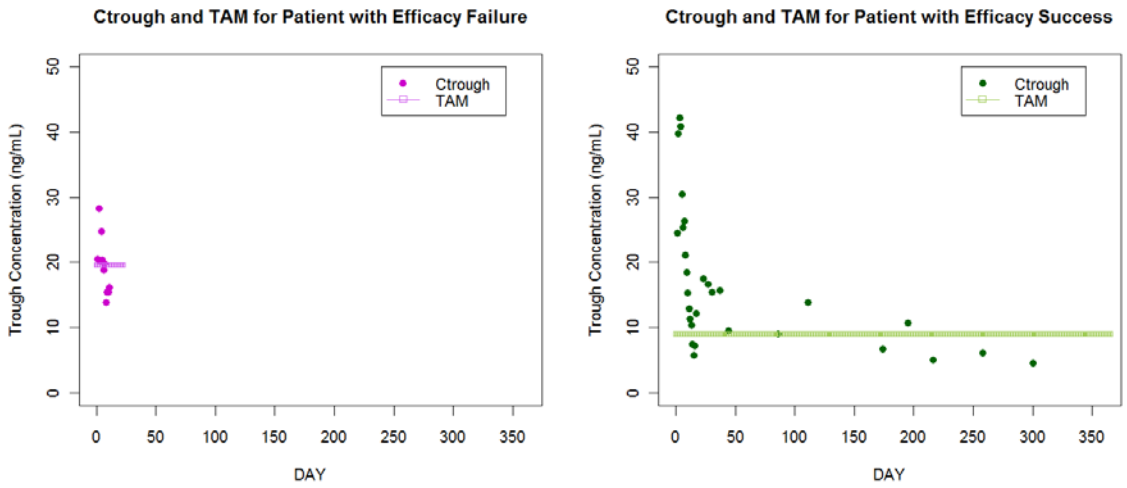

Figure 1. Comparison of Ctrough and TAM between a Patient with Acute Rejection (H8208, Left) and a Patient without Acute Rejection (H4015, Right)

4. REVIEWER'S ANALYSIS

Introduction

As explained above, the sponsor's exposure metric used for the exposure-response analyses, time-averaged mean trough concentrations, was inappropriate. The reviewer attempted to develop a population PK model to estimate daily concentrations of tacrolimus as the exposure metric for the exposure-response analyses. However, the records for the time of blood sampling to measure tacrolimus concentration were missing for all measurements except for the first measurement. The records for the time of daily administration of Prograf or Tac XL were also missing. Thus it was not feasible to develop a reliable population PK model to generate predicted concentrations either. Thus, the reviewer's analysis

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was limited to evaluate time-to-event for efficacy endpoints such as acute rejection or efficacy failure using various cutoffs of trough concentrations within the first month after the transplantation to minimize the impact of changing tacrolimus levels. Additionally, trough concentration profiles of tacrolimus in patients with AEs and in patients without AEs were compared for cytomegalovirus infection and bacterial pyelonephritis upon the clinical reviewer's request.

Objectives

Analysis objectives are:

1. To compare time-to-event for acute rejection or efficacy failure in patients whose mean trough concentrations of tacrolimus between Days 1 and 28 were above or below specified cutoffs: 7 ng/mL, 8 ng/mL, 9 ng/mL and 10 ng/mL for both Prograf and Tac XL treatment groups.
2. To compare mean trough concentration profiles of tacrolimus in patients with and without major AEs for Prograf and Tac XL treatment groups.

Methods

Kaplan-Meier survival curves were compared to evaluate the time-to-event for acute rejection or efficacy failure in patients whose mean trough concentrations were above or below specified cutoffs. Graphical assessments were performed for concentration profiles of patients with AEs or without AEs.

Data sets

The analysis was limited to Study 12-03 which was submitted as a new data set for the indication of prophylaxis of organ rejection in patients receiving allogeneic kidney transplantation and the key data set for safety evaluation.

Table 4. Analysis Data Sets

Study Number	Name	Link to EDR
FG-506E-12-03	eff.xpt trlev.xpt trlevi.xpt outcome.xpt adv.xpt dose.xpt	\\cdsesub1\evsprod\NDA204096\0000\m5\datasets\fg-506e-12-03-12m\analysis\datasets

Software

Graphical, statistical analyses were performed with R (version 2.13.2).

Reference ID: 3323950

Results

Time-to-event for acute rejection

Kaplan-Meier curves for acute rejection comparing patients with specified mean trough concentrations of tacrolimus up to Day 28 (Figure 2, Figure 3) show that increasing concentrations of tacrolimus show lower rate for acute rejection and the cutoff of 10 ng/mL did not separate the curves for both Prograf and Tac XL. These results support that the protocol specified lower limit (10 ng/mL) of the target concentration was reasonably set for Days between 1 and 28 after the first dose. It should be noted that this exploratory analysis did not control potential confounding factors that may be unbalanced between the two different exposure subgroups (below or above the cutoff). Another caveat of this exploratory analysis is that the contribution of tacrolimus concentrations after Day 28 is not accounted for.

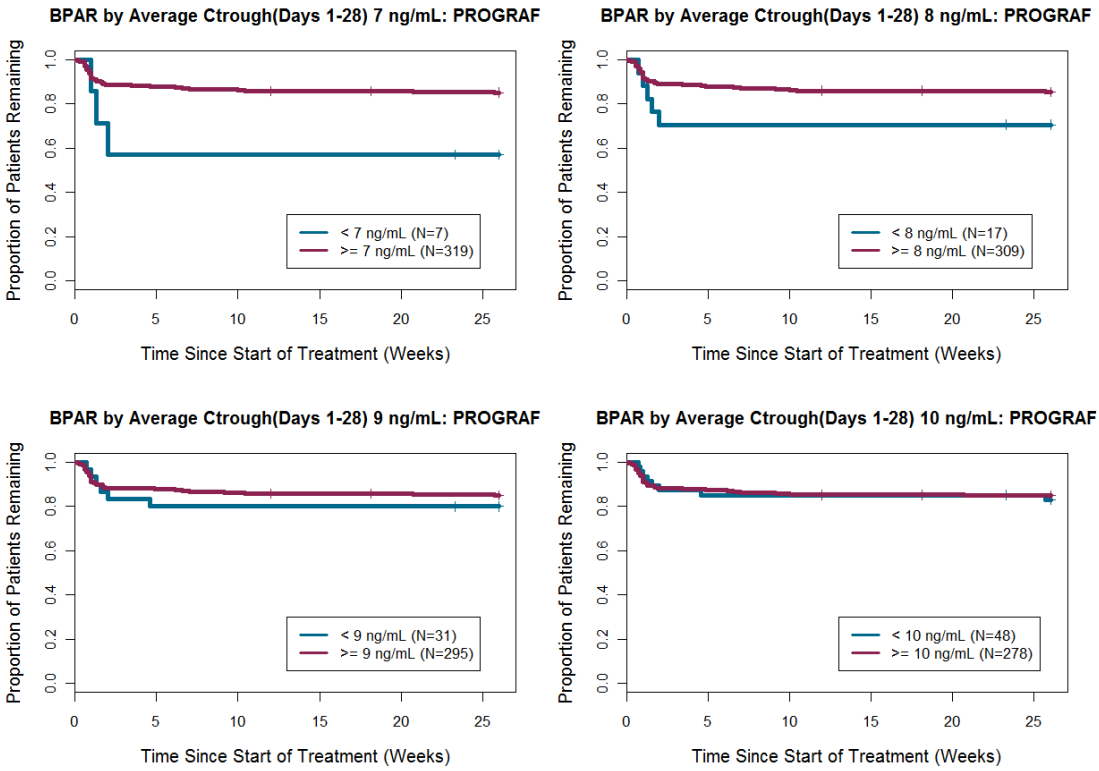

Figure 2. Kaplan-Meier curves for acute rejection comparing patients with various mean trough concentrations of tacrolimus up to Day 28 following administration of Prograf

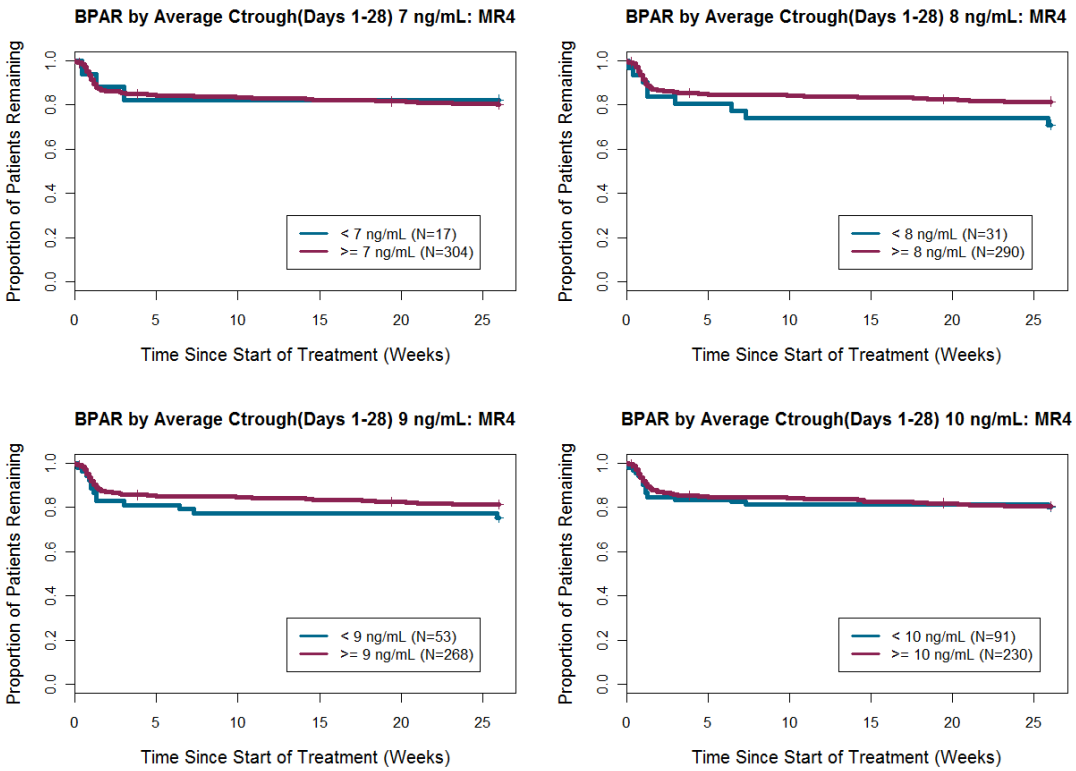

Figure 3. Kaplan-Meier curves for acute rejection comparing patients with various mean trough concentrations of tacrolimus up to Day 28 following administration of Tac XL (MR4)

Time-to-event for efficacy failure

As shown in Figure 4, the proportion of patients having an event for efficacy failure including death was higher in patients with lower exposure group compared to that in patients with higher exposure group up to the cutoff of 13 ng/mL, following administration of Prograf. From the cutoff of 14 ng/mL, the relationship is reversed: higher exposure of tacrolimus was associated with higher efficacy failure. For patients in Tac XL, the relationship is reversed at the cutoff of 15 ng/mL. These results indicate that the upper limit of the protocol-specified target concentrations for Days between 1 and 28 (15 ng/mL) seems reasonable. It should be noted that this exploratory analysis did not control potential confounding factors that may be unbalanced between the two different exposure subgroups (below or above the cutoff).

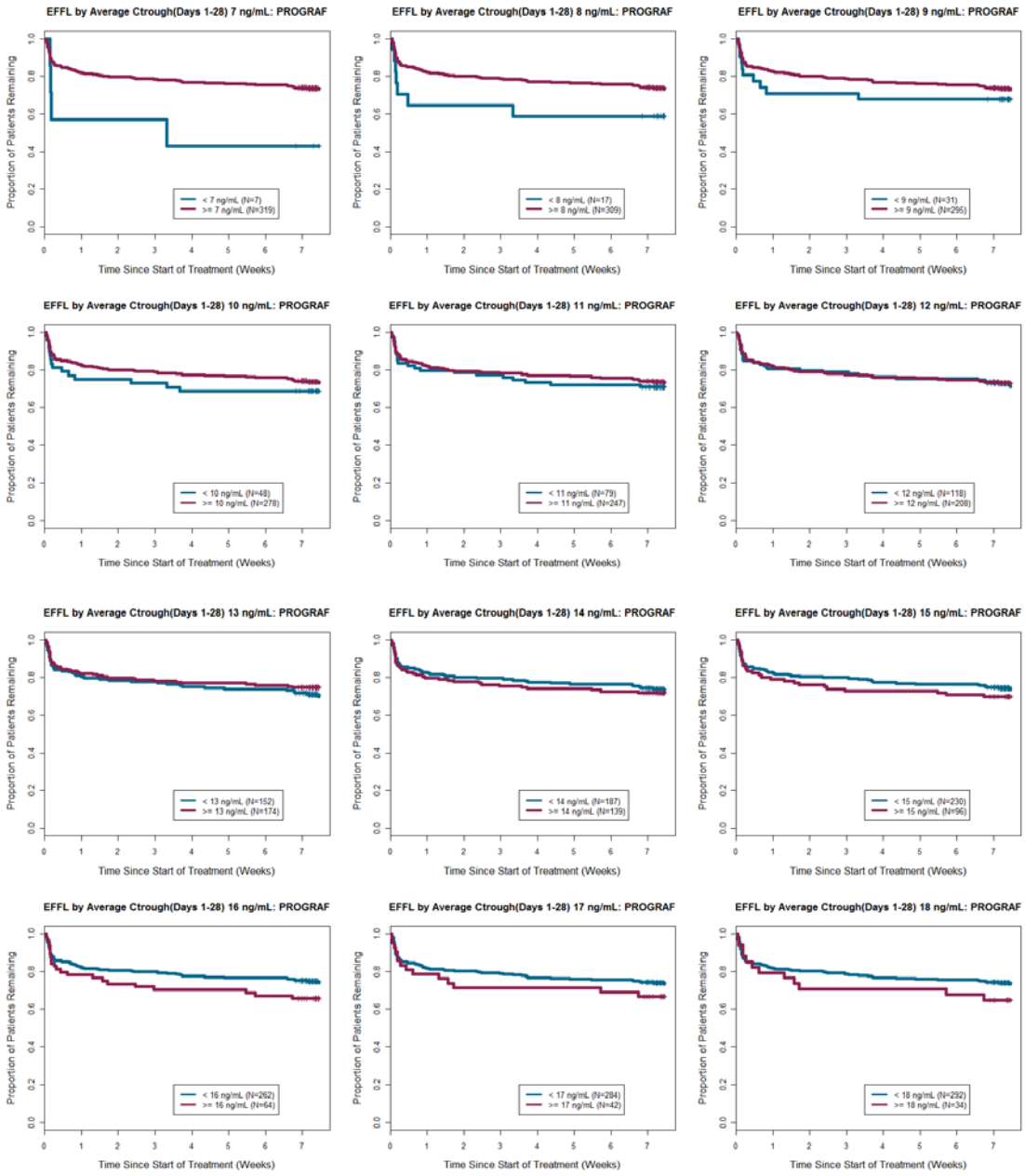

Figure 4. Kaplan-Meier curves for efficacy failure comparing patients with various mean trough concentrations of tacrolimus up to Day 28 following administration of Prograf

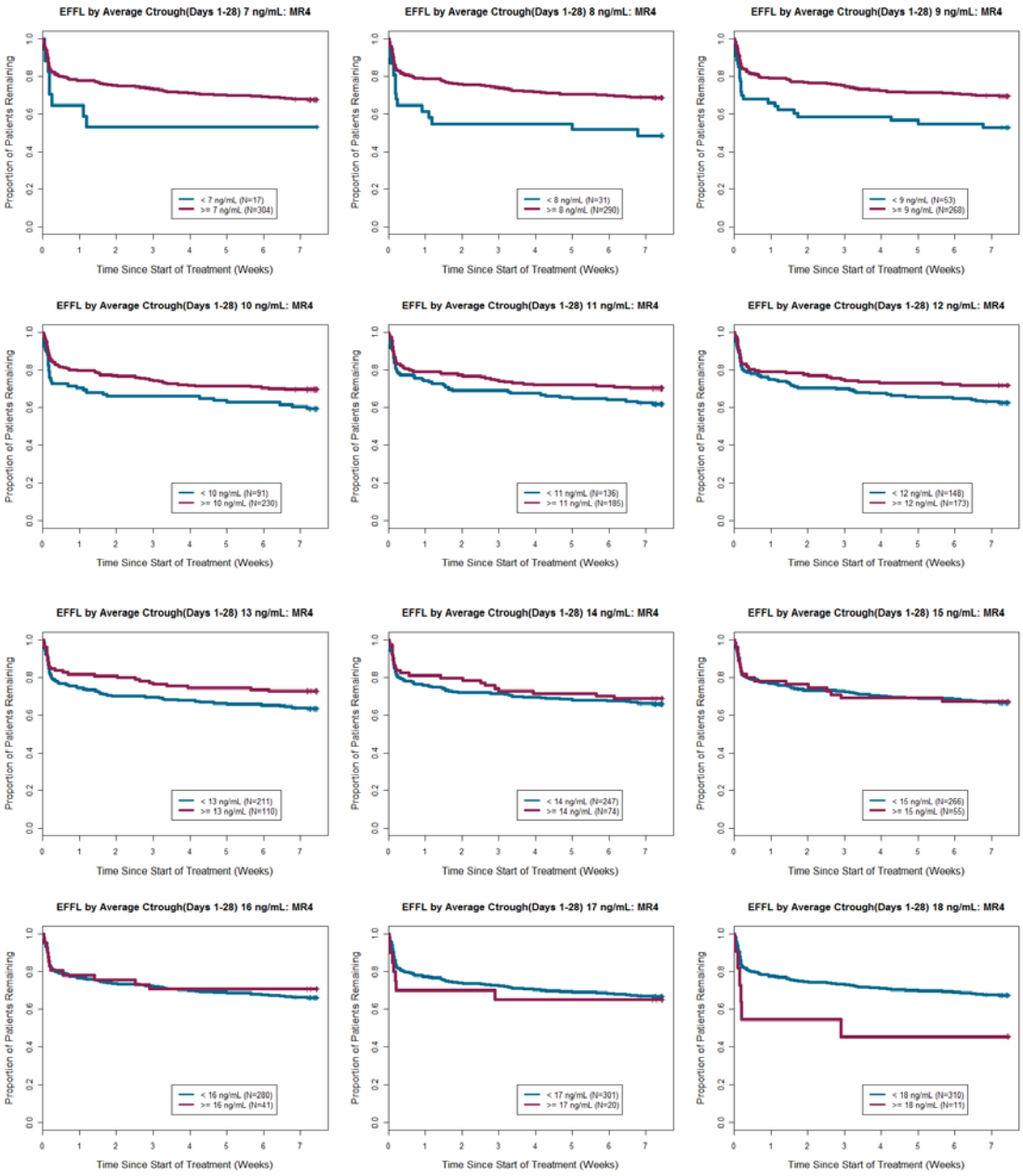

Figure 5. Kaplan-Meier curves for efficacy failure comparing patients with various mean trough concentrations of tacrolimus up to Day 28 following administration of Tac XL (MR4)

Based on the results of this analysis, the reviewer concludes that the recommended target trough concentration range of 10 –15 ng/mL up to 28 Day appears to be reasonable.

Relationships between trough concentrations and AEs

Visual assessments on the mean trough concentration profiles of tacrolimus for patients with cytomegalovirus infection or bacterial pyelonephritis comparing to patients without the adverse event were conducted. As seen in Figure 6 and Figure 7, there were no significant differences in mean concentration profiles between patients with AE and patients without AE for both cytomegalovirus infection and bacterial pyelonephritis. Given the small number of patients with the relevant safety events and the TDM design, this observation should be explained with caution.

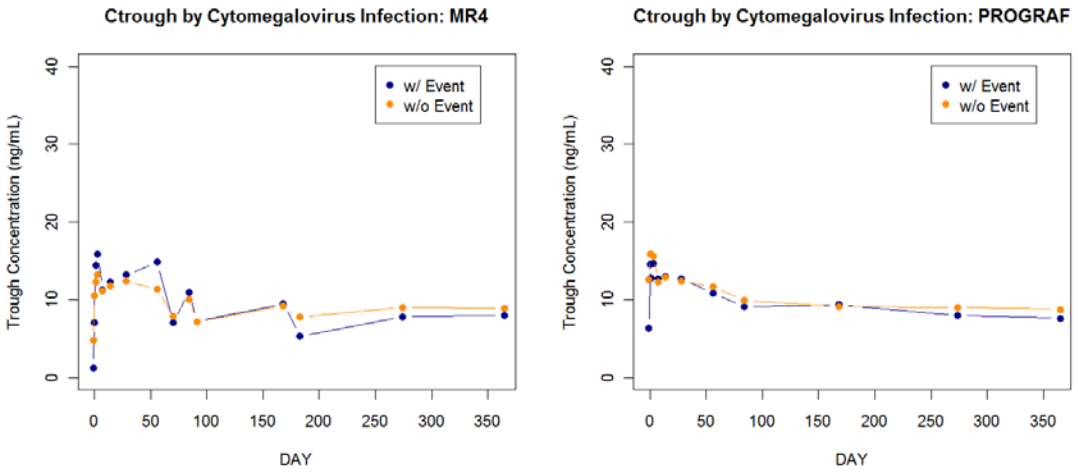

Figure 6. Mean trough concentration profiles of tacrolimus for patients with and without cytomegalovirus infection following Prograf of Tac XL (MR4)

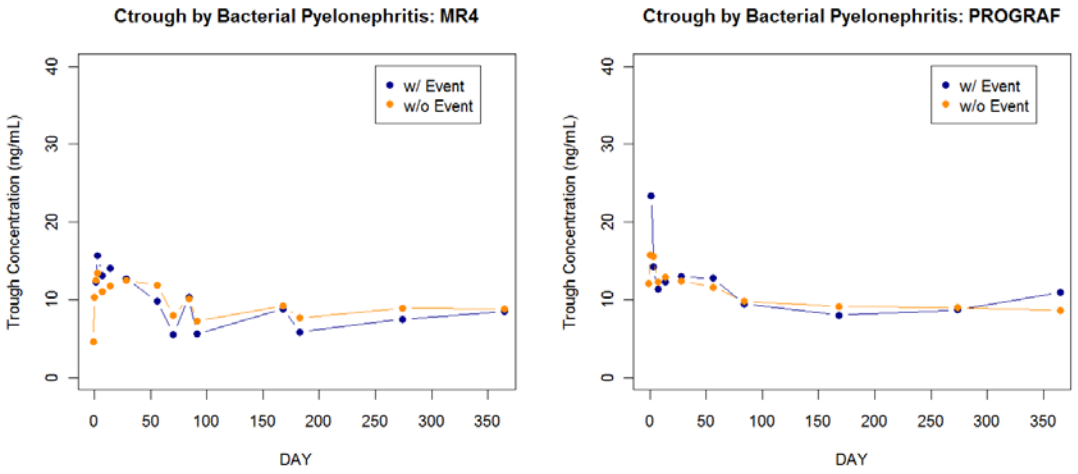

Figure 7. Mean trough concentration profiles of tacrolimus for patients with and without bacterial pyelonephritis following Prograf of Tac XL (MR4)

5. LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
NDA204096_1203_ER.R	Exposure-response analyses with data from Study 12-03	Reviews\Ongoing PM Reviews\Advagraf_NDA204096_JEL\ER Analyses

Reference ID: 3323950

4.4. OCPB/Filing /Review Form

(for both the kidney and liver transplant indications, prior to the withdrawal of the liver indication on 06 February 2013)

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	NDA 204096	**Brand Name**	Advagraf
OCP Division (I, II, III, IV, V)	IV	**Generic Name**	tacrolimus extended release
Medical Division	DTOP	**Drug Class**	calcineurin inhibitor immunosuppressant
OCP Reviewer	Gerlie Gieser, Ph.D.	**Indication(s)**	(b) (4)
OCP Team Leader	Philip Colangelo, PharmD, PhD	**Dosage Form**	(b) (4) capsules (0.5 mg, 1 mg, 5 mg)
Pharmacometrics Reviewer	Jee Eun Lee, PhD	**Dosing Regimen**	(b) (4)
Date of Submission	September 21, 2012	**Route of Administration**	oral
Estimated Due Date of OCP Review	May 24, 2013	**Sponsor**	Astellas
Medical Division Due Date		**Priority Classification**	standard
PDUFA Due Date	July 21, 2013		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	**X**			
Healthy Volunteers-				
single dose:	**X**			**(see Biopharmaceutics studies)**
multiple dose:	**X**			**(see Biopharmaceutic studies)**
Patients-				
single dose:	**X**			
multiple dose:	**X**			

Reference ID: 3323950

Dose proportionality -				
fasting / non-fasting single dose:	**X**	**1**		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	**2**		**ketoconazole (strong CYP3A inhibitor), rifampin (strong CYP inducer)**
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				**(subgroup analysis)**
gender:				**(subgroup analysis)**
pediatrics:	**X**	**1**		**stable liver conversion**
geriatrics:				**(subgroup analysis)**
renal impairment:				**(see Prograf)**
hepatic impairment:				**(see Prograf)**
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**8**		
Phase 3 and 4 clinical trial:	**X**	**2 +1+1**		**2 w/ PK substudy + 1 Ph3 w/ Cmin data + 1 Ph4 (post-approval ex-US) w/ Cmin data**
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**2**		**vs Prograf IR, vs MR4 oral suspension**
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**6**		**vs Prograf IR**
replicate design; single / multi dose:	**X**	**1**		**vs Prograf IR**
Food-drug interaction studies	**X**	**2**		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping	**X**			
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics	**X**	**1**		
Pediatric development plan	**X**			(b) (4) **; deferral (PMC study planned) for stable kidney transplant peds 5 to 16 y; waiver requested for peds 0- <5 y**
Literature References	**X**	**23 + 8**		**23 submitted in original NDA and 8 in response to reviewer's IR requests #1 and #2**
Total Number of Studies		**29 (excluding literature references)**		**14 studies in HVs, 15 studies in transplant patients (with PK profiles and/or tacrolimus Cmin & dose data)**

Reference ID: 3323950

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			Note: Astellas has right of reference to Prograf® (tacrolimus, IR) Clin Pharm data
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	X			
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	X			
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			

Reference ID: 3323950

	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?	X			

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? _____YES___

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

N/A

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

None

Gerlie Gieser, Ph.D.
Reviewing Clinical Pharmacologist

Philip Colangelo, Pharm.D., Ph.D.
Team Leader/Supervisor

Reference ID: 3323950

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

/s/

GERLIE GIESER
06/12/2013

JEE E LEE
06/12/2013

YANING WANG
06/12/2013

PHILIP M COLANGELO
06/13/2013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	NDA 204096	**Brand Name**	Advagraf
OCP Division (I, II, III, IV, V)	IV	**Generic Name**	tacrolimus extended release
Medical Division	DTOP	**Drug Class**	calcineurin inhibitor immunosuppressant
OCP Reviewer	Gerlie Gieser, Ph.D.	**Indication(s)**	(b) (4)
OCP Team Leader	Philip Colangelo, PharmD, PhD	**Dosage Form**	(b) (4) capsules (0.5 mg, 1 mg, 5 mg)
Pharmacometrics Reviewer	Jee Eun Lee, PhD	**Dosing Regimen**	(b) (4)
Date of Submission	September 21, 2012	**Route of Administration**	oral
Estimated Due Date of OCP Review	May 24, 2013	**Sponsor**	Astellas
Medical Division Due Date		**Priority Classification**	standard
PDUFA Due Date	July 21, 2013		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	**X**			
Healthy Volunteers-				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

single dose:	**X**			**(see Biopharmaceutics studies)**
multiple dose:	**X**			**(see Biopharmaceutic studies)**
Patients-				
single dose:	**X**			
multiple dose:	**X**			
Dose proportionality -				
fasting / non-fasting single dose:	**X**	**1**		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	**2**		**ketoconazole (strong CYP3A inhibitor), rifampin (strong CYP inducer)**
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				**(subgroup analysis)**
gender:				**(subgroup analysis)**
pediatrics:	**X**	**1**		**stable liver conversion**
geriatrics:				**(subgroup analysis)**
renal impairment:				**(see Prograf)**
hepatic impairment:				**(see Prograf)**
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**8**		
Phase 3 and 4 clinical trial:	**X**	**2 +1+1**		**2 w/ PK substudy + 1 Ph3 w/ Cmin data + 1 Ph4 (post-approval ex-US) w/ Cmin data**
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**2**		**vs Prograf IR, vs MR4 oral suspension**
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**6**		**vs Prograf IR**
replicate design; single / multi dose:	**X**	**1**		**vs Prograf IR**
Food-drug interaction studies	**X**	**2**		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping	**X**			
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics	**X**	**1**		
Pediatric development plan	**X**			**(b) (4) ; deferral (PMC study planned) for stable kidney transplant peds 5 to 16 y; waiver requested for peds 0- <5 y**
Literature References	**X**	**23**		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Total Number of Studies		**29 (excluding literature references)**		**14 studies in HVs, 15 studies in transplant patients (with PK profiles and/or tacrolimus Cmin data)**

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			Note: Astellas has right of reference to Prograf® (tacrolimus, IR) Clin Pharm data
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

	the pharmacokinetic or pharmacodynamics?				
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	X			
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	X			
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?	X			

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
_____YES___

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

N/A

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

None

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

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

/s/

GERLIE GIESER
11/06/2012

PHILIP M COLANGELO
11/06/2012