

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206406Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

ADDENDUM TO CLINICAL PHARMACOLOGY REVIEW

NDA:	206406
Submission Date:	30 December 2013
Drug Product:	Tacrolimus extended release oral tablets (0.75, 1.0, 4.0 mg)
Trade Name:	ENVARUSUS® XR
Sponsor:	Veloxis Pharmaceuticals, Inc.
Submission Type:	505(b)(2) NDA; Standard review
Pharmacometrics Reviewer	Jeffry Florian, PhD
Pharmacometrics Team Leader	Yaning Wang, PhD
OCP Team Leader:	Philip Colangelo, PharmD, PhD

Executive Summary

The following is an addendum to the Clinical Pharmacology Review for NDA 206406 that was previously entered into DARRTS September 25, 2014 for ENVARUSUS® XR (tacrolimus extended release) oral tablets administered once-daily for the prophylaxis of organ rejection in kidney transplant patients. Importantly, the Clinical Pharmacology Review (pp. 13 and 69) notes similarities between the respective analyses for ENVARUSUS XR oral tablets and for ASTAGRAF® XL (tacrolimus extended release) oral capsules with respect to handling of missed doses. However, it was not necessary to refer to ASTAGRAF XL for the analysis pertaining to the handling of missed doses for ENVARUSUS XR. This addendum is intended to supersede the previous analysis on missed doses in the Clinical Pharmacology review, clarify that the recommendation for the handling of missed dosing has been derived solely from data submitted in the ENVARUSUS XR NDA, and provide the Clinical Pharmacology review team's rationale for the proposed edits to the labeling regarding missed doses of ENVARUSUS XR.

The Sponsor performed modeling and simulation based on data from the LCP-Tacro Study 2011 to inform labeling recommendations regarding the handling of missed doses of ENVARUSUS XR (referred to as LCP-Tacro in the Sponsor's plots below). Details on the model development and data used in the analysis are summarized below and were adapted from the original Clinical Pharmacology NDA review (September 25, 2014, pages 109-113).

Overall, the Sponsor's analyses using data from LCP-Tacro Study 2011 provide support for the following Clinical Pharmacology edits to the original Sponsor proposed labeling recommendation for handling missed doses of ENVARUSUS XR under **Section 2. Dosage and Administration** (reviewer deletions noted as strikethrough and additions as underlined in red):

 (b) (4)

If a dose is missed, take it as soon as possible within 15 hours after missing the dose; beyond the 15-hour time frame, wait until the usual scheduled time to take the next regular daily dose. Do not double the next dose.

Clinical Pharmacology Evaluation of the Labeling Recommendation for Management of a Missed Dose of ENVARUSUS XR

In reviewing and editing the Sponsor's proposed labeling language, the Clinical Pharmacology Review team considered the following information and observations:

1. ENVARUSUS XR is recommended to be administered once daily in the morning.
2. The effect of diurnal variation on tacrolimus absorption following ENVARUSUS XR administration was not included in the sponsor's modeling and simulation.

3. The simulation scenario of doubling the dose is generally avoided in drug labeling.
4. The simulation scenarios of taking the missed ENVARSUS XR dose at 18- or 21-hours after the missed dose are close enough in proximity to the next dose administration (i.e., at 24 hours) so that it could be perceived by the prescriber that it may be acceptable to double the dose.
5. The Sponsor's model predicts that the highest maximum tacrolimus concentration (C_{max}) of ENVARSUS XR would occur in a scenario when the make-up dose is administered at 18 hours after the missed dose rather than at 24 hours after the missed dose.
6. Of the various simulation scenarios performed by the sponsor, the Clinical Pharmacology review team considers the simulation scenario of taking the missed ENVARSUS XR dose within 15 hours as providing the most appropriate balance between maintaining safe and efficacious tacrolimus trough concentrations and the aforementioned issues 1 to 5.

The Clinical Pharmacology Review team concludes that the Sponsor has provided information based on their product to support the handling of missed doses. Based on the review of the Sponsor's modeling and simulation report, the Clinical Pharmacology Review team recommends revising the Sponsor's original proposal regarding the management of missed doses, under **Section 2. Dosage and Administration** of the ENVARSUS XR labeling as is described above under **Executive Summary** of this review.

Summary of Sponsor's Analyses to Support Missed Dosing

To address the issue of how to handle missed ENVARSUS XR doses, the Sponsor developed a physiologically based pharmacokinetic model based on observed Prograf and ENVARSUS XR exposure data from ENVARSUS XR Study 2011. The model developed by the Sponsor included compartments for unreleased, released, dissolved, absorbed, and metabolized tacrolimus in the stomach, intestine, other organs, and plasma. Model calibration was achieved by altering transit compartment values and comparing model predictions with observations from Study 2011.

Study 2011 consisted of PK data from Prograf and ENVARSUS XR treatments from 47 patients. In this study, adult stable kidney transplant patients on tacrolimus capsules (Prograf) twice-daily were converted to tacrolimus tablets (ENVARSUS XR) once-daily. Patients continued on ENVARSUS XR once-daily for days 8-21; trough concentrations were to be maintained between 5-15 ng/mL; 24-hour pharmacokinetic (PK) assessments were done on days 7 (baseline pre-switch), 14, and 21. In Figure 1 below a summary of tacrolimus whole blood trough concentrations from the study is shown with model fits of the observed data shown in Figure 2.

Figure 1. Mean Tacrolimus Trough Concentrations from Patients on Days 7, 14, and 21 versus Time; Stable Kidney Transplant Patients from LCP-Tacro Study 2011

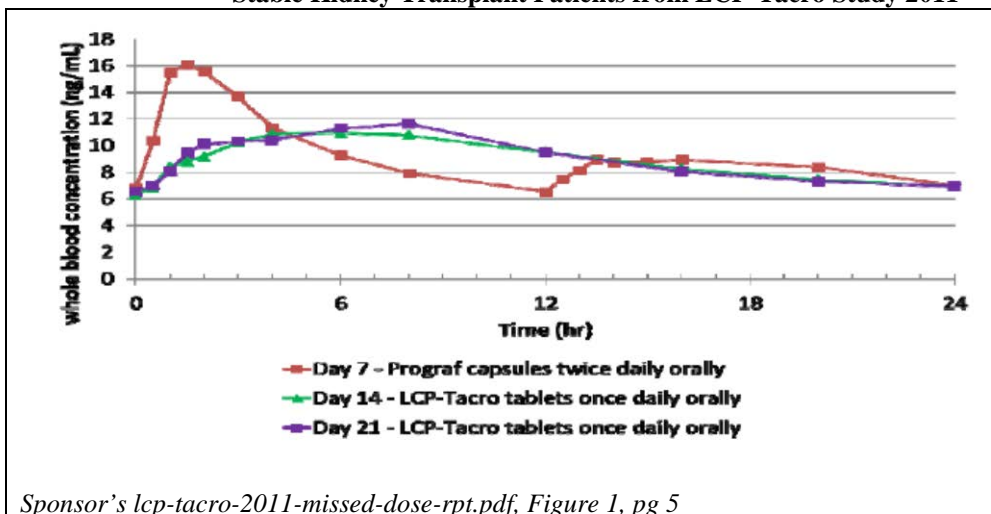
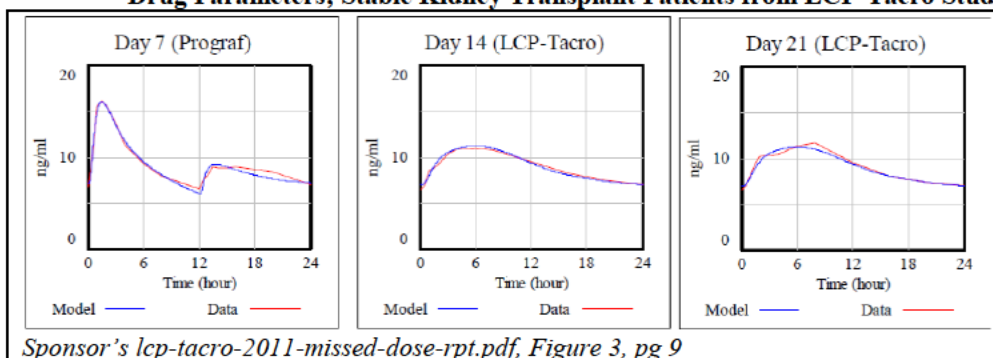


Figure 2. Comparison of Observed Study Data and Model Predictions Using Estimated Patient and Drug Parameters; Stable Kidney Transplant Patients from LCP-Tacro Study 2011



Based on the developed model, the Sponsor simulated various exposure scenarios assuming steady state tacrolimus trough concentrations ranging between 12 ng/mL to 6 ng/mL based on 2 ng/mL increments. In these figures, the Sponsor overlaid predicted whole blood concentrations for Prograf and ENVARSUS XR and included horizontal lines depicting the peak and trough concentrations that would be predicted for Prograf with the expectation that a proposal for handling missed doses should not result in tacrolimus concentrations exceeding peak observations for Prograf. The Sponsor considered the following scenarios (a)-(f) for handling missed dosing:

- (a) Perfect compliance of Prograf (blue curve, dose taken every 12 hours) and ENVARSUS® XR (red curve, dose taken every 24 hours).
- (b) A missed ENVARSUS® XR dose at $t=0$ with no make-up dose.
- (c) A missed dose at $t=0$ with a double dose taken at $t=24$ hours and a single dose taken at $t=48$ hours.
- (d) A missed dose at $t=0$, a make-up dose taken at 21 hours and normal doses taken at $t=24$ hours and $t=48$ hours.
- (e) A missed dose at $t=0$, a make-up dose taken at 18 hours and normal doses taken at $t=24$ hours and $t=48$ hours.
- (f) A missed dose at $t=0$, a make-up dose taken at 15 hours and normal doses taken at $t=24$ hours and $t=48$ hours.

In all analyses, the Prograf and ENVARSUS XR regular doses have been adjusted to obtain a target trough value (C_{min}) of 12ng/ml, 10ng/ml, 8ng/ml and 6ng/ml. Results are shown below for the simulations where C_{min} was 12 ng/mL (Figure 3) or 6 ng/mL (Figure 4) as these evaluations represent the cases which would result in the highest or lowest tacrolimus exposures. Each of the figures below contains six panels. Each panel of Figures 3 and 4 compares the tacrolimus concentration as a function of time over a 72 hour period for Prograf and ENVARSUS XR, for the same sequence of dose administration. In each panel, the red curve shows the tacrolimus concentration for perfect compliance of ENVARSUS XR (scenario (a)). From these analyses the Sponsor observed that doubling the dose at 24 hours after a missed dose (scenario (c)) results in prolonged elevation of tacrolimus concentrations over the following day. Missing a dose (scenario (b)) results in complete under exposure over an 8 to 12 hour window following the missed dose. Taking the missed dose at 15, 18, or 21 hours (scenarios (f), (e), and (d), respectively) reduces the window over which tacrolimus exposures may be less than the therapeutic window, but subsequently result in predicted C_{max} and AUC values on the following day that exceed that of the scenario where the dose is doubled. From these analyses the Sponsor concluded and proposed that subjects who miss a dose (b) (4)

The Sponsor also noted that maximum peak exposures (C_{max}) may occur by taking the regular ENVARSUS XR dose at 18-hours after the missed dose.

Figure 3. Simulation of non-compliance and make-up dose scenarios for a normal trough of 12 ng/mL

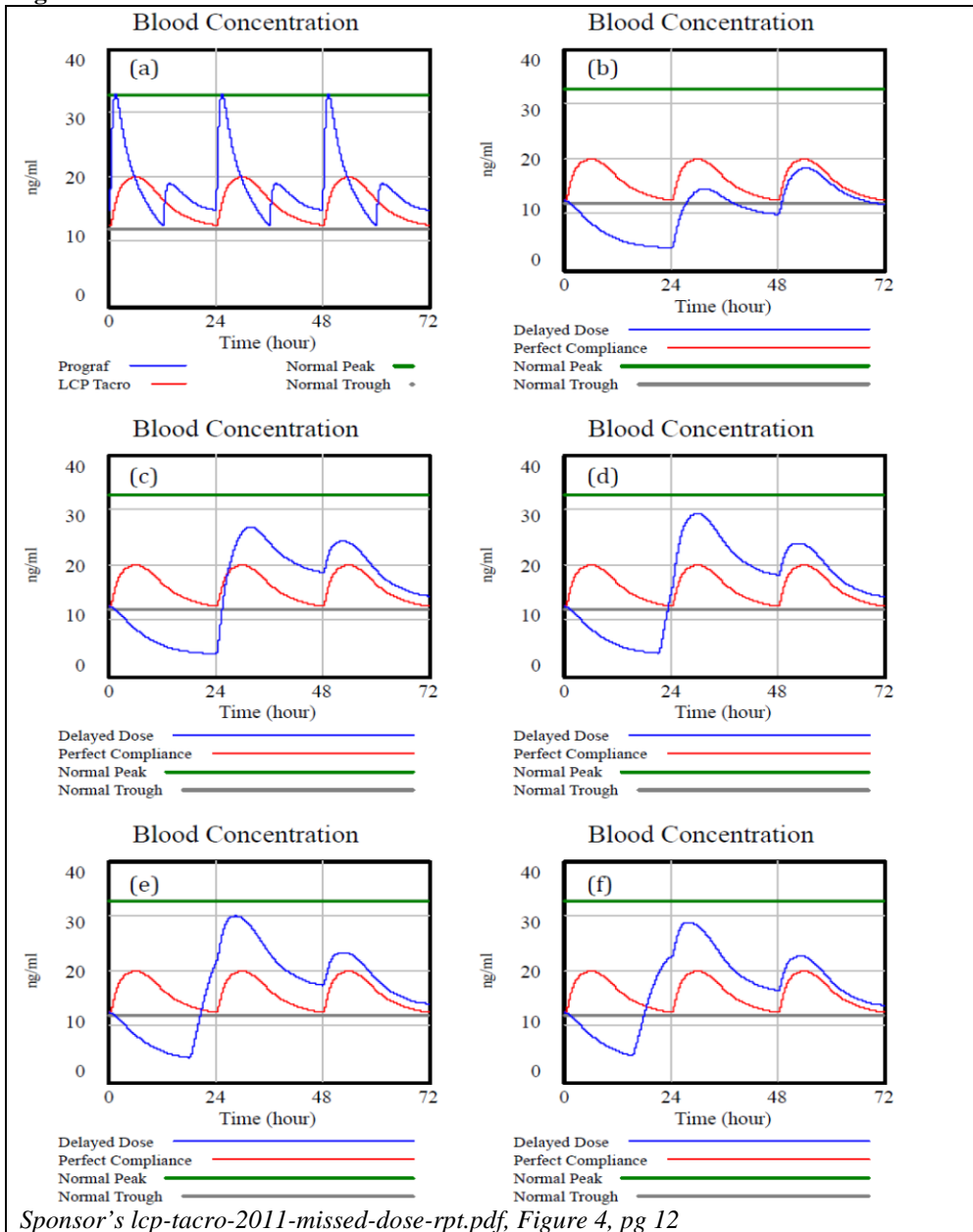
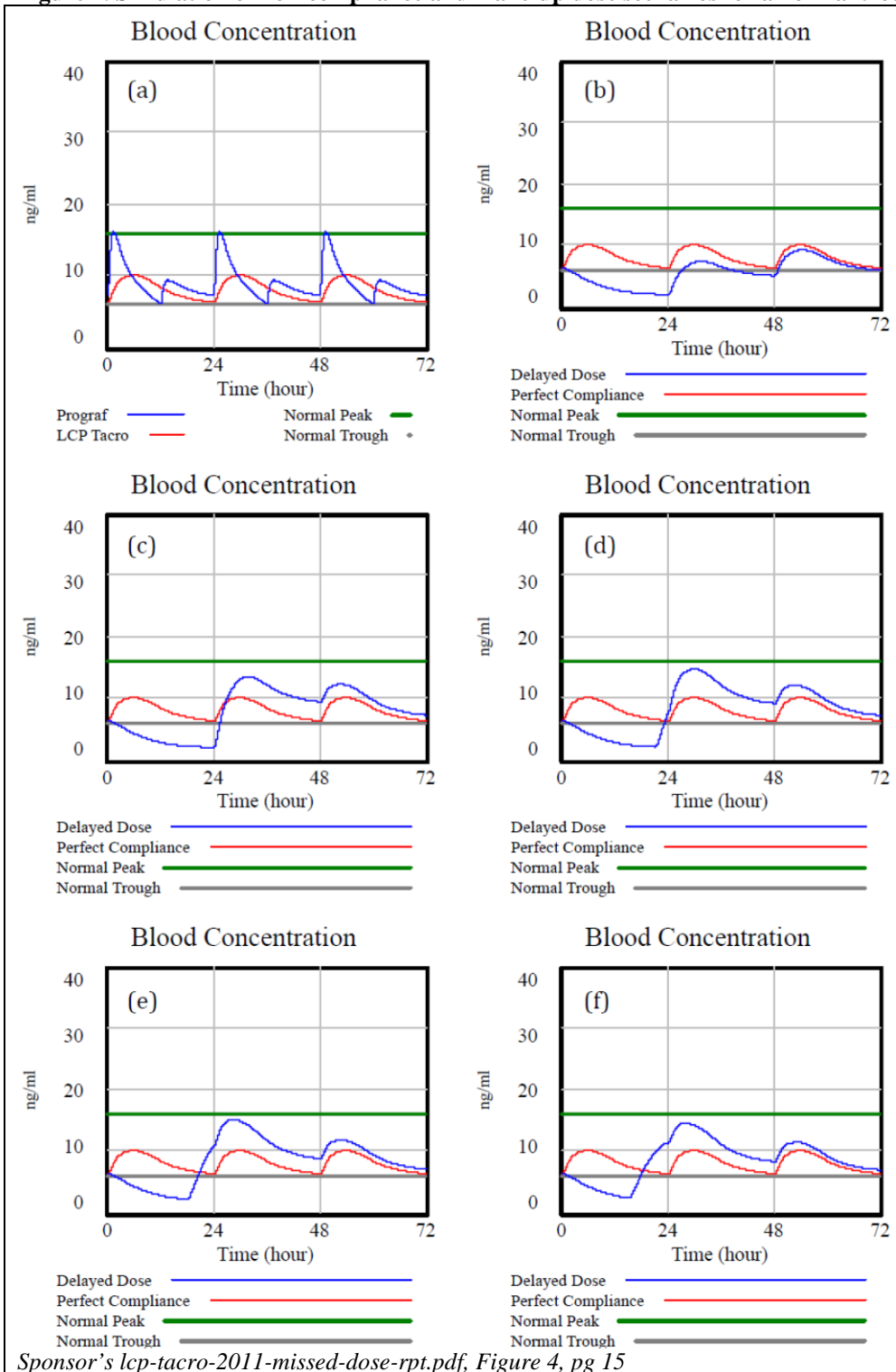


Figure 4. Simulation of non-compliance and make-up dose scenarios for a normal trough of 6 ng/mL



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

/s/

JEFFRY FLORIAN
07/09/2015

YANING WANG
07/09/2015

PHILIP M COLANGELO
07/09/2015

BIOPHARMACEUTICS REVIEW-Resubmission			
Division of Biopharmaceutics			
Office of New Drug Products, OPQ			
Application No.:	NDA 206406 Seq. 0046 Class 1 Resubmission	Reviewer: Banu Sizanli Zolnik, Ph.D.	
Resubmission Date:	June 12, 2015		
Division:	Division of Transplant and Ophthalmology	Team Lead (Acting): Elsbeth Chikhale, Ph.D.	
Applicant:	Veloxis Pharmaceuticals, Inc.		
Trade Name:	Envarsus XR	Acting Branch Chief: Angelica Dorantes, Ph.D.	
Generic Name:	Tacrolimus extended release tablets	Date Assigned:	June 17, 2015
Proposed Indication:	For the prophylaxis of transplant rejection in kidney transplant patients converted from tacrolimus immediate release preparations in combination with other immunosuppressants	Date of Review:	June 25, 2015
Dosage Form/strength	Extended Release Tablets/ 0.75 mg, 1 mg, and 4 mg	Route of Administration: Oral	
Background: NDA 206406 for Envarsus XR (tacrolimus extended release tablets), 0.75 mg, 1 mg, and 4 mg was tentatively approved on 10/30/2014 for prophylaxis of organ rejection in kidney transplant patients. Submission: The original NDA 206406 was tentatively approved because the use of Envarsus XR in de novo patients was blocked by Astragraf XL's exclusivity. In this class 1 Resubmission of NDA 206406 for Envarsus XR the Applicant proposes to omit the labeling information regarding the use of Envarsus XR in de novo patients (which is covered by Astragraf XL's exclusivity) while adding the use of Envarsus XR in patients converted from immediate release tacrolimus to Envarsus XR (which is not covered by Astragraf XL's exclusivity). Please note that an addendum to the original Biopharmaceutics review by Dr. Banu S. Zolnik, entered in DARRTS on 10/16/2014 recommended Approval for the original NDA during the first review cycle.			

Recommendation

Since the labeling changes (indication for the conversion of patients who are stable on immediate release tacrolimus to Envarsus XR and omission of the use of Envarsus in de novo patients) do not impact any of the Biopharmaceutics studies reviewed in the first cycle of the review, the Biopharmaceutics team's recommendation regarding approval of NDA 206406 remains unchanged.

From the Biopharmaceutics perspective, NDA 206406 for Envarsus XR (tacrolimus extended release tablets) 0.75 mg, 1 mg, and 4 mg is recommended for **APPROVAL**.

**Banu S.
Zolnik
-S**

Digitally signed by
Banu S. Zolnik -S
DN: c=US, o=U.S.
Government, ou=HHS,
ou=FDA, ou=People,
cn=Banu S. Zolnik -S,
0.9.2342.19200300.10
0.1.1=1300438310
Date: 2015.06.25
11:59:28 -04'00'

Banu Sizanli Zolnik, Ph. D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products , OPQ

**Elsbeth
G.
Chikhale
-S**

Digitally signed by
Elsbeth G. Chikhale -S
DN: c=US, o=U.S.
Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.
1.1=1300136142,
cn=Elsbeth G. Chikhale
-S
Date: 2015.06.25
16:50:59 -04'00'

Elsbeth Chikhale, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products, OPQ

cc: Angelica Dorantes, Ph.D.

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

/s/

NAVDEEP BHANDARI
06/30/2015

CLINICAL PHARMACOLOGY REVIEW

NDA: 206406	Submission Date: June 12, 2015
Brand Name	ENVARUSUS XR
Generic Name	Extended Release Tacrolimus
Reviewer	N/A
Team Leader	Philip M. Colangelo, Pharm.D, Ph.D.
OCP Division	DCP 4
OND Division	DTOP
Sponsor	Veloxis Pharmaceuticals, Inc.
Submission Type; Code	Class 1 Resubmission
Formulation; Strength(s)	Tablets; 0.75 mg, 1.0 mg, 4.0 mg
Proposed Indication	Prophylaxis of organ rejection in kidney transplant patients converted from tacrolimus immediate release formulations, in combination with other immunosuppressants
Dosage and Administration for Conversion from Tacrolimus Immediate Release Formulation	Dose of ENVARUSUS XR once daily (QD) is 80% of the total daily dose of the tacrolimus immediate release formulation

1. EXECUTIVE SUMMARY

The Sponsor, Veloxis Pharmaceuticals, Inc., submitted a Class 1 Resubmission for NDA 206406 for ENVARUSUS XR (extended release tacrolimus) that consisted of proposed labeling for the indication of prophylaxis of organ rejection in kidney transplant patients converted from tacrolimus immediate release formulations, in combination with other immunosuppressants. The Clinical Pharmacology review associated with this “conversion” indication was performed by Dr. Gerlie Gieser (*see review dated 09/25/2014*).

1.1. Recommendation

Section 7. Drug Interactions and Section 12.2. Pharmacokinetics of the Sponsor-proposed June 12, 2015 version of the “conversion” labeling were reviewed and were found to be generally acceptable. However, since this labeling pertains only to kidney transplant recipients who are converted from an immediate release tacrolimus formulation to ENVARUSUS XR, there is one reviewer proposed edit under Section 12.2. Pharmacokinetics, *Absorption* as follows (marked in red as a deletion):

Absorption

Absorption of tacrolimus from the gastrointestinal tract after oral administration is incomplete and variable. [REDACTED] (b) (4)

[REDACTED] In healthy subjects, the oral bioavailability of ENVARSUS XR was approximately 50% higher as compared with both tacrolimus immediate-release and extended-release formulations at steady state. In healthy subjects who received single ENVARSUS XR doses ranging from 5 mg to 10 mg, the mean AUC and C₂₄ of tacrolimus increased linearly and the elimination half-life did not change with increasing doses.

Philip M. Colangelo, Pharm.D., Ph.D.

Clinical Pharmacology Team Leader

OTS/OCP/DCP 4

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

/s/

PHILIP M COLANGELO
06/25/2015

**CLINICAL PHARMACOLOGY REVIEW
ADDENDUM**

NDA:	206-406
Submission Date:	30 December 2013
Drug Product:	Tacrolimus extended release oral tablets (0.75, 1.0, 4.0 mg)
Trade Name:	ENVARUSUS® XR
Sponsor:	Veloxis Pharmaceuticals, Inc.
Submission Type:	505(b)(2) NDA; Standard review
Indication:	Prevention of organ rejection in kidney transplant recipients
Pharmacometrics Reviewer	Jeffrey Florian, PhD
Pharmacometrics Team Leader	Yaning Wang, PhD
OCP Reviewer:	Gerlie Gieser, PhD
OCP Team Leader:	Philip Colangelo, PharmD, PhD

During labeling negotiations with the sponsor of the ENVARUSUS® XR NDA, the proportion of *de novo* kidney transplant patients with tacrolimus whole blood trough concentrations that were above 20 ng/mL or above 30 ng/mL at each study visit in Phase 3 Study 3002 was calculated by the reviewer. The reviewer's analysis results are summarized in Tables 1 and 2. During the first 1 to 2 weeks post-transplant, it was determined that there was a higher proportion of Envarsus XR patients with tacrolimus trough concentrations that were > 20 ng/mL or > 30 ng/mL compared to Prograf patients in Study 3002.

Table 1. Proportion of *de novo* kidney transplant patients with tacrolimus whole blood trough concentrations **above 20 ng/mL** in Study 3002

Study Visit	Study Visit (Target Day)	Study Visit (Window)	Envarsus XR			Prograf		
			≤20 ng/mL	>20 ng/mL	% >20 ng/mL	≤20 ng/mL	>20 ng/mL	% >20 ng/mL
Day 2	2	2	143	23	13.9	179	6	3.2
Day 3	3	3	186	44	19.1	223	5	2.2
Day 4	4	4	170	46	21.3	220	4	1.8
Day 7	7	6-11	187	24	11.4	228	3	1.3
Day 10	10	9-11	178	14	7.3	193	3	1.5
Week 2	14	12-17	233	7	2.9	246	2	0.8
Week 3	21	18 - 25	234	5	2.1	240	6	2.4
1 Month	30	26 - 37	229	5	2.1	244	2	0.8
1.5 Months	45	38 - 52	232	4	1.7	238	1	0.4
2 Months	60	53 - 74	230	4	1.7	236	1	0.4
3 Months	90	75 - 104	230	1	0.4	238	0	0
4 Months	120	105 - 149	222	3	1.3	236	0	0
6 Months	180	150 - 224	222	0	0	230	0	0
9 Months	270	225 - 314	214	2	0.9	222	0	0
12 Months	360	315 - 404	210	2	0.9	221	1	0.5

Table 2. Proportion of *de novo* kidney transplant patients with tacrolimus whole blood trough concentrations **above 30 ng/mL** in Study 3002

Study Visit	Study Visit (Target Day)	Study Visit (Window)	Envarsus XR			Prograf		
			≤30 ng/mL	>30 ng/mL	% >30 ng/mL	≤30 ng/mL	>30 ng/mL	% >30 ng/mL
Day 2	2	2	163	3	1.8	185	0	0
Day 3	3	3	220	10	4.4	227	1	0.4
Day 4	4	4	210	6	2.8	224	0	0
Day 7	7	6-11	209	2	1.0	231	0	0
Day 10	10	9-11	191	1	0.5	196	0	0
Week 2	14	12-17	240	0	0.0	248	0	0
Week 3	21	18 - 25	238	1	0.4	245	1	0.4
1 Month	30	26 - 37	234	0	0	246	0	0
1.5 Months	45	38 - 52	236	0	0	239	0	0
2 Months	60	53 - 74	234	0	0	237	0	0
3 Months	90	75 - 104	231	0	0	238	0	0
4 Months	120	105 - 149	225	0	0	236	0	0
6 Months	180	150 - 224	222	0	0	230	0	0
9 Months	270	225 - 314	216	0	0	222	0	0
12 Months	360	315 - 404	212	0	0	222	0	0

Gerlie Gieser, Ph.D.
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology 4
Office Clinical Pharmacology

Jeffry Florian, Pharm.D.
Acting Team Leader,
Division of Pharmacometrics,
Office Clinical Pharmacology

Yaning Wang, Ph.D.
Deputy Director,
Division of Pharmacometrics,
Office Clinical Pharmacology

Philip M. Colangelo, Pharm.D., Ph.D.
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology 4
Office Clinical Pharmacology

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
10/15/2014

JEFFRY FLORIAN
10/15/2014

YANING WANG
10/16/2014

PHILIP M COLANGELO
10/16/2014

BIOPHARMACEUTICS REVIEW-ADDENDUM			
Office of New Drug Quality Assessment			
Application No.:	NDA 206-406	Reviewer: Banu Sizanli Zolnik, Ph.D.	
Division:	Division of Transplant and Ophthalmology		
Applicant:	Veloxis Pharmaceuticals, Inc.	Team Leader: Angelica Dorantes, Ph.D.	
Trade Name:	Envarsus XR	Acting Supervisor: Paul Seo, Ph.D.	
Generic Name:	Tacrolimus extended release tablets	Date Assigned:	January 18, 2014
Indication:	For the prophylaxis of transplant rejection in adult kidney allograft recipients	Date of Review:	October 6, 2014
Formulation/strength	Extended Release Tablets, 0.75 mg, 1 mg, and 4 mg	Route of Administration: Oral	
Type of Submission: 505 (b)(2)		PDUFA DATE	October 30, 2014

SYNOPSIS

Submission:

NDA 206-406 is a 505(b)(2) submission for tacrolimus, an approved drug in a new extended release formulation.

Review:

This document is an Addendum to the original ONDQA-Biopharmaceutics review by Dr. Banu S. Zolnik, entered in DARRTS on 9/25/2014. The following recommendation was included in the original review:

*“At this time of the review process (GRMP date) the Office of Scientific Investigations has not provided inspection report for the clinical and analytical sites of bioequivalence studies No. 1020 and 1023 and therefore the information needed to finalize the review of these studies is lacking. From the Biopharmaceutics perspective, the recommendation on the approvability of NDA 206-406 for Tacrolimus ER Tablets is **PENDING**”*

This Addendum is focused on the evaluation of the information provided by the Office of Scientific Investigations (OSI) in their inspection report for BE for studies No.1020, and 1023.

The consult reports from the Office of Scientific Investigations (OSI) were log-in in DARRTS on October 3, 2014. The following studies were part of the OSI inspection:

Study No.: *LCP-Tacro 1020*

Study Title: *“A Two-Way Crossover, Open-Label, Multiple-Dose, Fasting, Bioequivalence Study of LCP Tacro™ 1 mg Tablets (Formulation F) Versus LCPTacro™ 1 mg Tablets (Formulation D) in Normal, Healthy, Non-Smoking Male and Female Caucasian Subjects.”*

Study No.: *LCP-Tacro 1023*

Study Title: *“A Two-Way Crossover, Open-Label, Multiple-Dose, Fasting, Bioequivalence Study of LCP Tacro™ 4 mg Tablets (Formulation G) Versus LCPTacro™ 4mg Tablets (Formulation F) in Normal, Healthy, Non-Smoking Male and Female Caucasian Subjects.”*

Study #: *LCP-Tacro 1024*

Study Title: *“The Determination of Tacrolimus in Human Whole Blood by High Performance Liquid Chromatography- Tandem Mass Spectrometry”*

The OSI inspection report concluded that the results from the clinical and bioanalytical portion of the aforementioned BE studies are adequate and recommended that the data from these BE studies be accepted.

Reviewer’s Overall Assessment of BE Studies: *SATISFACTORY*

This Reviewer concurs with the overall recommendation provided in the OSI’s Inspection Report and therefore, the clinical and analytical data for BE studies LCP-Tacro 1020 and 1023 are reliable and the studies are found acceptable.

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 206-406 for Envarsus XR (tacrolimus extended release tablets) is recommended for **APPROVAL**.

Banu Sizanli Zolnik, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: Paul Seo

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

/s/

BANU S ZOLNIK
10/16/2014

ANGELICA DORANTES
10/16/2014

BIOPHARMACEUTICS REVIEW			
Office of New Drug Quality Assessment			
Application No.:	NDA 206-406	Reviewer: Banu Sizanli Zolnik, Ph.D.	
Division:	Division of Transplant and Ophthalmology		
Applicant:	Veloxis Pharmaceuticals	Team Leader: Angelica Dorantes, Ph.D.	
Trade Name:	Envarsus XR; LCP-Tacro TM	Acting Supervisor: Paul Seo, Ph.D.	
Generic Name:	Tacrolimus extended release tablets	Date Assigned:	January 18, 2014
Indication:	For the prophylaxis of transplant rejection in adult kidney allograft recipients	Date of Review:	September 24, 2014
Formulation/strength	Extended Release Tablets, 0.75 mg, 1 mg, and 4 mg	Route of Administration: Oral	
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission Dates Original Submission dated 12/30/2014 S0006 dated 03/14/2014 S0009 dated 04/15/2014 S0010 dated 04/25/2014 S0018 dated 07/18/2014 S0023 dated 09/10/2014		Date of informal/Formal Consult	PDUFA DATE
		NA	October 30, 2014
Type of Submission:	505 (b) (2)		
Key review points	1. Dissolution acceptance criteria 2. In vitro alcohol dose-dumping 3. Biowaiver request supporting approval of the lower strengths 4. Bridging across phases of drug development 5. Evaluation of the data supporting the extended release claim		

TABLE OF CONTENTS

I) SUMMARY OF BIOPHARMACEUTICS FINDINGS	4
RECOMMENDATION	6
III) QUESTION BASED REVIEW – BIOPHARMACEUTICS EVALUATION	7
A) GENERAL ATTRIBUTES	7
1 What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?.....	7
2 Is there any information on BCS classification? What claim did the applicant make based on BCS classification? What data are available to support this claim?	8
3 Does the proposed product meet the extended release designation claim? What data are provided to support the Applicant’s claim?	8
B) DISSOLUTION INFORMATION	10
4 What is the proposed dissolution method?	10
5 What data are provided to support the adequacy of the proposed dissolution method (e.g. medium, apparatus selection, etc.)?	11
6 What information is available to support the robustness (e.g. linearity, accuracy, etc.) of the dissolution methodology?	11
7 What data are available to support the discriminating power of the method?.....	11
8 Is the proposed dissolution method bio-relevant? What data are available to support this claim?	12
9 Is the proposed method acceptable? If not, what are the deficiencies?	12
B.2. ACCEPTANCE CRITERIA	12
10 What are the proposed dissolution acceptance criteria for this product?	12
11 What data are available to support these criteria?	12
12 Are the acceptance criteria acceptable? If not, what are the recommended criteria? Is the setting of the dissolution acceptance criteria based on data from clinical and registration batches? If not, is the setting based on BE or IVIVC data?	15
C) DRUG PRODUCT FORMULATION DEVELOPMENT AND BRIDGING ACROSS PHASES	15
13 What are the highlights of the drug product formulation development?.....	15
14 Are there any manufacturing changes implemented (e.g. formulation changes, process changes, site change, etc.) to the clinical trial formulation? What information is available to support these changes?	15

NDA 206406 Biopharmaceutics Review

15 Bioanalytical Method Validation Data 22

16 Are all the strengths evaluated in the pivotal clinical trials? What data are available to support the approval of lower strengths? 22

D) DISSOLUTION APPLICATIONS..... 23

D.1 BIOWAIVERS..... 23

17 Is there a request for a waiver of the submission of in vivo BE data (Biowaiver)? What is the purpose of the biowaiver request?..... 23

18 Is there any in vitro alcohol dose-dumping information submitted? What data are provided to support the Applicant’s claim of lack of dose-dumping in the presence of alcohol?..... 27

D) SUMMARY OF BIOPHARMACEUTICS FINDINGS

Submission: This 505(b)(2) NDA submission contains tacrolimus, an approved drug in a new extended release formulation. FDA’s approved tacrolimus products include, Prograf® 0.5 mg, 1 mg, and 5 mg (NDA 50708, Approval Date April 8, 1994) and Astagraf XL (NDA 204096, 0.5 mg, 1 mg, and 5 mg, Approval date: July 19 2013).

Review: The Biopharmaceutics review is focused on;

- 1) The evaluation of the proposed acceptance criteria,
- 2) The evaluation of the biowaiver request for the lower strengths,
- 3) The evaluation of the dissolution data included in the in vitro alcohol induced dose dumping study,
- 4) The evaluation and acceptability of the bridging bioequivalence studies supporting the approval of the proposed drug product, and 5) evaluation of the data supporting the extended release claim.

Dissolution Method: ACCEPTABLE

It is noted that the data supporting the dissolution method was previously evaluated under the IND. The following method is acceptable for release and stability testing .

USP Apparatus	Rotation Speed	Medium Volume	Temperature	Medium
USP II (paddles)	100 rpm	900 mL	37°C ± 0.5°C	Water + 0.005% hydroxypropyl cellulose (HPC) + 0.50% SLS adjusted to pH 4.5 ± 0.2 (2N Acetic Acid)
Sampling Times: 0, 2.5, 6, and 12 hours				

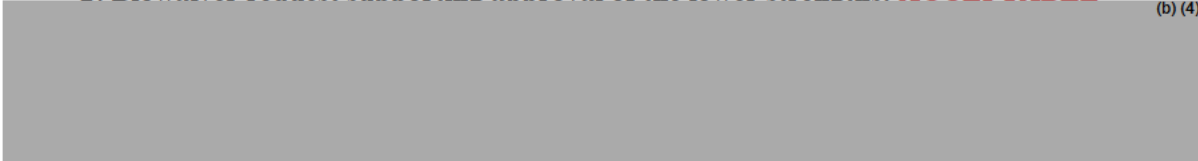
For specific information on the dissolution method, refer to Dr. John Duan’s reviews for IND 75-250/SDN029, SDN038 and SDN064 in DARRTS.

1) Dissolution acceptance criteria: ACCEPTABLE

The following proposed dissolution acceptance criteria limits are found acceptable.

Dissolution Acceptance Criteria	
2.5 hours:	(b) (4) %
6.5 hours:	%
12 hours	%

2) Biowaiver request supporting approval of the lower strengths: ACCEPTABLE



(b) (4)

Therefore, the Applicant supported the approval of the 1 mg and 0.75 mg lower strengths as follows:

- For the 1 mg strength, a BE study (No.1024) comparing the 4 mg and 1 mg strengths was conducted. The study results support the approval of the 1 mg strength. (a biowaiver is not needed).
- For the 0.75 mg strength, a biowaiver was requested. The following data were provided to support the approval of the biowaiver request for the 0.75 mg:
 - BE study No. 1024 for the 1 mg,
 - Information demonstrating the proportionality between the composition of the 1 mg and 0.75 mg formulations
 - Comparative dissolution profiles between the 1 mg and 0.75 mg with statistical f2 testing ^{(b) (4)} indicating similarity between these strengths.

3) In vitro alcohol dose-dumping: **SATISFACTORY**

The Applicant conducted in vitro alcohol dose dumping studies in presence of alcohol with varying concentrations (5%, 10%, 20% and 40%) in the dissolution media at two different pH conditions (pH 1.2 and 4.5). **The dissolution profile data show absence of alcohol induced dose dumping.** However, the results showed that drug release is increased from 5% to 15% at 2.5 hours in the presence of ~40% alcohol at pH 1.2 for the 0.75 mg strength. Similar trends were also observed for the 1 mg and 4 mg strengths.

4) Bridging throughout phases of drug product development: **PENDING**

The formulation changes throughout product's development are supported by the result of three BA/BE studies-Study 1018, 1020, and 1023 linking the early formulations to the to-be-marketed formulation as described in the section for drug product formulation development and bridging throughout product's development phases. However, it is noted that The Office of Scientific Investigation (OSI) inspection report supporting the data from the analytical and clinical sites of BE studies 1020 and 1023 is currently pending and therefore the final approval of the bridging BA/BE studies is also pending.

5) Evaluation of the data supporting the extended release claim: **SATISFACTORY**

The following information was reviewed in support of the extended release designation claim of the proposed product per stated in CFR 320.25 (f):

- 1) The data from multiple dose Study S1016, demonstrated that the tacrolimus steady-state performance show that degree of fluctuation is lower (84.72% versus 159.78%) as compared with immediate release tacrolimus formulation Prograf 0.5 mg given twice daily. Similar trends were observed in the study S2017 in stable kidney transplant patients.
- 2) The drug product has a less frequent dosing interval (i.e., once daily) as oppose to twice-daily for the commercial tacrolimus immediate release product.

RISK ASSESSMENT EVALUATION:

The Table below presents the risk assessment for the dissolution quality attribute of the proposed Tacrolimus extended release tablets.

From Initial Quality Assessment			Review Assessment		
Product attribute / CQA	Factors that can impact the CQA	Risk Ranking*	Risk Mitigation Approach	Risk Evaluation [Acceptable/ Unacceptable]	Lifecycle Considerations/ Comments**
Dissolution	Potential risk to crystalline conversion can impact the dissolution`	Medium	XRPD method will be used to monitor crystalline content throughout product's life cycle.	Acceptable	Post-marketing commitment to utilize XRPD method to monitor the crystalline content. See Dr. Mark Seggel CMC review for specific details

* Risk ranking applies to product attribute/CQA (L, M, H)

RECOMMENDATION

At this time of the review process (GRMP date) the Office of Scientific Investigations has not provided inspection report for the clinical and analytical sites of bioequivalence studies #1020 and 1023.and therefore the information needed to finalize the review of these studies is lacking. From the Biopharmaceutics perspective, the recommendation on the approvability of NDA 206-406 for Tacrolimus ER Tablets is **PENDING**.

After the report from OSI is received and reviewed, an Addendum to this Original Review with the final Biopharmaceutics recommendation on the approvability of this NDA will be filed in DARRTS.

Banu Sizanli Zolnik, Ph. D.
 Biopharmaceutics Reviewer
 Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
 Biopharmaceutics Team Leader
 Office of New Drug Quality Assessment

cc: Paul Seo

III) QUESTION BASED REVIEW – BIOPHARMACEUTICS EVALUATION

A) GENERAL ATTRIBUTES

- 1 What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?

Drug Substance

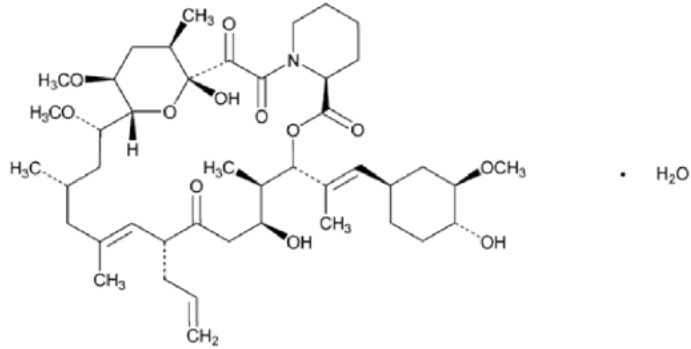


Figure 1: Structure of Tacrolimus

Description: Tacrolimus monohydrate is a white to off-white powder.

Solubility: Tacrolimus is insoluble in water

Drug Product

Table 1 Qualitative and quantitative composition of tacrolimus extended release tablets

Name of ingredient	Amount per extended-release tablet [mg/unit]		
	0.75 mg	1 mg	4 mg
Drug Substance			

(b) (4)

Reviewer's Comment



Therefore, the biowaiver request, which is discussed in Section D1, is only applicable to the lowest 0.75 mg strength because the 1 mg strength is supported by BE study #1024 comparing the 4 mg vs. the 1 mg strength. The biowaiver for the 0.75 mg strength is supported by BE study # 1024, the comparative dissolution profile data between the 0.75 mg and the 1 mg tablets, and the 1mg and 0.75 mg tablets, which are considered qualitatively the same and quantitatively dose proportional.

2 Is there any information on BCS classification? What claim did the applicant make based on BCS classification? What data are available to support this claim?

According to the Biopharmaceutics review by Dr. John Duan, tacrolimus is BCS Class II drug.

3 Does the proposed product meet the extended release designation claim? What data are provided to support the Applicant's claim?

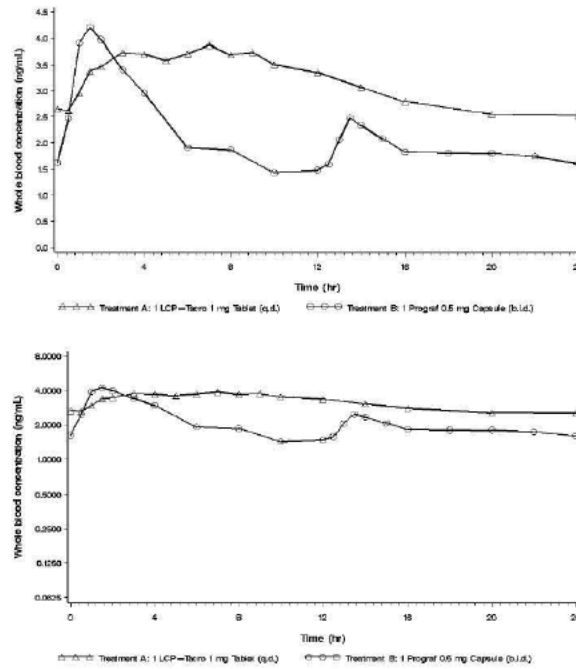
The following information was reviewed in support of the extended release designation claim of the proposed product per stated in CFR 320.25 (f):

- 1) The data from multiple dose Study S1016, demonstrated that the tacrolimus steady-state performance show that degree of fluctuation is lower (84.72% versus 159.78%) as compared with immediate release tacrolimus formulation Prograf 0.5 mg given twice daily. Similar trends were observed in the study S2017 in stable kidney transplant patients.
- 2) The drug product has a less frequent dosing interval i.e., once daily as oppose to twice-daily tacrolimus immediate release product.

¹ For more information refer to the IND 75,250 SDN 064 Biopharmaceutics Review dated 9/22/2010 by Dr. John Duan

**Mean whole blood tacrolimus concentration versus time
(as provided in the study report for Study 1016)**

Figure 11.4.2 – Mean Whole Blood Tacrolimus Concentration Versus Time, Linear Scale (upper panel), Semi-Log Scale (lower panel) (n=17) for Day 10



(b) (4)

Study No.: 3423 (LCP-Tacro 1016)
LCP-Tacro 1 mg Tablets

Table 11.4.2 – Pharmacokinetic Parameters for Tacrolimus on Day 10

Pharmacokinetic Parameter	Geometric Mean (%CV) Arithmetic Mean ± SD	
	LCP-Tacro 1 mg Tablets (q.d.) (A) (n=17)	Prograf [®] 0.5 mg Capsules (b.i.d.) (B) (n=15)
AUC _τ [‡] (ng·hr/mL)	70.67 (40.54) 75.50 ± 30.61	48.42 (32.54) 50.57 ± 16.45
AUC ₀₋₁₂ (ng·hr/mL)	39.74 (39.26) 42.39 ± 16.64	27.50 (26.82) 28.36 ± 7.60
AUC ₁₂₋₂₄ (ng·hr/mL)	30.51 (45.48) 33.12 ± 15.06	20.76 (41.01) 22.21 ± 9.11
C _{max} (ng/mL)	4.36 (37.84) 4.65 ± 1.76	4.42 (22.64) 4.53 ± 1.03
C _{min} (ng/mL)	2.32 (50.08) 2.53 ± 1.27	1.50 (40.24) 1.59 ± 0.64
C ₁₂ (ng/mL)	3.12 (42.10) 3.35 ± 1.41	1.39 (38.46) 1.47 ± 0.57
C _{avg} (ng/mL)	2.94 (40.54) 3.15 ± 1.28	2.02 (32.54) 2.11 ± 0.69
T _{max} (hr)*	6.00 (1.50 – 10.00)	1.55 (1.00 – 8.00)
t _{1/2} (hr)	36.89 ± 7.74	33.88 ± 7.51
K _{el} (hr ⁻¹)	1.96E-02 ± 4.02E-03	2.13E-02 ± 4.30E-03
Degree of Fluctuation (%)	84.72 ± 42.07	159.78 ± 49.48
Degree of Swing (%)	97.31 ± 64.18	204.54 ± 78.14
R	2.35 ± 0.83 [†]	2.21 ± 0.78
C _{max} /C _{min}	1.97 ± 0.64	3.05 ± 0.78
AUC ₀₋₁₂ /C ₁₂ (hr)	12.95 ± 2.53	19.93 ± 2.56
AUC _τ /C _{min} [‡] (hr)	30.80 ± 4.47	32.44 ± 3.56
AUC ₁₂₋₂₄ /C _{min} (hr)	13.27 ± 1.65	13.93 ± 1.68

* median (min – max)
[†] n = 16 [‡] τ = 24 hrs

B) DISSOLUTION INFORMATION

B.1. DISSOLUTION METHOD

4 What is the proposed dissolution method?

The dissolution method was accepted during the IND stage. For further information refer to the reviews by Dr. John Duan for IND 75-250/SDN029, SDN038 and SDN064 in DARRTS. The following table shows the approved dissolution method.

USP Apparatus	Rotation Speed	Medium Volume	Temperature	Medium
USP II (paddles)	100 rpm	900 mL	37°C ± 0.5°C	Water + 0.005% hydroxypropyl cellulose (HPC) + 0.50% SLS adjusted to pH 4.5 ± 0.2 (2N Acetic Acid)
Sampling Times: 0, 2.5, 6, and 12 hours				

Reviewer's Comment:

There is a concern about the possibility of the (b) (4) which could adversely impact the product performance. This concern was communicated to the Applicant in the August 2, 2013 Meeting's Preliminary Comments and also during Pre-NDA meeting dated August 7, 2013, and a number of recommendations were made regarding potential methodology (e.g. direct spectroscopic, calorimetric, and dissolution). However, the Applicant did not provide adequate information in the Original Submission. Therefore an Information Request (IR) Letter was sent on 04/01/2014. The comments for the dissolution methodology included in the IR letter are shown below.

- **Dissolution testing has also proven useful for detecting (b) (4) in drug products. We note that high paddle speeds and surfactant concentrations typically mask the discriminating power. Use of a discriminating dissolution test for control of (b) (4) form is consistent with ICH Q6A, Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, which states that dissolution testing may be a surrogate for a direct test for changes in (b) (4) form.**

Therefore, please submit 24-hour dissolution profiles of the drug product (and (b) (4) prepared with 0, 2.5, 5, 10, 15 and 20% crystalline content. Profiles should be obtained using the currently proposed regulatory method, as well as in dissolution media containing 0.01 to 0.1% sodium laurel

sulfate. The effect of paddle speed (50 rpm and 75 rpm) should also be evaluated. Comparison of results obtained by, for example, XRPD and dissolution testing will be informative.

The discriminating test method, whether XRPD, NIR, dissolution testing or other sensitive (i.e., (b) (4) % crystalline content), robust and validated procedure, should then be systematically applied to (b) (4) and drug product, including clinical batches, at release and on stability under long term, accelerated and stress storage conditions. Based on the results, please propose a clinically relevant acceptance criterion for crystalline content.

Reviewer's Comment on the Applicant's Response in an Amendment S0009 dated April 15, 2014: NOT SATISFACTORY

The Applicant claimed that their dissolution method is not able to discriminate between crystalline and (b) (4) forms of tacrolimus. However, their response is not satisfactory since the Applicant only provided data collected at (b) (4) rpm and did not attempt to develop an additional dissolution method with discriminating power.

Reviewer's Comment on the Applicant's Response in an Amendment S0018 dated July 18, 2014: SATISFACTORY

On July 14, 2014, T-con was held with the Applicant. In the slides, the Applicant provided XRPD data for detection of crystalline material in the proposed drug product. Following this t-con in an amendment (Seq. 0018 dated 07/18/2014), the Applicant proposed XRPD as a primary method for crystal detection (refer to the CMC review by Dr. Mark Seggel for more information). From the Biopharmaceutics team's perspective, utilizing a sensitive analytical method such as XRPD in lieu of dissolution method is an acceptable approach.

5 What data are provided to support the adequacy of the proposed dissolution method (e.g. medium, apparatus selection, etc.)?

The data were provided under the IND. The dissolution method development report was evaluated by Dr. John Duan and the proposed method was found acceptable. Please refer to the Biopharmaceutics Reviews by Dr. Duan².

6 What information is available to support the robustness (e.g. linearity, accuracy, etc.) of the dissolution methodology?

Refer to response #5.

7 What data are available to support the discriminating power of the method?

Refer to response #5.

² Biopharmaceutics review IND 75-250/SDN029, SDN038 and SDN064 by John Duan

8 Is the proposed dissolution method bio-relevant? What data are available to support this claim?

Refer to response #5.

9 Is the proposed method acceptable? If not, what are the deficiencies?

Yes, the proposed dissolution method is acceptable. Refer to response #5.

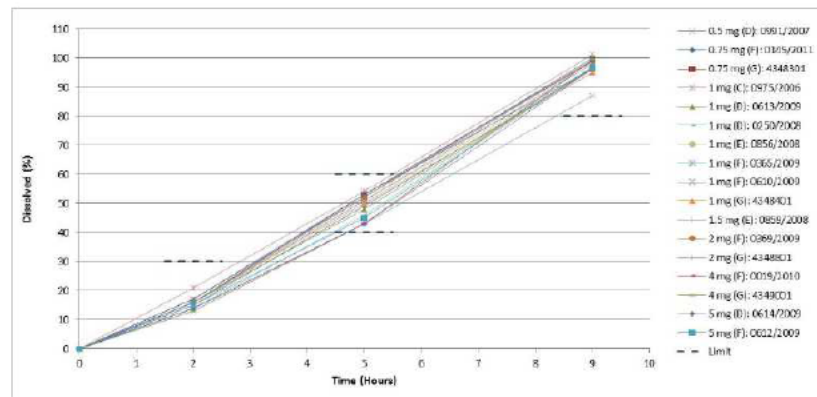
B.2. ACCEPTANCE CRITERIA

10 What are the proposed dissolution acceptance criteria for this product?

Proposed Dissolution Acceptance Criteria for Envarsus XR	
2.5 hours:	(b) (4) %
6.5 hours:	%
12 hours	

11 What data are available to support these criteria?

Figure 1: Dissolution profiles (mean values) from clinical batches including batches used for bioequivalence studies



In an IR letter dated April 18, 2014, the following comment was sent to the Applicant.

- *Provide the complete multipoint dissolution profile data from the bio-batches and registration stability batches supporting the selection of the sampling time-points and range vales for proposed acceptance criteria.*

Reviewer’s Assessment for the Applicant’s Response provided in an amendment S0010 dated April 25, 2014: NOT SATISFACTORY

The Applicant only provided mean drug release data collected at the acceptance criteria (2.5 hrs, 6 hrs, and 12 hours); therefore, the following IR comment was conveyed to the Applicant in an IR letter dated September 03, 2014.

- *We acknowledge the dissolution data from the registration batches you submitted on April 25, 2014 (Seq. 0010), however provide complete dissolution profile data (i.e. sampling time points at 0.5, 2.5, 4.5, 6.5, 8.5, 10, and 12 hour) in tabulated (raw and mean values) and graphical form (mean values) from the registration stability batches for each strength at the current stability time point or other more recent representative batches if available. Indicate the details for each batch such as age of batch, storage conditions, etc.*

Reviewer’s Assessment for the Applicant’s Response provided in an amendment S0023 dated September 10, 2014: SATISFACTORY

The Applicant re-iterated their selection of three time-point specification at 2.5 hrs, 6.5 hrs and 12 hours based on the justification that tacrolimus release is linear between 2.5 and 12 hours. The Applicant provided the dissolution data of the following batches at their current stability time point (ranging between 30-48 months). The drug dissolution data of one batch from each strength are shown here since drug release profiles are similar for each batch.

Envarsus XR, 0.75 mg, 30 Count Bottles

Dissolution (100 rpm): Envarsus XR, 0.75mg, 30ct bottle, bulk batch no. 0018-2010, packaging batch no. (b) (4) 25°C/60%RH, 48 months

	Time point (minutes)			
	0	150	390	720
% dissolved				(b) (4)
% dissolved				
% dissolved				
% dissolved				
% dissolved				
% dissolved				
Mean				
Rsd				



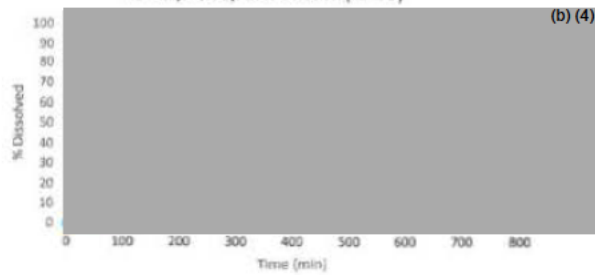
NDA 206406 Biopharmaceutics Review

Envarsus XR, 1mg, 30 Count Bottles

Dissolution (100 rpm): Envarsus XR, 1mg, 30ct bottle, bulk batch no. 0365/2009, packaging batch no. BE2044321i, 25°C/60%RH, 48 months

	Time point (minutes)
% dissolved	(b) (4)
% dissolved	(b) (4)
% dissolved	(b) (4)
% dissolved	(b) (4)
% dissolved	(b) (4)
% dissolved	(b) (4)
mean	(b) (4)
rsd	(b) (4)

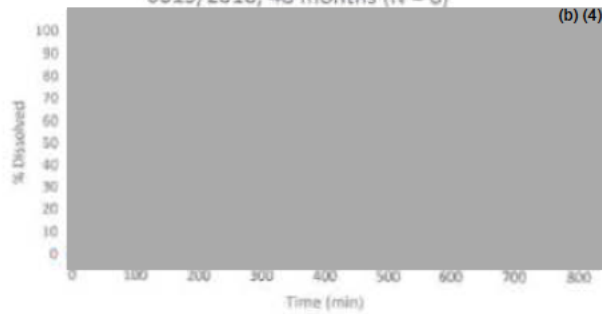
Envarsus XR, 1 mg Tablet, 30 ct bottle, 0365/2009, 48 months (N = 6)



Dissolution (100 rpm): Envarsus XR, 4mg, 30ct bottle, bulk batch no. 0019/2010, packaging batch no. BE2045263i, 25°C/60%RH, 48 months

	Time point (minutes)
% dissolved	(b) (4)
% dissolved	(b) (4)
% dissolved	(b) (4)
% dissolved	(b) (4)
% dissolved	(b) (4)
% dissolved	(b) (4)
mean	(b) (4)
rsd	(b) (4)

Envarsus XR, 4 mg Tablet, 30 ct bottle, 0019/2010, 48 months (N = 6)



- 12 Are the acceptance criteria acceptable? If not, what are the recommended criteria? Is the setting of the dissolution acceptance criteria based on data from clinical and registration batches? If not, is the setting based on BE or IVIVC data?**

The Applicant's proposed acceptance criteria limits for drug release comply with the FDA and ICH guidance recommendations. The following acceptance criteria are acceptable for batch release and on stability.

Dissolution Acceptance Criteria for Tacrolimus ER Tablets	
2.5 hours:	(b) (4)
6.5 hours:	%
12 hours:	

C) DRUG PRODUCT FORMULATION DEVELOPMENT AND BRIDGING ACROSS PHASES

- 13 What are the highlights of the drug product formulation development?**



(b) (4)



Reviewer's Comments:

The Applicant developed

(b) (4)



5 pages have been withheld immediately following this page as b4 (CCI/TS)

15 Bioanalytical Method Validation Data

The Applicant provided adequate information to support the validity of the bioanalytical methods used in bridging pharmacokinetic studies (Study 1018, 1020, 1023, and 1024). The analytical study reports can be found in the links below:

<\\cdsesub1\evsprod\nda206406\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\1018\1018-16-5.pdf>

<\\cdsesub1\evsprod\nda206406\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\1020\1020-16-5.pdf>

<\\cdsesub1\evsprod\nda206406\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\1023\1023-16-5.pdf>

<\\cdsesub1\evsprod\nda206406\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\1024\1024-16-5.pdf>

16 Are all the strengths evaluated in the pivotal clinical trials? What data are available to support the approval of lower strengths?

The Phase clinical studies -3002 and -3003 were conducted with all strengths (0.75, 1 and 4 mg). However, the Applicant conducted BE study 1024 to support the approval of 1 mg strength (b) (4)

D) DISSOLUTION APPLICATIONS

D.1 BIOWAIVERS

17 Is there a request for a waiver of the submission of in vivo BE data (Biowaiver)? What is the purpose of the biowaiver request?

The Applicant included a biowaiver request for (b) (4)

[REDACTED]

Therefore, the Applicant supported the approval of the 1 mg and 0.75 mg lower strengths as follows:

- A. For the 1 mg strength, a BE study (No.1024) comparing the 4 mg and 1 mg strengths was conducted. The study results support the approval of the 1 mg strength. (no biowaiver is needed).
- B. For the 0.75 mg strength, a biowaiver was requested. The following data were provided to support the approval of the biowaiver request for the 0.75 mg:
 - BE study No. 1024 for the 1 mg,
 - Information demonstrating the proportionality between the composition of the 1 mg and 0.75 mg formulations
 - Comparative dissolution profiles between the 1 mg and 0.75 mg with statistical f2 testing (b) (4) indicating similarity between these strengths.

➤ **Study 1024 – Bioequivalence between 4 mg and 1 mg formulations**

The Applicant conducted two-way cross over multiple-dose fasting relative bioavailability study between Formulation F LCP Tacro ER 1 X 4 mg vs. 4 X 1 mg in healthy subjects. It should be noted although Formulation F is not the to-be-marketed formulations as stated earlier, because of formulation F is shown to be bioequivalent to TBM formulation G, the BE study between 4 mg and 1 mg with Formulation F is appropriate.

STUDY RESULTS

The following tables summarize the mean data for the pharmacokinetic parameters for the 4 mg and 1 mg formulations for days 1 and 8, and the BA/BE results (tablets provided by the Applicant).

Table 11.4.1 – Pharmacokinetic Parameters for Tacrolimus on Day 1

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean $\pm$ SD	
	LCP-Tacro™ 4 mg Tablets (Formulation F) (B) (n=45)	LCP-Tacro™ 1 mg Tablets (Formulation F) (A) (n=46)
AUC ₀₋₂₄ (ng·hr/mL)	117.65 (27.55) 122.29 $\pm$ 33.69	119.13 (30.43) 125.45 $\pm$ 38.18
C ₂₄ (ng/mL)	3.20 (33.78) 3.41 $\pm$ 1.15	3.89 (40.41) 4.28 $\pm$ 1.73
C _{max} (ng/mL)	9.93 (33.10) 10.50 $\pm$ 3.47	8.05 (28.32) 8.41 $\pm$ 2.38
T _{max} (hr)*	6.00 (1.00 - 8.00)	8.00 (3.00 - 12.02)

* median (min – max)

Table 11.4.2 – Pharmacokinetic Parameters for Tacrolimus on Day 8

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean $\pm$ SD	
	LCP-Tacro™ 4 mg Tablets (Formulation F) (B) (n=45)	LCP-Tacro™ 1 mg Tablets (Formulation F) (A) (n=46)
AUC _{τ} (ng·hr/mL)	260.29 (23.08) 267.12 $\pm$ 61.64	257.29 (24.67) 265.36 $\pm$ 65.47
AUC _{τ} /C _{min}	36.21 (10.97) 36.40 $\pm$ 3.99	34.16 (15.92) 34.52 $\pm$ 5.49
C _{avg} (ng/mL)	10.83 (23.09) 11.12 $\pm$ 2.57	10.71 (24.70) 11.05 $\pm$ 2.73
C _{max} (ng/mL)	17.28 (25.85) 17.85 $\pm$ 4.61	14.71 (23.48) 15.12 $\pm$ 3.55
C _{max} /C _{min}	2.40 (21.04) 2.45 $\pm$ 0.52	1.95 (28.80) 2.02 $\pm$ 0.58
C _{min} (ng/mL)	7.19 (25.68) 7.42 $\pm$ 1.91	7.53 (30.02) 7.91 $\pm$ 2.38
T _{max} (hr)*	6.02 (1.00 - 12.02)	7.00 (1.00 - 16.02)
C _{pd} (ng/mL)	7.94 (30.06) 8.30 $\pm$ 2.49	7.93 (29.99) 8.32 $\pm$ 2.50
Degree of Fluctuation (%)	91.08 (26.14) 94.16 $\pm$ 24.61	63.53 (40.26) 67.75 $\pm$ 27.28
Degree of Swing (%)	137.21 (35.52) 145.18 $\pm$ 51.58	90.32 (57.13) 101.64 $\pm$ 58.06
R	2.21 (23.55) 2.27 $\pm$ 0.54	2.16 (34.34) 2.27 $\pm$ 0.78

* median (min – max)

Table 11.4.3 – Relative Bioavailability Analysis of LCP-Tacro™ 4 mg Tablets (Formulation F) (B) versus LCP-Tacro™ 1 mg Tablets (Formulation F) (A) for Tacrolimus on Day 8

Parameter	90% C.I.	Ratio of Means	Intra-Subject CV
AUC _τ	97.18% to 107.46%	102.19%	14.22%
C _{max}	112.49% to 124.62%	118.40%	14.49%

Bioequivalence Results calculated by the Reviewer

This Reviewer confirmed the BE results provided by the Applicant. The Phoenix software (Phoenix 64 Build 6.3.0.395) was used to re-analyze the raw data. The following results were obtained using Phoenix software.

Tacrolimus Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals (calculated by the reviewer)				
(Study No. 1024) Day 8				
Parameter	Treatment A (1 mg Formulation)	Treatment B (4 mg Formulation)	Ratio%	90% C.I.
AUC _{0-τ} (ng.h/mL)	253.28	259.15	102.32	97.28-107.62
C _{max} (ng/mL)	14.52	17.23	118.66	112.75-124.88

This Reviewer calculated BE results are in agreement with the Applicant's calculations for Day 8. The Applicant did not assess statistical analysis for Day 1. The Reviewer's calculated BE results for Day 1 show that 90% CI for C_{max} is within 113.66-132.50, and AUC 0-t is within 89.49-102.92.

Reviewer's Assessment for Study 1024 (4 vs. 1 mg Formulations): ACCEPTABLE

Although BE results for C_{max} is outside the regulatory boundaries for Day 1, these two strengths are considered BE to each other based on the Day 8.

Biowaiver Request for the Lowest 0.75 mg Strength

Adequate data were provided to support the biowaiver request for the 0.75 mg strength [i.e., BE data for the 1 mg strength (study No. 1024, information demonstrating the proportionality between the composition of the 1 mg and 0.75 mg formulations, and dissolution profile and f₂ data comparing the 1 mg and 0.75 mg drug products. The dissolution comparison profiles and f₂ values are presented below.

Dissolution Profiles for the 4 mg, 1 mg and 0.75 mg strengths

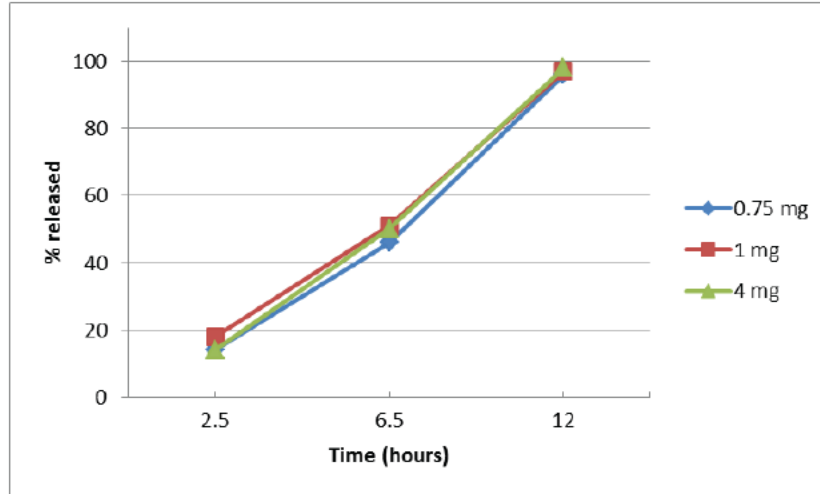


Table 1: Similarity Factors (F₂) between LCP-Tacro ER 0.75 mg, 1 mg and 4 mg

F ₂ Values in Support of In Vivo BE Waiver Request			
Dissolution Method for LCP-Tacro ER Tablets (FDA Database Monograph USP <111> Ph. Eur)	0.75 mg lot 4726601 (Formulation F*) Vs. 0.75 mg lot 4609801 (Formulation G)	1 mg lot 4609801 (Formulation G) Vs. 1 mg lot 4773601 (Formulation G)	4 mg lot 4773601 (Formulation F*) Vs. 4 mg lot 4773701 (Formulation G)
Apparatus II (Paddles) Ph. Eur Basket Sinkers			
Speed Rotation: 100 rpm	77	70	76
Medium: Water + 0.005% HPC+0.50% SLS adjusted to pH 4.5 ± 0.2 (2N Acetic Acid)			
Volume: Acid Stage: 710 mL Buffer Stage: 900 mL			
Temperature: 37°C ± 0.5°C			

* Difference between Formulation F and the commercial Formulation G is (b) (4)
(b) (4)

The similarity f₂ values comparing the 0.75 mg strength (test product) to the 1 mg strength (reference product) **indicate similarity between these strengths.**

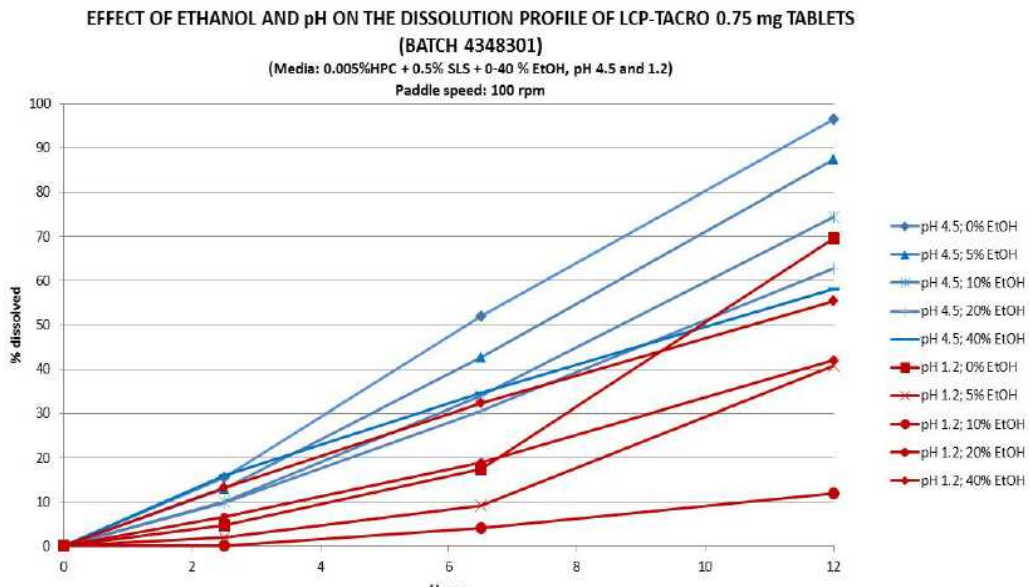
Reviewer’s Assessment on the Biowaiver Request: *ACCEPTABLE*

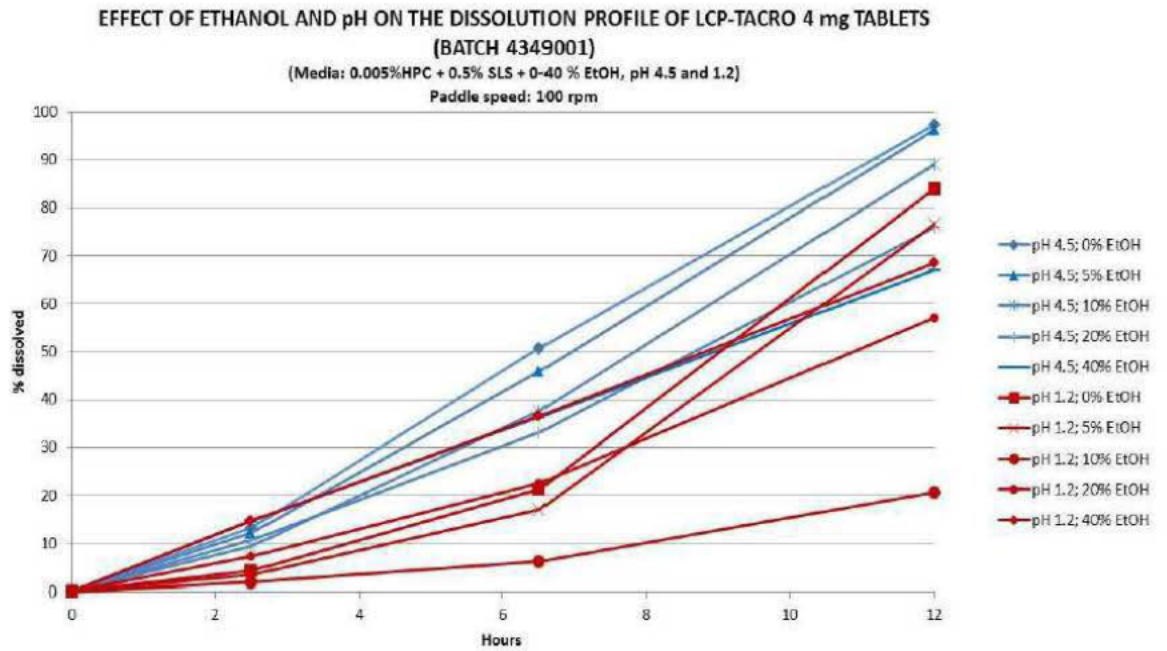
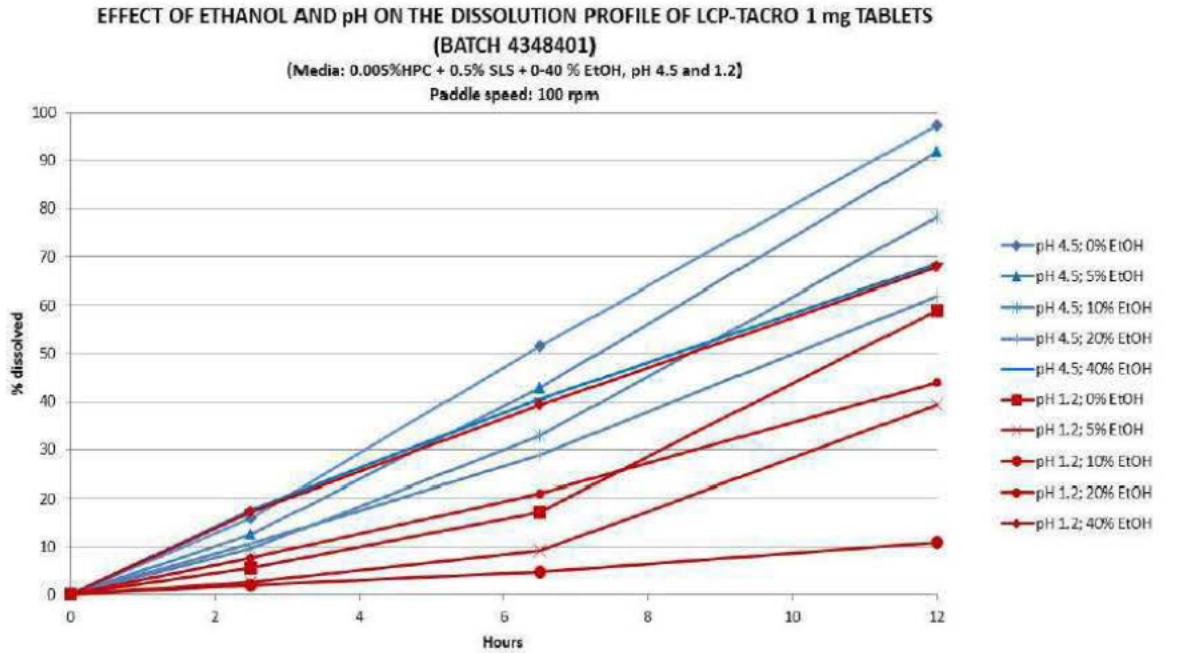
The overall BE, formulation, and dissolution data support the approval of the biowaiver request.

18 Is there any in vitro alcohol dose-dumping information submitted? What data are provided to support the Applicant’s claim of lack of dose-dumping in the presence of alcohol?

The Applicant conducted in vitro alcohol dose dumping studies in presence of alcohol with varying concentrations (5%, 10%, 20% and 40%) in the dissolution media at two different pH conditions (pH 1.2 and 4.5). Although the results show that for 0.75 mg tablets drug release increased from 5% to 15% at 2.5 hr. in presence of ~40% alcohol at pH 1.2 (similar trends are observed for 1 mg and 4 mg), **dose dumping is not observed with the tested alcohol concentrations.**

The following plots present the dissolution profiles for the 0.75 mg, 1 mg, and 4 mg tablets at several pH and alcohol concentrations.





APPENDIX 1

Composition information for all formulations used clinical development for 1 mg

Component	A	B	C	D	E	F	G
1 mg							

(b) (4)



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

/s/

BANU S ZOLNIK
09/25/2014

ANGELICA DORANTES
09/25/2014

CLINICAL PHARMACOLOGY REVIEW

NDA:	206-406
Submission Date:	30 December 2013
Drug Product:	Tacrolimus extended release oral tablets (0.75, 1.0, 4.0 mg)
Trade Name:	ENVARUSUS® XR
Sponsor:	Veloxis Pharmaceuticals, Inc.
Submission Type:	505(b)(2) NDA; Standard review
Pharmacometrics Reviewer	Jeffry Florian, PhD
Pharmacometrics Team Leader	Yaning Wang, PhD
OCP Reviewer:	Gerlie Gieser, PhD
OCP Team Leader:	Philip Colangelo, PharmD, PhD

Table of Contents

I. Executive Summary	1
A. Recommendations	2
B. Phase IV Commitments	2
C. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings	3
II. Question Based Review	14
A. General Attributes of the Drug	14
B. General Clinical Pharmacology	15
C. Intrinsic Factors	66
D. Extrinsic Factors	69
E. General Biopharmaceutics	71
F. Analytical Section	76
III. Detailed Labeling Recommendations	79
A. Proposed Package Insert (Annotated)	81
B. Individual Study Reviews	102
C. Consult Review (including Pharmacometric Reviews)	103
D. Cover Sheet and OCP Filing Review Form	115

I. Executive Summary

Prograf® (tacrolimus immediate release; Astellas) is a twice-a-day (BID) oral capsule formulation approved by FDA for the prophylaxis of organ rejection in liver transplant patients, kidney transplant patients and heart transplant patients. Astagraf® XL (tacrolimus-extended release; Astellas) is a once-a-day (QD) oral capsule formulation approved for the prophylaxis of organ rejection in kidney transplant patients.

Veloxis Pharmaceuticals is seeking approval of ENVARUSUS® XR (tacrolimus extended release) oral tablets administered once-daily for the prophylaxis of organ rejection in kidney transplant patients. In developing ENVARUSUS® XR, MeltDose® technology was used to increase the oral bioavailability of tacrolimus via (b) (4)

During the IND stage, ENVARUSUS® XR was known as LCP-Tacro. The pharmacokinetics of tacrolimus following single dose and/or multiple dose administration of ENVARUSUS® XR once daily were evaluated in *de novo* kidney transplant patients, stable kidney transplant patients and healthy subjects, in a total of 14 Clinical Pharmacology studies; (b) (4)

(u) (4)

This NDA review also includes an evaluation of the dose and concentration data from three Phase 2 and two Phase 3 pivotal kidney transplant trials in order to compare the administered tacrolimus

doses and the measured tacrolimus trough concentrations, as well as the doses of concomitantly administered immunosuppressive agents in the ENVARSUS® XR and active comparator (Prograf) treatment groups. Note that bioequivalence studies in healthy subjects between different ENVARSUS® XR formulations produced during clinical development of the proposed drug product, and the *in vitro* alcohol dose dumping study were evaluated by the assigned Biopharmaceutics reviewer.

A. Recommendations

The Clinical Pharmacology information submitted for NDA 206-406 of ENVARSUS® XR oral tablets is acceptable. From a Clinical Pharmacology perspective, approval of this NDA is recommended, provided satisfactory agreement is reached between the sponsor and FDA regarding the language in the package insert. See Part III of this NDA review for the Clinical Pharmacology reviewer's detailed labeling recommendations.

Based on the reviewer's analyses of tacrolimus PK, concentration and dose data from two Phase 2 studies and two Phase 3 studies in *de novo* kidney transplant patients and stable kidney transplant patients switched from tacrolimus immediate release capsules (Prograf®), as well as Phase 1 PK studies in healthy subjects, the reviewer's recommendations regarding the dosage and administration of ENVARSUS® XR are as follows.

ENVARSUS® XR Starting Dosage and Dosage Titration

(b) (4)

- ***Stable kidney transplant patients***

When switching from tacrolimus immediate release (e.g., Prograf) to ENVARSUS® XR, use a daily dose conversion ratio of 1:0.80 (i.e., upon conversion, the daily dose of ENVARSUS® XR should be 80% of the daily dose of Prograf prior to conversion).

If needed, adjust ENVARSUS® XR dosage to achieve tacrolimus trough concentrations within a 4 to 11 ng/mL range, and preferably similar to the pre-conversion level.

Administration:

- To achieve maximum possible and consistent tacrolimus exposures, take ENVARSUS® XR without food (i.e., at least 1 hour before a meal or 2 hours after a meal), and at the same time each day (preferably in the morning).

Therapeutic Drug Monitoring:

Monitor tacrolimus whole blood trough concentrations frequently during the first 7 days post-transplant. When interpreting measured concentrations, clinicians should be aware that the time to achieve steady state is approximately 7 days after initiating or changing the ENVARSUS® XR dose; however, administration of a higher ENVARSUS® XR starting dosage (e.g., ≥ 0.17 mg/kg/day) could potentially result in higher than expected initial tacrolimus concentrations and/or systemic exposure.

B. Phase IV Commitments

None.

C. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

1. De novo Kidney Transplant Patients

Recommended Dosing Regimen for *de novo* kidney transplant patients when ENVARSUS® XR is given

(b) (4)

Tacrolimus Pharmacokinetics of ENVARSUS® XR in *de novo* kidney transplant recipients

Phase 2 Study 2019

Phase 2 Study 2019 has the same design and used the same batches of ENVARSUS® XR tablets and Prograf capsules as the pivotal Phase 3 Study 3002.

Based on the results of the Phase 2 Study 2019 which determined tacrolimus PK parameters in *de novo* kidney transplant patients, a starting ENVARSUS® XR daily dose of 0.17 mg/kg/day (regardless of race) would result in a 2.0 to 2.6 -fold higher tacrolimus $AUC_{0-24}/C_{max}/C_{trough}$ on Day 1 (Table 1), as compared to Prograf starting at 0.1 mg/kg/day (given twice daily). At this starting dose, ENVARSUS® XR patients achieved a whole blood tacrolimus AUC on Day 1 that was close to that achieved at steady state. On Day 1, ENVARSUS® XR patients in Study 2019 received an average tacrolimus dose of 15.5 mg, which exceeds the dose range evaluated for linear PK of tacrolimus (i.e., up to 10 mg in healthy subjects; Study 1013).

Based on the reviewer's analysis of tacrolimus trough concentrations (as measured by the local laboratories) on Day 2 pre-dose, there was a higher proportion of patients with above-target levels and a

lower proportion of patients with below-target levels in the ENVARSUS® XR 0.17 mg/kg/day arm than in the Prograf 0.1 mg/kg/day arm (Figure 1).

Table 1. Mean ± SD Tacrolimus Pharmacokinetic Parameters of ENVARSUS® XR™ and Prograf® in *De novo* Kidney Transplant Patients (Study 2019)^a

	ENVARSUS® XR Once Daily Starting dose: 0.17 mg/kg/day (n=10)			Prograf Twice Daily Starting dose: 0.1 mg/kg/day (n=11)		
	Day 1	Day 14	Day 28	Day 1	Day 14	Day 28
AUC ₀₋₂₄ (ng·hr/mL)	376.66 ± 256.83	375.64 ± 140.32	396.23 ± 149.93	149.16 ± 89.34	243.13 ± 69.97	205.79 ± 36.25
C _{max} (ng/mL)	33.57 ± 21.83	31.13 ± 14.58	35.91 ± 18.67	13.09 ± 7.41	18.71 ± 6.84	17.38 ± 4.07
C ₂₄ (ng/mL)	11.03 ± 6.06	9.09 ± 3.02	10.49 ± 3.18	5.74 ± 5.54	7.46 ± 2.61	6.75 ± 2.22
C _{ave} (ng/mL)	15.69 ± 10.7	15.65 ± 5.85	16.51 ± 6.25	6.21 ± 3.72	10.13 ± 2.92	8.57 ± 1.51
T _{max} ^b (h)	6.02 (4.05 - 24)	4.04 (1.02 - 18)	4 (1.5 - 14.05)	4 (1.03 - 18)	2 (1 - 18)	4 (1 - 18)
Fluctuation (%)	-	132.06 ± 57.99	144.57 ± 67.49	-	113.8 ± 54.82	131.4 ± 75.96
Swing (%)	-	240.94 ± 136.52	246.69 ± 140.87	-	166.8 ± 87.32	189.15 ± 152.01

^a includes 10 ENVARSUS® XR patients and 11 Prograf patients with complete set of PK profiles on Days 1, 14, and 28; ^b median (range);

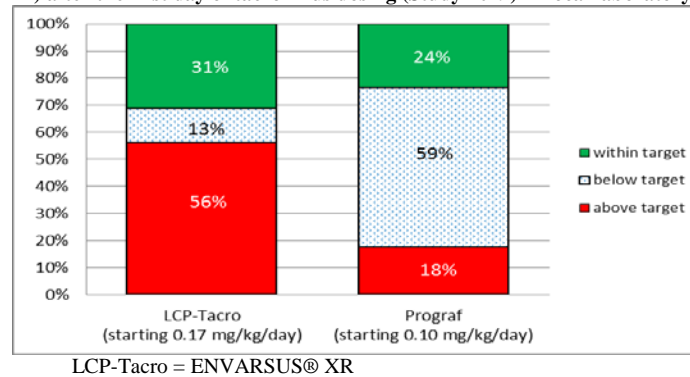
^c mean ± SD daily doses of ENVARSUS® XR vs Prograf (mg/day):

Day 1: 15.5 ± 3.1 vs 8 ± 1.9;

Day 14: 11.4 ± 5.4 vs 9.6 ± 4.2;

Day 28: 11.1 ± 6.4 vs 8.9 ± 5.0

Figure 1. Distribution of Patients Below/Within/Above the Target Tacrolimus Trough Concentration Range (6 – 11 ng/mL) after the first day of tacrolimus dosing (Study 2019) – Local laboratory assay results



Phase 2 Study 2017

Phase 2 Study 2017 was an open-label trial conducted earlier than Study 2019. In this study, the PK of tacrolimus, as well as the efficacy and safety of ENVARSUS® XR vs Prograf was investigated over 12 months in *de novo* kidney transplant patients. Majority of the PK evaluable patients, i.e., 20 non-African Americans/non-Blacks were administered an ENVARSUS® XR starting dose of 0.14 mg/kg/day, whereas 5 African-Americans/Blacks with evaluable PK data were initially given 0.17 mg/kg/day ENVARSUS® XR. Prograf was given at an initial daily dose of 0.2 mg/kg/day (administered twice daily) which was higher than the 0.1 mg/kg/day starting dosage regimen used for Prograf in Phase 3 Study 3002 and Phase 2 Study 2019. Compared to Studies 3002 and 2019, Study 2017 targeted a slightly higher tacrolimus whole blood trough concentration range (i.e., 7-20 ng/mL during the first 14 days during the PK profiling phase, 5-20 ng/mL from day 15 to day 90, then 5-15 ng/mL for the remainder of the 12-month study period).

Following the first ENVARSUS® XR dose, the mean tacrolimus AUC and C_{24h} were 127 ng·h/mL and 5.2 ng/mL, respectively (Table 2); if excluding the 5 African American (AA) patients who were given 0.17 mg/kg/day, the corresponding values would be 138 ng·h/mL and 5.2 ng/mL, respectively. The reviewer's linear interpolation analysis of ENVARSUS® XR PK data from Study 2019 and 2017 (with and without data from 0.17 mg/kg ENVARSUS® XR dosing of African American patients) suggests that an ENVARSUS® XR dose of approximately 0.142 to 0.143 mg/kg/day on Day 1 would produce a mean tacrolimus AUC and C_{24h} comparable to that following the first day of Prograf BID (0.1 mg/kg/day) in

Phase 2 Study 2019 (150 ng*h/mL and 5.7 ng/mL, respectively; see Table 1 above). In Study 2017, the administration of ENVARSUS® XR at the protocol-specified starting dose of 0.14 mg/kg/day resulted in steady state tacrolimus PK by Day 7 post-transplant; the actual mean ENVARSUS® XR dose on Day 1 was 12.4 mg/day (11.8 mg/day if excluding AAs who were given 0.17 mg/kg/day). In contrast, the administration of Prograf at 0.2 mg/kg/day (= 15.7 mg/day = 7.85 mg twice daily) in the same study resulted in tacrolimus AUC and C_{trough} on Day 1 that were close to those achieved at steady state. [See also the *Specific Populations/Race* subsection below for the separate evaluation of the PK parameters of tacrolimus in African American patients who received ENVARSUS® XR starting dose of 0.17 mg/kg/day in Phase 2 Studies 2017 and 2019.]

Per the sponsor, no patients in Phase 2 Study 2017 experienced graft failure or died during the 12-month study; there was no statistically significant difference between ENVARSUS® XR and Prograf in terms of the cumulative incidence of freedom from biopsy-proven acute rejection (BPAR), and severity of BPAR episodes. Additionally, the following lines of evidence suggest that ENVARSUS® XR patients in this study were not likely over-immunosuppressed: a) no cases of nephrotoxicity, b) no reported cases of malignancy (e.g., PTLN), c) low incidence of PVAN (i.e., n=1 Black/AA patient who received ENVARSUS® XR at a starting dose of 0.17 mg/kg/day), and no significant difference in the numbers of patients who experienced opportunistic infections (n=5 ENVARSUS® XR versus n=7 Prograf), d) no significant difference between treatments in the incidence of clinically significant laboratory abnormality, e) no evidence of QT prolongation in both treatment groups, f) no difference in the numbers of patients who discontinued due to adverse events (n=2 ENVARSUS® XR; n=2 Prograf).

Table 2. Mean ± SD Tacrolimus Pharmacokinetic Parameters of ENVARSUS® XR and Prograf® in *De novo* Kidney Transplant Patients (Study 2017)^{a,g}

	ENVARSUS® XR Once Daily starting 0.14 mg/kg/day ^b (n=26)			Prograf Twice Daily starting 0.2 mg/kg/day (n=27)		
	Day 1	Day 7	Day 14	Day 1	Day 7	Day 14
AUC ₀₋₂₄	126.6 ± 76.3 ^d	318.9 ± 126.4	354.1 ± 109.2	241.3 ± 97.1	282.9 ± 98.3	252.3 ± 80.4
C _{max}	11.0 ± 6.8 ^e	26.1 ± 17.5	28.1 ± 14.0	22.6 ± 10.6	23.8 ± 12.9	20.1 ± 6.6
C ₂₄	5.2 ± 2.8 ^f	9.2 ± 4.3	10.6 ± 4.1	8.7 ± 4.2	10.2 ± 5.2	8.0 ± 3.1
C _{ave}	5.3 ± 3.2	13.3 ± 5.3	14.8 ± 4.5	10.1 ± 4.0	11.8 ± 4.1	10.5 ± 3.3
T _{max} ^c	10 (4 - 24)	6 (1.5 - 12.1)	4 (1.3 - 8.1)	4 (1 - 24)	1.6 (0.5 - 24)	2 (0.5 - 14.1)
Fluctuation	94.2 ± 66.9	129.6 ± 119.2	124.5 ± 97.8	135.7 ± 77.4	107.4 ± 78.3	123.8 ± 60.6
Swing	125.2 ± 115.2	217.3 ± 241.3	195.7 ± 175.5	186.3 ± 127.0	153.6 ± 138.1	177.3 ± 101.7

^a includes 26 ENVARSUS® XR patients and 27 Prograf patients with complete set of PK profiles on Days 1, 7, and 14

^b 0.17 mg/kg/day for African Americans/Blacks (n=5)

^c median (range)

^d 138 ± 80.2 (if excluding 5 AA patients who received 0.17 mg/kg/day)

^e 11.8 ± 7.2 (if excluding 5 AA patients who received 0.17 mg/kg/day)

^f 5.2 ± 2.7 (if excluding 5 AA patients who received 0.17 mg/kg/day)

^g mean ± SD daily doses (mg/day) of ENVARSUS® XR vs Prograf administered on day of PK profiling:

Day 1: 12.4 ± 2.7 vs 15.7 ± 3.8

Day 7: 10.3 ± 4.4 vs 9.9 ± 3.9

Day 14: 10.3 ± 4.6 vs 8.4 ± 4.4

Reviewer's Comments:

The 12-month efficacy and safety findings, as well as the measured tacrolimus trough concentrations 24 hours after the first dose and during the first 3 to 7 days, in Study 2017 provide support to the Clinical Pharmacology reviewer's dosage recommendations to start ENVARSUS® XR at 0.14 mg/kg/day (regardless of race) and titrate the dose per protocol-specified target tacrolimus concentration ranges provided in Study 3002. Additionally, the reviewer notes that recommending an ENVARSUS® XR starting dose of 0.14 mg/kg/day for all-comers would not pose a lack of efficacy and/or increase risk of toxicity during the first few weeks post-transplant for the following reasons:

(1) A starting ENVARSUS® XR dose of 0.14 mg/kg/day (rather than 0.17 mg/kg/day as evaluated in Phase 2 Study 2019 and Phase 3 Study 3002) would achieve a Day 1 tacrolimus AUC and/or trough

concentration that are comparable to that achieved with Prograf 0.1 mg/kg/day of Study 2019 and Phase 3 Study 3002 (see below for further details of this study).

(2) As is the case with Prograf (starting dose: 0.1 mg/kg/day), ENVARSUS® XR will be labeled for use as a component of a combination immunosuppressive regimen including antibody induction, mycophenolate mofetil, and corticosteroids.

(3) Timely therapeutic drug monitoring (usually done more frequently during the first week post-transplant) would provide for individualization of the subsequent ENVARSUS® XR doses.

Tacrolimus AUC-C_{trough} correlation in *de novo* kidney transplant recipients

C_{trough} is used as a surrogate of AUC for tacrolimus therapeutic drug monitoring. A cross-study comparison of the AUC-C_{trough} correlation plots of ENVARSUS® XR in Study 2017 and Prograf in Study 2019 indicates that targeting the same tacrolimus C_{trough} range (e.g., 6 to 11 ng/mL) as Prograf at a starting dose 0.1 mg/kg/day would result in an AUC with ENVARSUS® XR at a starting dose 0.14 mg/kg/day that is 0 to 10% lower than that of Prograf on Day 1, and is approximately 15% higher than that of Prograf on Day 14 (steady state; See Figure 41). There was a substantial overlap in data points between the AUC-C_{trough} correlation plots of ENVARSUS® XR and Prograf; the correlation coefficients (r) of ENVARSUS® XR on Day 1 and at steady state were ≥ 0.638 and ≥ 0.899 , respectively.

On the contrary, the reviewer observed a substantial separation (i.e., difference in slopes) between the AUC-C_{trough} correlation lines with ENVARSUS® XR at starting dose of 0.17 mg/kg/day and Prograf at starting dose of 0.1 mg/kg/day on Day 1 and at steady state, based on PK data generated in Study 2019 (see Figure 47). The correlation coefficients (r) of ENVARSUS® XR on Day 1 and at steady state were ≥ 0.777 . Based on the AUC-C_{trough} correlation plots, targeting the same C_{trough} range as Prograf (e.g., 6 to 11 ng/mL) would result in a 35% to 65% higher AUC on Day 1, and a 15% to 40% higher AUC at steady state with ENVARSUS® XR than Prograf. Note that in Study 2019, the average tacrolimus trough concentrations of ENVARSUS® XR were consistently higher (i.e., on Days 1, 14 and 28 post-transplant) than that achieved with Prograf.

Tacrolimus and Concomitant Immunosuppressive Exposures in 12-month clinical trials (*de novo* kidney)

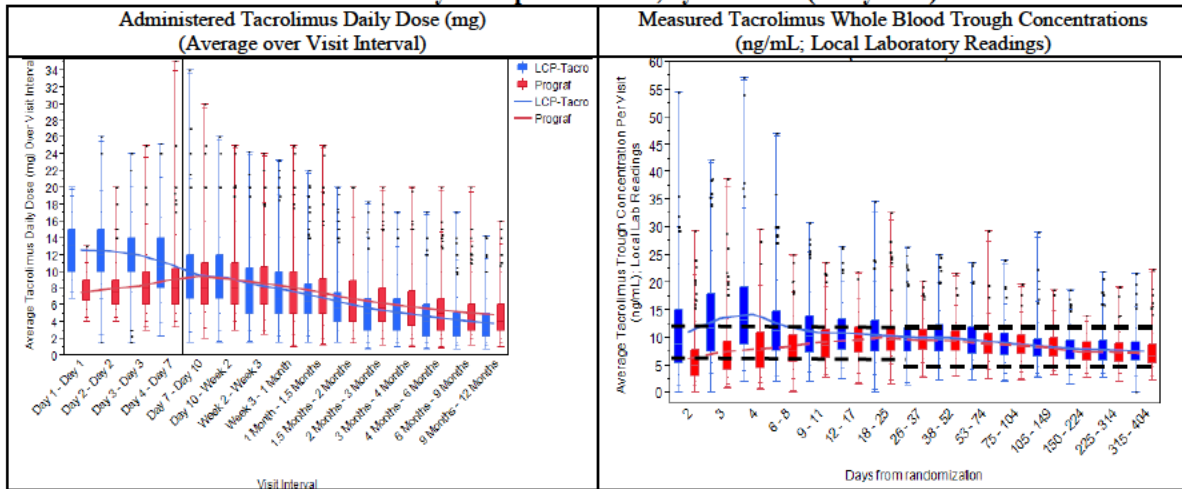
Phase 3 Study 3002

The following ENVARSUS® XR dosing regimen was prospectively evaluated in *de novo* kidney transplant patients in the 12-month Phase 3 Study 3002: ENVARSUS® XR at a starting dose of 0.17 mg/kg/day (given QD) vs. Prograf at a starting dose of 0.1 mg/kg/day (given BID), with subsequent dosage adjustments based on the attainment of the protocol-specified target tacrolimus trough concentration ranges of 6-11 ng/mL (first 30 days), and 4-11 ng/mL thereafter.

ENVARSUS® XR demonstrated non-inferiority to Prograf in terms of efficacy; however, there was an imbalance in the incidence of toxic nephropathy between the two treatment arms (i.e., 3.5% for ENVARSUS® XR versus 0% for Prograf), although it was noted that nephrotoxicity cases associated with high tacrolimus trough concentrations appeared to be reversible with a reduction in tacrolimus exposures. Additionally, there were higher rates of adverse events potentially related to over-immunosuppression, i.e., fatal Post-Transplant Lymphoproliferative Disease (PTLD), polyoma virus associated nephropathy (PVAN) in ENVARSUS® XR treated patients than in Prograf treated patients.

The mean/median tacrolimus whole blood trough concentrations measured in ENVARSUS® XR patients were higher than the upper limit of the protocol specified target range during the first 7 days, and higher than that achieved in the Prograf twice daily arm during the first 14 days, due at least in part to the higher administered daily doses of ENVARSUS® XR than Prograf during the first week post-transplant (Figure 2). The time course profile of the mean ENVARSUS® XR daily doses suggests that dosage reduction was minimal during the first week post-transplant, despite the high proportion of ENVARSUS® XR patients achieving tacrolimus trough concentrations above the protocol defined target range during the first 3 days of dosing.

Figure 2. Administered Tacrolimus Daily Dose (mg) and Measured Tacrolimus Trough Concentrations (ng/mL) of *De novo* Kidney Transplant Patients, by treatment (Study 3002)



Legend: LCP-Tacro = ENVARSUS® XR (blue bars with solid blue line); PROGRAF (red bars with broken red line); protocol defined target tacrolimus trough concentrations (dashed horizontal lines)
 *reviewer's analysis includes 12-month study completers

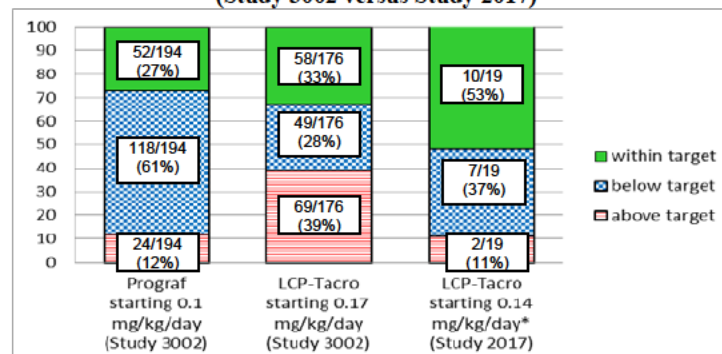
Based on the reviewer's confirmatory analyses, majority of the patients (96% ENVARSUS® XR and 99% Prograf) received two 20 mg doses of basiliximab for antibody induction. Additionally, the average daily doses of concomitant MMF and corticosteroids were comparable between the two tacrolimus treatment arms throughout the 12-month study period.

Phase 2 Study 2017

In Study 2017, the mean/median tacrolimus whole blood trough concentrations (C_{trough}) achieved in ENVARSUS® XR patients at a starting dose of 0.14 mg/kg/day were within the protocol defined target tacrolimus C_{trough} range (7-20 ng/mL), and increased steadily during the first 7 days post-transplant.

Based on the reviewer's exploratory analysis, during the first 3 days, these mean/median tacrolimus C_{trough} values measured in ENVARSUS® XR patients in Study 2017 were also within the range (6-11 ng/mL) that was targeted in Phase 3 Study 3002. Additionally, the reviewer's exploratory analysis of tacrolimus C_{trough} data across studies revealed that a starting ENVARSUS® XR dose of 0.14 mg/kg/day (as used in Study 2017) would result in a greater proportion of ENVARSUS® XR patients within the ideal target tacrolimus concentration range (6-11 ng/mL), and a lower proportion of patients below the ideal target range after the first day of tacrolimus dosing, as compared to Prograf patients given a starting dose of 0.1 mg/kg/day (as used in Study 3002; Figure 3).

Figure 3. Proportion (%) of *De novo* Kidney Transplant Patients with Tacrolimus Trough Concentrations Below/Within/Above Ideal Target Range (6-11 ng/mL) After the First Day of Tacrolimus Dosing (Study 3002 versus Study 2017)



*starting dose for majority (86%) of the PK-evaluable patients in Study 2017; within/below/above target rates if including 3 patients who received LCP-Tacro starting dose of 0.17 mg/kg/day: 45%/41%/14%, respectively; LCP-Tacro = ENVARSUS® XR

Based on the reviewer's analyses, almost (if not) all of the tacrolimus treated patients in Study 2017 received concomitant MMF, corticosteroids, and antibody induction. The mean/median daily MMF and prednisone equivalent doses and the antibody induction (mainly antithymocyte immunoglobulin) doses in this trial were similar between treatment groups.

Tacrolimus Exposure-Response: Efficacy

A Cox-proportional hazards analysis was conducted by the sponsor to describe the relationship between the risk of treatment failure, tacrolimus trough concentrations as a time-dependent covariate, and various baseline factors from Study 3002. Significant relationships were identified between lower tacrolimus trough concentrations, presence of diabetes, Black race, and non-US region and an increased likelihood of treatment failure. A significant impact of treatment effect between ENVARSUS® XR and Prograf was not identified from the analysis. The observed relationship between increased likelihood of treatment failure and lower tacrolimus trough concentrations is consistent with previous transplant studies involving tacrolimus. This relationship was predominantly driven by individuals outside of the specified tacrolimus target trough concentration range from Study 3002 and continues to support the use of therapeutic drug monitoring with tacrolimus for the prevention of organ graft rejection in kidney transplant recipients.

Tacrolimus Exposure-Response: Safety

A Cox-proportional hazards analysis was conducted by the reviewer to describe the relationship between nephropathy adverse events and tacrolimus trough concentrations as a time-dependent covariate from Study 3002. A relationship with regard to tacrolimus trough concentrations could not be identified, but that may have been due to the low number of nephropathy events (n=9) in the dataset. However, it was noted that there was an imbalance in nephropathy events between the ENVARSUS® XR (n=9) and Prograf (n=0) treatment arms. In addition, three of the events in the ENVARSUS® XR arm occurred during the initial first week of treatment when exposures in the ENVARSUS® XR arm exceeded those in the Prograf arm. These observations suggest that differences in the safety profiles may exist between the studied ENVARSUS® XR and Prograf regimens, but the available data is not sufficient to quantify the contribution of higher tacrolimus trough concentrations following administration of ENVARSUS® XR during the initial week of treatment to these adverse events.

2. Stable Kidney Transplant Patients Switched from Prograf to ENVARSUS® XR

Recommended Tacrolimus Dosing Regimen

Based on the reviewer's overall assessment of the PK and efficacy/safety findings of the Phase 2 and Phase 3 trials conducted by the sponsor, stable kidney transplant patients (≥ 3 months post-transplant) being switched from Prograf (tacrolimus immediate release twice daily) should receive a daily dose of ENVARSUS® XR (tacrolimus extended release once daily) equivalent to 80% of the daily dose of Prograf prior to conversion. Since the mean/median tacrolimus whole blood trough concentrations of tacrolimus treated patients in Phase 3 Study 3001 were maintained closer to the lower end of the protocol defined target range (4-15 ng/mL), and for consistency with the target tacrolimus C_{trough} recommendation for *de novo* kidney transplant patients beyond 30 days post-transplant, the target range for stable kidney transplant patients (≥ 3 months post-transplant) converted from Prograf twice daily to ENVARSUS® XR daily should be 4-11 ng/mL, preferably similar to the pre-conversion level.

Tacrolimus PK of ENVARSUS® XR in stable kidney transplant patients

Phase 2 Study 2011

In stable kidney transplant patients (43% African American; 53% Caucasian) who were converted to ENVARSUS® XR once daily at 67% to 80% of the daily dose of Prograf twice daily, the tacrolimus AUC_{0-24h} at steady state (7 days) after conversion was comparable to that prior to conversion (Table 3).

In the ENVARSUS® XR group, the mean steady state tacrolimus AUC and C_{trough} were comparable between African American (AA) and non-AA patients, suggesting that the same Prograf-to-ENVARSUS® XR conversion factor could be used for both racial subgroups (Table 3A). The reviewer notes that prior to switching to ENVARSUS® XR, the average Prograf daily dose of African-American patients in Study 2011 was already 2-fold higher than that being received by non-African American stable kidney transplant patients (10.7 ± 5.4 mg versus 5.0 ± 2.8 mg). [This differential tacrolimus dosing between AAs and non-

AAs pre-conversion is in line with the reviewer's observation that following 7 days of stable Prograf dosing in this study, the dose-normalized tacrolimus AUC_{0-24h} and C_{trough} of AAs were both ~30% lower than that of non-AAs.] The reviewer also notes that patients in this study were converted to the nearest whole mg ENVARSUS® XR dose, and that dosage adjustment was not permitted from the time of conversion to ENVARSUS® XR to the time of ENVARSUS® XR steady state PK profiling 7 days after conversion.

Table 3. Tacrolimus Pharmacokinetic Parameters after 7 days of fixed dosing with Prograf BID and 7 to 14 days following conversion to ENVARSUS® XR QD (daily dose conversion ratio: 1:0.67-0.80) – Study 2011 (ALL PATIENTS)

Parameter	Geometric Mean (%CV) Arithmetic Mean ± SD		
	Prograf Capsules twice-daily	ENVARSUS® XR Tablets	
	Day 7 (n=47)	Day 14 (n=47)	Day 21 (n=46)
AUC _t ^a (ng-hr/mL)	212.12 (25.59) 218.82 ± 55.99	206.79 (29.27) 215.71 ± 63.14	209.05 (31.30) 218.03 ± 68.23
C _{max} (ng/mL)	17.66 (42.59) 19.14 ± 8.15	12.64 (36.02) 13.45 ± 4.84	13.05 (41.91) 13.94 ± 5.84
C _{trough} (ng/mL)	6.82 (22.01) 7.00 ± 1.54	6.59 (33.41) 6.96 ± 2.32	6.64 (31.70) 6.94 ± 2.20
C _{avg} (ng/mL)	8.84 (25.59) 9.12 ± 2.33	8.62 (29.27) 8.99 ± 2.63	8.71 (31.29) 9.08 ± 2.84
T _{max} (hr) ^b	1.82 (0.50 - 24.00)	6.00 (1.00-16.00)	6.00 (1.50 - 16.00)
Degree of fluctuation (%)	127.41 ± 57.28	73.24 ± 44.96	77.04 ± 50.59
Degree of Swing (%)	174.55 ± 93.72	102.80 ± 75.24	110.07 ± 89.23
C _{max} /C _{trough}	2.75 ± 0.94	2.03 ± 0.75	2.10 ± 0.89

^a t=24 hours; ^b median (minimum – maximum); Source: NDA Study 2011 CSR (Table 7)
Prograf daily dose pre-conversion (Mean ± SD): 7.4 ± 4.9 mg/day

Table 3A. Tacrolimus Pharmacokinetic Parameters after 7 days of fixed dosing with Prograf BID and 7 to 14 days following conversion to ENVARSUS® XR QD (daily dose conversion ratio: 1: 0.67 to 0.8, regardless of race) – Study 2011 (African Americans versus Non-African Americans)

Parameter	Geometric Mean (%CV) Arithmetic Mean ±SD					
	African Americans/Blacks			Non-African Americans/Non-Blacks		
	Prograf Capsules twice-daily	ENVARSUS® XR Tablets once-daily		Prograf Capsules twice-daily	ENVARSUS® XR Tablets once-daily	
Day 7 (n=20)	Day 14 (n=20)	Day 21 (n=19)	Day 7 (n=27)	Day 14 (n=27)	Day 21 (n=27)	
AUC _t ^a (ng-hr/mL)	242.19 (24.78) 250.12 ± 61.98	204.13 (32.48) 214.78 ± 69.77	216.93 (39.32) 231.41 ± 90.99	192.28 (19.32) 195.64 ± 37.79	208.78 (27.32) 216.40 ± 59.11	203.68 (21.98) 208.62 ± 45.86
C _{max} (ng/mL)	21.72 (41.29) 23.73 ± 9.80	13.89 (41.05) 15.20 ± 6.24	14.48 (48.92) 15.91 ± 7.78	15.15 (27.81) 15.74 ± 4.38	11.79 (24.56) 12.14 ± 2.98	12.14 (27.91) 12.55 ± 3.50
C _{trough} (ng/mL)	7.43 (21.57) 7.62 ± 1.64	6.21 (37.53) 6.62 ± 2.49	6.68 (38.83) 7.09 ± 2.75	6.41 (19.98) 6.54 ± 1.31	6.88 (30.70) 7.20 ± 2.21	6.60 (25.79) 6.84 ± 1.76
C _{avg} (ng/mL)	10.09 (24.78) 10.42 ± 2.58	8.51 (32.49) 8.95 ± 2.91	9.04 (39.32) 9.64 ± 3.79	8.01 (19.31) 8.15 ± 1.57	8.70 (27.32) 9.02 ± 2.46	8.49 (21.98) 8.69 ± 1.91
T _{max} (hr) ^b	1.91 (0.50- 24.00)	4.00 (1.00- 12.00)	6.00 (1.50- 16.00)	1.52 (0.50 – 13.48)	6.00 (2.00- 16.00)	7.87 (1.53- 12.05)
Degree of Fluctuation (%)	145.87 ± 60.72	94.99 ± 54.11	91.42 ± 63.47	113.74 ± 51.53	57.13 ± 28.34	66.92 ± 37.20
Degree of Swing (%)	212.69 ± 108.38	138.16 ± 91.69	135.87 ± 114.34	146.30 ± 70.76	76.61 ± 46.88	91.92 ± 62.46
C _{max} /C _{trough}	3.13 ± 1.08	2.38 ± 0.92	2.36 ± 1.14	2.46 ± 0.71	1.77 ± 0.47	1.92 ± 0.62

^a t=24 hours; ^b median (minimum – maximum); Source: NDA Study 2011 CSR (Tables 12 and 13)
Prograf daily dose pre-conversion (Mean ± SD): 10.7 ± 5.4 mg/day (AAs); 5.0 ± 2.8 mg/day (non-AAs)
Prograf-to-ENVARSUS® XR daily dose conversion ratio: 1: 0.67 to 0.80 (for both AAs and non-AAs)

Tacrolimus AUC-C_{trough} correlation in stable kidney transplant patients

In Study 2011, the steady state AUC-C_{trough} correlation lines of ENVARSUS® XR and Prograf were superimposable (i.e, the slopes of the lines were comparable, and the data points comprising each line overlapped substantially); the AUC-C_{trough} correlation coefficients ($r \geq 0.79$) were satisfactory. *This observation suggests that targeting the same tacrolimus trough concentration range as Prograf would be appropriate for stable kidney transplant patients switched from Prograf to ENVARSUS® XR (at a daily dose conversion ratio of 1:0.8).*

Phase 3 Study 3001

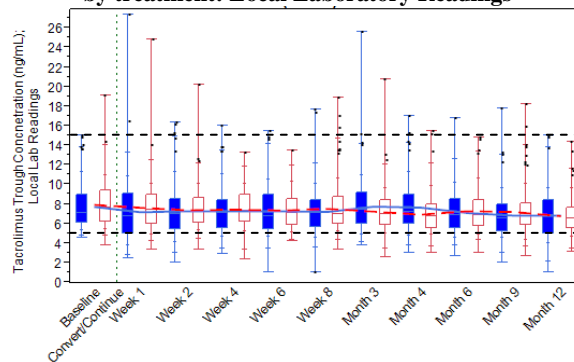
In Study 3001, stable kidney transplant patients (30 African Americans/Blacks and 120 non-African Americans/non-Blacks) receiving stable doses of Prograf twice daily and with tacrolimus trough concentration within 4-15 ng/mL at the end of the 7-day run-in period were randomized (1:1) at baseline to either continue treatment with Prograf twice daily at the current dose, or switch to ENVARSUS® XR once daily. The Prograf-to-ENVARSUS® XR daily dose conversion ratio was 1:0.85 for Blacks/African Americans, or 1:0.7 for non-African Americans/non-Blacks (slightly different from that used in Phase 2 Study 2011). ENVARSUS® XR dosage adjustment was not allowed during the first week post-conversion but was considered afterwards if tacrolimus trough concentration measured on Day 7 post-conversion deviated from the pre-conversion value by more than 25%. All subsequent dosage adjustments were based on the assessment of clinical factors and the maintenance of tacrolimus trough concentration within 4-15 ng/mL.

Per the sponsor, ENVARSUS® XR administered at the pre-specified conversion dosage to stable kidney transplant patients was non-inferior in terms of efficacy, and exhibited a safety profile that was comparable to Prograf.

Based on the reviewer's analysis, the baseline-to-Week 1 ratio of mean tacrolimus daily doses administered in Study 3001 were 0.8 for ENVARSUS® XR conversion patients and 1.0 for Prograf continuation patients. This observation provides support for the reviewer's proposal to recommend a Prograf-to-ENVARSUS® XR daily dose conversion ratio of 1:0.8 (regardless of race).

Throughout the 12-month study period, the tacrolimus daily doses and trough concentrations were stable, and were comparable between patients switched to ENVARSUS® XR and patients who continued to receive Prograf (Figure 4).

Figure 4. Daily Tacrolimus Trough Concentrations (ng/mL) in Stable Kidney Transplant Patients in Study 3001, by treatment: Local Laboratory Readings



Legend: ENVARSUS® XR (blue solid boxes with blue solid line); PROGRAF (red open boxes with red broken line); protocol defined target tacrolimus trough concentrations (black horizontal broken lines)

Based on the reviewer's analysis, the daily MMF equivalent doses and prednisone equivalent doses received by ENVARSUS® XR and Prograf patients during the 12-month study period were comparable.

3. Healthy Subjects

Tacrolimus PK of ENVARSUS® XR Once Daily

- Food effect
 - In healthy subjects, a high fat meal reduced the tacrolimus AUC of ENVARSUS® XR by 50 to 55% (Study 1011).
Reviewer Note: In de novo kidney transplant patients (Study 3002), it was recommended that tacrolimus be taken either at least 1 hour before or 2 hours after the morning/evening meal. In stable kidney transplant patients converted to ENVARSUS® XR from Prograf (Study 3001), it was recommended that tacrolimus be taken either at least 1 hour before or 2 hours after the morning meal. For both Phase 3 studies, patients needing to take the drug with meals may do so, but should follow a consistent routine each day. Breakfast was not to be taken prior to a C_{trough} measurement.
- Chronopharmacokinetic effect (diurnal variation)
 - In healthy subjects, evening dosing of ENVARSUS® XR produced a 15% lower AUC_{0-inf} and a 20% lower C_{24h} than after morning dosing (Study 1014).
Reviewer Note: In de novo kidney transplant patients (Study 3002), the study drug was to be administered on a consistent schedule with regard to time of day. Per the study protocol, the first study drug dose must be given as a morning dose (before noon) no later than 48 hours following transplantation. Similarly, per the protocol of Study 3001, stable kidney transplant patients were to take ENVARSUS® XR tablets orally once daily in the morning, with an interval of 24 hours (± 1 hour) between doses.
- Dose proportionality/PK Linearity:
 - In healthy subjects who received single doses of ENVARSUS® XR 5 mg, 7 mg, and 10 mg in a crossover fashion, there was a linear relationship between dose and tacrolimus AUC_{0-inf} and C_{max} (Study 1013). Additionally, the elimination half-lives did not change as a function of tacrolimus dose.
 - In one Phase 2 PK study (Study 2019) where the average ENVARSUS® XR dose on Day 1 exceeded 15 mg/day (given once daily), the mean tacrolimus AUC and C_{24h} values on Day 1 were higher than anticipated, and similar to those achieved at steady state, suggesting possible PK nonlinearity at high ENVARSUS® XR doses as administered in this study.
- Relative Bioavailability
 - When given to healthy subjects at the same tacrolimus daily dose, the steady state AUC and C_{24h} of ENVARSUS® XR given once daily are higher by 50% and by 60%, respectively, compared to Prograf given twice daily (Study 1016).
 - When given to healthy subjects at the same tacrolimus daily dose, the steady state AUC and C_{24h} of ENVARSUS® XR given once daily are higher by 45% and by 60%, respectively, compared to Astagraf XL given once daily (Study 1017). Astagraf XL is another extended release tacrolimus product that was recently approved in the U.S.
- Tacrolimus AUC-C_{trough} correlation

In Study 1016, the steady state AUC-C_{trough} correlation lines of ENVARSUS® XR and Prograf were superimposable; the AUC-C_{trough} correlation coefficients ($r \geq 0.89$) were acceptable.

4. Specific Populations

Race

In Phase 3 Study 3002, there were very few African-Americans who received ENVARSUS® XR (n=10) and who have tacrolimus trough concentration data (n = 3 to 8 per study visit) to warrant a meaningful race subgroup analysis of tacrolimus dose/concentration. *However, the reviewer notes that the protocol defined ENVARSUS® XR starting dose in the trial was not race dependent.*

In Phase 2 Studies 2017 and 2019, the pharmacokinetics of tacrolimus in African American/Black *de novo* kidney transplant patients who received ENVARSUS® XR at a starting dose of 0.17 mg/kg/day were

highly variable; the mean $\pm$ SD tacrolimus AUC values on Day 1 were 79 ± 27 ng*h/mL (n=5) and 270 ± 233 ng*h/mL (n=4), respectively. The reviewer's analysis of the pooled PK data from these two Phase 2 studies suggests that African American *de novo* kidney transplant patients would need a ENVARSUS® XR starting dose of approximately 0.14 mg/kg/day to achieve a mean tacrolimus AUC that is similar to the Day 1 AUC (150 ng*h/mL for all patients or 122 ng*h/mL for the African American subset) of patients treated initially with Prograf 0.1 mg/kg/day (the active comparator used in Phase 2 Study 2019 and also Phase 3 Study 3002). Thus, assuming tacrolimus PK-based racial differences are not product-dependent or formulation-dependent, and in order to simplify the *starting* ENVARSUS® XR dosage recommendation for *de novo* kidney transplant patients, the reviewer recommends that African American *de novo* kidney transplant patients be given the same ENVARSUS® XR starting dose (0.14 mg/kg/day) as that being recommended by the reviewer for non-AAAs. Such dosage recommendation is also consistent with the observation that the resulting tacrolimus exposure is comparable between African American (n=20) and non-African American (n=27) stable kidney transplant patients following switch from Prograf using the same daily dose conversion ratio in Phase 2 Study 2011. Because frequent therapeutic drug monitoring during the first week post-transplant is standard clinical practice for tacrolimus treated kidney transplant recipients (regardless of race), subsequent ENVARSUS® XR dosage will be titrated based on the attainment of the recommended target tacrolimus trough concentration range and the assessment of clinical factors.

Based on the findings of Study 3002, African-Americans (AA) *de novo* kidney transplant patients may need to be titrated to higher ENVARSUS® XR doses to achieve tacrolimus C_{trough} that are comparable to their non-AA counterparts, consistent with the observation for the Prograf comparator arm.

Gender

In Phase 3 Study 3002, males comprised about two-thirds of the study population. During the first 1 to 2 weeks post-transplant, males in the ENVARSUS® XR arm received a numerically higher mean tacrolimus daily dose (in mg) and consequently had slightly higher mean tacrolimus C_{trough} than their female counterparts. Both gender subgroups of ENVARSUS® XR had mean values that exceeded the upper bound of the target range during this early post-transplant period. Thereafter, tacrolimus exposures were comparable between the two gender subgroups of ENVARSUS® XR during the remainder of the 12-month study period.

No gender-dependent starting dosage adjustments are recommended for ENVARSUS® XR. Per standard clinical practice, tacrolimus whole blood trough concentration monitoring is recommended, regardless of gender.

Age

In Phase 3 Study 3002, there were very few elderly patients (≥ 65 years) who received ENVARSUS® XR and with tacrolimus trough concentration data (n = 10 to 14 per study visit) to warrant a meaningful age subgroup analysis. However, the reviewer observed that during the first two weeks post-transplant: 1) elderly patients (≥ 65 years) in the ENVARSUS® XR arm had substantially higher mean tacrolimus C_{trough} than younger patients, at comparable mean daily doses (in mg). 2) Both age subgroups of the ENVARSUS® XR arm had mean C_{trough} values that were above the protocol defined target range and consistently higher than that observed for the age subgroups of the Prograf arm.

Since the average Day 2 predose tacrolimus C_{trough} values were comparable between elderly patients and younger patients who received comparable ENVARSUS® XR doses in Study 3002, no adjustment in ENVARSUS® XR *starting* dose is recommended for elderly patients. Since the incidence of renal and/or hepatic impairment, concomitant disease, and concomitant drug use increase with age, the tacrolimus C_{trough} of elderly patients should be monitored closely to determine whether adjustment of subsequent ENVARSUS® XR dosages is necessary.

Renal Impairment and Hepatic Impairment

No PK studies in renal impairment and hepatic impairment were conducted specifically for ENVARSUS® XR. Per the labeling of Prograf, a reduction in starting dosage of tacrolimus will be recommended for patients with severe hepatic impairment (Child Pugh C); dosage reduction will also be recommended for patients who develop tacrolimus-associated nephrotoxicity.

5. Drug Interactions

No drug-drug interaction studies were conducted specifically for ENVARSUS® XR; the labeling will include the Forest plot prepared by the reviewer to summarize the drug-drug interaction data generated with the reference tacrolimus immediate release product (Prograf capsules).

In an *in vitro* study, alcohol enhanced the dissolution but did not induce dose dumping of tacrolimus from the ENVARSUS® XR tablets. As recommended for other tacrolimus products, ENVARSUS® XR patients should avoid alcohol consumption.

6. Missed dosing

The applicant proposed that missed dosing with ENVARSUS® XR could be mitigated by (b) (4). To support this proposal, the applicant conducted modeling and simulation to evaluate resulting pharmacokinetics under different scenarios for handling missed doses. The simulations provided by the applicant suggest that taking the missed dose within 15 hours will maintain trough and peak tacrolimus levels within a tacrolimus range of 4-25 ng/mL for a typical patient with steady state tacrolimus trough levels of 6-12 ng/mL. If the dose is not administered within 15 hours, the sponsor predicts that tacrolimus trough levels will fall below 4 ng/mL for up to 9 hours until the next dose is administered. In contrast, if the missed dose is immediately administered, tacrolimus trough levels will be maintained above the 4 ng/mL over all times, but elevated tacrolimus concentrations will be observed over the following dosing interval. The scenario of tacrolimus trough concentrations lower than the therapeutic range may impact graft rejection while the scenario involving higher tacrolimus trough concentrations may impact safety. There is not sufficient data available to determine the benefit of one scenario over the other; however, the already approved labeling for Astagraf XL (extended release tacrolimus) recommends that missed doses can be made up as normal up to 14 hours after the scheduled time, after which a patient should wait until the next dosing time to take their dose. To avoid confusion among health care providers regarding other similar approved products and as there is no clear benefit of one approach for handling missed doses, the review team recommends similar instructions for ENVARSUS® XR with regards to handling missed doses as that provided in the approved labeling for Astagraf XL.

Gerlie Gieser, Ph.D.
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology 4
Office Clinical Pharmacology

Jeffrey Florian, Pharm.D.
Acting Team Leader,
Division of Pharmacometrics,
Office Clinical Pharmacology

Yaning Wang, Ph.D.
Deputy Director,
Division of Pharmacometrics,
Office Clinical Pharmacology

Philip M. Colangelo, Pharm.D., Ph.D.
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology 4
Office Clinical Pharmacology

II. Question Based Review

A. General Attributes of the Drug

1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Prograf® (tacrolimus immediate release twice daily [BID] capsules; Astellas) 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. For *de novo* kidney transplant patients: Prograf (starting dose: 0.2 mg/kg/day) was originally approved for use with azathioprine (anti-proliferative agent); in May 2009, Prograf (starting dose: 0.1 mg/kg/day) was also approved for use with mycophenolate mofetil (anti-proliferative agent) and an IL-2 receptor antagonist (antibody induction agent).

Astagraf XL (tacrolimus extended release once daily [QD] capsules; Astellas) was approved by FDA in 2013 for the prophylaxis of organ rejection in kidney transplant patients.

ENVARUSUS® XR (tacrolimus extended release tablets) given once daily (QD) was known as LCP-Tacro during the IND phase. All clinical trials, except one, conducted for ENVARUSUS® XR used Prograf® twice daily (at a starting dose of either 0.2 mg/kg/day or 0.1 mg/kg/day) as the active comparator.

2. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Tacrolimus is a poorly water soluble drug. To develop ENVARUSUS® XR extended release once-daily oral tablets, MeltDose® technology was used to increase the oral bioavailability of tacrolimus via (b) (4)

During drug product development, (b) (4) Whereas Formulation F was used in the pivotal Phase 3 trial in *de novo* kidney transplant patients (Study 3002) and Formulation D was used in the Phase 3 trial in stable kidney transplant patients switched from immediate release tacrolimus (Study 3001), Formulation G is the to-be-marketed formulation. Per the sponsor, the only difference between the two formulations is (b) (4) Formulation G tablets resulting in a minor change in tablet shape without altering the surface to volume ratio. Two bioequivalence studies each were conducted between Formulations D and F, and between Formulations F and G. Of note, Formulation G was used in a Phase 3 clinical trial involving stable kidney transplant patients (Study 3003) but FDA does not consider this particular trial to be adequate for registration purposes. Phase 2 Studies 2017, 2019 and 2011 used ENVARUSUS® XR Formulations D, F, and C, respectively. Two BE studies were conducted between Formulations D and F; one BE study between Formulations C and D. See also *Section E. General Biopharmaceutics* for details regarding the specific extended release tacrolimus formulations and tablet strengths used in the individual clinical pharmacology studies and other clinical trials.

Both Prograf® and Astagraf XL capsules are commercially available in the following strengths: 0.5 mg, 1 mg, and 5 mg. A total of seven ENVARUSUS® XR tablet strengths were evaluated during drug product development. In consideration of the proposed 'lower than 1.0' daily dose conversion ratio of ENVARUSUS® XR when switched from immediate release tacrolimus oral dosage forms in stable kidney transplant recipients, the NDA sponsor intends to market ENVARUSUS® XR oral tablets in the following strengths: 0.75 mg, 1 mg, and 4 mg; such unit dose strengths would potentially allow for administration of tacrolimus doses rounded up/down to the nearest 0.25 mg.

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).

If approved, ENVARSUS® XR will be indicated for the prophylaxis of organ rejection in kidney transplant patients.

4. What are the proposed dosage(s) and route(s) of administration?

De novo kidney transplant patients

The sponsor proposed starting oral dose of [REDACTED] (b) (4)

Stable kidney transplant patients (conversion from immediate-release tacrolimus)

When switching patients from immediate-release tacrolimus oral dosage form to ENVARSUS® XR, the sponsor proposed daily dose conversion ratio is [REDACTED] (b) (4). Following conversion, tacrolimus whole blood trough concentrations should be monitored in order to maintain pre-conversion levels.

B. General Clinical Pharmacology

1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The NDA sponsor conducted a total of 18 clinical Phase 1 studies, including early pilot studies, in more than 500 healthy subjects and a total of six clinical Phase 2 studies in kidney [REDACTED] (b) (4) allograft recipients, comprising about 600 patients. The designs of these studies are summarized in Table 4. Note that the [REDACTED] (b) (4) [REDACTED] were not reviewed. See Section E. General Biopharmaceutics for the specific formulation of ENVARSUS® XR evaluated in each of these studies.

Tacrolimus PK parameters in kidney transplant patients were investigated in Phase 2 Studies 2017 and 2019 (*de novo* kidney transplant) and Study 2011 (stable kidney transplant patients switched from Prograf to ENVARSUS® XR). Table 5 summarizes the study design and the tacrolimus-based immunosuppressive regimens evaluated in the Phase 2 and Phase 3 clinical trials of the kidney transplant program of ENVARSUS® XR. Note that in these trials involving kidney transplant patients, tacrolimus was administered in combination with other immunosuppressive agents, i.e., mycophenolate, corticosteroids, with antibody induction (*de novo* patients) or without antibody induction (stable patients). Note also that the tacrolimus starting doses and the target tacrolimus C_{trough} used in Phase 2 Studies 2019 and 2011 were either the same or similar to those used in the corresponding Phase 3 clinical trials (Study 3002 and Study 3001, respectively).

Table 4. Pharmacokinetic Studies of Extended-release ENVARUS® XR tablets in Healthy Subjects and Organ Transplant Patients

Study	N*	Design
	(b) (4)	
		(b) (4)
Phase 1 Studies of Dose Linearity and Chronopharmacokinetics in Healthy Volunteers		
LCP-Tacro 1013	25	Open-label, randomized, single-dose, three-way crossover study in healthy volunteers to evaluate the dose-linearity of LCP-Tacro tablets at three dose levels (5 mg, 7 mg and 10 mg) under fasting conditions
LCP-Tacro 1014	26	Open-label, randomized, single-dose, two-way cross over study in healthy volunteers to evaluate the effect of morning vs. evening administration on the pharmacokinetics of tacrolimus from LCP-Tacro 2 mg tablets under fasting conditions.
Phase 1 Comparative Bioavailability Studies in Healthy Volunteers		
LCP-Tacro 1012	25	Two-way crossover, randomized, open-label, steady-state, multiple-dose study to evaluate and compare the bioavailability of tacrolimus from a test formulation of LCP-Tacro 2 mg tablets q.d. versus the reference Prograf 1 mg capsules b.i.d. under multiple dose, fasting conditions.
LCP-Tacro 1016	17	Two-way, crossover, open-label, randomized, multiple-dose, fasting comparative study to evaluate and compare the bioavailability of tacrolimus from a test formulation of LCP-Tacro 1 mg tablets q.d. versus the reference Prograf 0.5 mg capsules b.i.d. under multiple-dose, fasting conditions.
LCP-Tacro 1017	21	Two-way, crossover, open-label, randomized, multiple-dose, fasting comparative study to determine and compare the rate and extent of absorption of tacrolimus from LCP-Tacro 2 mg tablets versus Advagraf 1 mg capsules under multiple-dose, fasting conditions.
Phase 2 PK Studies in Kidney (b) (4) Transplant Patients		
LCP-Tacro 2011	47	Open-label, multi-center, prospective, conversion study in stable kidney transplant patients to compare the pharmacokinetics of LCP-Tacro tablets (q.d.) to Prograf capsules (b.i.d.)
		(b) (4)
LCP-Tacro 2017	61	Open-label, multi-center, randomized study to demonstrate the Pharmacokinetics of LCP-Tacro tablets (q.d.) and Prograf capsules (b.i.d.) in adult <i>de novo</i> kidney transplant patients
		(b) (4)
LCP-Tacro 2019	26	Double-blind, double-dummy, multicenter, prospective, randomized study of the pharmacokinetics of LCP-Tacro tablets q.d. compared to Prograf capsules b.i.d. for the prevention of acute allograft rejection in <i>de novo</i> adult kidney transplant recipients

*N=number of subjects included in the pharmacokinetic analysis; b.i.d.=twice daily; q.d.= once daily

Table 5. Dosing Regimens of Tacrolimus and Concomitant Immunosuppressive Agents in the Phase 2 and Phase 3 Clinical Trials in *De novo* Kidney Transplant Patients and Stable Kidney Transplant Patients (Per Study Protocol)

	Study 3002	Study 2017	Study 2019
Study Details (Study Period: Date of First patient enrolled to Date of Last patient completed)	Phase 3 – adult <i>de novo</i> kidney transplant patients (543 randomized;517 completed 12-month visit) 2-arm parallel group, prospective, randomized, double-blind, double-dummy, multicenter trial (October 2010 – March 2013)	Phase 2 – adult <i>de novo</i> kidney transplant patients (63 randomized;49 completed 12-month visit) randomized, parallel-group, open-label, multi-center study (October 2008 – February 2010)	Phase 2 – adult <i>de novo</i> kidney transplant patients (36 randomized; 31 completed D30 termination visit; 34 completed D60 safety follow-up) 2-arm parallel group, prospective, randomized, double-blind, double-dummy, multicenter study (December 2012 – June 2013)
ENVARUSUS® XR Formulation (strengths)	Formulation F (0.75, 1, 4 mg)	Formulation D (0.5, 1, 2, and 5 mg)	Formulation F (0.75, 1, 4 mg)
Starting Tacrolimus doses; Dosing and Administration	ENVARUSUS® XR : 0.17 mg/kg/day Prograf: 0.1 mg/kg/day (given BID) - First (AM) dose given before noon within 48 hours of transplantation - Highly recommended: take study drug either at least 1 h before or 2 hours after the morning or evening meal	ENVARUSUS® XR : 0.14 mg/kg/day (0.17 mg/kg/day for African-Americans/Blacks) Prograf: 0.2 mg/kg/day (given BID) - First (AM) dose given within 48 hours of graft reperfusion	ENVARUSUS® XR : 0.17 mg/kg/day Prograf: 0.1 mg/kg/day (given BID) - First (AM) dose given before noon within 48 hours of transplantation - Highly recommended: take study drug either at least 1 h before or 2 hours after the morning or evening meal
Target tacrolimus trough concentration range (ng/mL)	First 30 days post-transplant: 6-11 ng/mL; then, 4-11 ng/mL	Day 1 – 14: 7-20 ng/mL Day 15 – 90: 5-20 ng/mL then, 5-15 ng/mL	30-day treatment period: 6-11 ng/mL
MMF daily dose	Per current Cellcept USPI (1 gram BID)	Per center practice: MMF or MPS (or azathioprine) permitted but not required	Per current Cellcept USPI (1 gram BID)
Antibody induction (i.v.)	e.g., Basiliximab: 20 mg given within 2 hours prior to surgery, 20 mg given 4 days after transplantation	Per institution’s practice: permitted (except alemtuzumab)	Per investigator’s discretion
Corticosteroids	Based on the institution’s standard of care but must be ≥10mg/day for the first month; ≥5mg/day thereafter	Per investigator’s discretion	≥10mg/day

	Study 3001	Study 2011
Study Details (Study Period)	Phase 3 – adult stable kidney transplant (326 randomized;296 completed 12-month visit) Open-label, multicenter, prospective, randomized, dose conversion, (December 2008 – February 2011)	Phase 2 – adult stable kidney transplant (60 enrolled; 48 completed 52-day study) Open-label, multicenter, prospective,conversion, <u>crossover</u> (October 2008 – February 2010)
ENVARUSUS® XR Formulation (strengths)	Formulation D (0.5 mg, 1 mg, 2 mg, 5 mg)	Formulation C (1 mg, 2 mg, and 5 mg)
Daily Dose Conversion Ratio; Administration	ENVARUSUS® XR : 0.7 of Prograf dose (0.85 for African-Americans/Blacks) Prograf: continue existing dose - Recommended: take study drug either at least 1 hour before or 2 hours after the morning meal. Can take the drug with meals, but should follow a consistent routine each day	ENVARUSUS® XR (starting on Day 8): 0.66-0.80 of Prograf dose Prograf (starting on Day 22): continue pre-study dose -orally once daily either at least one hour before or two hours after the morning meal and to follow the same routine each day
Target tacrolimus trough concentration range (ng/mL)	4-15 ng/mL	5-15 ng/mL
Concomitant Immunosuppressive Agents	Per institution’s practice: MMF or MPS or azathioprine and/or corticosteroids allowed	maintain at usual doses of Cellcept or Myfortic, with or without corticosteroids

2. What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (collectively called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

For the Phase 3 Studies 3002 (*de novo* kidney transplant patients) and 3001 (stable kidney transplant patients converted from immediate release tacrolimus twice daily), the primary efficacy endpoint was efficacy failure 12 months after the first dose of the extended release tacrolimus once daily. Efficacy failure was a composite endpoint, defined as any patient experiencing one of the following during the 12-month study period: death, graft failure (return to dialysis for >30 days, allograft nephrectomy or re-transplantation), biopsy proven acute rejection (BPAR) Banff grade $\geq 1A$, or lost to follow up. For Study 3002, BPAR assessments for the primary efficacy endpoint were based on a blinded central biopsy reading.

3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, refer to Section II.F. Analytical section.

Tacrolimus C_{trough}

3.a. Were the observed whole blood trough concentrations (C_{trough}) of tacrolimus with ENVARSUS® XR (tacrolimus extended release) once daily comparable to Prograf® (tacrolimus immediate release) twice daily in the Phase 3 clinical trials involving *de novo* kidney transplant patients (Study 3002) and stable kidney transplant patients (Study 3001)? Were the C_{trough} achieved in these Phase 3 studies within the protocol-specified target ranges?

Study 3002: *De novo* Kidney Transplant

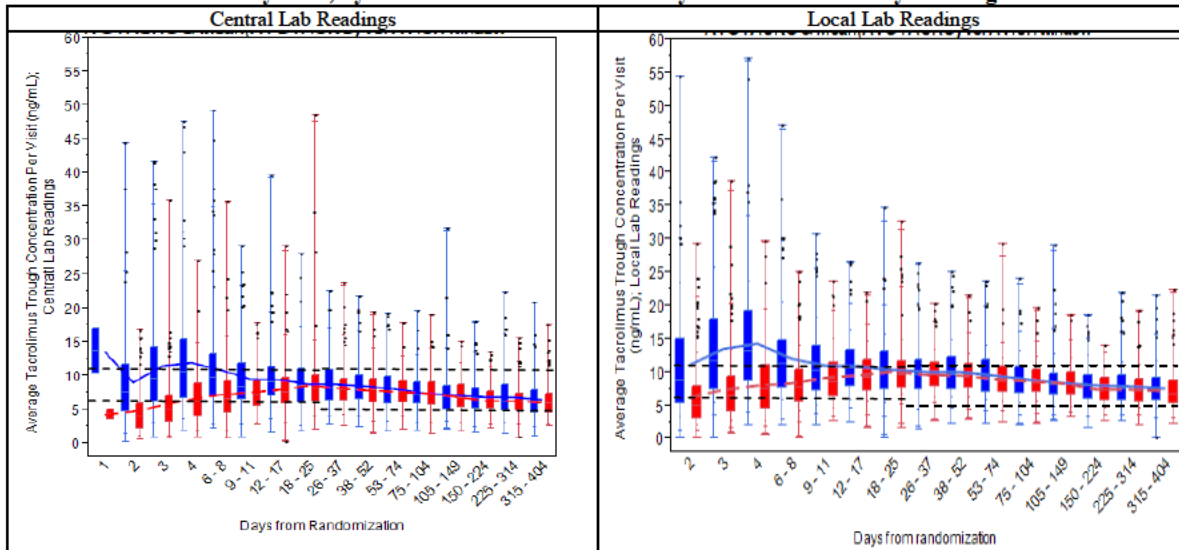
In Study 3002 (*de novo* kidney transplant), the protocol-specified target tacrolimus C_{trough} range was 6-11 ng/mL for the first 30 days, and 4-11 ng/mL thereafter. For measurement of tacrolimus whole blood trough concentrations, blood samples were to be collected daily within 30 minutes before the morning dose of tacrolimus, starting 24 hours after the first tacrolimus dose, i.e., on Days 2, 3, 4, 7 $\pm$ 1, 10 $\pm$ 1, 14 $\pm$ 2, 21 $\pm$ 3, 30 $\pm$ 3, 45 $\pm$ 3, 60 $\pm$ 4, 90 $\pm$ 5, 120 $\pm$ 5, 180 $\pm$ 7, 270 $\pm$ 7, and 360 $\pm$ 7. Tacrolimus dose adjustments were based on local laboratory C_{trough} readings, although sample aliquots were archived for central laboratory analysis. Note that the protocol defined starting daily dose was higher for ENVARSUS® XR than for Prograf (0.17 mg/kg/day versus 0.10 mg/kg/day).

Table 6 summarizes the reviewer’s calculated mean $\pm$ sd and median (10th to 90th percentile) tacrolimus whole blood C_{trough} values based on central laboratory and local laboratory measurements by protocol defined time periods. Table 7 and Figure 5 depict the tacrolimus C_{trough} in each treatment group by study visit. During the first 2 weeks, the tacrolimus whole blood trough concentrations (both the central and the local laboratory readings) were higher in ENVARSUS® XR patients than in Prograf patients; the tacrolimus C_{trough} between treatments were comparable thereafter. However, except for Days 3, 4 and 7 (when the mean/median local laboratory trough concentration readings for ENVARSUS XR patients were slightly above the protocol specified target, yet not exceeding 15 ng/mL), mean/median trough concentration values were generally within the target ranges for both treatment groups during the 12-month study period.

Table 6. Observed Tacrolimus Whole Blood Trough Concentrations (ng/mL) in *De novo* Kidney Transplant Patients in Study 3002, by time period [Mean $\pm$ SD; Median (10th – 90th percentile)]:

Time period	ENVARSUS® XR once daily				PROGRAF twice daily			
	n	Central Lab Reading	n	Local Lab Reading	n	Central Lab Reading	n	Local Lab Reading
Days 1 - 30	1463	9.99 $\pm$ 5.87; 8.74 (4.5-16.71)	1728	11.73 $\pm$ 6.36; 10.5 (5.4-19.9)	1559	7.16 $\pm$ 3.87; 6.7 (2.87-11.57)	1804	8.7 $\pm$ 4.32; 8.2 (3.6-14)
Months 2 - 12	1412	7.35 $\pm$ 3.01; 6.9 (4.11-11.04)	1576	8.72 $\pm$ 3.39; 8.2 (5-13)	1512	6.97 $\pm$ 2.5; 6.6 (4.09-10.2)	1624	8.31 $\pm$ 2.84; 8.08 (4.9-11.8)

Figure 5. Box plots of Daily Tacrolimus Trough Concentrations (ng/mL) in De novo Kidney Transplant Patients in Study 3002, by treatment: Central Laboratory vs Local Laboratory Readings



Legend: ENVARUSUS® XR (blue bars with solid blue line); PROGRAF (red bars with broken red line); protocol defined target tacrolimus trough concentrations (dashed black horizontal lines)
 Day 1 is the day of randomization. Patients were to take the first tacrolimus dose within 48 hours of transplant.

Table 7. Observed Tacrolimus Whole Blood Trough Concentrations (ng/mL) in De novo Kidney Transplant Patients in Study 3002, by Visit [Mean ± SD; Median (10th – 90th percentile)]:
Central Laboratory vs Local Laboratory Readings

VISIT*	ENVARUSUS® once daily				PROGRAF twice daily			
	n	Central Lab Reading	n	Local Lab Reading	n	Central Lab Reading	n	Local Lab Reading
Day 1	2	13.64 ± 4.79; 13.64 (10.25-17.03)	0	-	2	4.29 ± 1.09; 4.29 (3.52-5.06)	0	-
Day 2	156	9.05 ± 6.64; 7.52 (2.16-18.03)	166	11.14 ± 8.26; 8.75 (3.24-23.41)	169	4.75 ± 3.49; 3.76 (1.55-9.68)	185	6.28 ± 4.98; 4.9 (2-12.94)
Day 3	180	11.51 ± 7.5; 9.47 (4.5-21.19)	230	13.58 ± 8.04; 11.55 (5.31-25.59)	190	5.7 ± 3.91; 4.98 (2.05-10.03)	228	7.44 ± 4.98; 6.3 (2.59-13.21)
Day 4	183	11.97 ± 7.31; 10.48 (4.86-20.45)	216	14.4 ± 7.99; 13.05 (5.67-23.56)	182	6.58 ± 3.69; 5.98 (2.63-11.28)	224	8.07 ± 4.73; 7.35 (2.67-13.6)
Day 7	183	10.88 ± 7.08; 9.59 (4.46-17.08)	211	12.14 ± 6.45; 11.1 (5.76-20.38)	203	7.22 ± 4.23; 6.42 (2.95-12.01)	231	8.44 ± 4.11; 7.7 (4-13.9)
Day 10	154	9.54 ± 4.94; 8.26 (4.44-16.47)	192	11.08 ± 5.48; 10.2 (5-18.15)	165	7.57 ± 3.15; 7.03 (3.98-12.36)	196	9.22 ± 4.05; 8.5 (4.57-15.03)
Week 2	204	9.46 ± 4.16; 8.99 (5.1-13.8)	240	10.94 ± 4.21; 10.55 (5.8-16.19)	216	7.96 ± 3.36; 7.47 (4.28-11.71)	248	9.64 ± 3.49; 9.05 (5.6-14.6)
Week 3	203	8.79 ± 3.85; 8.46 (4.52-13.42)	239	10.44 ± 4.3; 10 (5.4-15.6)	213	8.63 ± 4.45; 8.01 (5-11.93)	246	10.2 ± 3.9; 9.5 (6.59-14.66)
Month 1	198	8.76 ± 3.38; 8.17 (4.96-13.23)	234	10.14 ± 3.81; 9.6 (5.98-14.92)	219	8.19 ± 2.82; 7.87 (5.37-11.34)	246	9.68 ± 2.93; 9.5 (6.27-13.33)
Month 1.5	200	8.5 ± 3.13; 7.73 (5-12.75)	236	10.12 ± 3.7; 9.6 (6.2-14.66)	223	7.88 ± 2.61; 7.84 (4.86-11.06)	239	9.59 ± 2.83; 9.5 (6.2-12.7)
Month 2	206	8.06 ± 3.18; 7.44 (4.48-12.27)	234	9.59 ± 3.6; 8.9 (5.67-13.95)	216	7.68 ± 2.52; 7.51 (4.61-11.05)	237	9.03 ± 2.93; 8.8 (5.5-12.12)
Month 3	204	7.43 ± 2.68; 7.09 (4.18-11.28)	231	8.94 ± 3.2; 8.6 (5.3-13.14)	223	7.43 ± 2.63; 7.08 (4.57-10.46)	238	8.76 ± 2.71; 8.7 (5.6-12.17)
Month 4	203	7.18 ± 3.17; 6.85 (4.14-10.3)	225	8.49 ± 3.28; 8.1 (4.76-12.74)	219	6.96 ± 2.34; 6.7 (4.03-10.1)	236	8.4 ± 2.72; 8.1 (4.8-11.95)
Month 6	208	6.88 ± 2.65; 6.58 (3.86-10.48)	222	8.11 ± 2.89; 7.9 (4.8-12.5)	215	6.36 ± 2.1; 6.13 (3.71-9.35)	230	7.51 ± 2.32; 7.3 (4.57-10.6)
Month 9	194	6.85 ± 2.99; 6.12 (3.78-10.22)	216	7.95 ± 3.07; 7.52 (4.7-11.5)	208	6.28 ± 2.27; 6.04 (3.85-9)	222	7.48 ± 2.62; 7.23 (4.53-10.94)
Month 12	197	6.5 ± 2.77; 6.08 (3.54-9.4)	212	7.64 ± 3.13; 7 .13 (4.4-11.57)	208	6.07 ± 2.3; 5.75 (3.6-8.57)	222	7.28 ± 2.88; 6.6 (4.6-10.71)

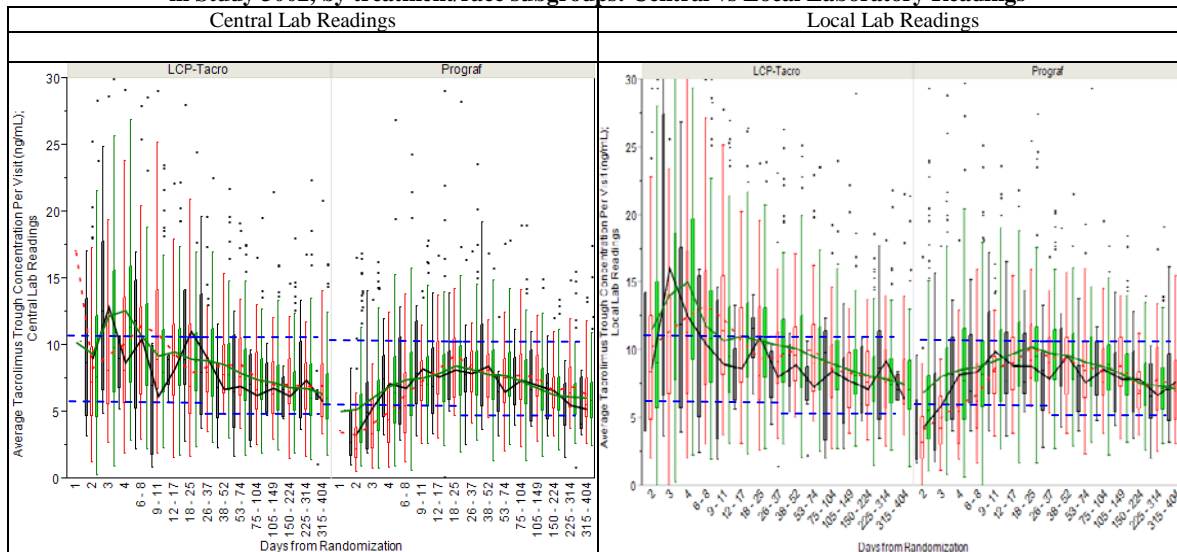
*Week 2 (Days 18-25); Week 3 (Days 18-25); Month 1 (Days 26-37); Month 1.5 (Days 38-52); Month 2 (Days 53-74); Month 3 (Days 75-104); Month 4 (Days 105-149); Month 6 (Days 150-224); Month 9 (Days 225-314); Month 12 (Days 315-404)

On Days 2 and 3, close to half of the ENVARSUS® XR patients had tacrolimus trough concentrations that were above the protocol specified target range (6-11 ng/mL), whereas during the first 7 days, there were 47% to 75% of Prograf patients who were below the protocol defined target range (although the reviewer notes that in the Prograf USPI, the recommended target tacrolimus whole blood trough concentration range is 4-11 ng/mL during the first 12 months).

By Treatment/Race

In Study 3002, there were 3 to 8 ENVARSUS® XR patients of African American descent (per study visit) and with tacrolimus C_{trough} data. Figure 6 depicts the reviewer’s calculated tacrolimus C_{trough} for each treatment/race subgroup by study visit. In general, tacrolimus whole blood trough concentrations in Study 3002 were comparable between racial subgroups. It is noted that the mean tacrolimus trough concentrations per local laboratory readings were slightly above the protocol specified target range (yet not over 16 ng/mL) for all treatment/race subgroups of ENVARSUS® XR during the first week.

Figure 6. Box plots of Daily Tacrolimus Trough Concentrations (ng/mL) in *De novo* Kidney Transplant Patients in Study 3002, by treatment/race subgroups: Central vs Local Laboratory Readings

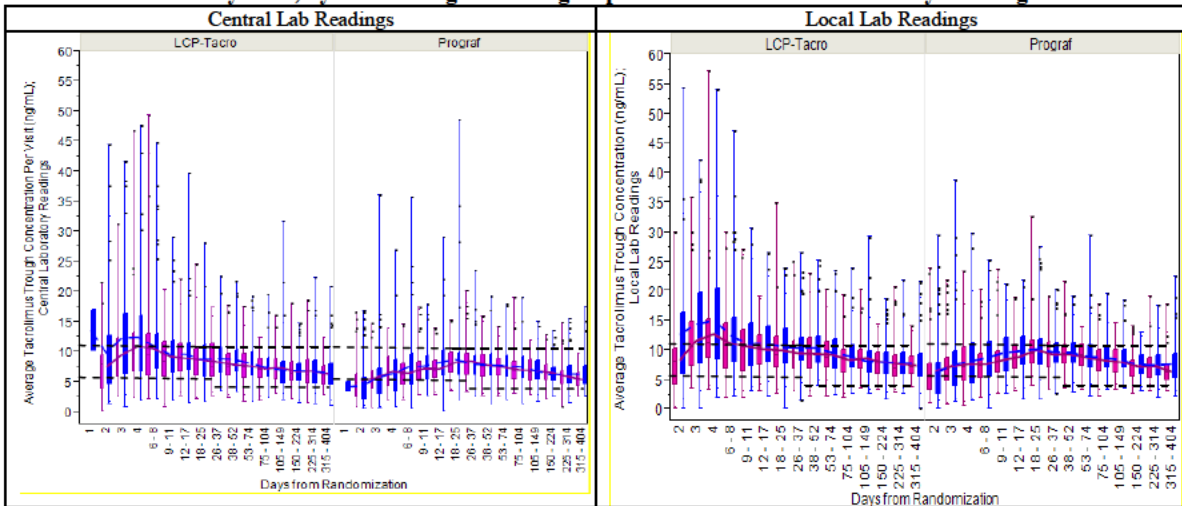


Legend: African-Americans (black boxes/line); Caucasians (green boxes/line); Other Races (red bars/ broken line); protocol defined target tacrolimus trough concentrations (dashed blue horizontal lines)
LCP-Tacro = ENVARSUS® XR

By Treatment/Gender

In Study 3002, about a third of the patients were females. Figure 7 depicts the reviewer’s calculated tacrolimus C_{trough} in each treatment/gender subgroup by study visit. In general, tacrolimus whole blood trough concentrations in Study 3002 were comparable between gender subgroups. In the ENVARSUS® XR treatment group, there was a trend of numerically higher tacrolimus C_{trough} in males than females during the first 1 to 2 weeks post-transplant. It is noted that both male and female subgroups of the ENVARSUS® XR arm achieved slightly higher-than-target mean tacrolimus C_{trough} (per local laboratory readings) during the first week.

Figure 7. Box plots of Daily Tacrolimus Trough Concentrations (ng/mL) in *De novo* Kidney Transplant Patients in Study 3002, by treatment/gender subgroups: Central vs Local Laboratory Readings

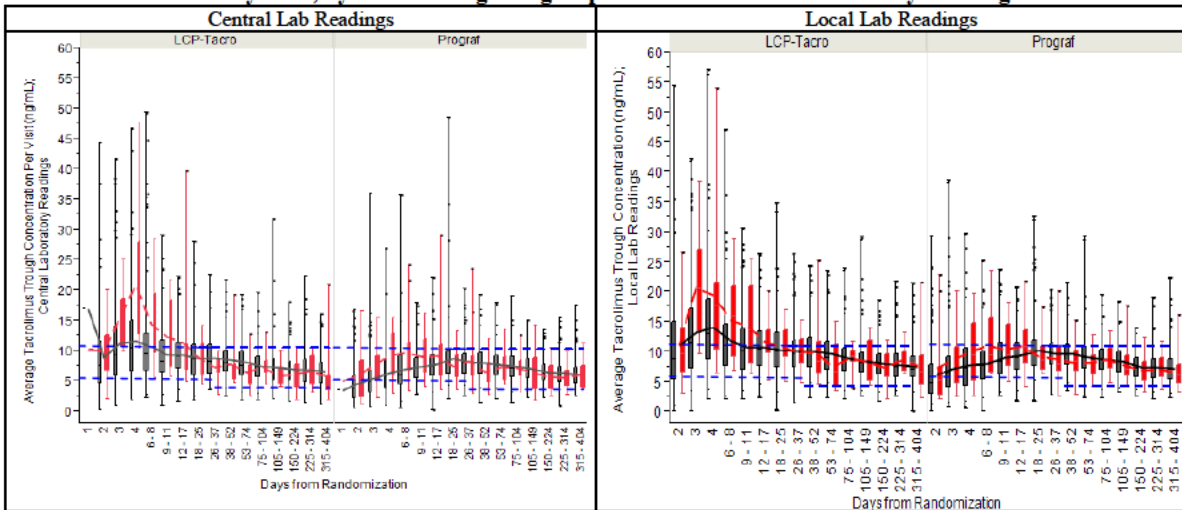


Legend: Females (pink boxes with pink solid line); Males (blue boxes with blue broken line); protocol defined target tacrolimus trough concentrations (dashed black horizontal lines)
LCP-Tacro = ENVARSUS® XR

By Treatment/Age

Figure 8 depicts the tacrolimus C_{trough} in each treatment/age subgroup by study visit. During the first two weeks post-transplant, tacrolimus whole blood trough concentrations in Study 3002 were higher for patients ≥ 65 years than younger patients for both tacrolimus treatment groups. Additionally, it is noted that in the ENVARSUS® XR treatment group, both age subgroups achieved mean tacrolimus C_{trough} values that were slightly higher-than-target, yet not exceeding 21 ng/mL (per both local and central laboratory readings) during the first to second week(s).

Figure 8. Box plots of Daily Tacrolimus Trough Concentrations (ng/mL) in *De novo* Kidney Transplant Patients in Study 3002, by treatment/age subgroups: Central vs Local Laboratory Readings



Legend: Age < 65 years (gray boxes with gray solid line); Age ≥ 65 years (red boxes with red broken line); protocol defined target tacrolimus trough concentrations (dashed blue horizontal lines)
LCP-Tacro = ENVARSUS® XR

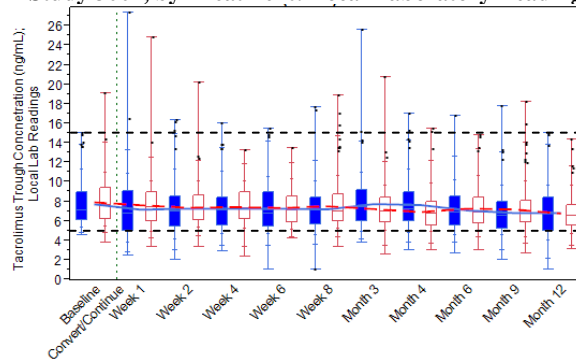
Study 3001: Stable Kidney Transplant

Stable kidney transplant patients receiving a stable dose of Prograf® twice daily (at least 2 mg daily) and with a tacrolimus whole blood trough concentration within the 4-15 ng/mL target range at the end of the 7-day run-in period were either converted to ENVARSUS® XR QD or continued to receive their current dose

of Prograf® BID. After initial dosing, patients taking Prograf had their dose adjusted to maintain tacrolimus whole blood trough levels within the predefined therapeutic range of 4 to 15 ng/mL for the duration of the study, following standards of care at each participating site. Tacrolimus whole blood trough concentrations were measured at every study visit thereafter (i.e., at Weeks 1, 2, 4, 6, 8, end of Months 3, 4, 6, 9, 12).

Table 8 and Figures 9 to 12 summarize the reviewer’s calculated tacrolimus whole blood C_{trough} measured at each protocol specified visit. Tacrolimus trough concentrations were stable in both treatment groups, generally within the target range, and were comparable between ENVARSUS® XR conversion patients and Prograf continuation patients throughout the 12-month study period. African-Americans who were converted to ENVARSUS® XR from Prograf at baseline had tacrolimus C_{trough} concentrations that were slightly numerically higher at certain times and fluctuated more (but were still within the target range) as compared to non-African American patients who received ENVARSUS®XR and all patients who received Prograf. There were no notable trends observed between gender subgroups and between age subgroups in this trial.

Figure 9. Box plots of Daily Tacrolimus Trough Concentrations (ng/mL) in Stable Kidney Transplant Patients in Study 3001, by Treatment: Local Laboratory Readings

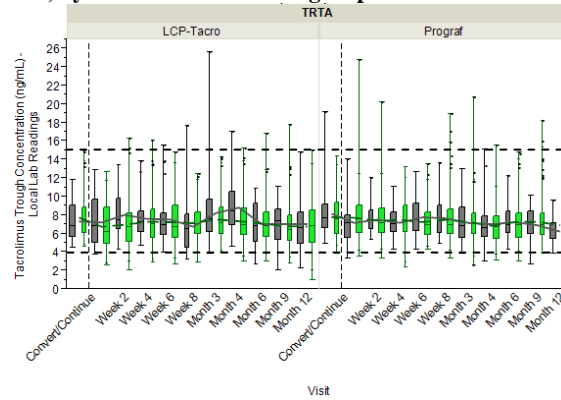


Legend: ENVARSUS® XR (blue solid boxes with blue solid line); Prograf (red open boxes with red broken line); protocol defined target tacrolimus trough concentrations (black horizontal dashed lines)

Table 8. Observed Tacrolimus Trough Concentrations in Stable Kidney Transplant Patients in Study 3001, by Visit and by Treatment Group [Mean ± SD; Median (10th – 90th percentile)]

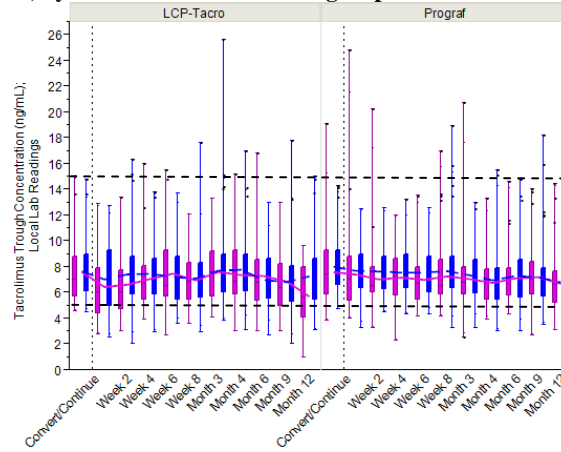
Study Visit	n	ENVARSUS® XR once daily	n	Prograf® twice daily
Baseline	142	7.71 ± 2.27 ;	154	7.91 ± 2.25 ;
		7.1 (5.23 - 11.2)		7.6 (5.4 - 10.65)
Week 1	133	6.89 ± 2.52 ;	143	7.65 ± 2.48 ;
		6.4 (3.7 - 10.6)		7.4 (4.84 - 10)
Week 2	127	7.25 ± 2.61 ;	141	7.48 ± 2.1 ;
		7 (4.08 - 11.12)		7.2 (5.3 - 10)
Week 4	133	7.4 ± 2.49 ;	141	7.47 ± 1.98 ;
		7.1 (4.7 - 11.16)		7.2 (5.2 - 10)
Week 6	131	7.36 ± 2.49 ;	140	7.41 ± 1.98 ;
		6.7 (4.7 - 10.5)		7.15 (5.1 - 10.29)
Week 8	136	7.11 ± 2.13 ;	145	7.58 ± 2.46 ;
		7 (4.5 - 9.43)		7 (5.2 - 10.24)
Month 3	130	7.74 ± 2.83 ;	133	7.29 ± 2.18 ;
		7.25 (4.81 - 10.99)		7 (5.04 - 9.6)
Month 4	126	7.71 ± 2.47 ;	141	6.94 ± 2.07 ;
		7.2 (4.87 - 11.26)		6.7 (4.82 - 9.76)
Month 6	116	7.13 ± 2.28 ;	127	7.29 ± 2.24 ;
		6.8 (4.44 - 10.26)		6.9 (4.88 - 10.6)
Month 9	112	6.9 ± 2.32 ;	120	7.25 ± 2.5 ;
		6.5 (4.5 - 9.57)		7 (4.32 - 10.07)
Month 12	114	6.88 ± 2.59 ;	118	6.81 ± 2 ;
		6.8 (4 - 9.6)		6.5 (4.6 - 9.6)

Figure 10. Box plots of Daily Tacrolimus Trough Concentrations (ng/mL) in Stable Kidney Transplant Patients in Study 3001, by treatment/RACE subgroups: Local Laboratory Readings



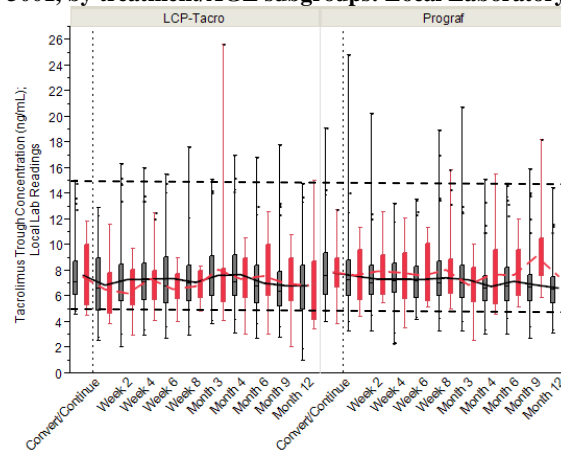
Legend: African Americans/Blacks (gray solid boxes with black solid line); non-African Americans/non-Blacks (green boxes with green broken line); protocol defined target tacrolimus trough concentrations (dashed black horizontal lines)
LCP-Tacro = ENVARSUS® XR

Figure 11. Box plots of Daily Tacrolimus Trough Concentrations (ng/mL) in Stable Kidney Transplant Patients in Study 3001, by treatment/GENDER subgroups: Local Laboratory Readings



Legend: Females (pink solid boxes/lines); Males (blue boxes/broken lines); protocol defined target tacrolimus trough concentrations (dashed black horizontal lines)
LCP-Tacro = ENVARSUS® XR

Figure 12. Box plots of Daily Tacrolimus Trough Concentrations (ng/mL) in Stable Kidney Transplant Patients in Study 3001, by treatment/AGE subgroups: Local Laboratory Readings



Legend: Age < 65 years (gray boxes with gray solid line); Age ≥ 65 years (red boxes with red broken line); protocol defined target tacrolimus trough concentrations (dashed black horizontal lines)
LCP-Tacro = ENVARSUS® XR

Tacrolimus Dose

3.b. Were the (starting and subsequent) total daily tacrolimus doses of ENVARSUS® XR once daily comparable to Prograf® twice daily in Study 3002 and in Study 3001?

Study 3002: De novo Kidney Transplant

In Study 3002, *de novo* kidney transplant patients assigned to ENVARSUS® XR once daily tablets received -- per protocol-- a higher starting tacrolimus daily dose (0.17 mg/kg/day) than the patients assigned to Prograf® twice daily capsules (0.1 mg/kg/day). Table 9 and Figure 13 compare the total tacrolimus daily doses received by ENVARSUS® XR and Prograf® patients during the 12-month study. The mean tacrolimus daily doses (mg) continued to be higher in the ENVARSUS® XR than in the Prograf group during the first week. Such higher daily doses resulted in measured tacrolimus C_{trough} that were slightly above the target C_{trough} range in ENVARSUS® XR patients (see Figure 5 above). After the first month, the mean tacrolimus daily doses (mg) were numerically lower in the ENVARSUS® XR than in the Prograf group, when the measured tacrolimus C_{trough} were comparable between treatment arms.

Note that in majority (98%; 251/255) of the patients, the first tacrolimus dose was received within 24 hours post-transplant, the remainder received the first tacrolimus dose within 48 hours post-transplant (per the last protocol amendment).

The racial distribution in this trial was as follows: 77% Caucasian; 4.5% African-Americans; 8.5% others. Regardless of race, patients in the ENVARSUS® XR arm received the same starting tacrolimus daily dose (mg/kg/day), and comparable average daily tacrolimus doses (mg/day) up to Day 7 which resulted in apparently comparable tacrolimus C_{trough} (see Table 10 below and Figure 6 above). Thereafter, numerically higher tacrolimus daily doses of ENVARSUS® XR and Prograf® were administered to African-Americans (AA) than Caucasians or non-AA patients after the first 7 days and first 3 days, respectively. Though generally consistent with data obtained with other oral tacrolimus products, these comparative racial subgroup findings should be interpreted with caution due to the very low numbers of African-Americans included in the trial.

Males comprised about two-thirds (65%) of the study population. For both ENVARSUS® XR and Prograf treatment arms, males received higher tacrolimus daily doses (mg) than their female counterparts during the first 1 to 2 weeks, which could explain (at least in part) the numerically higher mean tacrolimus C_{trough} in male patients in the ENVARSUS® XR arm measured during the first 1 to 2 weeks (see Table 11 below and Figure 7 above). The mean tacrolimus daily doses were comparable between gender subgroups thereafter, regardless of treatment.

Approximately 6% of the ENVARSUS® XR patients and 9% of the Prograf patients in this trial were 65 years or older at baseline. Additionally, for both ENVARSUS® XR and Prograf arms, comparable to slightly higher tacrolimus daily doses (mg) during the first 1 to 2 weeks resulted in higher tacrolimus C_{trough} in elderly patients ≥ 65 years than younger patients (see Table 12 below and Figure 8 above). Thereafter, to maintain comparable C_{trough} between age subgroups, lower mean tacrolimus daily doses were needed in the elderly patients, regardless of treatment arm. Though consistent with general expectations, these comparative age subgroup findings should be interpreted with caution due to the very low numbers of patients ≥ 65 years old included in the trial.

Figure 13. Average Tacrolimus Daily Dose (TDD; mg) Over Visit Interval in Study 3002, by Treatment Group

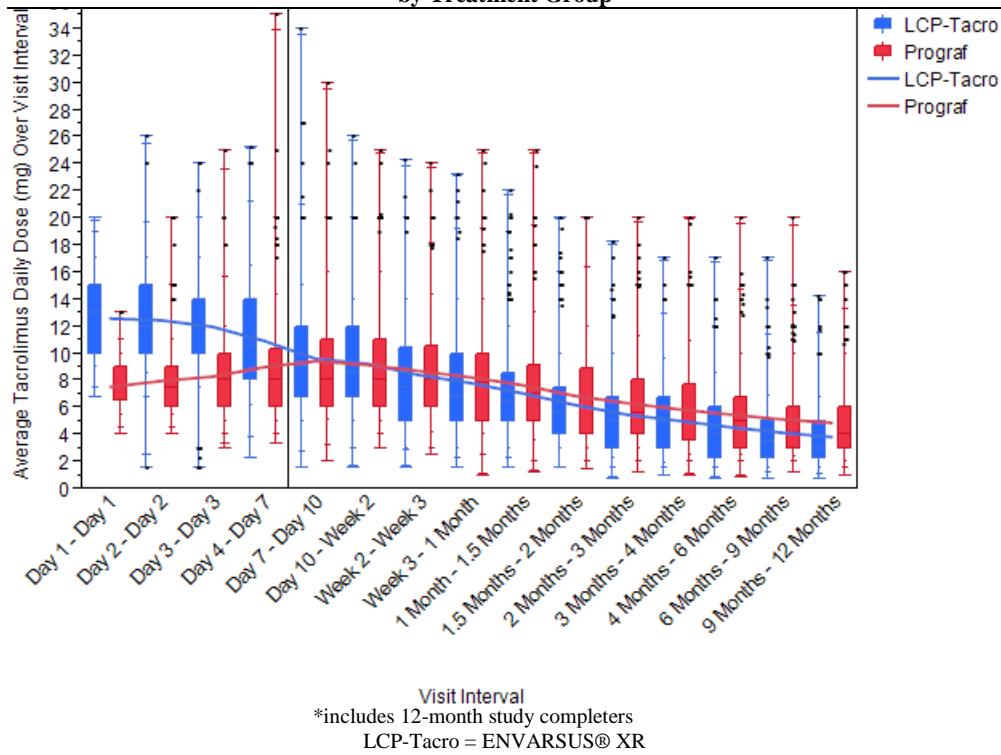


Table 9. Mean ± SD Tacrolimus Daily Doses (mg) per visit interval in Study 3002, by treatment

Visit Interval	n	ENVARSUS® XR	n	Prograf
Day 1 - Day 1	251	12.66 ± 2.84	252	7.59 ± 1.7
Day 2 - Day 2	253	12.52 ± 3.43	255	8.02 ± 2.5
Day 3 - Day 3	252	12.04 ± 3.87	254	8.35 ± 3.06
Day 4 - Day 7	214	11 ± 4.23	222	9.06 ± 4.13
Day 7 - Day 10	213	9.67 ± 4.78	220	9.49 ± 4.5
Day 10 - Week 2	234	9.31 ± 4.17	238	9.22 ± 4.25
Week 2 - Week 3	228	8.46 ± 4.21	236	8.77 ± 3.99
Week 3 - 1 Month	231	7.88 ± 4.22	238	8.3 ± 4.16
1 Month - 1.5 Months	233	7.12 ± 3.82	239	7.72 ± 4.02
1.5 Months - 2 Months	231	6.26 ± 3.43	235	6.94 ± 3.7
2 Months - 3 Months	230	5.55 ± 3.13	233	6.41 ± 3.47
3 Months - 4 Months	223	5.1 ± 3	231	5.95 ± 3.35
4 Months - 6 Months	219	4.62 ± 2.85	223	5.56 ± 3.24
6 Months - 9 Months	214	4.22 ± 2.53	220	5.2 ± 3.07
9 Months - 12 Months	203	3.88 ± 2.41	214	4.93 ± 3.01

Figure 14. Average Tacrolimus Daily Dose (TDD; mg) Over Visit Interval in Study 3002, by Treatment Group and by Race

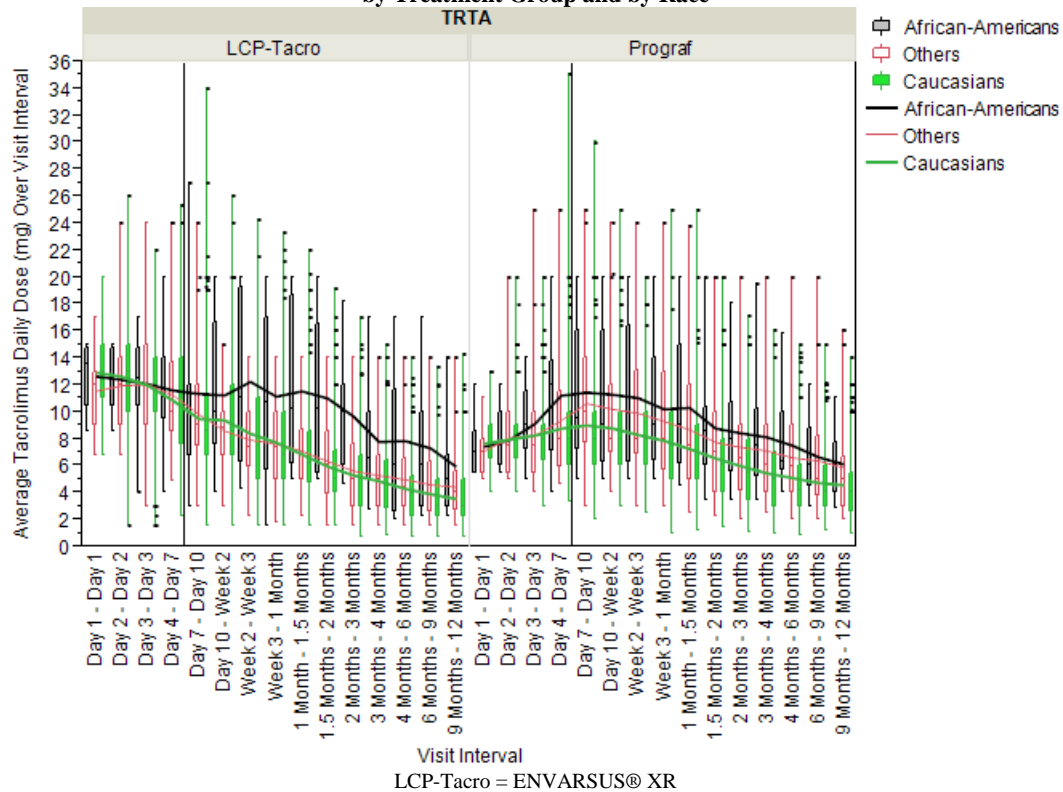


Table 10. Mean $\pm$ SD Tacrolimus Daily Doses (mg) per visit interval in Study 3002, by treatment/race

Visit Interval	ENVARUSUS® XR						Prograf					
	n	African Americans	n	Caucasians	n	Others	n	African Americans	n	Caucasians	n	Others
Day 1 - Day 1	8	12.69 $\pm$ 2.37	188	12.97 $\pm$ 2.85	55	11.59 $\pm$ 2.65	13	7.46 $\pm$ 2.12	196	7.69 $\pm$ 1.67	43	7.13 $\pm$ 1.65
Day 2 - Day 2	8	12.44 $\pm$ 2.32	190	12.68 $\pm$ 3.44	55	12 $\pm$ 3.5	13	7.96 $\pm$ 2.19	199	8.01 $\pm$ 2.4	43	8.1 $\pm$ 3.03
Day 3 - Day 3	8	12.13 $\pm$ 3.91	190	12.02 $\pm$ 3.74	54	12.08 $\pm$ 4.34	13	9.19 $\pm$ 2.61	198	8.31 $\pm$ 2.9	43	8.3 $\pm$ 3.84
Day 4 - Day 7	7	11.64 $\pm$ 4.89	159	10.88 $\pm$ 4.08	48	11.28 $\pm$ 4.67	12	11.25 $\pm$ 5.25	169	8.82 $\pm$ 3.93	41	9.4 $\pm$ 4.48
Day 7 - Day 10	7	11.39 $\pm$ 7.53	158	9.53 $\pm$ 4.81	48	9.87 $\pm$ 4.22	12	11.5 $\pm$ 5.27	167	9.06 $\pm$ 4.29	41	10.68 $\pm$ 4.86
Day 10 - Week 2	8	11.28 $\pm$ 5.43	172	9.43 $\pm$ 4.38	54	8.63 $\pm$ 3.09	12	11.33 $\pm$ 5.55	183	8.83 $\pm$ 4	43	10.25 $\pm$ 4.66
Week 2 - Week 3	8	12.29 $\pm$ 6.19	166	8.44 $\pm$ 4.34	54	7.97 $\pm$ 3.11	12	11.08 $\pm$ 5.15	182	8.34 $\pm$ 3.62	42	9.95 $\pm$ 4.76
Week 3 - 1 Month	8	11.19 $\pm$ 6.48	169	7.78 $\pm$ 4.29	54	7.68 $\pm$ 3.42	13	10.25 $\pm$ 5.1	183	7.91 $\pm$ 3.78	42	9.35 $\pm$ 5.09
1 Month - 1.5 Months	8	11.59 $\pm$ 6.08	171	6.9 $\pm$ 3.78	54	7.14 $\pm$ 3.18	13	10.35 $\pm$ 5.22	183	7.3 $\pm$ 3.58	43	8.73 $\pm$ 4.94
1.5 Months - 2 Months	8	11.05 $\pm$ 5.66	170	6 $\pm$ 3.29	53	6.38 $\pm$ 2.94	12	8.83 $\pm$ 4.31	180	6.61 $\pm$ 3.38	43	7.79 $\pm$ 4.54
2 Months - 3 Months	7	9.72 $\pm$ 4.7	170	5.35 $\pm$ 3.01	53	5.67 $\pm$ 2.95	12	8.47 $\pm$ 3.95	178	6.02 $\pm$ 3.15	43	7.42 $\pm$ 4.21
3 Months - 4 Months	7	7.82 $\pm$ 4.71	164	4.91 $\pm$ 2.9	52	5.33 $\pm$ 2.95	12	8.17 $\pm$ 4.37	176	5.5 $\pm$ 2.92	43	7.16 $\pm$ 4.12
4 Months - 6 Months	7	7.9 $\pm$ 5.33	161	4.35 $\pm$ 2.62	51	5.02 $\pm$ 2.84	12	7.55 $\pm$ 3.38	169	5.15 $\pm$ 2.93	42	6.64 $\pm$ 3.93
6 Months - 9 Months	7	7.35 $\pm$ 5.05	158	3.95 $\pm$ 2.28	49	4.64 $\pm$ 2.53	12	6.69 $\pm$ 2.65	167	4.79 $\pm$ 2.7	41	6.42 $\pm$ 4.08
9 Months - 12 Months	7	5.96 $\pm$ 3.87	149	3.6 $\pm$ 2.25	47	4.47 $\pm$ 2.44	12	6.16 $\pm$ 2.45	163	4.61 $\pm$ 2.75	39	5.9 $\pm$ 3.87

Figure 15. Average Tacrolimus Daily Dose (TDD; mg) Over Visit Interval in Study 3002, by Treatment Group and by Gender

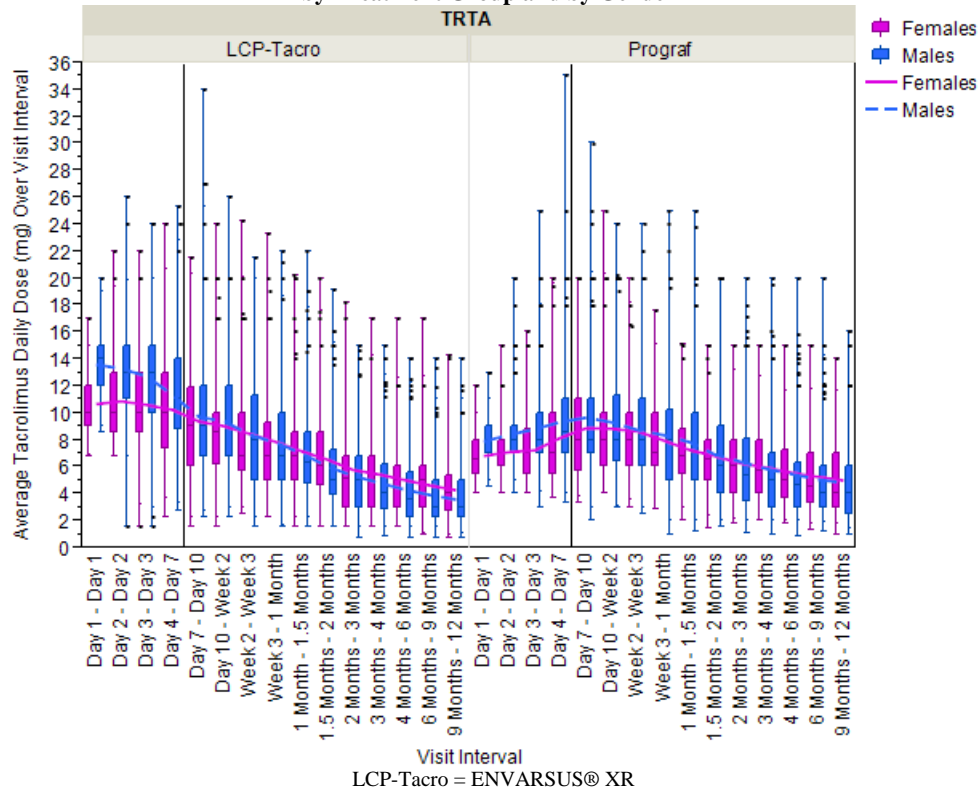


Table 11. Mean ± SD Tacrolimus Daily Doses (mg) per visit interval in Study 3002, by treatment/gender

Visit Interval	ENVARUSUS® XR				Prograf			
	n	Females	n	Males	n	Females	n	Males
Day 1 - Day 1	86	10.73 ± 2.32	165	13.66 ± 2.55	85	6.87 ± 1.59	167	7.95 ± 1.64
Day 2 - Day 2	87	10.93 ± 2.94	166	13.35 ± 3.38	85	7.16 ± 1.96	170	8.45 ± 2.63
Day 3 - Day 3	87	10.66 ± 3.49	165	12.77 ± 3.87	84	7.3 ± 2.52	170	8.87 ± 3.17
Day 4 - Day 7	72	10.29 ± 3.98	142	11.36 ± 4.31	66	8.23 ± 3.85	156	9.4 ± 4.21
Day 7 - Day 10	72	9.44 ± 4.74	141	9.79 ± 4.8	65	8.94 ± 4.37	155	9.72 ± 4.55
Day 10 - Week 2	80	9.08 ± 4.48	154	9.43 ± 4.02	76	8.89 ± 4.24	162	9.37 ± 4.26
Week 2 - Week 3	78	8.5 ± 4.45	150	8.44 ± 4.09	76	8.7 ± 3.9	160	8.8 ± 4.05
Week 3 - 1 Month	79	7.91 ± 4.34	152	7.86 ± 4.18	77	8.03 ± 3.34	161	8.42 ± 4.5
1 Month - 1.5 Months	79	7.22 ± 3.96	154	7.06 ± 3.76	77	7.32 ± 2.91	162	7.91 ± 4.45
1.5 Months - 2 Months	78	6.6 ± 3.53	153	6.09 ± 3.37	76	6.87 ± 2.87	159	6.97 ± 4.04
2 Months - 3 Months	78	5.83 ± 3.3	152	5.41 ± 3.04	76	6.33 ± 2.71	157	6.44 ± 3.79
3 Months - 4 Months	76	5.51 ± 3.06	147	4.89 ± 2.96	76	6 ± 2.68	155	5.92 ± 3.64
4 Months - 6 Months	74	5.09 ± 2.85	145	4.38 ± 2.82	73	5.62 ± 2.73	150	5.53 ± 3.47
6 Months - 9 Months	73	4.68 ± 2.62	141	3.98 ± 2.46	71	5.32 ± 2.69	149	5.14 ± 3.24
9 Months - 12 Months	70	4.33 ± 2.5	133	3.64 ± 2.34	71	5.05 ± 2.72	143	4.88 ± 3.16

Figure 16. Average Tacrolimus Daily Dose (TDD; mg) Over Visit Interval in Study 3002, by Treatment Group and by Age Subgroup (cut-off: 65 years)

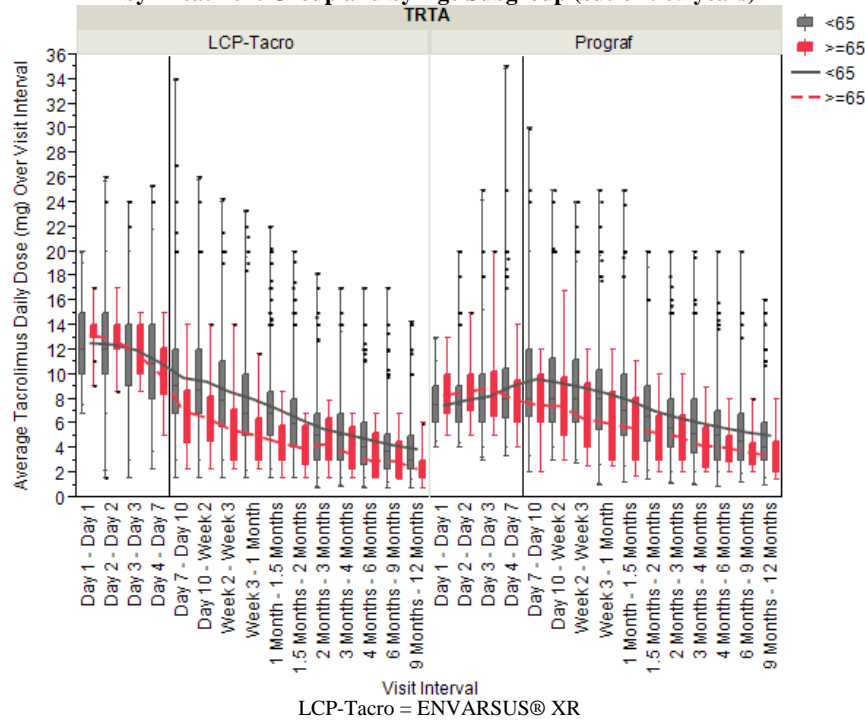


Table 12. Mean ± SD Tacrolimus Daily Doses (mg) per visit interval in Study 3002, by treatment /age

Visit Interval	ENVARUSUS® XR				Prograf			
	n	< 65 years old	n	≥ 65 years old	n	< 65 years old	n	≥ 65 years old
Day 1 - Day 1	236	12.62 ± 2.89	15	13.27 ± 1.83	231	7.52 ± 1.66	21	8.36 ± 1.94
Day 2 - Day 2	238	12.49 ± 3.49	15	12.97 ± 2.21	233	7.97 ± 2.51	22	8.64 ± 2.41
Day 3 - Day 3	238	12.05 ± 3.95	14	11.82 ± 2.27	232	8.3 ± 3	22	8.95 ± 3.69
Day 4 - Day 7	204	11.04 ± 4.28	10	10.1 ± 2.91	202	9.15 ± 4.22	20	8.05 ± 2.95
Day 7 - Day 10	203	9.79 ± 4.8	10	7.11 ± 3.42	200	9.68 ± 4.61	20	7.58 ± 2.64
Day 10 - Week 2	221	9.47 ± 4.17	13	6.54 ± 3.15	218	9.37 ± 4.3	20	7.49 ± 3.37
Week 2 - Week 3	215	8.64 ± 4.21	13	5.59 ± 3.1	216	8.98 ± 4.01	20	6.46 ± 3.11
Week 3 - 1 Month	218	8.04 ± 4.25	13	5.14 ± 2.59	216	8.52 ± 4.19	22	6.1 ± 3.13
1 Month - 1.5 Months	220	7.27 ± 3.86	13	4.59 ± 1.96	217	7.92 ± 4.06	22	5.73 ± 2.96
1.5 Months - 2 Months	218	6.39 ± 3.46	13	4.1 ± 1.79	213	7.1 ± 3.77	22	5.36 ± 2.47
2 Months - 3 Months	218	5.62 ± 3.17	12	4.38 ± 2.01	211	6.55 ± 3.55	22	5.03 ± 2.23
3 Months - 4 Months	211	5.18 ± 3.04	12	3.69 ± 1.93	211	6.1 ± 3.4	20	4.3 ± 2.2
4 Months - 6 Months	207	4.71 ± 2.86	12	3.04 ± 2.09	203	5.7 ± 3.32	20	4.12 ± 1.72
6 Months - 9 Months	202	4.29 ± 2.55	12	3.03 ± 1.86	200	5.34 ± 3.15	20	3.74 ± 1.49
9 Months - 12 Months	191	3.98 ± 2.42	12	2.35 ± 1.62	195	5.08 ± 3.08	19	3.4 ± 1.65

Study 3001: Stable Kidney Transplant

Following a 7-day run in period, stable kidney transplant patients receiving Prograf® oral capsules twice daily were randomized 1:1 either to continue on Prograf® twice daily at the current dose, or be converted to ENVARUSUS® XR oral tablets once daily using a daily dose conversion ratio of 1:0.70 for non-African Americans/non-Blacks, and 1:0.85 for African Americans/Blacks.

Tables 13 to 16 show the reviewer’s calculated tacrolimus daily doses received by Prograf® patients before their conversion (at baseline) and 1 week after conversion to ENVARSUS® XR, as compared to a parallel group of patients who continued receiving Prograf® during study participation. The calculated ratios of the mean tacrolimus daily doses between baseline and 1 week visits confirm that upon conversion to ENVARSUS® XR, the mean starting daily doses were: a) approximately 11% and 30% lower in African-American and non-African American patients, respectively, than prior to conversion from Prograf®, b) comparable between male and female patients, and c) numerically slightly lower in patients ≥ 65 years old than their younger counterparts. Note that in the ENVARSUS® XR conversion arm of this trial, 20% were African-Americans/Blacks, 30% were females, and 11% were elderly patients (≥ 65 years).

Note that dosage adjustments were not allowed in Study Week 1 but were considered afterwards, if the ENVARSUS® XR post-conversion tacrolimus trough concentration at Visit 5 (Day 7±2) was more than 25% above or below the pre-conversion tacrolimus trough level, even if the post-conversion tacrolimus C_{trough} was within the target range (if appropriate after assessment of clinical factors). All subsequent study drug dose adjustments were based on clinical assessment of the patient and maintenance of target tacrolimus whole blood trough levels within the predefined therapeutic range of 4 - 15 ng/mL (5-15 ng/mL in the original protocol; as determined by the local laboratory).

See also Figures 17 to 20 for a comparison of the 12-month time course profiles of the tacrolimus daily doses in the ENVARSUS® XR and Prograf groups received at each study visit prior to measurement of tacrolimus trough concentration, as a function of race, gender, and age subgroupings. Per protocol, tacrolimus daily doses in the ENVARSUS® XR group were reduced starting at Week 1 post-conversion compared to during the 7-day run-in phase with Prograf, more in non-African American than African American patients. The measured tacrolimus C_{trough} over the 12-month study were generally comparable between ENVARSUS® XR and Prograf, and were within the protocol specified target range of 4-15 ng/mL (see Figures 9 to 12 above).

Table 13. Tacrolimus Daily Doses (mg/day), and Baseline-to-Week 1 Ratio of Mean Tacrolimus Daily Doses received by stable kidney transplant patients (Study 3001)*

Study period	ENVARSUS® XR once daily (conversion)			Prograf® twice daily (continuation)		
	n	[Mean ± SD; Median (10th – 90th percentile)]	Mean Dose ratio	n	[Mean ± SD; Median (10th – 90th percentile)]	Mean Dose ratio
Baseline	150	5.68 ± 3.41; 4 (2-10)	0.77	147	5.16 ± 3.02; 4 (2-10);	1.01
Week 1	150	4.35 ± 2.8; 3.5 (1.5-9)		147	5.23 ± 3.02; 4 (2-10);	

*post-conversion to ENVARSUS® XR once daily (or continuation with Prograf® twice daily); paired comparisons between baseline and Week 1 doses

Table 14. Tacrolimus Daily Doses (mg/day), and Baseline-to-Week 1 Ratio of Mean Tacrolimus Daily Doses received by stable kidney transplant patients (Study 3001 - by RACE Subgroup)*

Study period	ENVARSUS® XR once daily (conversion) – African Americans			ENVARSUS® XR once daily (conversion) – non-African Americans		
	n	[Mean ± SD; Median (10th – 90th percentile)]	Mean Dose ratio	n	[Mean ± SD; Median (10th – 90th percentile)]	Mean Dose ratio
Baseline	30	8.33 ± 3.74; 9 (3.1 - 12)	0.89	120	5.02 ± 3; 4 (2 - 8)	0.71
Week 1	30	7.43 ± 3.25; 8 (2.6 - 10.9)		120	3.58 ± 2.05; 3 (1.5 - 6)	
Study period	Prograf® twice daily (continuation) – African Americans			Prograf® twice daily (continuation) – non-African Americans		
	n	[Mean ± SD; Median (10th – 90th percentile)]	Mean Dose ratio	n	[Mean ± SD; Median (10th – 90th percentile)]	Mean Dose ratio
Baseline	32	6.81 ± 3.14; 6 (2.3 - 12)	1.01	115	4.7 ± 2.83; 4 (2 - 8.4)	1.02
Week 1	32	6.88 ± 3.14; 6.5 (2.3 - 12)		115	4.77 ± 2.83; 4 (2 - 9)	

* post-conversion to ENVARSUS® XR once daily (or continuation with Prograf® twice daily); paired comparisons between baseline and Week 1 doses

Table 15. Tacrolimus Daily Doses (mg/day), and Baseline-to-Week 1 Ratio of Mean Tacrolimus Daily Doses received by stable kidney transplant patients (Study 3001 - by GENDER Subgroup)*

Study period	ENVARUSUS® XR once daily (conversion) – Females			ENVARUSUS® XR once daily (conversion) – Males		
	n	[Mean ± SD; Median (10th – 90th percentile)]	Mean Dose ratio	n	[Mean ± SD; Median (10th – 90th percentile)]	Mean Dose ratio
Baseline	44	5.39 ± 3.68; 4 (2-12);	0.78	106	5.8 ± 3.31; 5 (2-10);	0.76
Week 1	44	4.19 ± 3.02; 3 (1.5-9.5);		106	4.42 ± 2.71; 3.5 (1.85-9);	
Study period	Prograf® twice daily (continuation) – Females			Prograf® twice daily (continuation) – Males		
	n	[Mean ± SD; Median (10th – 90th percentile)]	Mean Dose ratio	n	[Mean ± SD; Median (10th – 90th percentile)]	Mean Dose ratio
Baseline	52	4.94 ± 2.45; 4 (2-9.4);	1.03	95	5.27 ± 3.3; 4 (2-10);	1.01
Week 1	52	5.08 ± 2.46; 5 (2-9.7);		95	5.32 ± 3.29; 4 (2-10);	

** post-conversion to ENVARUSUS® XR once daily (or continuation with Prograf® twice daily); paired comparisons between baseline and Week 1 doses

Table 16. Tacrolimus Daily Doses (mg/day), and Baseline-to-Week 1 Ratio of Mean Tacrolimus Daily Doses received by stable kidney transplant patients (Study 3001 - by AGE Subgroup)*

Study period	ENVARUSUS® XR once daily (conversion) – < 65 years			ENVARUSUS® XR once daily (conversion) – ≥ 65 years		
	n	[Mean ± SD; Median (10th – 90th percentile)]	Mean Dose ratio	n	[Mean ± SD; Median (10th – 90th percentile)]	Mean Dose ratio
Baseline	133	5.77 ± 3.34; 5 (2-10)	0.76	17	5 ± 4.02; 4 (2-11.6)	0.82
Week 1	133	4.38 ± 2.68; 3.5 (1.5-9)		17	4.09 ± 3.67; 3 (1.5-10.4)	
Study period	Prograf® twice daily (continuation) – < 65 years			Prograf® twice daily (continuation) – ≥ 65 years		
	n	[Mean ± SD; Median (10th – 90th percentile)]	Mean Dose ratio	n	[Mean ± SD; Median (10th – 90th percentile)]	Mean Dose ratio
Baseline	123	5.25 ± 2.77; 4 (2-10)	1.02	24	4.67 ± 4.09; 3.5 (2-10)	0.99
Week 1	123	5.35 ± 2.78; 4 (2-10)		24	4.63 ± 4.04; 3.5 (2-10)	

** post-conversion to ENVARUSUS® XR once daily (or continuation with Prograf® twice daily); paired comparisons between baseline and Week 1 doses

Figure 17. Last Daily Dose of Tacrolimus (mg/day) received during Study Visit prior to measurement of Tacrolimus trough Concentration in Stable Kidney Transplant Patients converted from Prograf® BID to ENVARUSUS® XR QD compared to those who continued to receive Prograf® BID in Study 3001 (by Treatment)

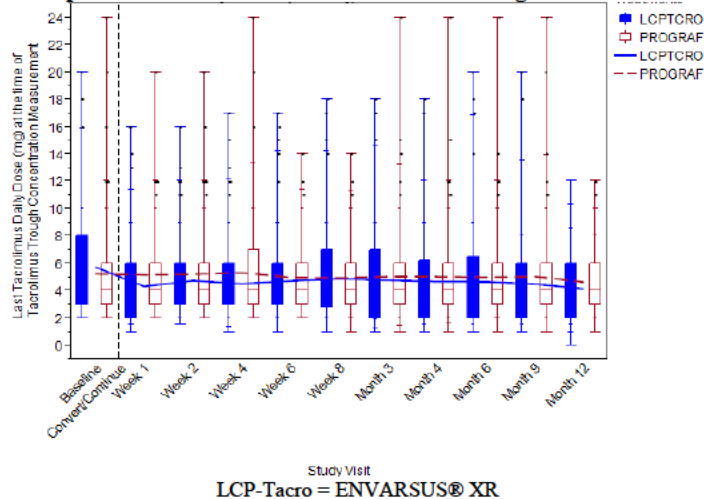


Figure 18. Last Daily Dose of Tacrolimus (mg/day) received during Study Visit prior to measurement of Tacrolimus trough Concentration in Stable Kidney Transplant Patients converted from Prograf® BID to ENVARSUS® XR QD compared to those who continued to receive Prograf® BID in Study 3001 (by Treatment/Race Subgroups)

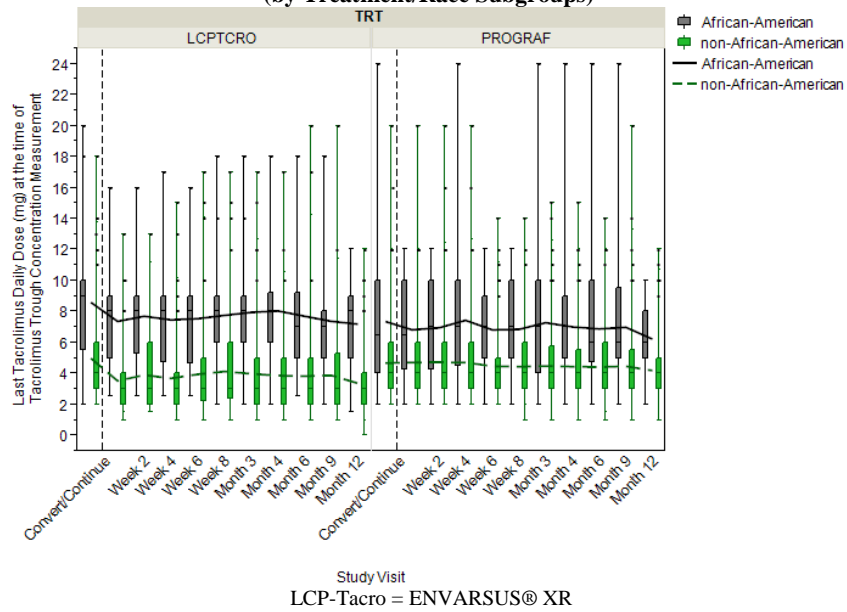


Figure 19. Last Daily Dose of Tacrolimus (mg/day) received during Study Visit prior to measurement of Tacrolimus trough Concentration in Stable Kidney Transplant Patients converted from Prograf® BID to ENVARSUS® XR QD compared to those who continued to receive Prograf® BID in Study 3001 (by Treatment/Gender Subgroups)

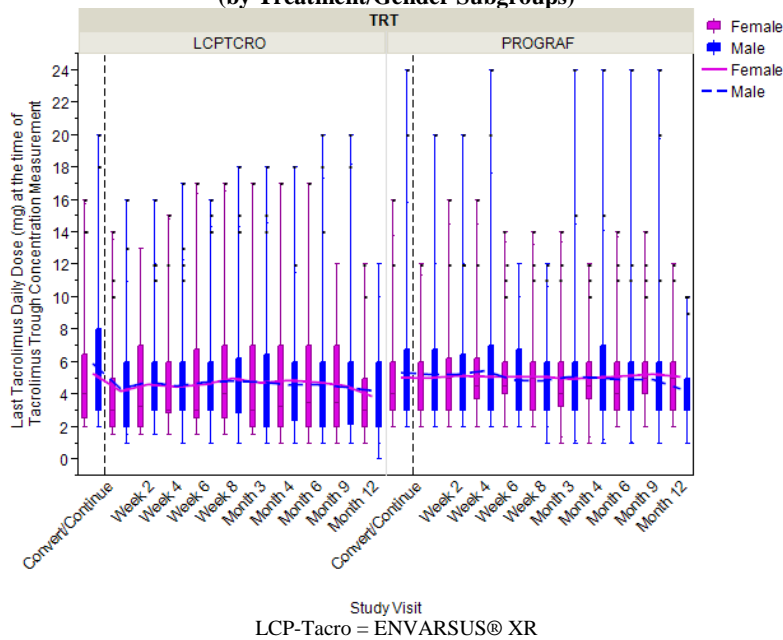
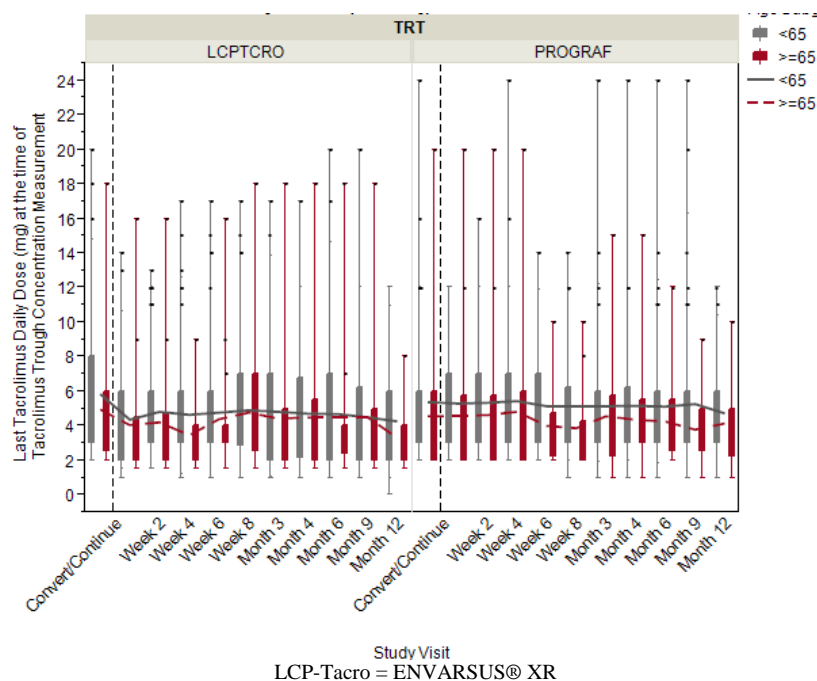


Figure 20. Last Daily Dose of Tacrolimus (mg/day) received during Study Visit prior to measurement of Tacrolimus trough Concentration in Stable Kidney Transplant Patients converted from Prograf® BID to ENVARSUS® XR QD compared to those who continued to receive Prograf® BID in Study 3001 (by Treatment/Age Subgroups)



Mycophenolate Mofetil (MMF) Dosing

3.c. Were the mycophenolate mofetil (MMF) equivalent doses comparable between the Prograf®/mycophenolate treatment group and ENVARSUS® XR/mycophenolate treatment group in Study 3002 and in Study 3001? Was mycophenolate dosing in these studies consistent with the protocol?

Study 3002: De novo Kidney Transplant

According to the protocol of Study 3002, MMF dosing was to be administered per the most current product label. In the 09 May 2011 amendment of the protocol, MMF dosing was specified as follows: 1 gram twice daily. The study protocol did not explicitly state whether MMF dosage adjustments were permitted or not, particularly based on intolerability concerns, although a gradual decrease in average mycophenolate equivalent doses was observed over the 12-month study period. By Month 6, median and mean mycophenolate doses were approximately 1.5 grams daily for both tacrolimus treatment arms.

The mean mycophenolate doses were comparable between males and females, regardless of tacrolimus treatment. There were very few non-Caucasian patients and elderly patients in this trial; comparisons of mycophenolate doses based on race subgroups and based on age subgroups should be interpreted with caution (Table 17; Figures 21 to 24).

Figure 21. Daily Mycophenolate Mofetil Equivalent Doses (mg/day) co-administered with ENVARSUS® XR and Prograf® in *De novo* Kidney Transplant Patients in Study 3002, by treatment

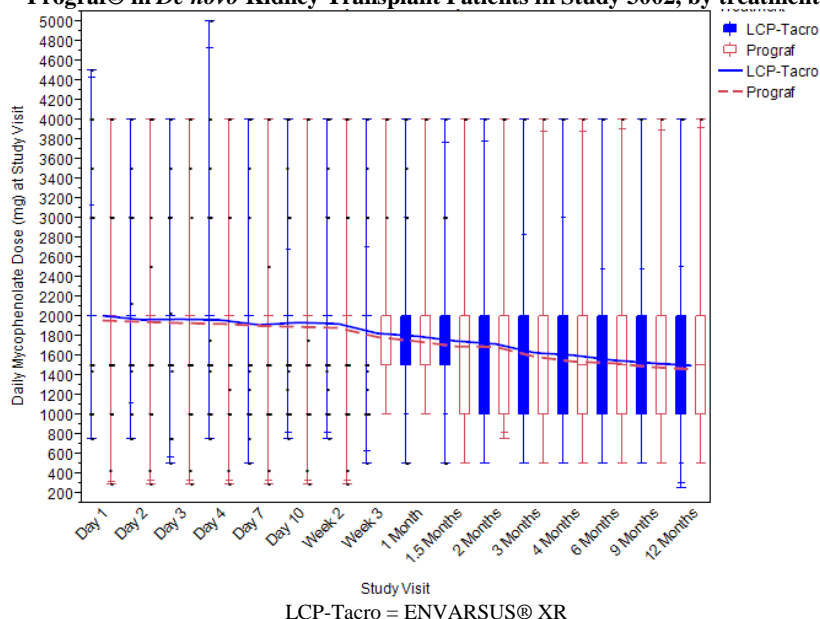


Table 17. Daily Mycophenolate Mofetil Equivalent Doses (mg/day) co-administered with ENVARSUS® XR and Prograf® in *De novo* Kidney Transplant Patients, by treatment [Study 3002 [Mean ± SD; Median (10th – 90th percentile)]]

Study Visit	n	ENVARSUS® XR	n	Prograf
Day 1	229	2012.8 ± 402.3; 2000(2000 - 2000)	240	1963.4 ± 381.8; 2000(1500 - 2000)
Day 2	249	1971.1 ± 328.8; 2000(1500 - 2000)	251	1951.1 ± 339.5; 2000(1500 - 2000)
Day 3	252	1976 ± 317.4; 2000(1500 - 2000)	252	1937.4 ± 338; 2000(1500 - 2000)
Day 4	253	1969.1 ± 378; 2000(1500 - 2000)	253	1930.7 ± 333.4; 2000(1500 - 2000)
Day 7	251	1918.1 ± 356.4; 2000(1500 - 2000)	253	1909.9 ± 342.8; 2000(1500 - 2000)
Day 10	252	1944.2 ± 359.3; 2000(1500 - 2000)	252	1898.7 ± 347.9; 2000(1500 - 2000)
Week 2	252	1930.3 ± 387.6; 2000(1500 - 2000)	250	1888.9 ± 393.6; 2000(1500 - 2000)
Week 3	251	1833.4 ± 461.1; 2000(1000 - 2000)	249	1795.2 ± 447; 2000(1000 - 2000)
1 Month	249	1804 ± 492.1; 2000(1000 - 2000)	250	1752 ± 459.7; 2000(1000 - 2000)
1.5 Months	246	1754.8 ± 489; 2000(1000 - 2000)	250	1700 ± 488.8; 2000(1000 - 2000)
2 Months	245	1725.3 ± 497.5; 2000(1000 - 2000)	250	1696 ± 497.1; 2000(1000 - 2000)
3 Months	246	1635.9 ± 566.3; 2000(1000 - 2000)	248	1595.8 ± 533; 2000(1000 - 2000)
4 Months	244	1609.6 ± 584.5; 2000(1000 - 2000)	248	1545.4 ± 539.6; 1500(1000 - 2000)
6 Months	242	1559.9 ± 580.7; 1500(1000 - 2000)	240	1529.2 ± 554.3; 1500(1000 - 2000)
9 Months	243	1529.8 ± 582; 1500(1000 - 2000)	242	1488.6 ± 543.8; 1500(1000 - 2000)
12 Months	239	1505.7 ± 592.1; 1500(1000 - 2000)	235	1468.1 ± 550.9; 1500(1000 - 2000)

Figure 22. Daily Mycophenolate Mofetil Equivalent Doses (mg/day) co-administered with ENVARUSUS® XR and Prograf® in *De novo* Kidney Transplant Patients in Study 3002, by treatment/race

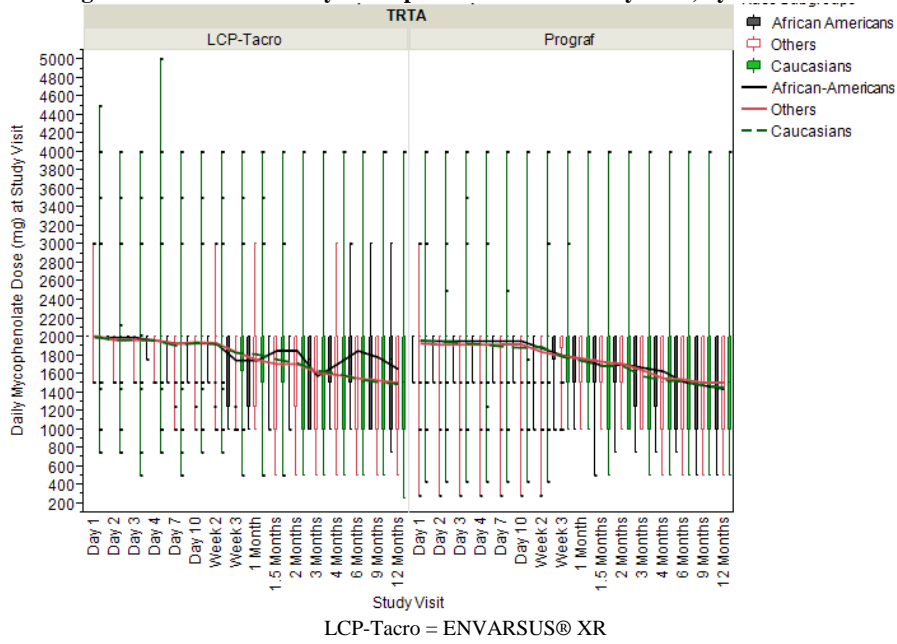


Figure 23. Daily Mycophenolate Mofetil Equivalent Doses (mg/day) co-administered with ENVARUSUS® XR and Prograf® in *De novo* Kidney Transplant Patients in Study 3002, by treatment/gender

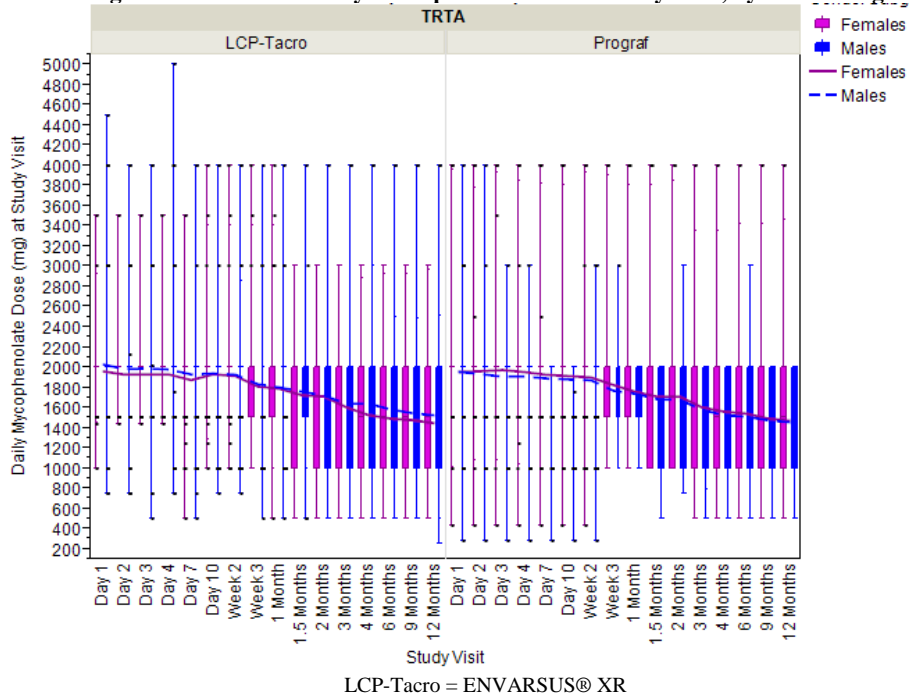
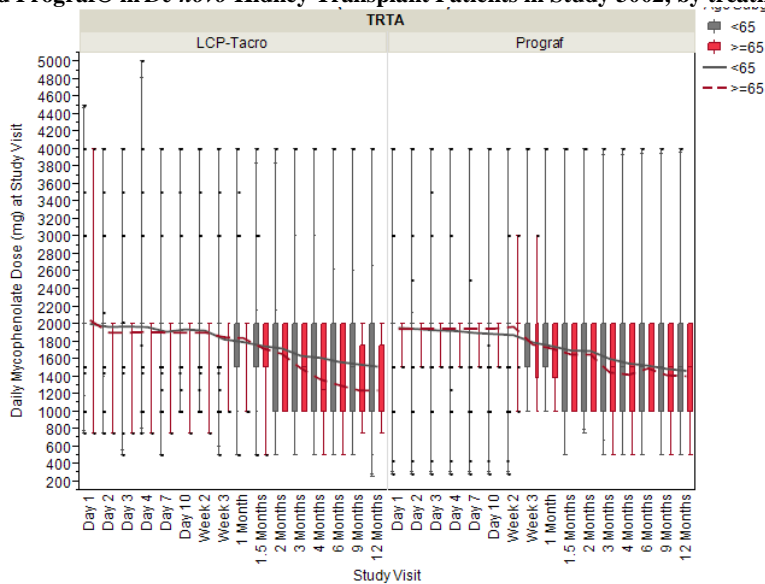


Figure 24. Daily Mycophenolate Mofetil Equivalent Doses (mg/day) co-administered with ENVARSUS® XR and Prograf® in *De novo* Kidney Transplant Patients in Study 3002, by treatment/age



LCP-Tacro = ENVARSUS® XR

Study 3001: Stable Kidney Transplant

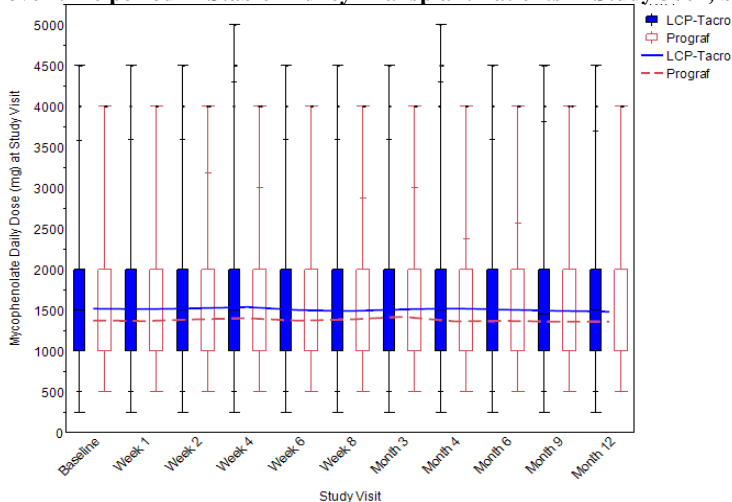
In Study 3001, the daily MMF equivalent doses received by ENVARSUS® XR and Prograf patients were comparable (Table 22; Figure 25).

In the ENVARSUS® XR arm, the African-American patients received numerically higher daily MMF equivalent doses than other patients (Figure 26). Note that approximately 22% of the ENVARSUS® XR patients in this trial were African-Americans.

Likewise, in the ENVARSUS® XR arm, elderly patients (≥ 65 years old) received numerically higher mean/median daily MMF equivalent doses than their younger counterparts (Figure 28), although this observation should be interpreted with caution as the elderly patients comprised approximately only 10% of the analysis population.

Regardless of tacrolimus treatment received, the males received comparable to numerically higher mean/median daily MMF equivalent doses than females (Figure 27). Note that in each tacrolimus treatment arm, females comprised about a third of the analysis population.

Figure 25. Daily Mycophenolate Mofetil Equivalent Doses (mg/day) co-administered with ENVARSUS® XR and Prograf® over time period in Stable Kidney Transplant Patients in Study 3001, by treatment

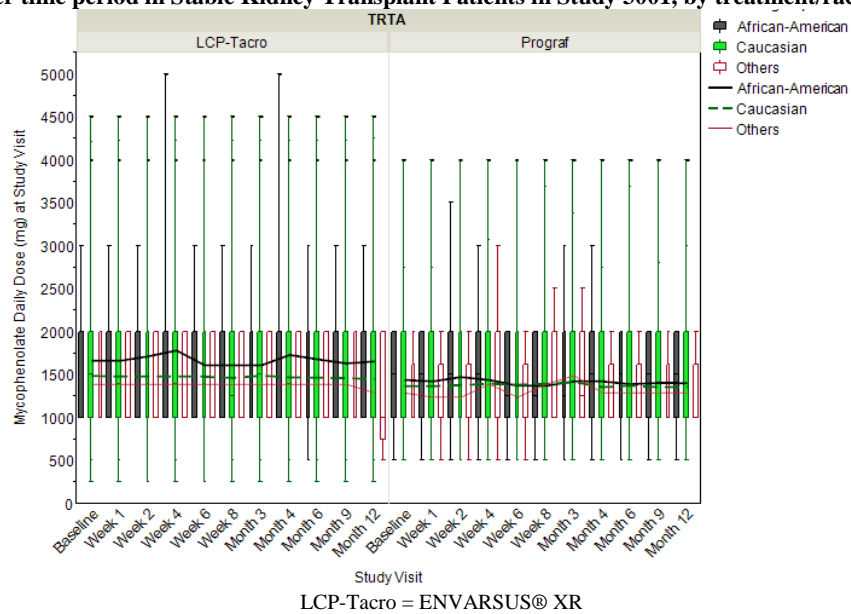


LCP-Tacro = ENVARSUS® XR

Table 22. Daily Mycophenolate Mofetil Equivalent Doses (mg/day) co-administered with ENVARUSUS® XR and Prograf® over time period in Stable Kidney Transplant Patients in Study 3001, by treatment [Mean ± SD; Median (10th – 90th percentile)]

Study Visit	n	ENVARUSUS® XR	n	Prograf
Baseline	136	1532.1 ± 690.8; 1500(1000 - 2000)	144	1386.7 ± 573.1; 1000(1000 - 2000)
Week 1	135	1524.9 ± 699; 1500(1000 - 2000)	144	1379.8 ± 580.8; 1000(1000 - 2000)
Week 2	135	1536 ± 702.5; 1500(1000 - 2000)	144	1400.6 ± 619.6; 1000(1000 - 2000)
Week 4	135	1550.8 ± 757.8; 1500(1000 - 2000)	144	1414.5 ± 618.8; 1000(1000 - 2000)
Week 6	135	1513.8 ± 687.2; 1500(1000 - 2000)	144	1383.3 ± 577; 1000(1000 - 2000)
Week 8	135	1502.7 ± 686; 1500(1000 - 2000)	144	1400.6 ± 605.3; 1000(1000 - 2000)
Month 3	135	1523 ± 683.2; 1500(1000 - 2000)	144	1431.9 ± 630.8; 1000(1000 - 2000)
Month 4	135	1534.1 ± 742.9; 1500(1000 - 2000)	144	1376.3 ± 584.6; 1000(1000 - 2000)
Month 6	135	1519.3 ± 720.5; 1500(1000 - 2000)	144	1381.5 ± 594.9; 1000(1000 - 2000)
Month 9	134	1504.5 ± 706.4; 1444(1000 - 2000)	143	1372 ± 565.9; 1000(1000 - 2000)
Month 12	131	1495.1 ± 696.4; 1500(1000 - 2000)	138	1370.9 ± 571.6; 1000(1000 - 2000)

Figure 26. Daily Mycophenolate Mofetil Equivalent Doses (mg/day) co-administered with ENVARUSUS® XR and Prograf® over time period in Stable Kidney Transplant Patients in Study 3001, by treatment/race



LCP-Tacro = ENVARUSUS® XR

Figure 27. Daily Mycophenolate Mofetil Equivalent Doses (mg/day) co-administered with ENVARUSUS® XR and Prograf® over time period in Stable Kidney Transplant Patients in Study 3001, by treatment/gender

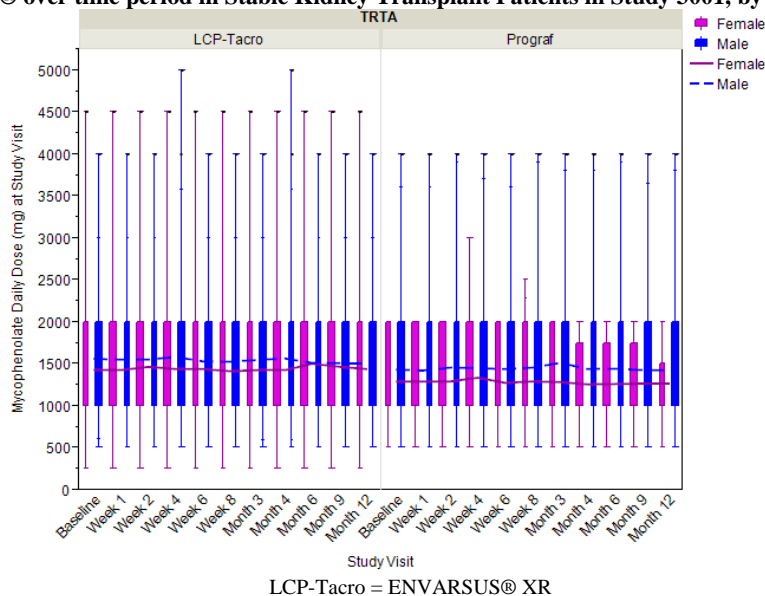
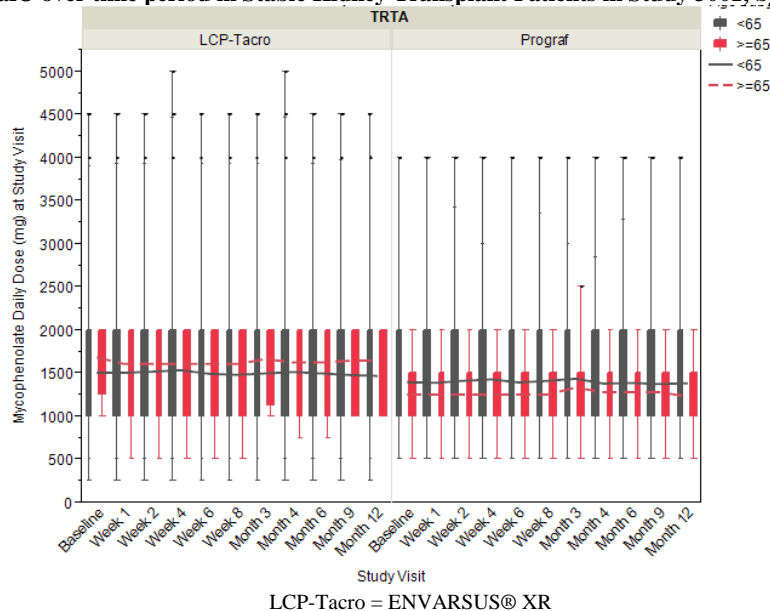


Figure 28. Daily Mycophenolate Mofetil Equivalent Doses (mg/day) co-administered with ENVARUSUS® XR and Prograf® over time period in Stable Kidney Transplant Patients in Study 3001, by treatment/age



Steroid Doses

3.d. Were the doses of maintenance corticosteroids comparable between the Prograf®/mycophenolate/steroid treatment group and ENVARUSUS® XR/mycophenolate/steroid treatment group in Study 3002, and in Study 3001? Were the doses used for corticosteroid taper in these studies consistent with the protocol?

Study 3002: De novo Kidney Transplant

According to the protocol of Study 3002, all patients must be maintained for the first month on a minimum of 10 mg and, thereafter, on a minimum of 5 mg of prednisone or equivalent for the 360-day duration of the study. During the 12 month treatment extension period, the corticosteroid treatment will be based on the standard of care at the participating site.

In Study 3002, the mean/median daily prednisone equivalent doses were comparable between ENVARSUS® XR and Prograf arms. In the ENVARSUS® XR arm, there were no significant differences in daily prednisone equivalent doses associated with gender subgroups. The results of the race subgroup and age subgroup analyses should be interpreted with caution due to the limited numbers of non-Caucasians and elderly subjects enrolled in this trial. See Table 19 and Figures 29 to 32.

Figure 29. Daily Prednisone Equivalent Doses (mg/day) co-administered with ENVARSUS® XR and Prograf® in *De novo* Kidney Transplant Patients in Study 3002, by treatment

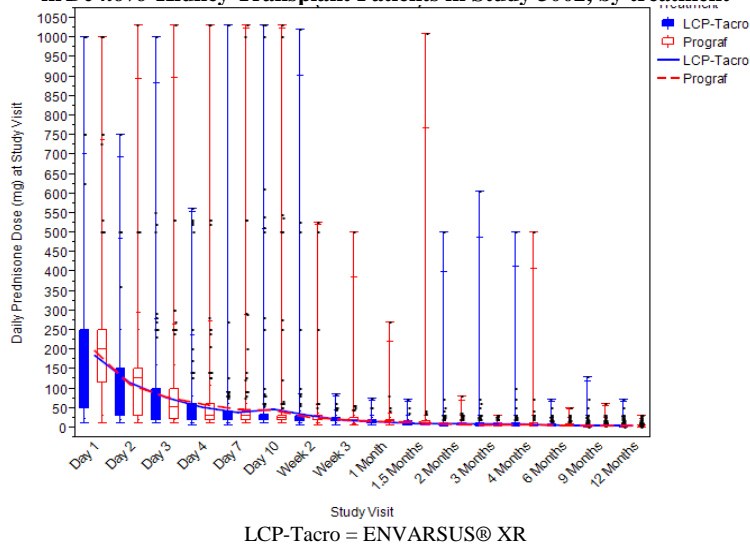


Table 19. Daily Prednisone Equivalent Doses (mg/day) co-administered with ENVARSUS® XR and Prograf® in *De novo* Kidney Transplant Patients in Study 3002, by treatment [Mean ± SD; Median (10th – 90th percentile)]

Study Visit	n	ENVARSUS® XR	n	Prograf
Day 1	215	188 ± 154.8; 200(21.5 - 250)	221	200.3 ± 160.4; 200(30 - 250)
Day 2	244	116.3 ± 104.5; 125(20 - 250)	250	111.7 ± 105.2; 125(20 - 250)
Day 3	251	78.5 ± 100; 40(20 - 160)	252	80.1 ± 97.7; 52.5(20 - 160)
Day 4	249	53.9 ± 76.5; 30(20 - 80)	251	61.8 ± 109.4; 30(20 - 108)
Day 7	247	40 ± 92.8; 30(10 - 60)	250	48.4 ± 107.3; 30(10 - 60)
Day 10	245	48.6 ± 129; 20(10 - 50)	249	45.7 ± 113.8; 25(10 - 40)
Week 2	247	32.4 ± 79.1; 20(10 - 40)	250	27.7 ± 46.8; 20(10 - 34.7)
Week 3	248	19.9 ± 9.7; 20(10 - 30)	251	21.5 ± 31.5; 20(10 - 30)
1 Month	248	15.9 ± 8.2; 15(9.8 - 25)	251	17.1 ± 18; 15(10 - 25)
1.5 Months	248	11.9 ± 7.5; 10(5 - 20)	249	15.6 ± 63.6; 10(5 - 20)
2 Months	246	11.8 ± 32.1; 8(5 - 16.45)	245	9.8 ± 7.6; 8(5 - 15)
3 Months	243	11.1 ± 39; 5(5 - 15)	240	7.7 ± 5; 5(5 - 15)
4 Months	243	10.2 ± 32.8; 5(4 - 15)	242	9.5 ± 32.3; 5(5 - 10)
6 Months	241	7.2 ± 6.6; 5(4 - 10)	240	6.9 ± 5; 5(5 - 10)
9 Months	236	7.4 ± 10.4; 5(4 - 10)	238	6.5 ± 5.3; 5(5 - 10)
12 Months	228	6.8 ± 6.9; 5(4 - 10)	229	6.3 ± 4.2; 5(5 - 10)

Figure 30. Daily Prednisone Equivalent Doses (mg/day) co-administered with ENVARUSUS® XR and Prograf® in *De novo* Kidney Transplant Patients in Study 3002, by treatment/race

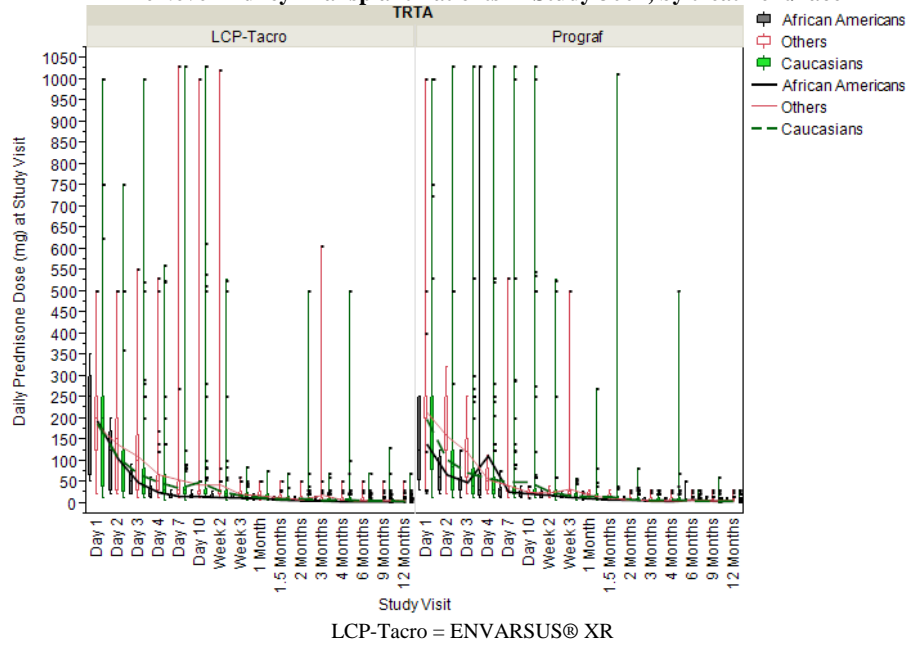


Figure 31. Daily Prednisone Equivalent Doses (mg/day) co-administered with ENVARUSUS® XR and Prograf® in *De novo* Kidney Transplant Patients in Study 3002, by treatment/gender

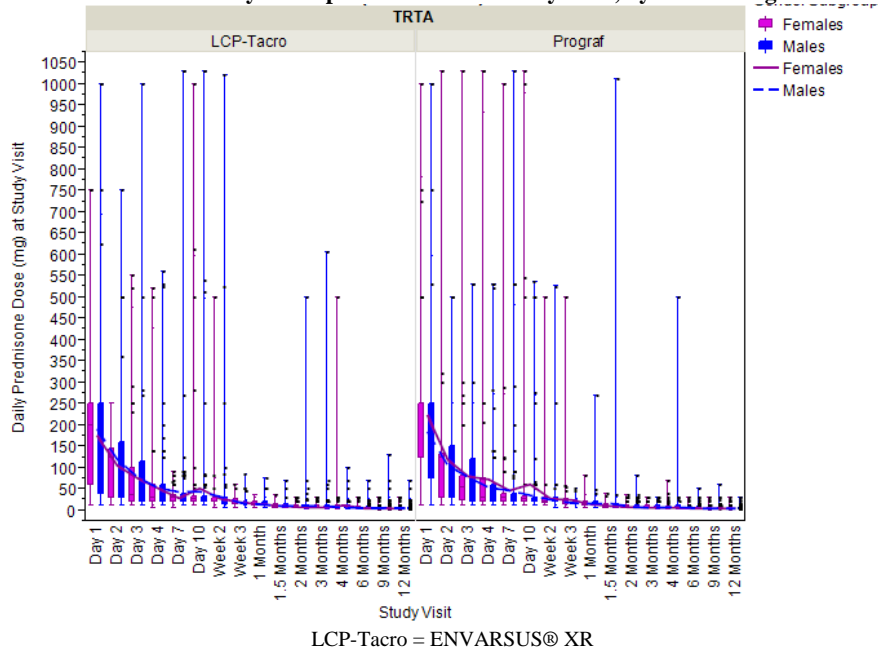
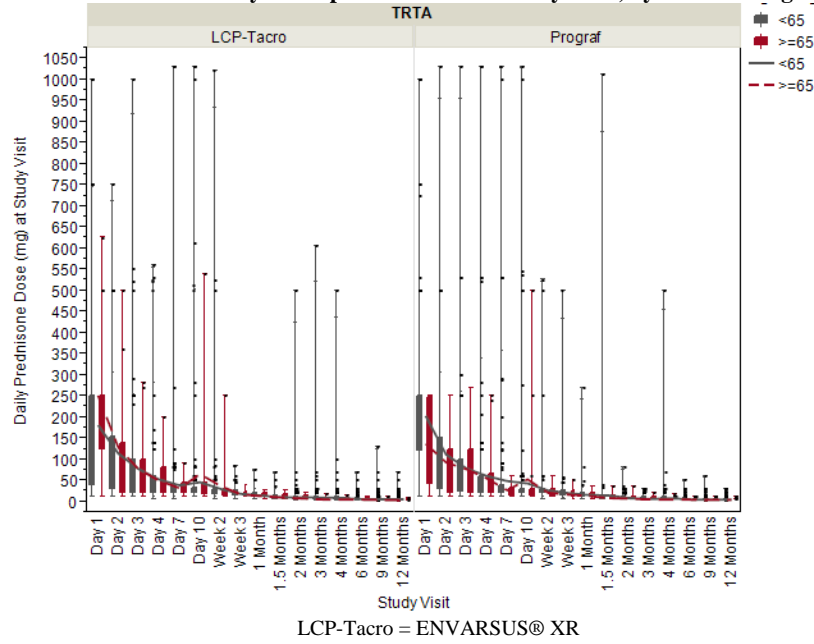


Figure 32. Daily Prednisone Equivalent Doses (mg/day) co-administered with ENVARSUS® XR and Prograf® in *De novo* Kidney Transplant Patients in Study 3002, by treatment/age



Study 3001: Stable Kidney Transplant

In Study 3001, the mean/median daily prednisone equivalent doses were comparable between the ENVARSUS® XR and Prograf arms. In the ENVARSUS® XR arm, there were no significant differences in daily prednisone equivalent doses associated with gender, race or age subgroups. See Table 20 and Figures 33 to 36.

Figure 33. Daily Prednisone Equivalent Doses (mg/day) co-administered with ENVARSUS® XR and Prograf® in Stable Kidney Transplant Patients in Study 3001, by treatment

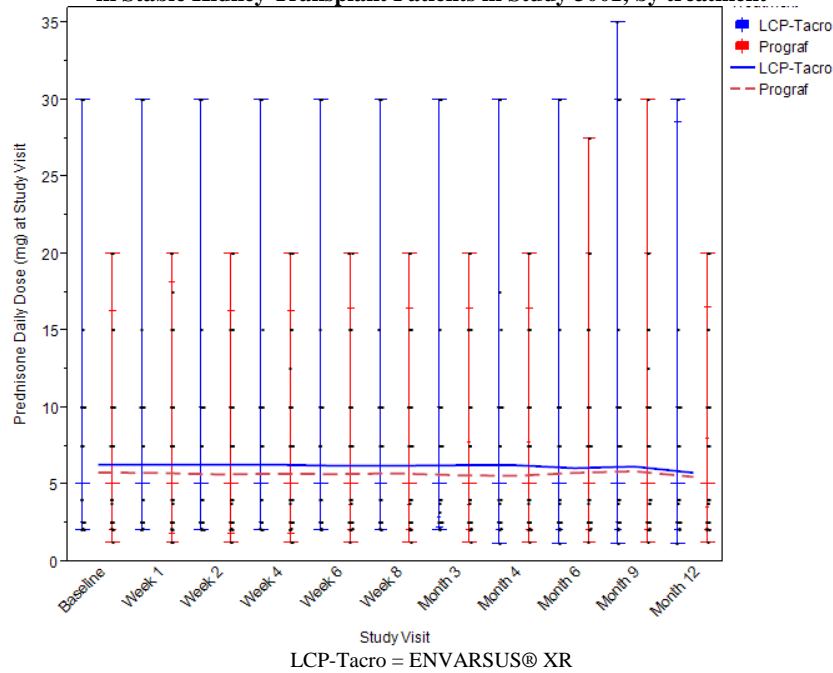


Table 20. Daily Prednisone Equivalent Doses (mg/day) co-administered with ENVARUSUS® XR and Prograf® in Stable Kidney Transplant Patients in Study 3001, by treatment [Mean ± SD; Median (10th – 90th percentile)]

Study Visit	n	ENVARUSUS® XR	n	Prograf
Baseline	84	6.3 ± 5.1; 5(2.5 - 10)	109	5.8 ± 3.1; 5(2.5 - 10)
Week 1	84	6.3 ± 5.1; 5(2.5 - 10)	109	5.8 ± 3.2; 5(2.5 - 10)
Week 2	84	6.3 ± 5.1; 5(2.5 - 10)	109	5.7 ± 3; 5(2.5 - 10)
Week 4	84	6.3 ± 5.1; 5(2.5 - 10)	109	5.8 ± 3.1; 5(2.5 - 10)
Week 6	84	6.3 ± 5.1; 5(2.5 - 10)	108	5.7 ± 3; 5(3.6 - 10)
Week 8	84	6.3 ± 5.1; 5(2.5 - 10)	108	5.8 ± 3.1; 5(3.6 - 10)
Month 3	84	6.3 ± 5.1; 5(2.8 - 10)	108	5.7 ± 3; 5(3.6 - 7.8)
Month 4	84	6.3 ± 5.2; 5(2.5 - 10)	108	5.6 ± 3; 5(2.5 - 7.8)
Month 6	85	6.1 ± 5.1; 5(2.5 - 10)	108	5.8 ± 3.7; 5(2.5 - 10)
Month 9	84	6.2 ± 5.4; 5(2.5 - 10)	108	5.9 ± 3.9; 5(2.5 - 10)
Month 12	83	5.8 ± 4.4; 5(2.5 - 10)	107	5.5 ± 2.9; 5(3.5 - 8)

Figure 34. Daily Prednisone Equivalent Doses (mg/day) co-administered with ENVARUSUS® XR and Prograf® in Stable Kidney Transplant Patients in Study 3001, by treatment/race

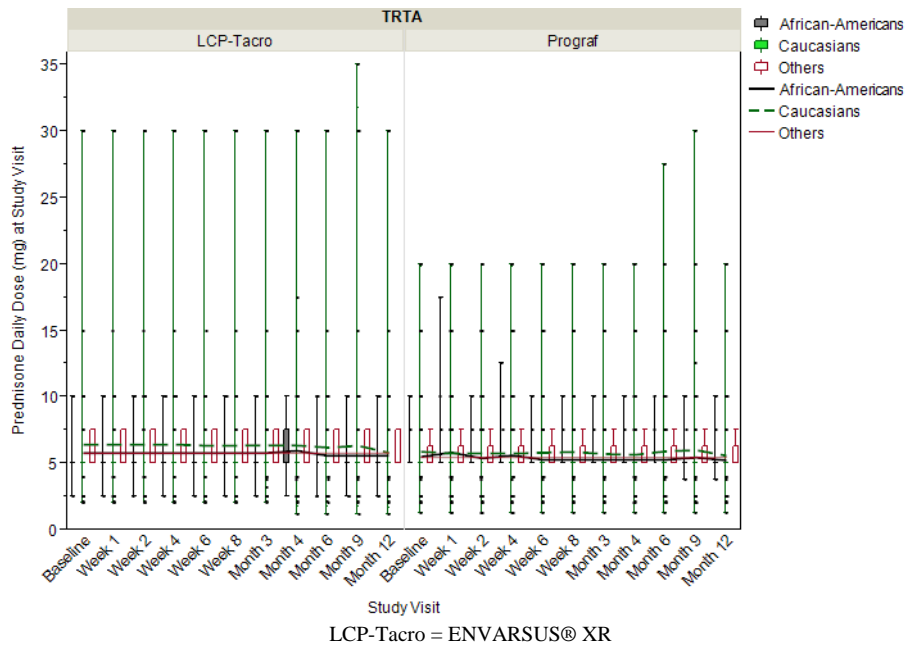


Figure 35. Daily Prednisone Equivalent Doses (mg/day) co-administered with ENVARUSUS® XR and Prograf® in Stable Kidney Transplant Patients in Study 3001, by treatment/gender

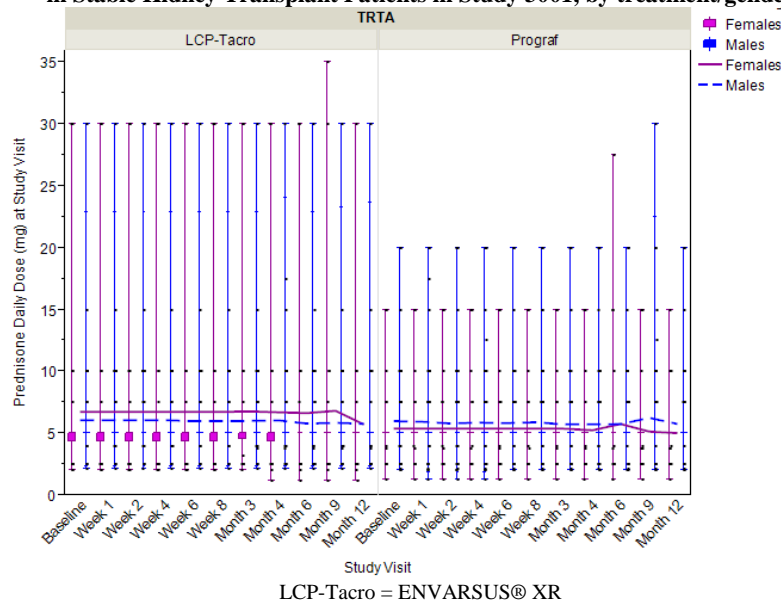
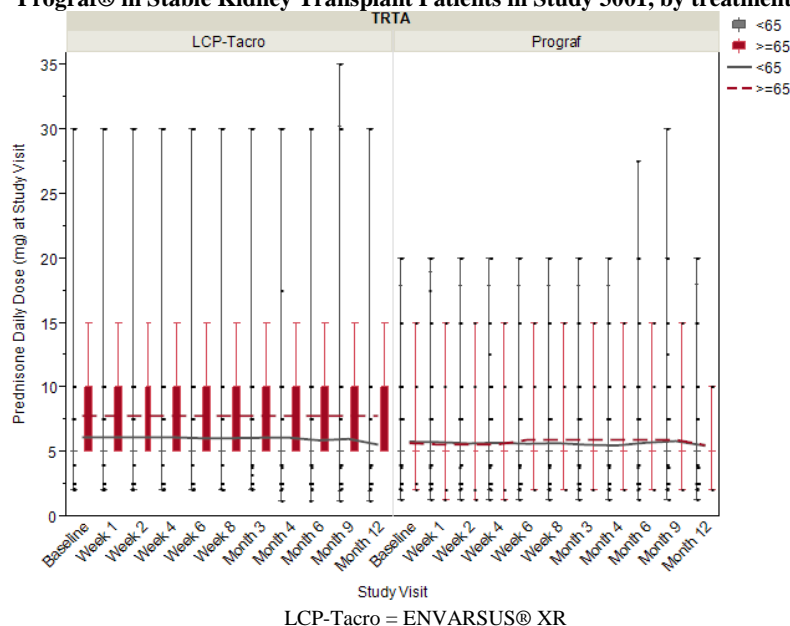


Figure 36. Daily Prednisone Equivalent Doses (mg/day) co-administered with ENVARUSUS® XR and Prograf® in Stable Kidney Transplant Patients in Study 3001, by treatment/age



Antibody Induction

3.e. Was antibody induction in Study 3002 comparable between the Prograf and the ENVARUSUS® XR treatment groups, and consistent with the study protocol?

Study 3002: De novo Kidney Transplant

According to the protocol of Study 3002, the IL-2 receptor antagonist (e.g., basiliximab) was to be administered per the most current product label. In the 09 May 2011 amendment of the protocol, basiliximab dosing was specified as follows: 2 doses of 20 mg each, the first 20 mg dose given within 2 hours prior to transplantation surgery, and the second 20 mg dose given 4 days after transplantation.

Use of polyclonal or monoclonal T-cell depleting antibodies, including but not limited to Thymoglobulin® (rabbit antithymocyte globulin) or Campath® (alemtuzumab) for induction, was not permitted. Antilymphocyte antibody therapy for patients with biopsy-confirmed rejection as per local standard of care was allowed.

Based on the reviewer's analysis, majority of the patients (96% ENVARSUS® XR and 99% Prograf) received two doses of basiliximab 20 mg each.

Study 3001: Stable Kidney Transplant

Note that antibody agents were not used for induction therapy of stable kidney transplant patients during participation in Study 3001.

Exposure-Response

4. Exposure-Response

- a) What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.**

The sponsor conducted post-hoc exposure-response analyses to evaluate the relationship between tacrolimus trough concentrations and time to event of biopsy proven acute rejection (BPAR), death, lost to follow-up, and/or graft loss as requested by FDA during pre-NDA discussion.

Given that both treatment arms are titrated to a target trough exposure, as tacrolimus trough concentrations vary between initial and maintenance portions of treatment, and as most events occur during the initial month of treatment, it was decided that time-averaged mean tacrolimus trough concentrations would not be appropriate for exploring the relationship between tacrolimus exposure and efficacy. Instead, tacrolimus trough concentration was included as a time-varying covariate in a Cox-proportional hazard model analysis along with other baseline covariates of interest including treatment arm, diabetes, body mass index, race, geographic region, age, sex, and CMV or EBV IgG status at baseline. Baseline tacrolimus concentrations were set as the earliest available trough concentration (day 2, 3, or 4). Subjects without a tacrolimus trough concentration available prior to event time were not included in the analysis.

The sponsor identified tacrolimus C_{trough} as a significant predictor of treatment failure, with a 1 ng/mL change associated with a hazard ratio of 0.86 (95% CI: 0.82; 0.95). Other covariates of significance identified by the sponsor that were associated with an increased likelihood of treatment failure included diabetes status (yes), race (Black versus White or Other), and geographic region (Latin America or Asia Pacific versus US). A significant impact of treatment effect between Envarsus® XR and Prograf was not identified from the analysis. The observed relationship between increased likelihood of treatment failure and lower tacrolimus trough concentrations is consistent with previous transplant studies involving tacrolimus. The reviewer identified similar covariates of interest during an independent analysis of the same efficacy measure (any treatment failure) and covariates of lower tacrolimus C_{trough} and region (Asia Pacific versus US) as associated with an increased likelihood of BPAR. Analyses for the other components of the primary endpoint (graft loss, all-cause mortality, and lost to follow-up) could not be performed due to the low number of events in each category. These observations underscore the importance of therapeutic drug monitoring with tacrolimus but do not suggest that alternative target thresholds than those used in Study 3002 (6 to 11 ng/mL over the first 30 days; 4 to 11 ng/mL out to 12 months) are necessary based on the available data.

- b) 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.**

Nephrotoxicity

In Study 3002, there was a higher incidence of treatment-emergent adverse events due to increased tacrolimus trough concentrations (e.g., toxic nephropathy, overdose) for the ENVARSUS® XR treatment group (0.17 mg/kg/day starting dose). See Table 21 below.

Table 21. Treatment-Emergent Adverse Events Reported Due to Increased Tacrolimus Trough Concentrations (Study 3002 ITT Set) – n (%)

Preferred Term	LCP-Tacro (N=268)	Prograf (N=275)
Nephropathy toxic	9 (3.4)	0
Toxicity to various agents	10 (3.7)	3 (1.1)
Overdose	9 (3.4)	1 (0.4)
Immunosuppressant drug level increased	5 (1.9)	0

Table 12-23 of the CSR of Study 3002
LCP-Tacro = ENVARSUS® XR

Nephrotoxicity due to tacrolimus is concentration or exposure-dependent, and is managed by reduction of tacrolimus dosage. Figure 37 compares the tacrolimus trough concentrations of the 9 ENVARSUS® XR *de novo* kidney transplant patients who experienced toxic nephropathy to those who did not experience toxic nephropathy. Of note, none of the patients on Prograf were reported as having toxic nephropathy during the trial. During the 12-month study period, the average tacrolimus trough concentrations from the 9 patients with toxic nephropathy were numerically lower or comparable to those without the AE, except during the Month 1 and Month 1.5 visits. During the Month 1 and Month 1.5 visits, some patients who did not experience the AE of interest had higher tacrolimus C_{trough} than all 9 nephropathy cases at the same timepoints.

When scrutinizing the tacrolimus C_{trough} - time profiles of individual cases (Figure 37A), the reported onset of the AE in 4 of the 9 cases either coincided with or was preceded by a “spike” in tacrolimus trough concentrations with at least 1 measured tacrolimus C_{trough} value above the 90th percentile (5 of 9 if with at least 1 measured C_{trough} above the 75th percentile); 1 (or 2) of these 5 cases had an onset day during the first week post-transplant. Of the total 9 toxic nephropathy cases, 4 had an onset day during the 1st month post-transplant and 3 had an onset during the first two weeks when tacrolimus exposures differed between the ENVARSUS XR and Prograf treatment arms (see Figure 5). The nephrotoxicity cases associated with relatively high tacrolimus trough concentrations appeared to be reversible with a reduction in tacrolimus exposures.

A Cox-proportional hazards analysis was conducted by the Pharmacometrics reviewer to describe the relationship between nephropathy adverse events and tacrolimus trough concentrations as a time-dependent covariate. A relationship with regard to tacrolimus trough concentrations could not be identified, but that may have been due to the low number of nephropathy events (n=9) in the dataset. However, the imbalance in event rates between the treatment arms suggest that differences in the safety profiles may exist between the studied ENVARSUS® XR and Prograf regimens, but the available data is not sufficient to determine the extent to which higher concentrations from the ENVARSUS® XR treatment arm during the first two weeks may have contributed to these events.

Figure 37. Tacrolimus Trough Concentration – Time Profiles of *De novo* Kidney Transplant Patients, with or without toxic nephropathy (Study 3002)

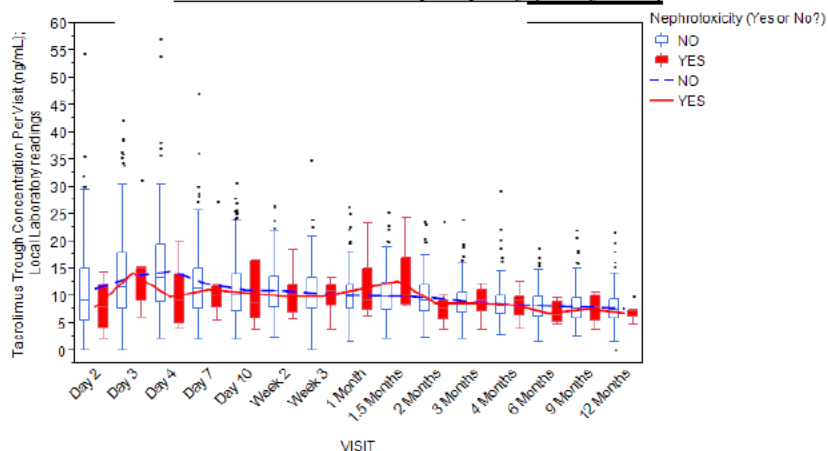
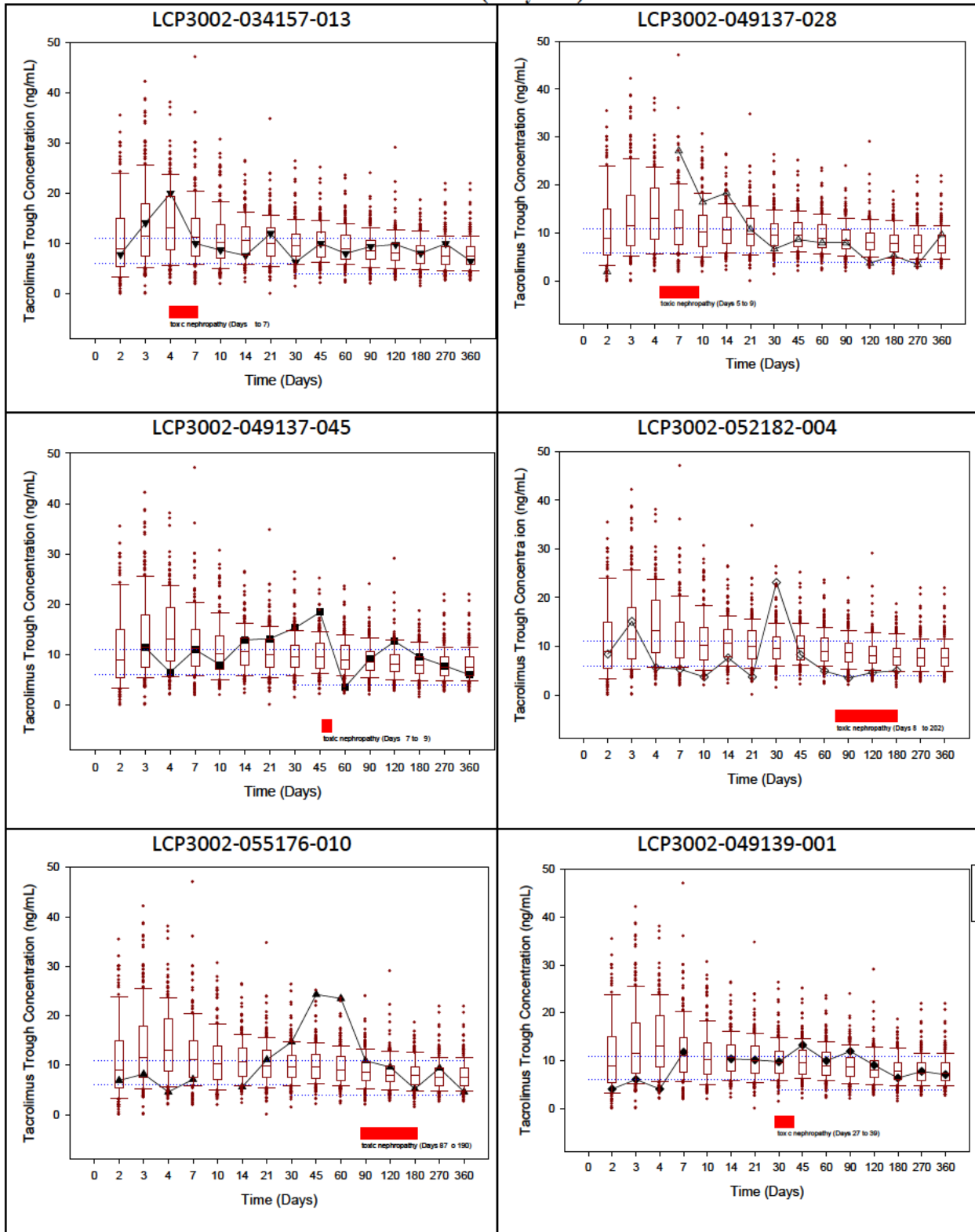
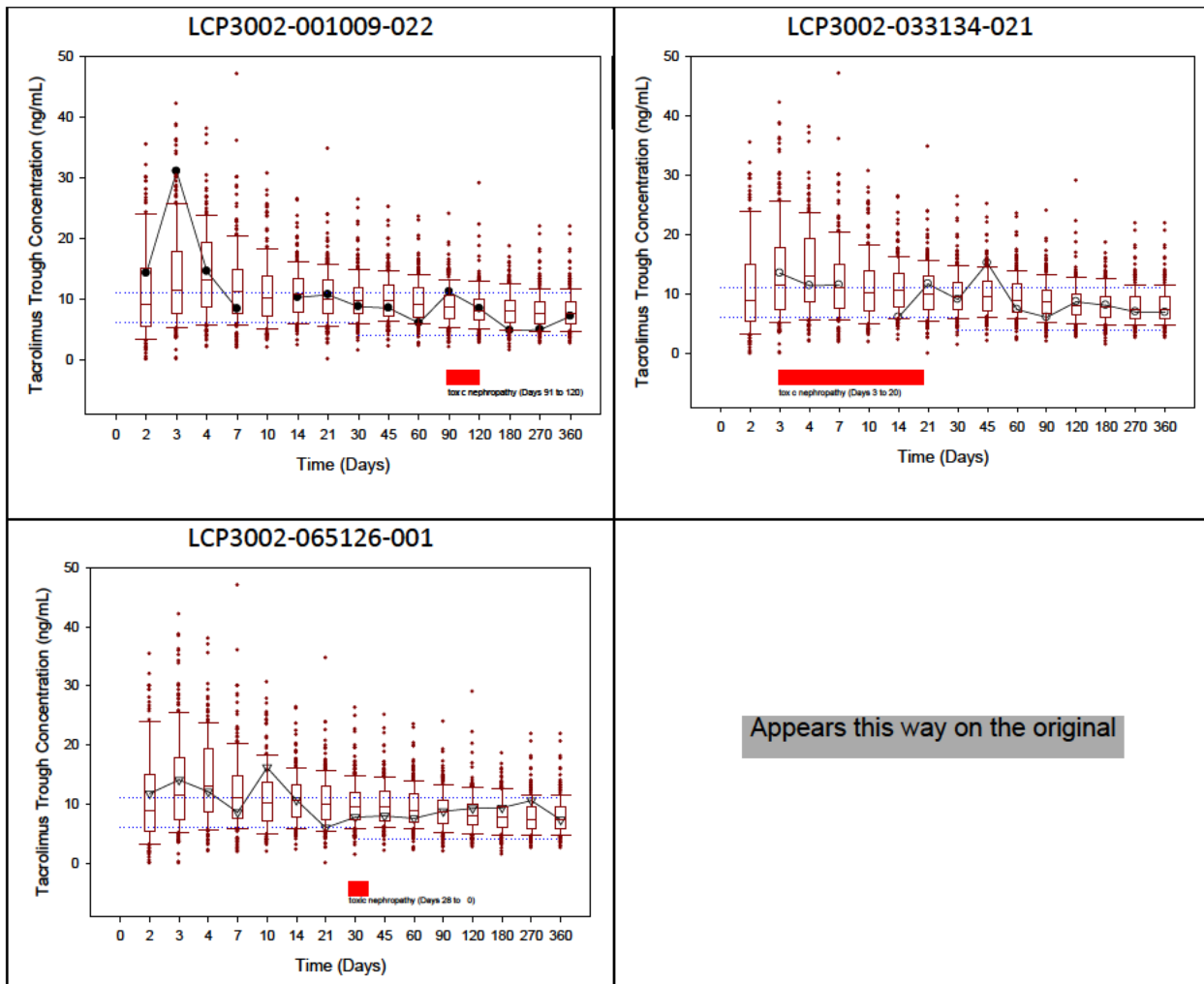


Figure 37A. Tacrolimus Trough Concentration (C_{trough}) – Time Profiles of 9 ENVARUSUS® XR cases of toxic nephropathy, overlaid with box plot for the tacrolimus C_{trough} – time profiles of ENVARUSUS® XR patients without the AE (Study 3002)





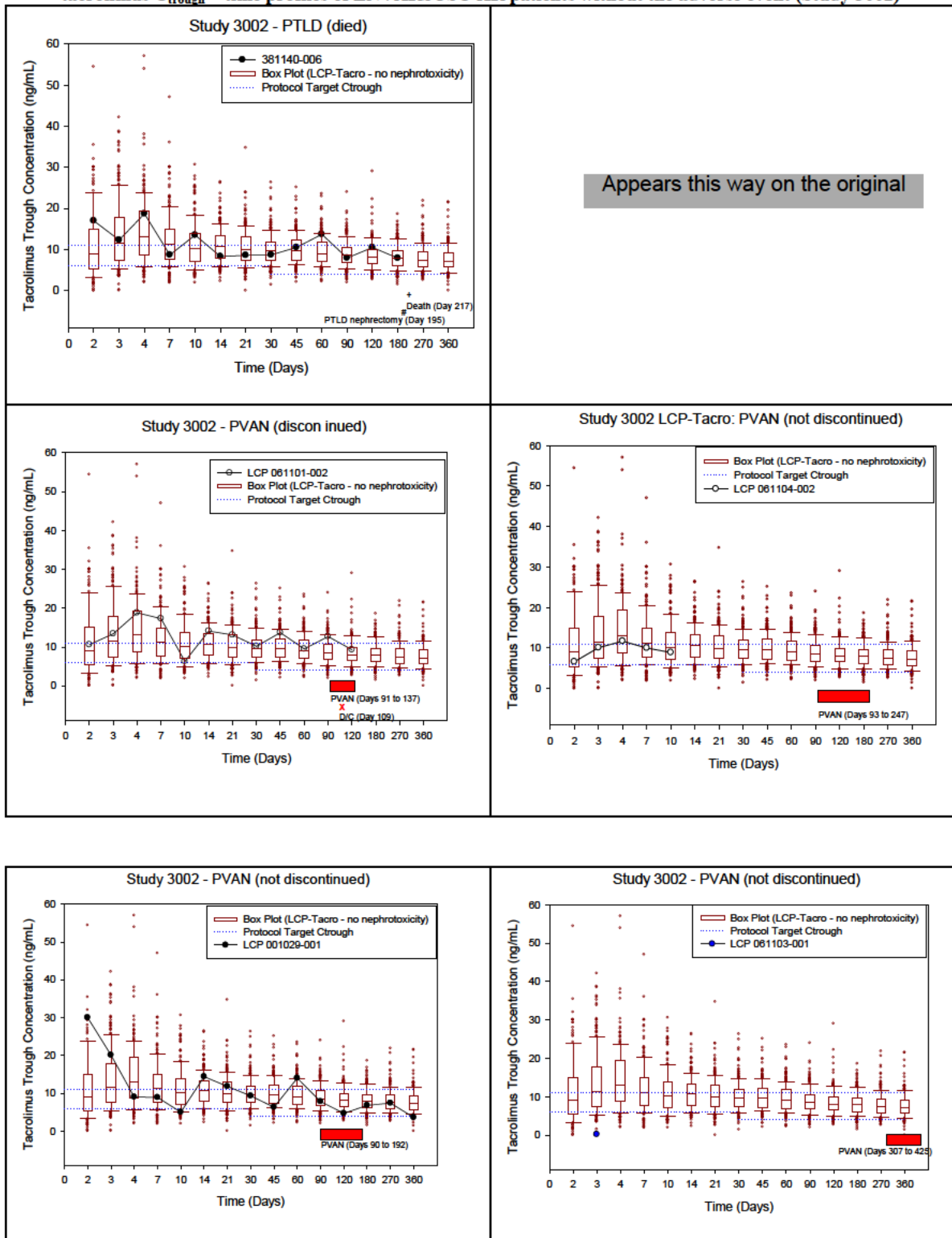
Post-Transplant Lymphoproliferative Disease (PTLD)

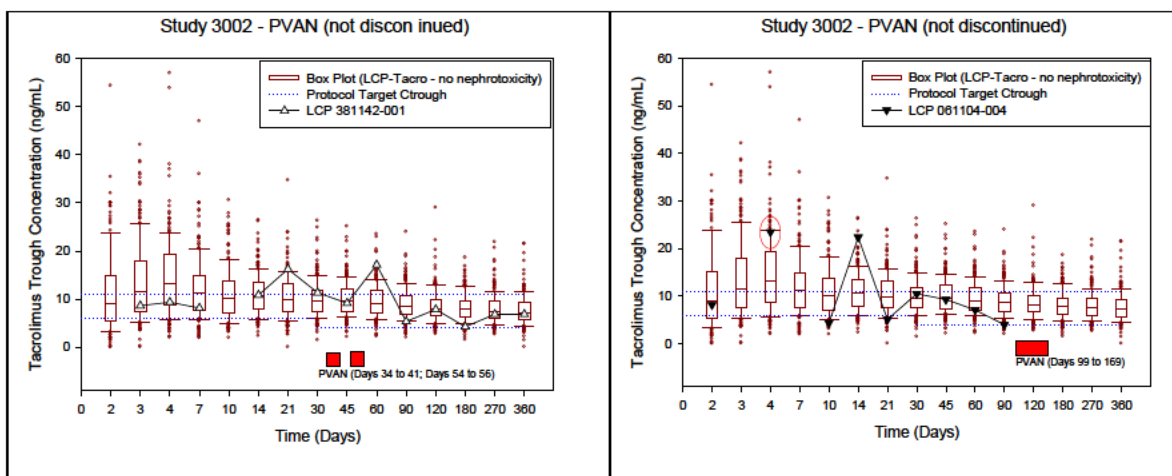
Pre-transplant EBV-seronegative status of the patient and prolonged high intensity of overall immunosuppression are risk factors of PTLD. The lone case of post-transplant lymphoproliferative disease (PTLD) in the ENVARSUS® XR arm was EBV-seropositive at the time of transplant. Judging from the profile of this particular patient, there were several occasions (during the 12-month study period including the first week post-transplant) when tacrolimus trough concentrations were above the protocol-specified target range, although no individual measurement exceeded 20 ng/mL prior to PTLD diagnosis or death (Figure 38).

Polyoma Virus Associated Nephropathy (PVAN)

Prolonged high intensity of total immunosuppression is a known risk factor of PVAN. In the lone case of polyoma virus associated nephropathy (PVAN) that led to discontinuation (which was reported in the ENVARSUS® XR arm), there were several occasions during the 12-month study period including the first week post-transplant when the tacrolimus trough concentrations were above the protocol-specified target range, although no individual measurement exceeded 20 ng/mL prior to PVAN diagnosis or discontinuation from study participation (Figure 38). Three of the 5 additional reported PVAN cases in the ENVARSUS® XR arm had an adequate number of tacrolimus trough concentration measurements; all 3 patients had 2 to 3 occasions (during the 12-month study period, not necessarily including the first week) when the trough concentrations were above the protocol-specified target range. Two of these 3 additional PVAN cases had measured tacrolimus trough concentrations above 20 ng/mL during the first 7 days.

Figure 38. Tacrolimus Trough Concentration (C_{trough}) – Time Profiles of cases of Post-Transplant Proliferative Disease (PTLD) and Polyoma Virus Associated Nephropathy (PVAN), overlaid with box plot for the tacrolimus C_{trough} – time profiles of ENVARUSUS® XR patients without the adverse event (Study 3002)





Potential influence of concomitant disease

The endogenous hormone thyroxin is considered a potent activator of CYP3A (the major enzyme for the metabolism of tacrolimus). Hypothyroidism had been reported to induce tacrolimus intoxication in one lung-transplant patient who subsequently developed anuric acute renal failure, with concomitant pancytopenia (Haas et al., 2000). Parathyroid hormone was shown to be the major mediator responsible for the down regulation of hepatic CYP450 in rats with chronic renal failure (Michaud et al, 2006).

Based on the review of the medical histories of these nephrotoxicity/PTLD/PVAN cases, the reviewer notes that both ENVARSUS® XR patients who experienced either PTLD/death or PVAN/discontinuation had ongoing hyperparathyroidism. Additionally, 6 of the 8 (75%) nephrotoxicity cases, as well as 2 of the 4 (50%) additional PVAN cases who did not discontinue, with available CRFs for review had one of several conditions, i.e., hepatorenal syndrome, hyperparathyroidism, hypothyroidism, parathyroidectomy (surgical removal of gland due to excessive parathyroid hormone) that could have potentially inhibited the CYP450-mediated metabolism of tacrolimus (thereby contributing to the observed increased tacrolimus trough concentration) in these patients. *In the reviewer's exploratory analysis, 104/268 ENVARSUS® XR patients had hyperparathyroidism and/or hypothyroidism, and ~8% were reported to have experienced nephrotoxicity, PTLD, or PVAN, compared to 4.8% in those ENVARSUS® XR patients without these types of endocrine dysfunction. The reviewer acknowledges that the interpretation of this particular observation is rather limited because the patients in Study 3002 were not randomized for the presence or absence of abnormal thyroid function and other concomitant illnesses that could have potentially contributed to altered tacrolimus exposures.*

QT Interval

c) Does this drug prolong the QT or QTc interval?

Yes. The labeling of approved tacrolimus products recommend obtaining ECGs and monitoring electrolytes in tacrolimus treated patients at risk for QT prolongation, as well as in patients who are taking concomitant medications with known QT prolongation potential.

PK in Transplant Patients and Healthy Volunteers

5. What are the PK characteristics of the drug and its major metabolite?

a) What are the single dose and multiple dose PK parameters?

De novo kidney transplant patients

Study 2017 (de novo)

The PK of ENVARSUS® XR once daily and Prograf twice daily were characterized in Phase 2 Study 2017, an open-label, multicenter, randomized 12-month trial involving adult *de novo* kidney transplant patients. Compared to Phase 3 Study 3002 and Phase 2 study 2019, *de novo* kidney transplant patients in this Phase 2 trial were administered starting tacrolimus doses that were on average lower for

ENVARUSUS® XR, i.e., 0.14 mg/kg/day for non-African Americans and 0.17 mg/kg/day for African Americans (versus 0.17 mg/kg/day regardless of race), and higher for Prograf, i.e., 0.2 mg/kg/day (versus 0.1 mg/kg/day). Compared to Studies 3002 and 2019, the target tacrolimus whole blood trough concentration ranges in Study 2017 was slightly higher (7 – 20 ng/mL through Study Day 14, 5 – 20 ng/mL from Day 15 to Day 90, and 5 – 15 ng/mL thereafter). Tacrolimus PK profiling (under fasting condition) was performed on Days 1, 7, and 14 post-transplant. The comparative tacrolimus PK profiles and PK parameters of the two treatment groups are shown in Figure 39 and Table 22, respectively. Table 22A provides the tacrolimus AUC, C_{max} and C_{trough} by racial subgroup; however, the results of this subgroup analysis for African-Americans (AA) should be interpreted with extreme caution due to the very low number (n=5) of AA patients included.

Note that on Day 1 of dosing Prograf (0.2 mg/kg/day), the tacrolimus AUC was similar to that achieved at steady state conditions. Note also that in the current Prograf USPI, the recommended starting dose of Prograf is lower (0.1 mg/kg/day when given with concomitant MMF and antibody induction) than that used in this trial. Thus, it would be justified to compare the PK of the ENVARUSUS® XR patients in this study to that obtained for Prograf (starting 0.1 mg/kg/day) in Study 2019.

The linear AUC – C_{trough} correlation plots for Days 1, 7 and 14 of tacrolimus dosing in Study 2017 are shown in Figure 40; the linear regression parameters are shown in the table below the figure. There was a substantial overlap of points between the linear plots of ENVARUSUS® XR and Prograf representing the two treatments. Based on the reviewer’s linear regression calculations, targeting the same tacrolimus C_{trough} range (e.g., 6 to 11 ng/mL) would result in a 5% to 22% lower AUC on Day 1, and a 10% to 20% higher AUC at steady state (Day 7) in patients who received ENVARUSUS® XR at a starting dose of 0.14 mg/kg/day, as compared to race-matched patients receiving Prograf at a starting dose of 0.2 mg/kg/day. *A cross-study comparison of the AUC-C_{trough} correlation plots of ENVARUSUS® XR in Study 2017 and Prograf in Study 2019 indicates that targeting the same tacrolimus C_{trough} range (e.g., 6 to 11 ng/mL) as Prograf would result in an AUC with ENVARUSUS® XR that is 0 to 10% lower than that of Prograf on Day 1, and is approximately 15% higher than that of Prograf on Day 14 (steady state). See Figures 41 and 41A, as well as tables below the figures for the linear regression plots and parameters with and without the patients who received a starting ENVARUSUS® XR dose of 0.17 mg/kg/day in Study 2017.*

In addition to the full PK assessments on Study Days 1, 7 and 14, whole blood tacrolimus trough levels were monitored on Days 2, 3, 4, 10 and 12. The target tacrolimus trough concentration ranges were as follows: 7 – 20 ng/mL through Study Day 14, 5 – 20 ng/mL from Day 15 to Day 90, and 5 – 15 ng/mL thereafter.

Table 22. Mean ± SD Tacrolimus Pharmacokinetic Parameters of ENVARUSUS® XR™ and Prograf® in De novo Kidney Transplant Patients in Study 2017^a

	ENVARUSUS® XR 0.14 mg/kg/day ^b (n=26)			Prograf 0.2 mg/kg/day (n=27)		
	Day 1	Day 7	Day 14	Day 1	Day 7	Day 14
AUC ₀₋₂₄	126.6 ± 76.3	318.9 ± 126.4	354.1 ± 109.2	241.3 ± 97.1	282.9 ± 98.3	252.3 ± 80.4
C _{max}	11.0 ± 6.8	26.1 ± 17.5	28.1 ± 14.0	22.6 ± 10.6	23.8 ± 12.9	20.1 ± 6.6
C ₂₄	5.2 ± 2.8	9.2 ± 4.3	10.6 ± 4.1	8.7 ± 4.2	10.2 ± 5.2	8.0 ± 3.1
C _{ave}	5.3 ± 3.2	13.3 ± 5.3	14.8 ± 4.5	10.1 ± 4.0	11.8 ± 4.1	10.5 ± 3.3
T _{max} ^c	10 (4 - 24)	6 (1.5 - 12.1)	4 (1.3 - 8.1)	4 (1 - 24)	1.6 (0.5 - 24)	2 (0.5 - 14.1)
Fluctuation	94.2 ± 66.9	129.6 ± 119.2	124.5 ± 97.8	135.7 ± 77.4	107.4 ± 78.3	123.8 ± 60.6
Swing	125.2 ± 115.2	217.3 ± 241.3	195.7 ± 175.5	186.3 ± 127.0	153.6 ± 138.1	177.3 ± 101.7

^a includes 26 ENVARUSUS® XR patients and 27 Prograf patients with complete set of PK profiles on Days 1, 7, and 14

^b 0.17 mg/kg/day LCP starting dose for African American/Black patients

^c median (range)

^d mean ± SD daily doses (mg/day) of ENVARUSUS® XR vs Prograf administered on day of PK profiling:

Day 1: 12.4 ± 2.7 vs 15.7 ± 3.8

Day 7: 10.3 ± 4.4 vs 9.9 ± 3.9

Day 14: 10.3 ± 4.6 vs 8.4 ± 4.4

Table 22A. Mean ± SD Tacrolimus Pharmacokinetic Parameters of ENVARSUS® XR™ in *De novo* Kidney Transplant Patients in Study 2017 – by Race Subgroup^a

Parameter	ENVARSUS® XR (starting dose 0.17 mg/kg/day) African Americans/Blacks (n=5)			ENVARSUS® XR (starting dose 0.14 mg/kg/day) Non-African Americans/Non-Blacks (n=21)		
	Day 1	Day 7	Day 14	Day 1	Day 7	Day 14
AUC ₀₋₂₄ ^b (ng·hr/mL)	79.1 ± 27.3	252.5 ± 98.1	282.4 ± 111	137.9 ± 80.2	334.7 ± 129.2	371.2 ± 104.1
C _{max} (ng/mL)	7.7 ± 3	30.2 ± 23.6	32 ± 17.2	11.8 ± 7.2	25.1 ± 16.3	27.1 ± 13.4
C _{trough} (ng/mL)	5.3 ± 3.3	6.6 ± 2.9	7.1 ± 2.3	5.2 ± 2.7	9.9 ± 4.4	11.4 ± 4.1
C _{ave}	3.3 ± 1.1	10.5 ± 4.1	11.7 ± 4.6	5.7 ± 3.3	13.9 ± 5.4	15.5 ± 4.3
T _{max} ^c	16 (12-24)	3.1 (3-12)	3.0 (1.5-6)	8 (4-24)	6 (1.5-12.1)	4 (1.3-8.1)
Fluctuation	64 ± 75	207 ± 195	200 ± 63	101 ± 65	111 ± 91	107 ± 97
Swing	71 ± 90	385 ± 725	330 ± 134	138 ± 119	117 ± 167	164 ± 171

^a includes ENVARSUS® XR patients with complete set of PK profiles on Days 1, 7, and 14

^b mean ± SD daily doses (mg/day) of ENVARSUS® XR received by AA versus non-AA on day of PK profiling:

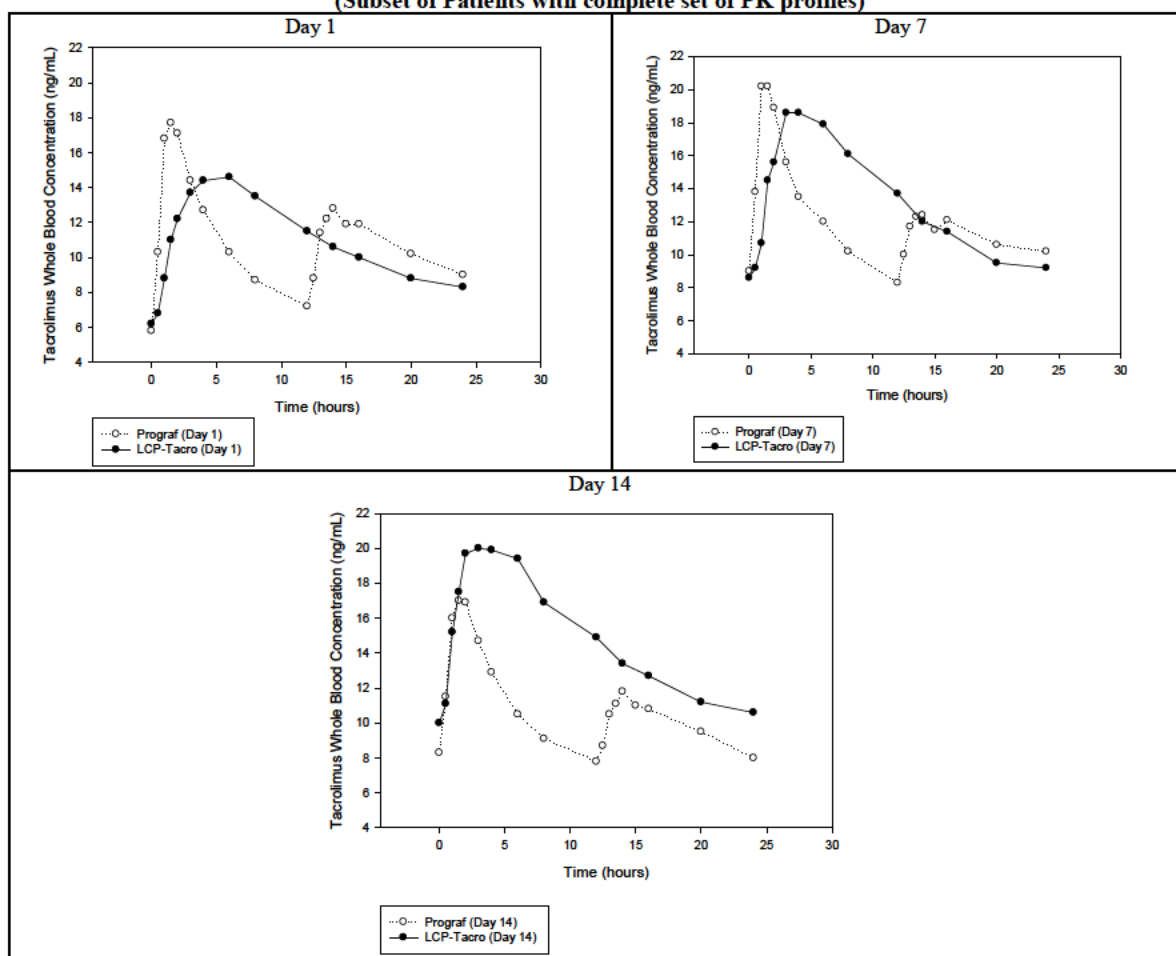
Day 1: 14.6 ± 2.2 vs 11.8 ± 2.7

Day 7: 12.4 ± 5.7 vs 10 ± 4.2

Day 14: 13.8 ± 5.4 vs 9.5 ± 4.3

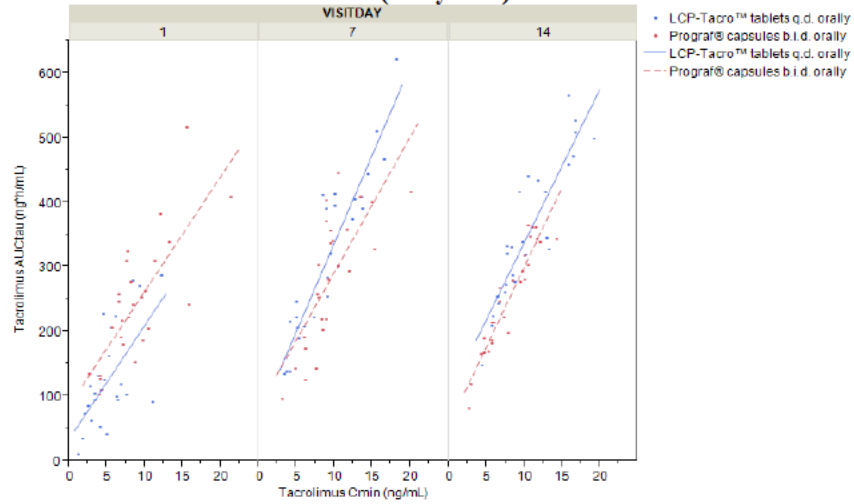
^c median (range)

Figures 39. Time Course Profiles of Mean Tacrolimus Whole Blood Concentrations after administration of ENVARSUS® XR™ and Prograf® during the first 14 days post-transplant in Study 2017 (Subset of Patients with complete set of PK profiles)



Reviewer's note: Tacrolimus concentration profiles of LCP-Tacro = ENVARSUS® XR vs Prograf on the 3 days of PK profiling were similar, regardless of inclusion/exclusion of 5 African American patients who received an ENVARSUS® XR-starting dose of 0.17 mg/kg/day, or African American patients in both ENVARSUS® XR and Prograf arms.

Figure 40. AUC-C_{trough} Correlation Plots, by Day of PK profiling in *de novo* kidney transplant patients (Study 2017)



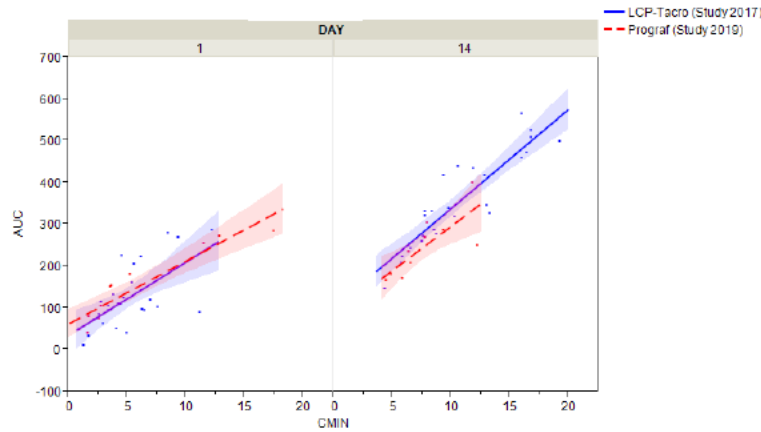
LCP-Tacro = ENVARUSUS® XR

Linear regression equations and correlation coefficients:

VISIT DAY	n	ENVARUSUS® XR once daily starting dose: 0.14 mg/kg/day*	n	Prograf twice daily starting dose: 0.2 mg/kg/day
Day 1	26	AUCtau = 35.423568 + 17.55472*C _{trough} r ² = 0.4067	27	AUCtau = 87.065047 + 17.657667*C _{trough} r ² = 0.5820
Day 7	26	AUCtau = 67.666323 + 27.186748*C _{trough} r ² = 0.8634	27	AUCtau = 184.3884 + 9.6499028*C _{trough} r ² = 0.2611
Day 14	26	AUCtau = 102.479 + 23.719891*C _{trough} r ² = 0.8134	27	AUCtau = 56.162954 + 24.601023*C _{trough} r ² = 0.8929

*For African Americans: ENVARUSUS® XR starting dose 0.17 mg/kg/day; analysis including only those patients with complete set of PK profiles for Days 1, 7, and 14

Figure 41. Cross-Study Comparison of Prograf and ENVARUSUS® XR AUC-C_{trough} correlations (Study 2017 versus Study 2019)



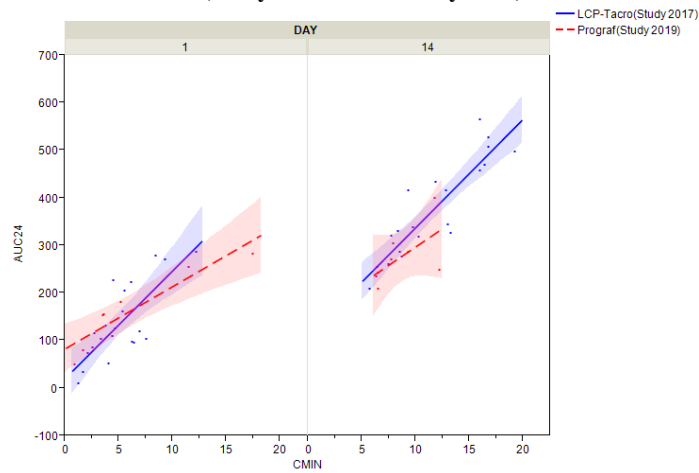
LCP-Tacro = ENVARUSUS® XR

Linear regression equations and correlation coefficients:

VISIT DAY	n	ENVARUSUS® XR once daily starting dose: 0.14 mg/kg/day* Study 2017	n	Prograf twice daily starting dose: 0.1 mg/kg/day Study 2019
Day 1	26	AUC = 35.423568 + 17.55472*C _{trough} r ² = 0.4067	11	AUC = 62.87539 + 15.040007*C _{trough} r ² = 0.8687
Day 14	26	AUC = 102.479 + 23.719891*C _{trough} r ² = 0.8135	11	AUC = 85.221722 + 21.166186*C _{trough} r ² = 0.6241

* 0.17 mg/kg/day for African Americans/Blacks; analysis including only those patients with complete set of PK profiles for Days 1 and 14

Figure 41A. Cross-Study Comparison of Prograf and ENVARSUS® XR AUC-C_{trough} correlations (Study 2017 versus Study 2019)



LCP-Tacro = ENVARSUS® XR;
analysis excludes patients who received starting dose of 0.17 mg/kg/day in Study 2017

Linear regression equations and correlation coefficients:

VISIT DAY	n	ENVARSUS® XR once daily starting dose: 0.14 mg/kg/day* Study 2017	n	Prograf twice daily starting dose: 0.1 mg/kg/day Study 2019
Day 1	20	$AUC = 20.621427 + 22.675415 * C_{trough}$ $r^2 = 0.5890$	11	$AUC = 62.87539 + 15.040007 * C_{trough}$ $r^2 = 0.8687$
Day 14	20	$AUC = 109.98019 + 22.854233 * C_{trough}$ $r^2 = 0.8083$	11	$AUC = 85.221722 + 21.166186 * C_{trough}$ $r^2 = 0.6241$

*analysis including only ENVARSUS® XR patients who received 0.14 mg/kg/day and with a complete set of PK profiles for Days 1 and 14

The results were similar, regardless of inclusion/exclusion of African American patients who received an ENVARSUS® XR starting dose of 0.17 mg/kg/day, or African American patients in both ENVARSUS® XR and Prograf arms.

The proportion of *de novo* kidney transplant patients in Phase 2 Study 2017 and pivotal Phase 3 Study 3002 with measured tacrolimus trough concentrations that were within, below, and above the protocol specified 6-11 ng/mL target range after the first day of dosing (i.e., Study Day 2 predose) was evaluated (Tables 23 and 24). When comparing the 0.14 mg/kg/day (Study 2017) versus the 0.17 mg/kg/day (Study 3002) ENVARSUS® XR starting dosages, a higher percentage of patients were within and a substantially lower percentage of patients were above the target range with 0.14 mg/kg/day of ENVARSUS® XR. However, a higher percentage of patients were below the target range at 0.14 mg/kg/day. *This observation suggests that 0.14 mg/kg/day ENVARSUS® XR may be a potentially safer starting dosage regimen than the 0.17 mg/kg/day regimen.*

When comparing ENVARSUS® XR at 0.14 mg/kg/day (Study 2017) versus Prograf 0.1 mg/kg/day (Study 3002), there was a greater percentage of patients who were within, and a lower percentage below the target trough concentration range for ENVARSUS® XR at 0.14 mg/kg/day; the percentage of patients above the target range were similar for the two treatment groups.

When comparing ENVARSUS® XR at 0.17 mg/kg/day versus Prograf 0.1 mg/kg/day (both in Study 3002), there was a similar percentage of patients within, and a substantially lower percentage of patients below the target range for the ENVARSUS® XR patients. However, the percentage of patients with trough concentrations above the target range was substantially higher for ENVARSUS® XR 0.17 mg/kg/day vs. Prograf 0.1 mg/kg/day.

In totality, these results of tacrolimus trough concentrations, coupled with the increased incidence of toxic nephropathy, PTLD and PVAN observed in Study 3002 with ENVARSUS® XR (0.17 mg/kg/day), suggest that 0.14 mg/kg/day may be a more suitable ENVARSUS® XR starting dosage regimen for de novo kidney transplant patients than the sponsor-proposed starting regimen of 0.17 mg/kg/day.

Table 23. Proportion of Patients Below/Within/Above the “Target” Tacrolimus Trough Concentration Range After First Day of Dosing [Study Day 2, Study 2017; n/N(%)]

ENVARUSUS® XR once daily Starting dose: 0.14 mg/kg/day*			Prograf twice daily Starting dose: 0.2 mg/kg/day		
below 6-11 ng/mL	within 6-11 ng/mL	above 6-11 ng/mL	below 6-11 ng/mL	within 6-11 ng/mL	above 6-11 ng/mL
9/22 (41)	10/22 (45)	3/22 (14)	4/26 (15)	10/26 (38)	12/26 (46)
below 7-20 ng/mL	within 7-20 ng/mL	above 7-20 ng/mL	below 7-20 ng/mL	within 7-20 ng/mL	above 7-20 ng/mL
14/22 (64)	8/22 (36)	0/22 (0)	7/26 (27)	15/26 (58)	4/26 (15)

*starting dose for majority of the PK-evaluable patients in Study 2017; within/below/above target rates if excluding 3 patients who received LCP starting dose of 0.17 mg/kg/day: 53%/37%/11%
analysis includes only those patients with trough concentration reading by local laboratory by Day 3 (predose), from the subset with a complete set of PK profiles on Days 1, 7, and 14
Target tacrolimus trough concentration range of Study 3002 during the first 30 days: 6-11 ng/mL
Target tacrolimus trough concentration range of Study 2017 during the first 14 days: 7-20 ng/mL

Table 24. Proportion of Patients Below/Within/Above the Target Tacrolimus Trough Concentration Range (6 – 11 ng/mL) After the First Day of Dosing [(Study Day 2, Study 3002; n/N(%))]

Treatment	Starting dose	below target range	within target range	above target range
ENVARUSUS® XR once daily	0.17 mg/kg/day	49/176 (28)	58/176 (33)	69/176 (39)
Prograf twice daily	0.1 mg/kg/day	118/194 (61)	52/194 (27)	24/194 (12)

Figure 42 compares the time course profiles of tacrolimus trough concentrations of the two treatment arms in Study 2017 and in Study 3002. It appears that tacrolimus concentrations in the ENVARUSUS® XR arm of Study 2017 (following a starting dose of 0.14 mg/kg/day for majority of the patients) was achieved by 7 days post-transplant in majority of the patients (see also Table 25).

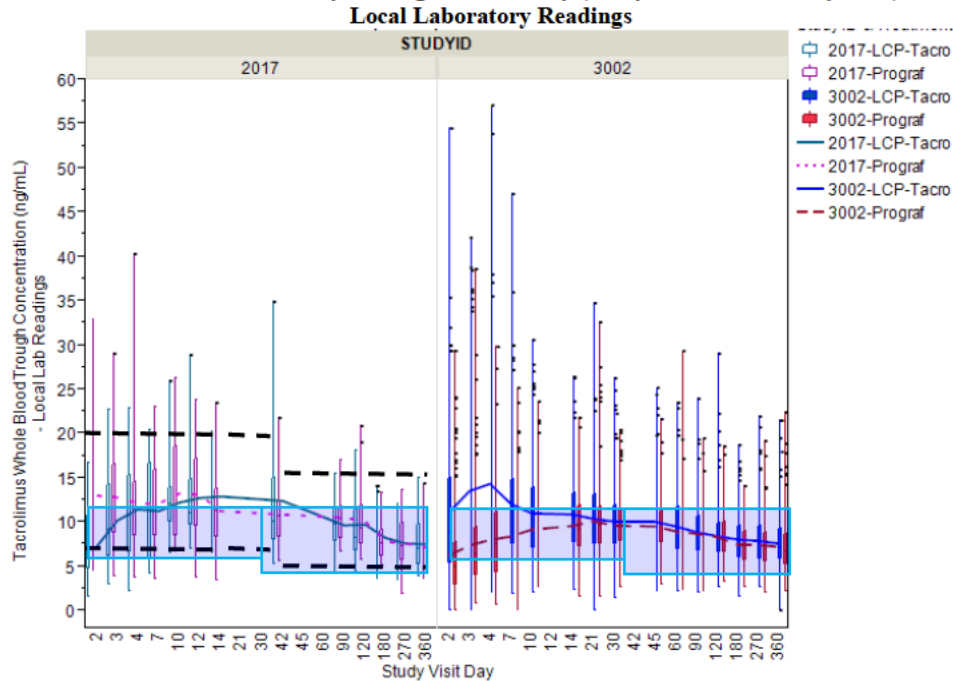
At a starting ENVARUSUS® XR dose of 0.14 mg/kg/day for majority of the ENVARUSUS® XR patients in this study, the mean/median tacrolimus trough concentrations during the first 7 days would be within that targeted in the Phase 3 trial (Study 3002), as was also observed for the Prograf comparator arm in Study 3002. Thus, it is anticipated that the efficacy of ENVARUSUS® XR when initiated at 0.14 mg/kg/day would be satisfactory. Note that there were a limited number of African American/Black patients included in this trial.

ENVARUSUS® XR exhibited a higher relative bioavailability than Prograf in healthy subjects and stable kidney transplant patients. Additionally, the tacrolimus T_{max} is prolonged with ENVARUSUS® XR compared to Prograf. That an ENVARUSUS® XR starting daily dose higher than 0.1 mg/kg/day (i.e., 0.14 mg/kg/day) would be necessary to achieve the same tacrolimus AUC on Day 1 as Prograf 0.1 mg/kg/day in *de novo* kidney transplant patients could be explained at least in part by the potentially greater impact of surgery-associated delayed gastric emptying time on the oral bioavailability of tacrolimus from extended release products given once daily than from immediate release products given twice daily.

In the ENVARUSUS® XR arm of Study 2017, the mean tacrolimus trough concentrations were comparable between 26 non-African Americans/non-Blacks and 5 African Americans/Blacks during the first 3 days of dosing, following starting tacrolimus doses of 0.14 mg/kg/day and 0.17 mg/kg/day, respectively (Figure 43 and Table 26).

See Figure 44 and Table 27 for a comparison of the tacrolimus daily doses in the two treatment arms of Study 2017; see also Figure 45 and Table 28 for the corresponding racial subgroup analysis.

Figure 42. Box plots of Tacrolimus Trough Concentrations (ng/mL) in *De novo* Kidney Transplant Patients treated with ENVARUSUS® XR once daily or Prograf twice daily (Study 2017 versus Study 3002):



Starting LCP-Tacro = ENVARUSUS® XR daily dose: 0.17 mg/kg/day (regardless of race; Study 3002) versus 0.14 mg/kg/day (0.17 mg/kg/day for Blacks/African Americans; Study 2017)

Starting Prograf daily dose (given twice daily): 0.1 mg/kg/day (Study 3002) versus 0.2 mg/kg/day (Study 2017)

Study 2017 protocol defined target tacrolimus trough concentration range (dashed black horizontal lines)

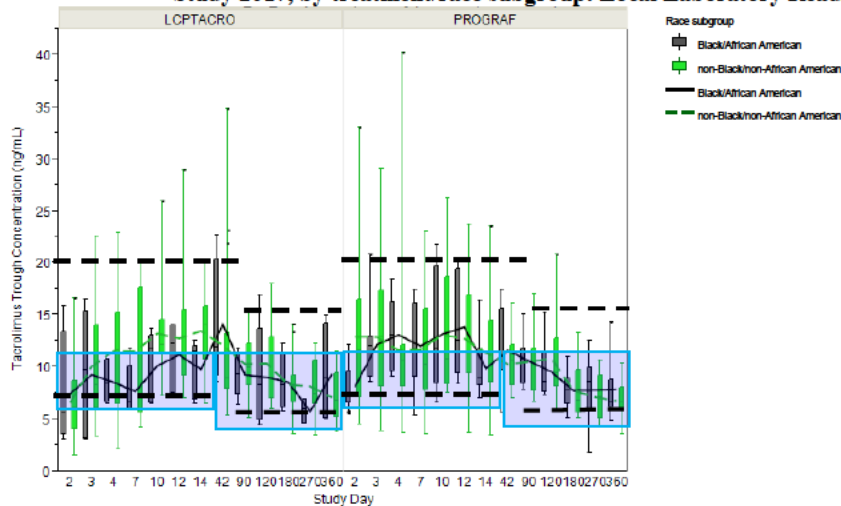
Study 3002 target tacrolimus trough concentration range (translucent green boxes)

Table 25. Observed Tacrolimus Whole Blood Trough Concentrations (ng/mL) in *De novo* Kidney Transplant Patients in Study 2017, by Visit [Mean ± SD; Median (10th – 90th percentile): Local Laboratory Readings

VISIT DAY	n	ENVARUSUS® XR 0.14 mg/kg/day	n	Prograf 0.2 mg/kg/day
Day 2	30	7.3 ± 3.9; 6.5(2.9 - 13.8)	28	13.1 ± 7.4; 11.2(5.6 - 24.8)
Day 3	26	10.2 ± 5.2; 9.1(3.3 - 18.8)	30	12.9 ± 5.6; 12.8(5.6 - 20.6)
Day 4	27	11.5 ± 6.2; 10.6(4.7 - 22)	26	12.2 ± 6.7; 11.5(6.5 - 16.4)
Day 7	31	11.3 ± 5.3; 11.2(4.9 - 19.4)	31	12.2 ± 4.8; 11.1(5.7 - 19.8)
Day 10	25	12.3 ± 4.1; 12.1(7 - 17.8)	26	13.3 ± 5.4; 11.6(7.8 - 21.4)
Day 12	21	12.8 ± 5.2; 10.9(7.7 - 20.7)	27	13.2 ± 5; 11.5(8 - 20.6)
Day 14	28	13 ± 3.9; 13(7.1 - 18.7)	29	11.3 ± 4.6; 11.3(5.1 - 18.8)
Day 42	26	12.5 ± 6.8; 10(6.6 - 22.8)	30	10.9 ± 3.6; 10.6(7 - 16.7)
Day 90	26	9.7 ± 3; 9.7(5 - 14.4)	25	10.6 ± 2.8; 10.3(7.2 - 15.4)
Day 120	24	9.8 ± 4.2; 8.2(5.7 - 17.3)	26	10.2 ± 3.8; 9.3(6.9 - 17.4)
Day 180	23	8.3 ± 2.8; 7.7(5.4 - 13.8)	26	7.9 ± 2.2; 7.5(5.1 - 11.2)
Day 270	22	7.6 ± 2.6; 7.2(3.9 - 11.4)	23	7.7 ± 2.8; 7.3(4.4 - 11.8)
Day 360	22	7.6 ± 2.9; 7(4.2 - 12)	24	7.2 ± 2.3; 6.7(4.3 - 10.2)

*analysis includes all patients in Study 2017 with measured tacrolimus trough concentrations; mean values are comparable when including only those patients with a complete set of PK profiles on Days 1, 7 and 14.

Figure 43. Box plots of Tacrolimus Trough Concentrations (ng/mL) in *De novo* Kidney Transplant Patients in Study 2017, by treatment/race subgroup: Local Laboratory Readings



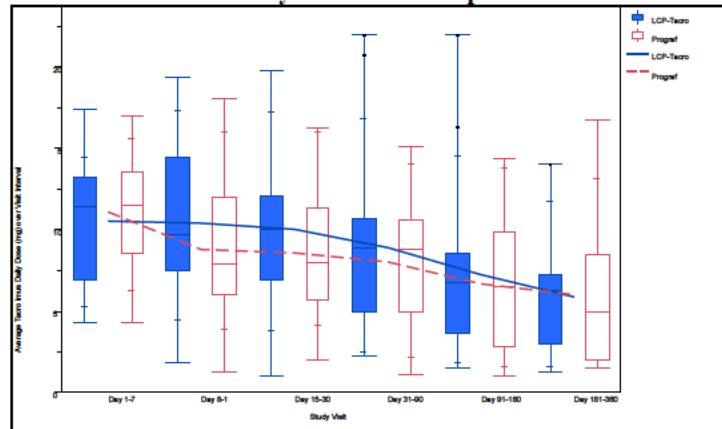
*analysis includes the subset of patients who have a complete set of PK profiles on Days 1, 7 and 14
 Study 2017 protocol defined target tacrolimus trough concentration range (dashed black horizontal lines)
 Study 3002 target tacrolimus trough concentration range (translucent green boxes)
 LCP-Tacro = ENVARUSUS® XR

Table 26. Observed Tacrolimus Whole Blood Trough Concentrations (ng/mL) in *De novo* Kidney Transplant Patients in Study 2017, by Visit and by treatment/race subgroup [Mean ± SD; Median (10th – 90th percentile): Local Laboratory Readings

VISIT DAY	ENVARUSUS® XR				Prograf			
	n	Black/African American (Starting dose: 0.17 mg/kg/day)	n	non- Black/non-African American (Starting dose: 0.14 mg/kg/day)	n	Black/African American	n	non- Black/non-African American
Day 2	4	7.5 ± 5.7; 6(3 - 15.9)	26	7.3 ± 3.7; 7(2.6 - 12.3)	7	8.1 ± 2.2; 8(5.6 - 12.1)	21	14.7 ± 7.8; 14(5.5 - 25.4)
Day 3	5	9.3 ± 6.1; 10(3 - 16.5)	21	10.5 ± 5.1; 8(5.1 - 19.6)	8	12.2 ± 3.9; 12(8.6 - 20.8)	22	13.1 ± 6.2; 13(4.4 - 22)
Day 4	4	8.6 ± 2.1; 8(6.5 - 11.2)	23	12 ± 6.5; 12(4 - 22.1)	6	13.2 ± 3.6; 13(9.1 - 18.4)	20	11.9 ± 7.4; 11(5 - 15.6)
Day 7	5	7.7 ± 2.5; 7(5.9 - 11.8)	26	12 ± 5.5; 12(4.8 - 19.5)	8	12.1 ± 4.1; 12(5.3 - 17.4)	23	12.2 ± 5.2; 11(5.8 - 21)
Day 10	5	10.2 ± 3.4; 12(6.5 - 13.7)	20	12.8 ± 4.2; 12(8 - 18.6)	8	13.2 ± 5.7; 12(6.6 - 21.7)	18	13.3 ± 5.4; 11(7.9 - 20.5)
Day 12	3	11.2 ± 3.4; 12(7.5 - 14)	18	13.1 ± 5.5; 11(8.2 - 21.5)	7	13.9 ± 4.9; 13(8.4 - 20)	20	12.9 ± 5.1; 12(6.8 - 22.2)
Day 14	5	9.8 ± 2.8; 12(6.5 - 12.5)	23	13.6 ± 3.8; 14(7.9 - 19.3)	8	9.9 ± 3.1; 9(7 - 16.4)	21	11.9 ± 5; 12(4.9 - 19.8)
Day 42	5	14.2 ± 6; 12(8.6 - 22.7)	21	12.1 ± 7; 9(6.5 - 22.8)	8	11.7 ± 3.9; 11(5.6 - 17.4)	22	10.7 ± 3.6; 10(7 - 15.6)
Day 90	5	9.3 ± 2.1; 9(6.4 - 11.8)	21	9.8 ± 3.2; 10(4.9 - 14.7)	8	10.6 ± 2.3; 11(7.8 - 15)	17	10.6 ± 3; 10(6.9 - 16.2)
Day 120	5	9.1 ± 5; 8(4.4 - 16.9)	19	10 ± 4; 8(6.1 - 17.6)	8	9.6 ± 2.7; 9(7.3 - 15.2)	18	10.5 ± 4.3; 9(6.7 - 19.2)
Day 180	4	8.6 ± 2.7; 8(5.7 - 12.2)	19	8.2 ± 2.9; 8(5.2 - 14.1)	8	7.8 ± 1.8; 8(5.1 - 11)	18	7.9 ± 2.4; 7(5.1 - 11.9)
Day 270	3	5.8 ± 1.2; 6(4.6 - 6.9)	19	7.9 ± 2.7; 7(3.8 - 11.5)	7	7.8 ± 3.4; 9(1.8 - 12.5)	16	7.6 ± 2.6; 7(4.5 - 11.6)
Day 360	4	9.4 ± 4.9; 9(5 - 14.9)	18	7.2 ± 2.3; 7(4 - 10.6)	7	7.9 ± 3.1; 7(4.8 - 14.3)	17	6.9 ± 1.9; 7(3.7 - 10.1)

*analysis includes the subset of patients who have a complete set of PK profiles on Days 1, 7 and 14

Figure 44. Average Tacrolimus Daily Dose (mg) Over Visit Interval in Study 2017, by Treatment Group



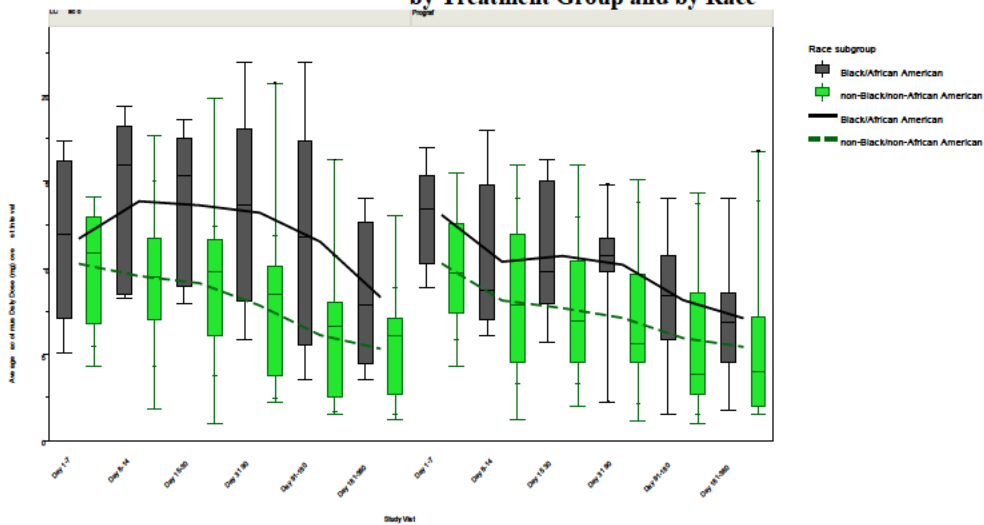
*analysis includes subset of patients with complete set of PK profiles on Days 1, 7 and 14
LCP-Tacro = ENVARSUS® XR

Table 27. Mean ± SD Tacrolimus Daily Doses (mg) per visit interval in Study 2017, by treatment

VISIT INTERVAL	n	ENVARSUS® XR	n	Prograf
Day 1-7	26	10.5 ± 3.6	27	11.1 ± 3.4
Day 8-14	25	10.4 ± 4.5	27	8.8 ± 4.3
Day 15-30	25	10 ± 4.5	27	8.6 ± 3.9
Day 31-90	25	8.9 ± 5.1	27	8 ± 3.9
Day 91-180	24	7.2 ± 4.9	24	6.7 ± 4.2
Day 181-360	22	5.9 ± 3.4	23	6 ± 4.3

*includes subset of patients with complete set of PK profiles on Days 1, 7 and 14

Figure 45. Average Tacrolimus Daily Dose (mg) Over Visit Interval by Treatment Group and by Race



*includes subset of patients with complete set of PK profiles on Days 1, 7 and 14
LCP-Tacro = ENVARSUS® XR

Table 28. Mean ± SD Tacrolimus Daily Doses (mg) per visit interval in Study 2017, by treatment/race

VISIT INTERVAL	ENVARUSUS® XR				Prograf			
	n	Blacks/ African Americans	n	non-Blacks/ non-African Americans	n	Blacks/ African Americans	n	non-Blacks/ non-African Americans
Day 1-7	5	11.7 ± 4.9	21	10.3 ± 3.3	8	13.1 ± 2.8	19	10.3 ± 3.3
Day 8-14	5	13.9 ± 5.1	20	9.5 ± 4	8	10.4 ± 4.4	19	8.1 ± 4.1
Day 15-30	5	13.7 ± 4.5	20	9.1 ± 4.1	8	10.7 ± 3.9	19	7.7 ± 3.6
Day 31-90	5	13.2 ± 5.9	20	7.8 ± 4.4	8	10.2 ± 3.6	19	7.1 ± 3.7
Day 91-180	5	11.5 ± 6.9	19	6.1 ± 3.6	8	8.1 ± 3.8	16	5.9 ± 4.2
Day 181-360	4	8.3 ± 4.3	18	5.3 ± 3.1	8	7.1 ± 3.6	15	5.4 ± 4.6

*includes subset of patients with complete set of PK profiles on Days 1, 7 and 14

Concomitant immunosuppressive agents in Study 2017

According to the protocol of Study 2017, concomitant therapy with either MMF or MPS or azathioprine was permitted but not required; the participating site should apply their protocol for use of maintenance immunosuppressant regimen uniformly to patients randomized to either study arm. Based on the reviewer's analysis, the mean or median daily MMF equivalent doses in ENVARUSUS® XR patients were comparable to or numerically lower than that received by Prograf patients. Based on the review of the MMF dosing dataset, almost all if not all of the tacrolimus treated patients in Study 2017 received concomitant MMF during the 12-month study.

Per the study protocol, corticosteroid therapy was at the discretion of the investigator; the participating site should apply their protocol for use of maintenance immunosuppressant regimen uniformly to patients randomized to either study arm. Based on the reviewer's analysis, the mean and median daily prednisone equivalent doses in this trial were similar between treatment groups.

Antibody induction according to center practice was permitted in the trial but must be applied uniformly to patients randomized to either study arm. Use of alemtuzumab (Campath®) was not permitted. Based on the reviewer's analysis, almost all if not all of the patients (29 ENVARUSUS® XR, 30 Prograf) received antibody induction; the mean daily doses of antibody induction agents (mainly antithymocyte immunoglobulin) in the study were similar between treatment groups. The mean durations of antibody induction therapy were also similar (3 days for ENVARUSUS® XR and 3.2 days for Prograf).

Study 2019 (de novo)

The PK of ENVARUSUS® XR once daily and Prograf twice daily were characterized in Phase 2 Study 2019, a double-blind, double dummy, randomized, multicenter trial in adult *de novo* kidney transplant patients. The starting doses of ENVARUSUS® XR (0.17 mg/kg/day) and Prograf (0.1 mg/kg/day), the target tacrolimus whole blood trough concentration range, and the batch number of the study medications in this Phase 2 trial were identical to those used in the pivotal Phase 3 Study 3002, also in *de novo* kidney transplant patients. Tacrolimus PK profiling (under fasting condition) was performed on Day 1 post-transplant, as well as on Days 14, and 28 post-transplant (after at least 5 days of stable tacrolimus dosing). The comparative tacrolimus PK profiles and PK parameters of the two treatment groups are shown in Figure 46 and Table 29, respectively. Ten (10) ENVARUSUS® XR patients and 11 Prograf patients had a complete set of tacrolimus PK profiles.

The higher tacrolimus AUC and higher C₂₄ achieved with ENVARUSUS® XR is related in part to the higher starting and average daily doses with ENVARUSUS® XR, as compared to Prograf. A comparison of the Day 1 and the Day 14 tacrolimus AUC and C_{max} values suggest that the higher starting dose of 0.17 mg/kg/day for ENVARUSUS® XR once daily results in higher than expected tacrolimus exposures in ENVARUSUS® XR patients. Additionally, even after normalizing for the tacrolimus dose difference on Day 1, the mean AUC and C_{max} of tacrolimus on Day 1 was still 50% higher in ENVARUSUS® XR patients than in Prograf patients, *similar to the observed 50% higher relative bioavailability at steady state in healthy subjects* (Studies 1012 and 1016). The dose-normalized tacrolimus AUC and C_{max} on Days 14 and 28 were comparable between the two treatment groups. *The reviewer notes that an ENVARUSUS® XR*

starting dose of **Appears this way on the original** for de novo kidney transplant patients **Appears this way on the original**

Figure 46. Time Course Profiles of Mean Tacrolimus Whole Blood Concentrations after administration of ENVARSUS® XR™ and Prograf® during the first 30 days post-transplant in Study 2019 (Subset of Patients with complete set of PK profiles)

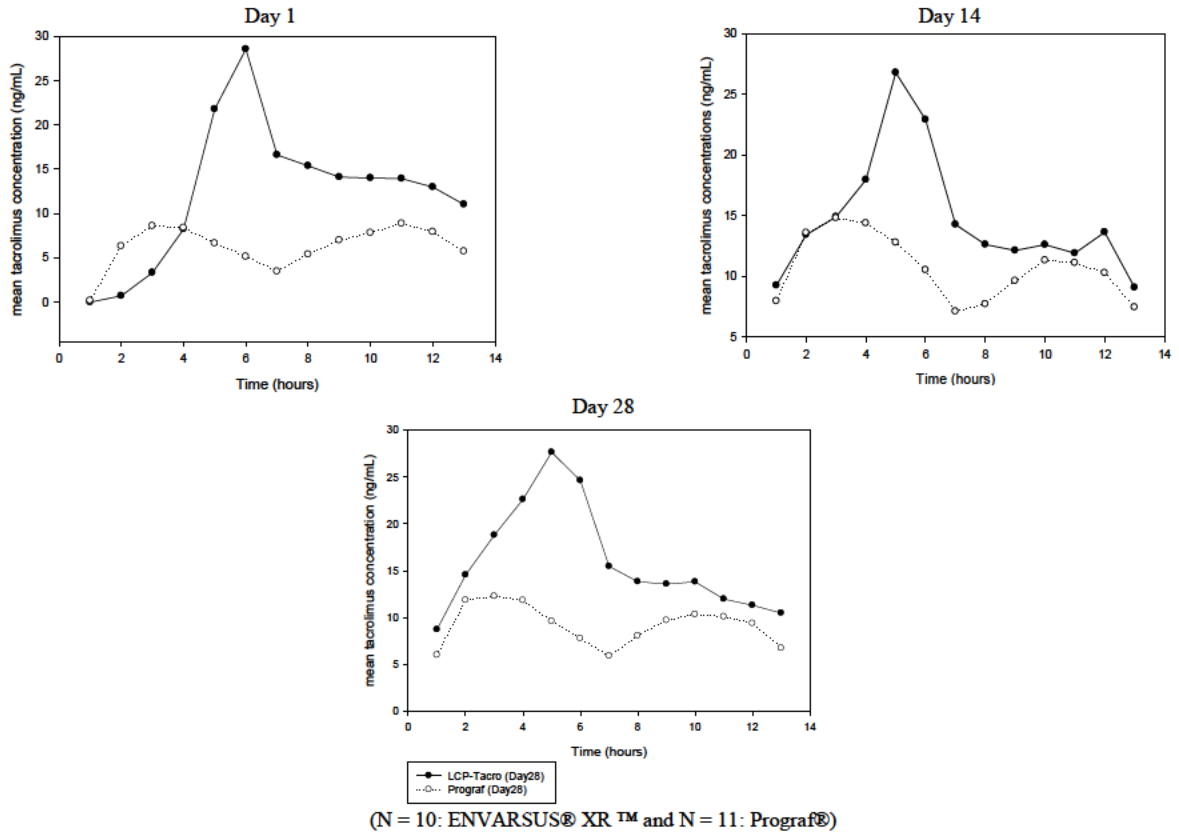


Table 29. Mean ± SD Tacrolimus Pharmacokinetic Parameters of ENVARSUS® XR™ and Prograf® in De novo Kidney Transplant Patients in Study 2019^a

	ENVARSUS® XR (n=10)			Prograf (n=11)		
	Day 1	Day 14	Day 28	Day 1	Day 14	Day 28
AUC ₀₋₂₄	376.66 ± 256.83	375.64 ± 140.32	396.23 ± 149.93	149.16 ± 89.34	243.13 ± 69.97	205.79 ± 36.25
C _{max}	33.57 ± 21.83	31.13 ± 14.58	35.91 ± 18.67	13.09 ± 7.41	18.71 ± 6.84	17.38 ± 4.07
C ₂₄	11.03 ± 6.06	9.09 ± 3.02	10.49 ± 3.18	5.74 ± 5.54	7.46 ± 2.61	6.75 ± 2.22
C _{ave}	15.69 ± 10.7	15.65 ± 5.85	16.51 ± 6.25	6.21 ± 3.72	10.13 ± 2.92	8.57 ± 1.51
T _{max} ^b	6.02 (4.05 - 24)	4.04 (1.02 - 18)	4 (1.5 - 14.05)	4 (1.03 - 18)	2 (1 - 18)	4 (1 - 18)
Fluctuation	-	132.06 ± 57.99	144.57 ± 67.49	-	113.8 ± 54.82	131.4 ± 75.96
Swing	-	240.94 ± 136.52	246.69 ± 140.87	-	166.8 ± 87.32	189.15 ± 152.01

^a includes 10 ENVARSUS® XR patients and 11 Prograf patients with complete set of PK profiles on Days 1, 14, and 28

^b median (range)

^c mean ± SD daily doses of ENVARSUS® XR vs Prograf (mg/day):

Day 1: 15.5 ± 3.1 vs 8 ± 1.9

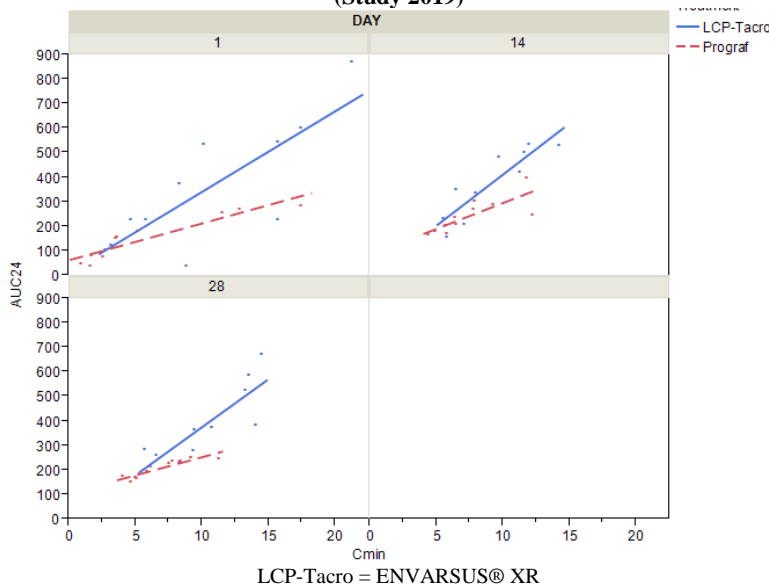
Day 14: 11.4 ± 5.4 vs 9.6 ± 4.2

Day 28: 11.1 ± 6.4 vs 8.9 ± 5.0

Note that in Study 2019, four African American /Black patients who received ENVARSUS® XR 0.17 mg/kg/day achieved a mean ± sd AUC and C₂₄ on Day 1 of 270 ± 233 ng*h/mL and 8.9 ± 5.1 ng/mL, respectively.

The linear AUC – C_{trough} correlation plots for Days 1, 14 and 28 of tacrolimus dosing in Study 2019 are shown in Figure 47; the linear regression parameters are shown in the table below the figure. The apparently higher slope for the lines of ENVARSUS® XR (0.17 mg/kg/day) than for Prograf (0.1 mg/kg/day) as early as Day 1 (as well as the attainment of tacrolimus AUC and C_{max} close to those achieved at steady state, after the first dose of ENVARSUS® XR in this trial) is unexpected, and suggests that targeting the same C_{trough} range as Prograf (e.g., 6 to 11 ng/mL) would result in a 35% to 65% higher AUC on Day 1, and a 15% to 40% higher AUC at steady state with ENVARSUS® XR than Prograf. Note that in Study 2019, the average tacrolimus trough concentrations of ENVARSUS® XR were consistently higher (i.e., on Days 1, 14 and 28 post-transplant) than that achieved with Prograf. Linear pharmacokinetics had been demonstrated in healthy subjects for tacrolimus up to 10 mg single dose (Study 1013); the administration of ENVARSUS® XR doses >15 mg/day could have been responsible (at least to part) for the observed higher than expected tacrolimus exposures in ENVARSUS® XR patients in Study 2019. It is not clear whether the sponsor’s decision to increase the ENVARSUS® XR starting daily dose paired with the decision to decrease the Prograf starting daily dose, the investigator’s inability to expeditiously manage the higher than expected tacrolimus trough concentrations during the first 7 days of dosing in ENVARSUS® XR patients, and/or the higher oral bioavailability of ENVARSUS® XR (as observed in healthy subjects and stable kidney transplant patients) could have also contributed to the significant separation of the ENVARSUS® XR and the Prograf AUC-C_{trough} correlation lines as observed in this study.

Figure 47. AUC-C_{trough} Correlation Plots, by Day of PK profiling in *de novo* kidney transplant patients (Study 2019)



Linear regression equations and correlation coefficients:

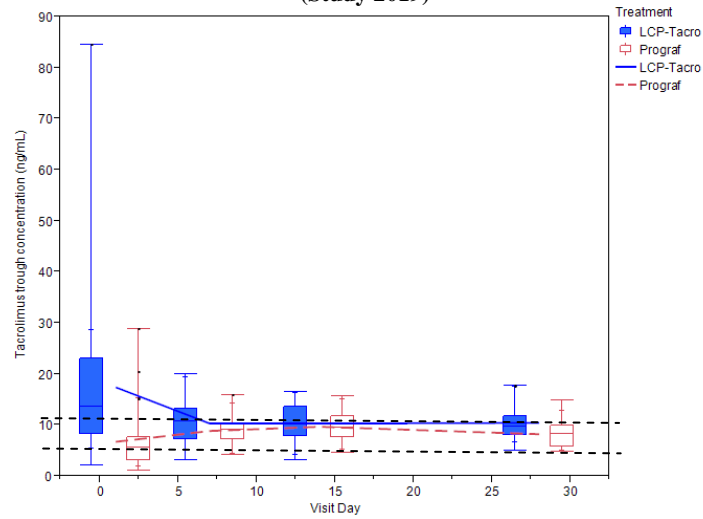
DAY	n	ENVARSUS® XR once daily starting dose: 0.17 mg/kg/day	n	Prograf twice daily starting dose: 0.1 mg/kg/day
Day 1	10	AUC ₂₄ = 13.519501 + 32.914016*C _{trough} r ² = 0.6033	11	AUC ₂₄ = 62.87539 + 15.040007*C _{trough} r ² = 0.8687
Day 14	10	AUC ₂₄ = -3.929137 + 41.746851*C _{trough} r ² = 0.8060	11	AUC ₂₄ = 85.221722 + 21.166186*C _{trough} r ² = 0.6240
Day 28	10	AUC ₂₄ = -15.47048 + 39.258306*C _{trough} r ² = 0.6942	11	AUC ₂₄ = 105.84816 + 14.8051*C _{trough} r ² = 0.8236

*analysis including only those patients with complete set of PK profiles for Days 1, 14, and 28

In Study 2019, pre-dose tacrolimus whole blood concentrations were measured at each visit by the local laboratory. As observed in Phase 3 Study 3002, the measured tacrolimus trough concentrations were numerically higher for ENVARSUS® XR than Prograf during the first 28 days (especially, during the first

7 days) of tacrolimus dosing (Figure 48; Table 30). Such tacrolimus exposure profiles were reflective of the relative dosing between ENVARSUS® XR and Prograf patients in this study (Figure 49). *The reviewer notes that the average ENVARSUS® XR starting dose administered on Day 1 exceeded 15 mg once daily in Study 2019 but not in Study 3002, so assuming nonlinear PK at ENVARSUS® XR dosage > 15 mg once daily, it is not clear whether the Day 1 tacrolimus exposures in the Phase 2 study is an overestimate of the actual tacrolimus exposures in ENVARSUS® XR patients who received the same 0.17 mg/kg/day starting dose (equivalent to 12.7 mg once daily) in the Phase 3 study (Study 3002).*

Figure 48. Tacrolimus Whole Blood Trough Concentration* (ng/mL) at Study Visit by Treatment Group (Study 2019)



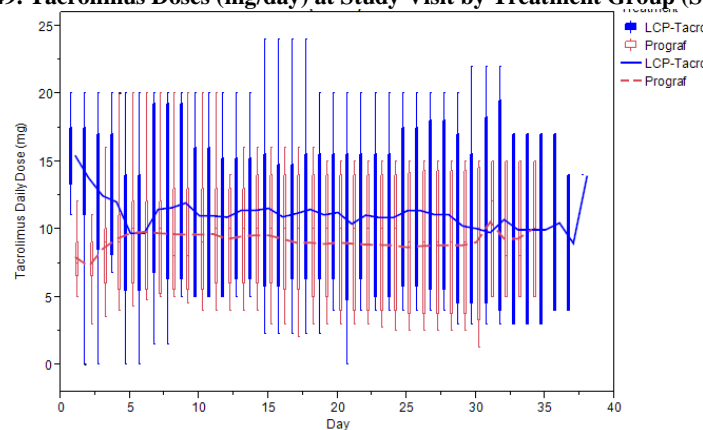
protocol specified target tacrolimus trough concentration range (dashed black horizontal lines)
LCP-Tacro = ENVARSUS® XR

Table 30. Tacrolimus Trough Concentrations of ENVARSUS® XR™ and Prograf® in De novo Kidney Transplant Patients in Study 2019 [Mean ± SD; Median (10th to 90th percentile)]- Local Lab assay results

Visit Day*	ENVARSUS® XR (ng/mL)	Prograf (ng/mL)
1	17.5 ± 14.8; 14 (5.3 - 28.7)	6.8 ± 6; 6 (1.8 - 15.2)
7	10.4 ± 4.7; 11 (3.1 - 19.3)	8.9 ± 3.2; 9 (4.3 - 14.2)
14	10.4 ± 4; 10 (4 - 16.3)	9.8 ± 3; 10 (5.1 - 15)
28	10.5 ± 3.7; 10 (6.5 - 17.5)	8.3 ± 2.6; 8 (4.9 - 12.7)

*Visit Day 1 = Day 2 predose = 24 hours after the first tacrolimus dose

Figure 49. Tacrolimus Doses (mg/day) at Study Visit by Treatment Group (Study 2019)



LCP-Tacro = ENVARSUS® XR

The proportions of patients in Study 2019 with measured tacrolimus trough concentrations that were within, below and above the protocol specified target range (6-11 ng/mL during the first 30 days) are depicted in Figure 50. On Day 1 (Day 2 predose), a higher proportion of ENVARSUS® XR patients in Study 2019 were either within target or above target, as compared to Prograf patients. For both ENVARSUS® XR and Prograf patients, the proportion of patients achieving tacrolimus trough concentrations within the target range increased by Day 7. By Day 28, both the above-target and below-target rates were lower than those observed on Day 1 for both ENVARSUS® XR and Prograf patients.

Figure 51 compares the proportions of patients in Phase 2 Study 2019 and Phase 3 Study 3002 with measured tacrolimus trough concentrations on Day 2 predose that were within, below and above the protocol specified target range (6-11 ng/mL during the first 30 days). The proportions within, below and above the target range observed by Day 2 predose were similar between the Phase 2 study and the Phase 3 study for Prograf patients. For ENVARSUS® XR patients (0.17 mg/kg/day), the percentage of patients within the protocol specified target range of tacrolimus trough concentrations and the total percentage of patients not within the target range were comparable between the two studies. Of note is that the percentage of patients above the target range in Studies 2019 and 3002 was 56% and 39%, respectively, which suggests a potentially increased risk of tacrolimus associated adverse events with the initial ENVARSUS® XR dosage regimen of 0.17 mg/kg/day.

Figure 50. Distribution of Patients Below/Within/Above the Target Tacrolimus Trough Concentration Range (6 – 11 ng/mL) by Study Day (Study 2019: ENVARSUS® XR versus Prograf) – Local Lab Assay Results

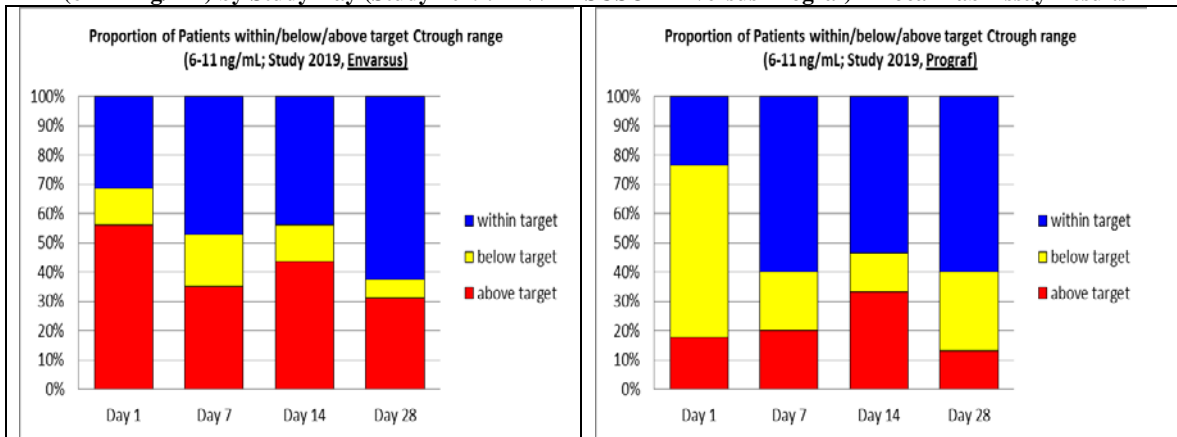
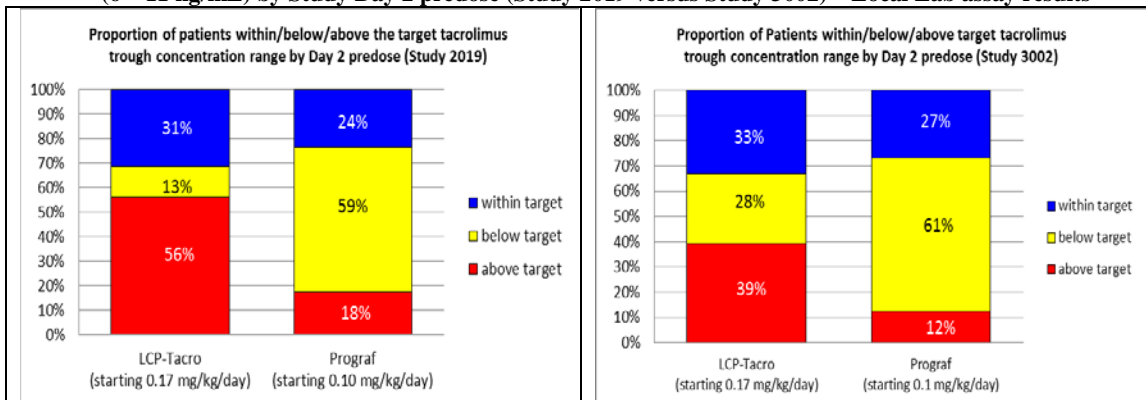


Figure 51. Distribution of Patients Below/Within/Above the Target Tacrolimus Trough Concentration Range (6 – 11 ng/mL) by Study Day 2 predose (Study 2019 versus Study 3002) – Local Lab assay results



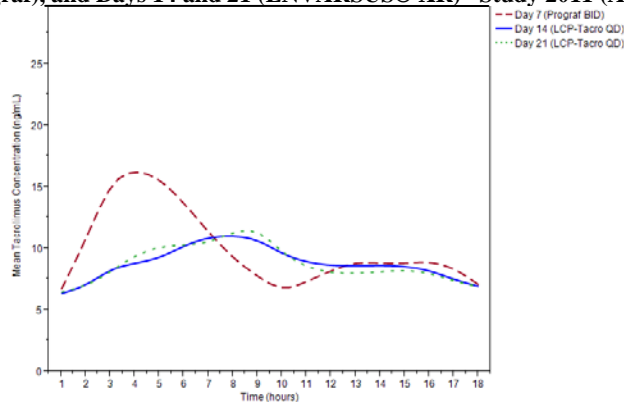
LCP-Tacro = ENVARSUS® XR

Stable Kidney transplant patients switched from immediate release tacrolimus to ENVARSUS® XR Study 2011

The PK of ENVARSUS® XR once daily and Prograf twice daily were characterized in Phase 2 Study 2011, an open-label, multicenter, 3-sequence conversion study in stable kidney transplant patients. Like in

Study 3001, patients on stable doses of Prograf BID and achieving a tacrolimus C_{trough} within the target range at screening were converted to ENVARSUS® XR QD (nearest whole mg dose). The daily dose conversion ratio (0.67 to 0.80 or ~ 0.71) from Prograf to ENVARSUS® XR in this study was slightly different from that used in Phase 3 Study 3001 involving also stable kidney transplant patients switched from Prograf BID to ENVARSUS® XR once daily (1: 0.85 for African-Americans; 1:0.70 for non-AAAs). The target tacrolimus whole blood trough concentration range (5 – 15 ng/mL) following conversion to ENVARSUS® XR in Study 2011 was also similar to that targeted in Study 3001 (4-15 ng/mL). The PK parameters of tacrolimus were determined (under fasted conditions) after 7 days of stable dosing of the study drug on Day 7 (Prograf), as well as on Days 14, and 21 (ENVARSUS® XR). If needed, dosage adjustment of ENVARSUS® XR was allowed on Day 15. The tacrolimus PK profiles and PK parameters of Prograf (Day 7) and ENVARSUS® XR (Days 14 and 21) are shown in Figure 52 and Table 31, respectively. The linear AUC – C_{trough} correlation parameters are shown in Table 32. Note that the reviewer was able to verify the sponsor’s reported PK parameters and relative bioavailability calculations using a subset of patients with PK profiles for both Day 7 (Prograf) and Day 14 (ENVARSUS® XR).

Figure 52. Time Course of Mean Tacrolimus Whole Blood Concentrations in Stable Kidney Transplant Patients following 7 days of fixed dosing with Prograf and then ENVARSUS® XR, i.e., Day 7 (Prograf), and Days 14 and 21 (ENVARSUS® XR) –Study 2011 (ALL PATIENTS)



*Prograf to ENVARSUS® XR daily dose conversion ratio (1: 0.67 to 0.8)
LCP-Tacro =ENVARSUS® XR

Table 31. Tacrolimus Pharmacokinetic Parameters after 7 days of fixed dosing with Prograf BID and 7 to 14 days following conversion to ENVARSUS® XR QD (daily dose conversion ratio: 1:0.67-0.80) – Study 2011 (ALL PATIENTS)

Parameter	Geometric Mean (%CV) Arithmetic Mean ± SD		
	Prograf Capsules twice-daily	ENVARSUS® XR Tablets	
	Day 7 (n=47)	Day 14 (n=47)	Day 21 (n=46)
AUC _t ^a (ng·hr/mL)	212.12 (25.59) 218.82 ± 55.99	206.79 (29.27) 215.71 ± 63.14	209.05 (31.30) 218.03 ± 68.23
C _{max} (ng/mL)	17.66 (42.59) 19.14 ± 8.15	12.64 (36.02) 13.45 ± 4.84	13.05 (41.91) 13.94 ± 5.84
C _{trough} (ng/mL)	6.82 (22.01) 7.00 ± 1.54	6.59 (33.41) 6.96 ± 2.32	6.64 (31.70) 6.94 ± 2.20
C _{ava} (ng/mL)	8.84 (25.59) 9.12 ± 2.33	8.62 (29.27) 8.99 ± 2.63	8.71 (31.29) 9.08 ± 2.84
T _{max} (hr) ^b	1.82 (0.50 - 24.00)	6.00 (1.00-16.00)	6.00 (1.50 - 16.00)
Degree of fluctuation (%)	127.41 ± 57.28	73.24 ± 44.96	77.04 ± 50.59
Degree of Swing (%)	174.55 ± 93.72	102.80 ± 75.24	11007 ± 89.23
C _{max} /C _{trough}	2.75 ± 0.94	2.03 ± 0.75	2.10 ± 0.89

^a t=24 hours; ^b median (minimum – maximum)

Source: NDA Study 2011CSR (Table 7)

Table 31A. Relative Tacrolimus Bioavailability –Day 14 versus Day 7 (Study 2011;ALL PATIENTS)

Parameter	90% CI	Ratio of Means	Intra-Patient CV
AUC _t ^a	88.63% to 107.23%	97.49%	28.44%
C _{max}	63.09% to 81.23%	71.59%	38.29%
C _{trough}	87.33% to 106.70%	96.53%	29.97%

^a t=24 hours; Source: NDA Study 2011CSR (Table 8)

Table 32. Correlation Between Tacrolimus AUC_t and C_{trough} (Study 2011;ALL PATIENTS)

Parameter	Day 7		Day 14		Day 21	
	AUC _t (ng·hr/mL)	C _{trough} (ng/mL)	AUC _t (ng·hr/mL)	C _{trough} (ng/mL)	AUC _t (ng·hr/mL)	C _{trough} (ng/mL)
Mean	5.35716	1.92049	5.33171	1.88517	5.34260	1.89238
SD	0.25141	0.23353	0.29591	0.33707	0.28751	0.29989
Correlation	0.78656		0.91380		0.86471	
P-value	<0.0001		<0.0001		<0.0001	

Source: NDA Study 2011CSR (Table 11)

Approximately half of the patients in this study were African Americans. Based on the sponsor’s race subgroup analysis, when Prograf patients were switched to ENVARSUS® XR at an actual daily dose conversion ratio that was 67% to 80% of the Prograf dose, the mean steady state tacrolimus AUC values were comparable between African-American and non-African American patients (Table 33). This PK finding suggests that it would not be necessary to tailor the ENVARSUS® XR dose conversion factor in stable kidney transplant patients by race. The reviewer notes that prior to conversion, the African-American patients in this study were already receiving a mean Prograf daily dose that was approximately 2-fold higher than their non-African American counterparts (10.7 ± 5.4 mg versus 5.0 ± 2.8 mg). Seven days after stable Prograf dosing, the *dose-normalized* tacrolimus AUC_{0-24h} and C_{trough} of AAs were both ~30% lower than non-AAs.

Table 33. Tacrolimus Pharmacokinetic Parameters after 7 days of fixed dosing with Prograf BID and 7 to 14 days following conversion to ENVARSUS® XR QD – Study 2011 (African Americans versus Non-African Americans)

Parameter	Geometric Mean (%CV)					
	Arithmetic Mean ± SD					
	African Americans/Blacks			Non-African Americans/Non-Blacks		
	Prograf Capsules twice-daily	ENVARSUS® XR Tablets once-daily		Prograf Capsules twice-daily	ENVARSUS® XR Tablets once-daily	
Day 7 (n=20)	Day 14 (n=20)	Day 21 (n=19)	Day 7 (n=27)	Day 14 (n=27)	Day 21 (n=27)	
AUC _t ^a (ng·hr/mL)	242.19 (24.78) 250.12 ± 61.98	204.13 (32.48) 214.78 ± 69.77	216.93 (39.32) 231.41 ± 90.99	192.28 (19.32) 195.64 ± 37.79	208.78(27.32) 216.40 ± 59.11	203.68 (21.98) 208.62 ± 45.86
C _{max} (ng/mL)	21.72 (41.29) 23.73 ± 9.80	13.89 (41.05) 15.20 ± 6.24	14.48 (48.92) 15.91 ± 7.78	15.15 (27.81) 15.74 ± 4.38	11.79 (24.56) 12.14 ± 2.98	12.14 (27.91) 12.55 ± 3.50
C _{trough} (ng/mL)	7.43 (21.57) 7.62 ± 1.64	6.21 (37.53) 6.62 ± 2.49	6.68 (38.83) 7.09 ± 2.75	6.41 (19.98) 6.54 ± 1.31	6.88 (30.70) 7.20 ± 2.21	6.60 (25.79) 6.84 ± 1.76
C _{avg} (ng/mL)	10.09 (24.78) 10.42 ± 2.58	8.51 (32.49) 8.95 ± 2.91	9.04 (39.32) 9.64 ± 3.79	8.01 (19.31) 8.15 ± 1.57	8.70 (27.32) 9.02 ± 2.46	8.49 (21.98) 8.69 ± 1.91
T _{max} (hr) ^b	1.91 (0.50- 24.00)	4.00 (1.00- 12.00)	6.00 (1.50- 16.00)	1.52 (0.50 – 13.48)	6.00 (2.00- 16.00)	7.87 (1.53- 12.05)
Degree of Fluctuation(%)	145.87 ± 60.72	94.99 ± 54.11	91.42 ± 63.47	113.74 ± 51.53	57.13 ± 28.34	66.92 ± 37.20
Degree of Swing (%)	212.69 ± 108.38	138.16 ± 91.69	135.87 ± 114.34	146.30 ± 70.76	76.61 ± 46.88	91.92 ± 62.46
C _{max} /C _{trough}	3.13 ± 1.08	2.38 ± 0.92	2.36 ± 1.14	2.46 ± 0.71	1.77 ± 0.47	1.92 ± 0.62

^a t=24 hours; ^b median (minimum – maximum); Source: NDA Study 2011CSR (Tables 12 and 13)

Healthy subjects

Study 1016 (Relative Bioavailability vs Prograf BID)

Study 1016 is a two-way crossover, single dose and multiple dose, relative BA study of ENVARSUS® XR1mg QD versus Prograf 0.5 mg BID in healthy male/female *Caucasian* subjects. Table 34 provides the statistical comparison of the PK parameters obtained on Day 10. Figure 53 shows the time course of the mean tacrolimus concentrations, by treatment.

In the 15 healthy Caucasian subjects with paired PK data in Phase 1 Study 1016, the steady state systemic AUC₀₋₂₄ and C₂₄ of ENVARSUS® XR 1 mg Tablets (q.d.) was ~ 52% and 64% higher, respectively, than that of Prograf® 0.5 mg Capsules (b.i.d.). The relative bioavailability data in this Phase 1 study suggest that the total tacrolimus daily dose should be approximately 25% lower in ENVARSUS® XR than Prograf patients (i.e., Caucasians) in Phase 2 and 3 clinical trials.

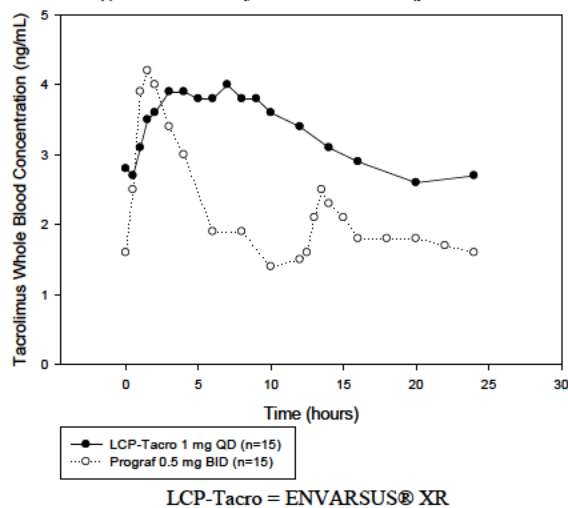
Table 34. Tacrolimus Pharmacokinetic Parameters of ENVARSUS® XR QD and Prograf BID after 10 days of dosing in 15 Healthy Caucasian Subjects under Fasting Conditions (Study 1016)

Pharmacokinetic Parameter	Geometric Mean (%CV) Arithmetic Mean ± SD		Geometric Mean Ratio (90% CI)
	ENVARSUS® XR™ 1 mg Tablets (q.d.) (n=15)	Prograf® 0.5 mg Capsules (b.i.d.) (n=15)	
AUC _T (ng·hr/mL)	73.0 (40.3) 78 ± 31.4	48.42 (32.5) 50.6 ± 16.5	1.51 (1.33 -1.68)
C _{max} (ng/mL)	4.49 (38) 4.8 ± 1.82	4.42 (22.7) 4.54 ± 1.03	1.02 (0.88 - 1.15)
C ₂₄ (ng/mL)	1.44 (48.8) 2.65 ± 1.29	1.5 (40.2) 1.59 ± 0.64	1.63 (1.41 - 1.84)
T _{max} (hr)*	5 (1.5 - 9)	1.55 (1 - 8)	NC

* median (min - max); n=15 subjects with paired comparison

NC - not calculated

Figure 53. Mean Tacrolimus Whole Blood Concentration – Time over 24 hour Profiles of ENVARSUS® XR QD and Prograf BID on Day 10 of dosing in 15 Healthy Caucasian Subjects under Fasting Conditions (Study 1016)



Study 1017 (Relative Bioavailability vs Astagraf XL QD)

Study 1017 is a two-way crossover, single dose and multiple dose, relative BA study of ENVARSUS® XR 2mg tablets QD versus Astagraf XL 2 x 1 mg capsules QD in healthy male *Caucasian* subjects. Table 35 shows the tacrolimus PK parameters and the statistical comparison of ENVARSUS® XR versus Astagraf XL after 1 day dosing and after 10 days of daily dosing. Figure 54 shows the time course of the mean tacrolimus concentrations, by treatment.

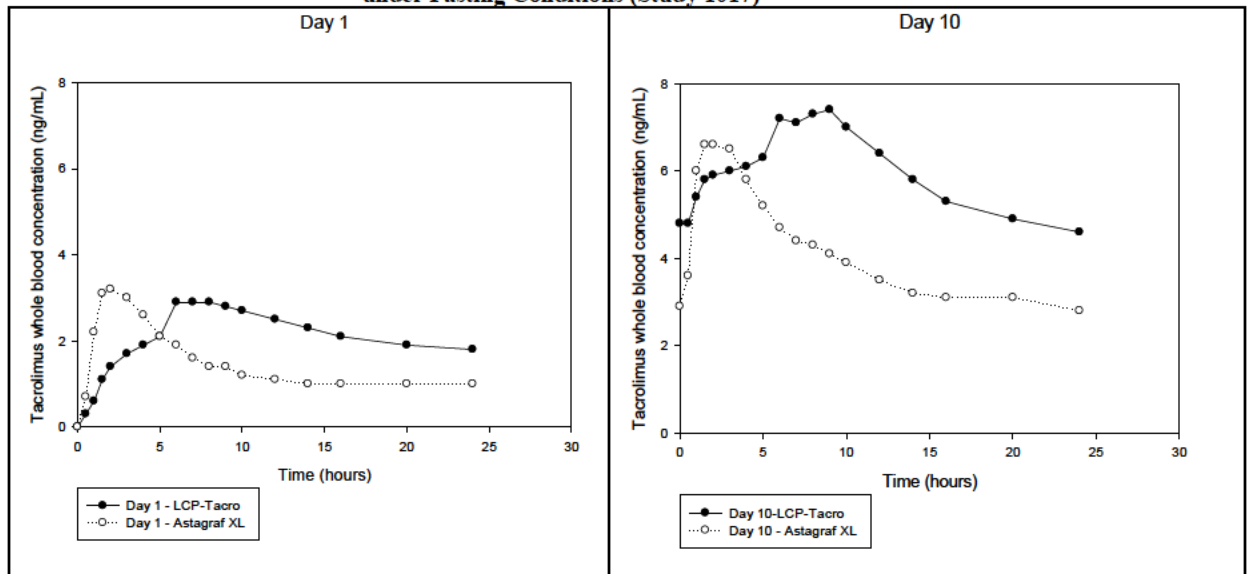
In the 19 healthy male Caucasian subjects with paired PK data for both Days 1 and 10, both the Day 1 and the Day 10 (steady state) AUC over the dosing interval period of 24 hours of ENVARSUS® XR 2 mg Tablets (q.d.) were 45% higher, and the C₂₄ were 60 to 90% higher than that of an equivalent dose of Astagraf XL 1 mg Capsules (q.d.).

Table 35. Tacrolimus Pharmacokinetic Parameters of ENVARSUS®XR QD and Astagraf XL QD after 1 day and 10 days of dosing in 19 Healthy Male Caucasian Subjects under Fasting Conditions (Study 1017)

Pharmacokinetic Parameter	DAY 1		Geometric Mean Ratio (90% CI)
	Geometric Mean (%CV) Arithmetic Mean ± SD		
	ENVARSUS® XR™ 2 mg Tablets (q.d.) (n=19)	Astagraf XL 1 mg Capsules #2(q.d.) (n=19)	
AUC ₀₋₂₄ (ng·hr/mL)	48.2 (27.9) 49.9 ± 14.0	33.3 (28.3) 34.4 ± 9.8	1.45 (1.24 – 1.66)
C _{max} (ng/mL)	11.4 (32) 11.9 ± 3.8	10.3 (27.2) 10.6 ± 2.9	1.11 (1.0 – 1.22)
C ₂₄ (ng/mL)	1.7 (31.5) 1.8 ± 0.6	0.91 (41.3) 0.97 ± 0.4	1.91 (1.54 – 2.28)
T _{max} (hr)*	14 (5.5 – 28)	5 (2.5 – 9)	NC
Pharmacokinetic Parameter	DAY 10		Geometric Mean Ratio (90% CI)
	Geometric Mean (%CV) Arithmetic Mean ± SD		
	ENVARSUS® XR™ 2 mg Tablets (q.d.) (n=19)	Astagraf XL 1 mg Capsules #2(q.d.) (n=19)	
AUC _T (ng·hr/mL)	132 (36) 140.2 ± 49.9	90.9 (30) 95.3 ± 28.5	1.45 (1.30 – 1.60)
C _{max} (ng/mL)	7.8 (36) 8.3 ± 2.9	6.9 (28) 7.1 ± 2.0	1.14 (1.02 – 1.27)
C ₂₄ (ng/mL)	4.3 (38) 4.6 ± 1.7	2.7 (35) 2.8 ± 1.0	1.61 (1.14 – 1.81)
T _{max} (hr)*	8 (1 – 12)	2 (1 – 6)	NC

* median (min – max); n=19 subjects with paired comparison
NC – not calculated

Figure 54. Mean Tacrolimus Whole Blood Concentration – Time over 24 hour Profiles of ENVARSUS® XR QD and Astagraf XL QD on Day 1 and Day 10 of dosing in 19 Healthy Caucasian Subjects under Fasting Conditions (Study 1017)

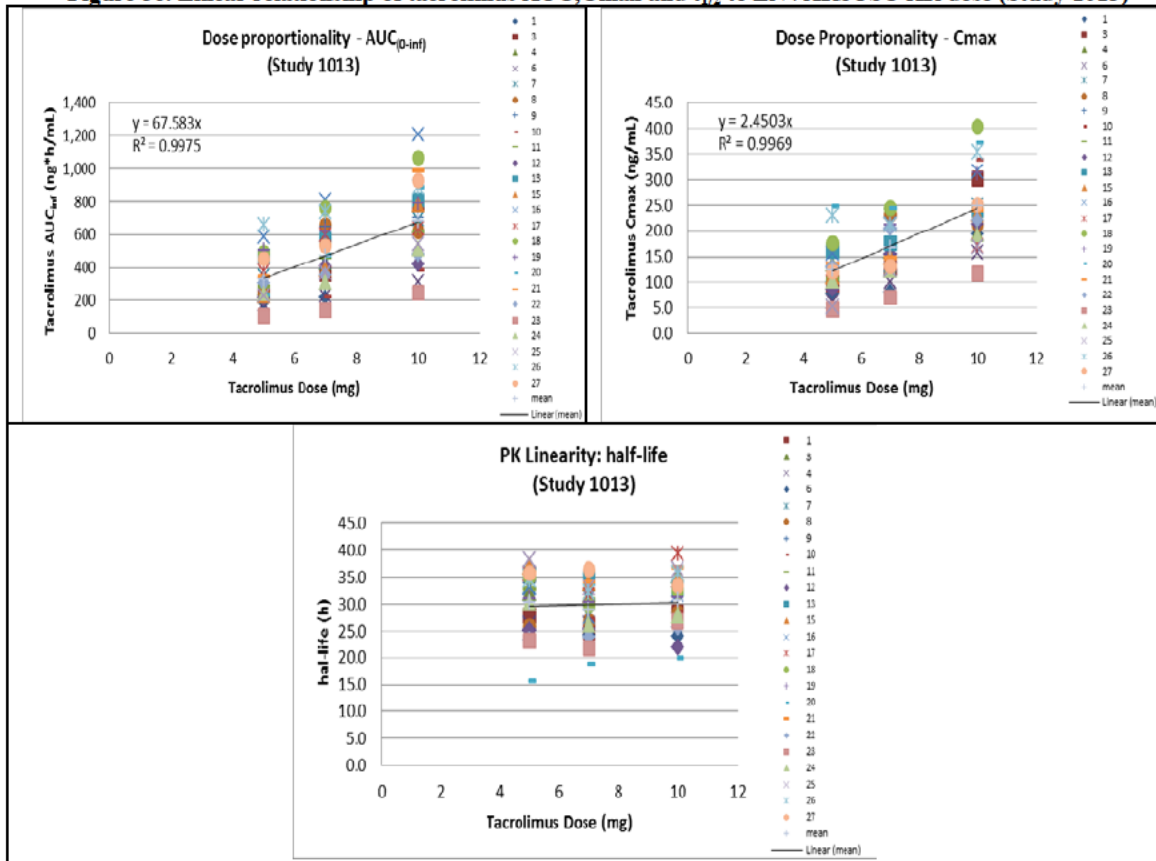


LCP-Tacro = ENVARSUS® XR

Study 1013 (Dose proportionality/PK Linearity)

In healthy subjects who received single doses of ENVARSUS® XR 5 mg, 7 mg, and 10 mg in a crossover fashion (Study 1013), there was a linear relationship between LCP-Tacro (ENVARSUS® XR) dose and tacrolimus AUC_(0-inf) and C_{max} (Figure 55.) Additionally, the elimination half-lives did not vary as a function of tacrolimus dose.

Figure 56. Linear relationship of tacrolimus AUC, C_{max} and t_{1/2} to ENVARSUS® XR dose (Study 1013)



*Analysis includes 24 healthy subjects with a complete set of PK parameters for all three doses.
LCP-Tacro = ENVARSUS® XR

C. Intrinsic Factors

1. What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response and what is the impact of any differences in exposure on efficacy or safety responses?

Race

A limited number of African-American/Black *de novo* kidney transplant patients were included in the Phase 2 and 3 clinical trials of ENVARSUS® XR; the PK parameters in these patients were highly variable. The available PK data do not support recommending a race-based ENVARSUS® XR starting dose for *de novo* kidney transplant patients nor a race-based daily dose conversion factor for stable kidney transplant patients switched from Prograf to ENVARSUS®XR.

Consistent with the labeling of already approved tacrolimus immediate release and extended release products, African-American *de novo* kidney transplant patients may need to be titrated to higher tacrolimus doses in order to achieve tacrolimus whole blood trough concentrations that are comparable to that achieved in non-African American/non-Black patients.

Hepatic Impairment

No PK study was conducted with ENVARSUS® XR in subjects with hepatic impairment. Based on the labeling of approved tacrolimus immediate release and extended release products, lower starting doses of tacrolimus are recommended for patients with severe hepatic impairment (i.e., Child Pugh score > 10) but not patients with mild hepatic impairment.

2. **Based upon what is known about exposure-response relationships and their variability, and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.**

a) **elderly**

No adjustment in starting ENVARSUS® XR dose is recommended for elderly patients. However, frequent monitoring of tacrolimus whole blood trough concentrations in elderly patients is recommended to determine whether dosage titration is needed.

b) **pediatric patients; Also- what is the status of pediatric studies and/or any pediatric plan for study?**

(b) (4)
Since ENVARSUS® XR was granted an orphan designation, PREA does not apply and a Pediatric Study Plan (PSP) is not required. (b) (4)

c) **gender**

None.

d) **race, in particular differences in exposure and/or response in Caucasians, African-Americans and/or Asians**

See C.1 above.

e) **renal impairment**

No PK study was conducted with ENVARSUS® XR in subjects with renal impairment. Per the labeling of approved tacrolimus products: Due to the nephrotoxic potential of tacrolimus, renal function of patients should be monitored; tacrolimus dosage should be reduced if indicated.

f) **hepatic impairment**

See C.1 above.

g) **what pharmacogenetics information is there in the application and is it important or not**

None.

h) **what pregnancy and lactation use information is there in the application?**

Per the labeling of approved tacrolimus products: Tacrolimus is transferred across the placenta.

i) **other human factors that are important to understanding the drug's efficacy and safety**

1. **What is the effect of administering ENVARSUS® XR in the morning vs. evening?**

Administration of ENVARSUS® XR tablets in the evening resulted in a 15% lower AUC_{0-inf} , a 20% lower C_{24} , and a 10% higher C_{max} when compared to morning dosing. ENVARSUS® XR should be taken once daily consistently at the same time of the day, preferably in the morning for maximal tacrolimus exposures. The pharmacokinetic parameters for tacrolimus following evening dosing and following morning dosing of ENVARSUS® XR (2 mg) tablets are compared in Table 36. The relative bioavailability analysis results for AUC_{0-4} , AUC_{0-inf} , AUC_{0-12} , AUC_{0-24} , $AUC_{\%Extrap}$, C_{max} , C_{12} , and C_{24}

are summarized in Table 36A. Note that the 90% CI of the (evening –to-morning) ratios of the geometric means of tacrolimus AUC_{0-t}, AUC_{0-inf}, and C₂₄ were below 80%.

According to the protocol of Study 3002, study drug was to be administered on a consistent schedule with regard to time of day and in relation to meals. It was highly recommended that patients take assigned study drug either at least 1 hour before or 2 hours after the morning/evening meal. Patients needing to take study drug with meals may have done so, but were to follow a consistent routine each day. The protocol also stated that the first study drug dose must be given as a morning dose (before noon) no later than 24 to 48 hours following transplantation.

According to the protocol of Study 3001, ENVARSUS® XR was to be administered orally once daily in the morning, with an interval of 24 hours (± 1 hour) between doses. It was recommended that patients take ENVARSUS® XR tablets either at least 1 hour before or 2 hours after the morning meal. Patients accustomed to taking tacrolimus with meals who continue to do so should follow a consistent routine each day.

Table 36. Pharmacokinetic Parameters for Tacrolimus: evening versus morning dosing (Study 1014)

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD	
	ENVARSUS® XR 2 mg Tablets (evening dose at 20:00)	ENVARSUS® XR 2 mg Tablets (morning dose at 08:00)
AUC _{0-t} (ng·hr/mL)	88.20 (36.40) 94.52 ± 34.41	102.74 (37.14) 112.46 ± 41.77
AUC _{0-inf} (ng·hr/mL)	99.30 (33.62) 105.39 ± 35.43 [†]	119.32 (31.35) 126.85 ± 39.77 [‡]
AUC ₀₋₁₂ (ng·hr/mL)	26.87 (29.38) 28.17 ± 8.28	28.49 (30.81) 29.85 ± 9.20
AUC ₀₋₂₄ (ng·hr/mL)	48.34 (29.19) 50.51 ± 14.75	51.65 (30.82) 54.50 ± 16.80
C _{max} (ng/mL)	4.21 (27.63) 4.39 ± 1.21	3.97 (34.71) 4.20 ± 1.46
C ₁₂ (ng/mL)	2.33 (39.29) 2.54 ± 1.00	2.37 (43.18) 2.66 ± 1.15
C ₂₄ (ng/mL)	1.24 (38.81) 1.34 ± 0.52	1.53 (39.72) 1.69 ± 0.67
T _{max} (hr)*	6.00 (2.00 - 14.00)	6.00 (1.50 - 12.00)
t _{1/2} (hr)	26.83 ± 5.18 [†]	28.20 ± 5.03 [‡]
K _{el} (hr ⁻¹)	2.68E-02 ± 5.60E-03 [†]	2.54E-02 ± 4.71E-03 [‡]
CL/F (L/hr)	21.52 ± 8.45 [†]	18.35 ± 10.32 [‡]

* median (min – max); [†] n = 25; [‡] n = 24
(Source: NDA 1014 CSR. Table 11.4.1)

Table 36A. Statistical Comparison of Tacrolimus PK Parameters of ENVARSUS® XR 2 mg Tablets (evening dose at 20:00) (A) versus ENVARSUS® XR 2 mg Tablets (morning dose at 08:00) (B) [Study 1014]

Parameter	90%	Ratio of Means
AUC _{0-t}	72.16% to 104.43%	86.81%
AUC _{0-inf}	71.62% to 101.28%	85.17%
AUC ₀₋₁₂	86.15% to 111.35%	97.95%
AUC ₀₋₂₄	84.25% to 108.65%	95.68%
C _{max}	95.32% to 126.14%	109.65%
C ₁₂	81.71% to 120.56%	99.25%
C ₂₄	65.43% to 99.64%	80.74%

(Source: NDA 1014 CSR. Table 11.4.2)

2. What is the recommendation for managing a missed dose of ENVARSUS® XR?

The applicant proposed that missed dosing with LCP-Tacro could be mitigated by (b) (4)
To support this proposal, The

Applicant provided simulations considering the following scenarios for handling missed dosing for subjects with trough tacrolimus concentrations ranging between 6 to 12 ng/mL:

- (a) Perfect compliance of Prograf (dose taken every 12 hours) and LCP-Tacro (dose taken every 24 hours).
- (b) A missed LCP-Tacro dose at t=0 with no make-up dose.
- (c) A missed dose at t=0 with a double taken at t=24 hours and a single dose taken at t=48.
- (d) A missed dose at t=0, a make-up dose taken at 21 hours and normal doses taken at t=24 hours and t=48.
- (e) A missed dose at t=0, a make-up dose taken at 18 hours and normal doses taken at t=24 hours and t=48.
- (f) A missed dose at t=0, a make-up dose taken at 15 hours and normal doses taken at t=24 hours and t=48.

From these analyses the applicant observed that doubling the dose at 24 hours after a missed dose result in prolonged elevation of tacrolimus concentrations over the following dosing interval. In contrast, missing a dose completely results in under exposure over an 8-12 hour window following the missed dose. Taking a missed dose at 15, 18, or 21 hours reduced the window over which tacrolimus exposures may be less than the therapeutic window, but subsequently resulted in tacrolimus exposures on the following day that exceed that of the scenario where the dose is doubled. None of the proposed approaches will simultaneously maintain a patient within the therapeutic range. As the benefit risk of low tacrolimus exposures versus high tacrolimus exposures for a short period of time is unknown, it is not possible to evaluate the trade-off between these scenarios.

The Pharmacometrics reviewer evaluated alternative scenarios involving a half-dose of tacrolimus between the 15-24 hour window following a missed dose as a means of maintaining tacrolimus levels within the therapeutic range, with a full dose administered at the subsequent dosing interval. While such an approach offers a mathematical solution to maintaining tacrolimus levels within the therapeutic range, the solution was rejected as: i) half-dose increments of tacrolimus may not be available to a patient based on the available formulation strengths; ii) labeling of half-dosing may lead to confusion in usage and further impact maintaining tacrolimus levels within the therapeutic range; iii) the proposed morning dosing would imply that 15-24 hours post-missed dose are during hours when patients are likely to be sleeping and wouldn't note that a tacrolimus dose has been missed.

Given the provided simulations, simulations evaluated by the Pharmacometrics reviewer, and proposed labeling for other tacrolimus products, the reviewer recommends the dosing for a missed dose should be to take the dose as normal if it is within 14 hours of when the dose should have been administered. Otherwise, wait until the next dosing interval and take that dose as normally. In addition, doubling of the tacrolimus at the next dosing time as a means of managing the missed dose should not be recommended. These dosing recommendations are similar to those determined in the clinical pharmacology review for Astagraf XL (NDA 204096; 6/13/2013).

D. Extrinsic Factors

1. What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response and what is the impact of any differences in exposure on response?

Based on the findings of *in vitro* studies, alcohol increased tacrolimus dissolution but did not induce dose dumping from ENVARSUS® XR tablets (see Biopharmaceutics review). Thus, ENVARSUS® XR treated patients should avoid alcohol consumption.

2. Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

3. Drug-Drug Interactions

a) is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

Tacrolimus is a CYP3A substrate. Co-administered drugs that inhibit or induce CYP3A-mediated metabolism may alter tacrolimus concentrations.

b) is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Tacrolimus is a CYP3A substrate. There are literature reports suggesting that CYP3A5 polymorphism may influence the metabolism of tacrolimus. However, in clinical practice, tacrolimus dosing is already being individualized via therapeutic drug monitoring. Note that the sponsor plans to conduct Study 3004 to investigate the steady state PK of tacrolimus in African-American stable kidney transplant patients receiving ENVARSUS® XR tablets or generic tacrolimus; all study participants will be genotyped for CYP3A5 allelic variants.

c) is the drug an inhibitor and/or an inducer of CYP enzymes?

No.

d) is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

No.

e) are there other metabolic/transporter pathways that may be important?

None.

f) does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

In addition to ENVARSUS® XR, the *de novo* or stable kidney transplant patients in the Phase 2 and Phase 3 clinical trials also received other immunosuppressive drugs including mycophenolate (MMF or MPS), corticosteroids, with or without antibody induction. No drug-drug interaction studies were conducted specifically for ENVARSUS® XR but the package insert will include information (mentioned in the labeling of other approved tacrolimus products) regarding the potential alteration in mycophenolate concentrations when MMF or MPS is co-administered with tacrolimus, as well as in tacrolimus concentrations when methylprednisolone is coadministered with tacrolimus.

g) what other co-medications are likely to be administered to the target patient population?

Commonly used concomitant medications include those used to treat common side-effects [including new-onset diabetes after transplant (NODAT), nephrotoxicity, neurotoxicity], and to prevent infections after surgery.

h) are there any *in vivo* drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

In an *in vivo* study, repeated dosing with methylprednisolone was shown to decrease triazolam exposures. Since tacrolimus is a CYP3A substrate, the current labeling of approved tacrolimus products suggest monitoring patients for potentially reduced tacrolimus exposures when co-administered with methylprednisolone. Additional potential interactions with other coadministered drugs as mentioned in the package insert of approved tacrolimus products will be included in the labeling of ENVARSUS® XR.

i) is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

Since tacrolimus has potential to induce QT prolongation, nephrotoxicity, neurotoxicity and other adverse events, caution should be exercised when tacrolimus is used concomitantly with drugs that exhibit the same toxicity potential.

j) are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

None

- k) **What issues related to dose, dosing regimens or administration are unresolved, and represent significant omissions?**
None

E. General Biopharmaceutics

The sponsor developed various formulations and tablet strengths during clinical development. Formulation G is the to-be-marketed formulation with three tablet strengths (0.75 mg, 1 mg, and 4 mg). Formulation D (0.5 mg, 1 mg, 2 mg, 5 mg) and Formulation F (0.75 mg, 1 mg and 4 mg, with matching placebo) were used in the pivotal Phase 3 trials 3001 and 3002, respectively. Formulation G was used in a non-pivotal Phase 3b trial 3003. See the schematic diagram (Figure 56) below from the Biopharmaceutics reviewer (Dr. Banu Zolnik) for the overview of all the formulations and bioequivalence (BE) studies conducted to bridge these various formulations. At the time of the Pre-NDA meeting, it was determined by FDA that an *in vivo* BA/BE study between Formulations D and G would not be needed in view of the comparable *in vitro* dissolution profiles and chemical compositions between Formulations D and G and the demonstration of an indirect *in vivo* BA/BE link, unless the indirect bioequivalence claim between Formulation D and F could not be confirmed and/or “biocreep/biodrift” concerns arise during the NDA review.

BE study 1024 was also conducted to bridge the 4 mg and the 1 mg strengths of Formulation F. A biowaiver to demonstrate bioequivalence was requested for lower strengths (0.75 mg and 1 mg) since they are qualitatively the same and quantitatively dose-proportional to the highest strength (4 mg).

Note that Formulation B was used for the food-effect study. At the time of the Pre-NDA meeting with FDA, it was determined that an *in vitro* dissolution or another food effect study with Formulation G may need to be conducted if there was a substantive (i.e. SUPAC Level 3) change between Formulations B and G.

At the time of NDA filing, the Biopharmaceutics reviewer recommended to the sponsor the use of dissolution to monitor potential crystallization of (b) (4) tacrolimus which could impact bioavailability.

Figure 56

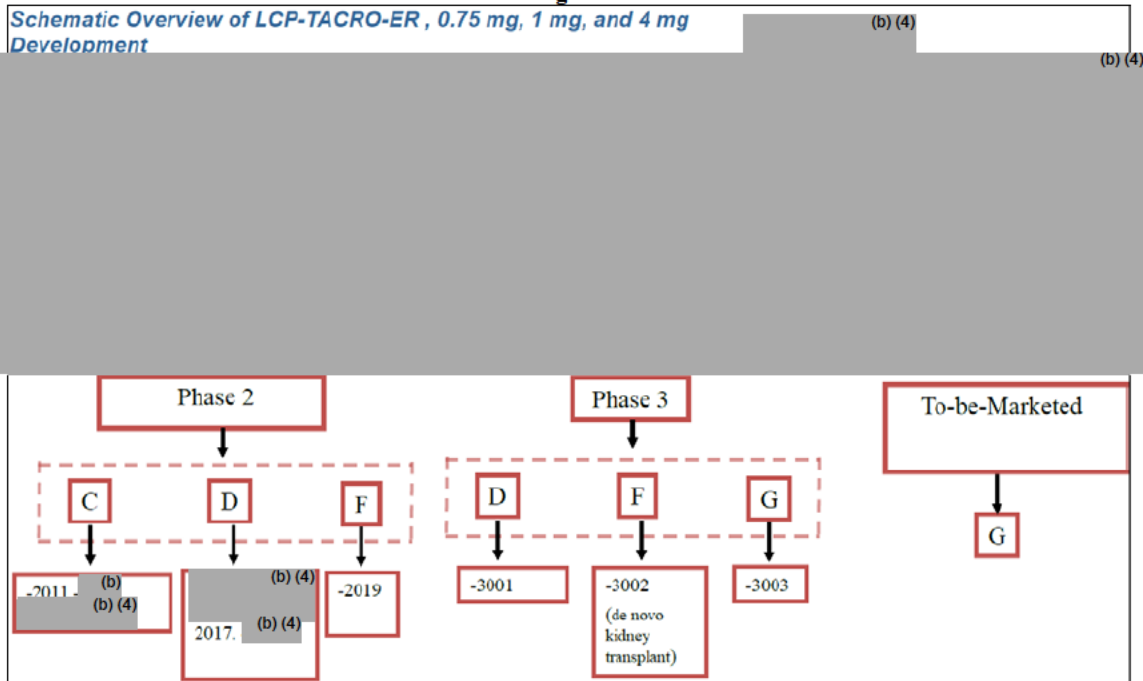


Diagram adapted from the FDA Biopharmaceutics Filing Review of Dr. Banu Zolnik; LCP-Tacro-ER = ENVARSUS® XR

1. Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

See the Biopharmaceutics review of the NDA.

2. What is the relative bioavailability of the proposed to-be-marketed formulation to that used in the pivotal clinical trial?

a) What data support or do not support a waiver of *in vivo* BE data?

- BCS classification system
- formulation ingredient information
- dissolution profiles
- others

See the Biopharmaceutics review of the NDA.

b) what are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

See the Biopharmaceutics review of the NDA.

c) if the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

Bioequivalence Studies 1022 and 1023 were conducted to bridge the 2 mg and the 4 mg tablet strengths, respectively, of Formulation F (used in the pivotal Phase 3 clinical trials) to Formulation G (the to-be-marketed product). Based on the Biopharmaceutics reviewer's assessment of Study 1023, Formulations F and G appear to be bioequivalent.

Formulation G (0.75 mg, 1 mg, 4 mg) was used in the non-registration/non-pivotal open-label Phase 3 clinical trial (Study 3003) involving stable kidney transplant patients 1 month to 5 years post-transplant at screening, and taking a stable dose of Prograf or generic twice daily for at least 7 days with tacrolimus trough concentration within 3 – 12 ng/mL. After receiving Prograf/generic twice daily for another 7 days, patients were switched to ENVARSUS® XR once daily at a daily dose conversion rate equivalent to 70% of the previous total daily dose Prograf/generic for non-African-Americans (85% for African-Americans), as per the starting dosage instructions in Study 3001. [Note however that there were only 4 African American patients in the MITT population.] Patients were instructed to ingest ENVARSUS® XR tablets whole in the morning (before noon) either at least 1 hour before or 2 hours after a meal, and to either avoid consumption of grapefruit or grapefruit juice or consume the same amount at the same time of the day for the duration of the study participation. Tacrolimus whole blood trough concentrations after 7-day dosing with Prograf® and with ENVARSUS® XR were to be maintained within the target range of 3 – 12 ng/mL; measurements were made on Visit Days 1, 7, and 14. Dosage adjustment was not permitted during the Prograf/generic phase but was allowed at an unscheduled visit per clinical practice during the ENVARSUS® XR dosing phase.

As was observed for pivotal Study 3001, the tacrolimus whole blood trough concentrations were similar pre-conversion and post-conversion to ENVARSUS® XR once daily (Table 37). Only 1 (2.4%) patient needed dosage adjustment on day 4 after conversion to ENVARSUS® XR. Also, the “steady state” tacrolimus whole blood trough concentration (C_{trough}) range attained in this study (3 – 15.5 ng/mL) is comparable to the pre-specified target range in Study 3001 (4 – 15 ng/mL).

Table 37. Tacrolimus whole blood trough concentrations before and after conversion from Prograf/generic immediate release tacrolimus twice daily to ENVARUSUS® XR once daily in stable kidney transplant patients ≥ 1 month post-transplant; daily dose conversion factor 1: 0.7 for non-African Americans; 1: 0.85 for African Americans (Study 3003)

	Prograf / generic tacrolimus		LCP-Tacro
	Day 1	Day 7	Day 14
Safety Population			
n	44	43	40
Mean (SD) (ng/mL)	6.70 (1.828)	6.53 (2.345)	6.12 (2.638)
Median	6.50	6.20	5.45
Min, Max	3.5, 10.6	2.5, 11.9	3.0, 15.5
mITT Population			
n	38	38	38
Mean (SD)	6.73 (1.912)	6.61 (2.320)	5.92 (2.404)
Median	6.55	6.25	5.15
Min, Max	3.5, 10.6	3.3, 11.9	3.0, 15.5

Source: Study 3003 CSR (Table 15)

3. What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Food significantly reduced both AUC and C_{max} of tacrolimus after the administration of ENVARUSUS® XR 5 mg Tablets. As expected for extended release products, ENVARUSUS® XR 5 mg Tablets produced overall similar AUC but statistically significantly lower C_{max} with delayed T_{max} relative to the immediate release product Prograf®. Table 38, Table 38A, and Figure 57 compare the tacrolimus PK parameters and whole blood concentrations of ENVARUSUS® XR when administered under fasted conditions versus when administered with a high-fat meal and versus Prograf when administered under fasted conditions.

According to the protocol of Study 3002, study drug was to be administered on a consistent schedule with regard to time of day and relation to meals. It was highly recommended that patients take assigned study drug either at least 1 hour before or 2 hours after the morning/evening meal. Patients needing to take study drug with meals may do so, but should follow a consistent routine each day. Note that on the mornings when trough level measurements of tacrolimus will be taken, patients were not to eat breakfast and were not to take their morning dose of study drug until after the trough level blood sample had been drawn.

Table 38. Tacrolimus Pharmacokinetic Parameters following single 5 mg doses of ENVARUSUS® XR (fed), ENVARUSUS® XR (fasted), and Prograf (fasted) in Healthy Subjects (Study 1011)

Pharmacokinetic Parameters	Geometric Mean (%CV)		
	Arithmetic Mean ± SD		
	ENVARUSUS® XR 5 mg Tablet – Fed (A)	ENVARUSUS® XR 5 mg Tablet – Fasting (B)	Prograf® 5 mg Capsules – Fasting (C) (n=26)
AUC ₀₋₁₂ (ng·hr/mL)	46.88 (27.57) 48.72 ± 13.43	96.49 (25.66) 99.78 ± 25.61	130.40 (30.60) 137.59 ± 42.10
AUC ₀₋₂₄ (ng·hr/mL)	70.58 (28.39) 73.65 ± 20.91	153.10 (28.33) 159.10 ± 45.08	169.96 (31.35) 180.01 ± 56.43
AUC _{0-t} (ng·hr/mL)	131.56 (38.92) 141.85 ± 55.20	296.65 (35.72) 316.77 ± 113.14	292.05 (33.87) 313.41 ± 106.15
AUC _{0-inf} (ng·hr/mL)	145.58 (37.85) 155.83 ± 58.98	328.17 (32.81) † 344.76 ± 113.10	308.64 (34.46) 330.89 ± 114.03
C _{max} (ng/mL)	10.86 (33.83) 11.43 ± 3.87	13.73 (30.01) 14.31 ± 4.29	30.59 (27.73) 31.76 ± 8.81
T _{max} (hr)*	5.00 (1.67 - 9.00)	5.00 (1.67 - 8.00)	1.33 (1.00 - 2.00)
t _{1/2} (hr)	33.32 ± 6.40	35.12 ± 6.95 †	35.15 ± 8.39
K _{el} (hr ⁻¹)	2.15E-02 ± 4.06E-03	2.06E-02 ± 4.43E-03 †	2.05E-02 ± 3.81E-03

* median (min – max)

† n = 25 (excludes 1 subject with AUC_{extrap} greater than 20%)

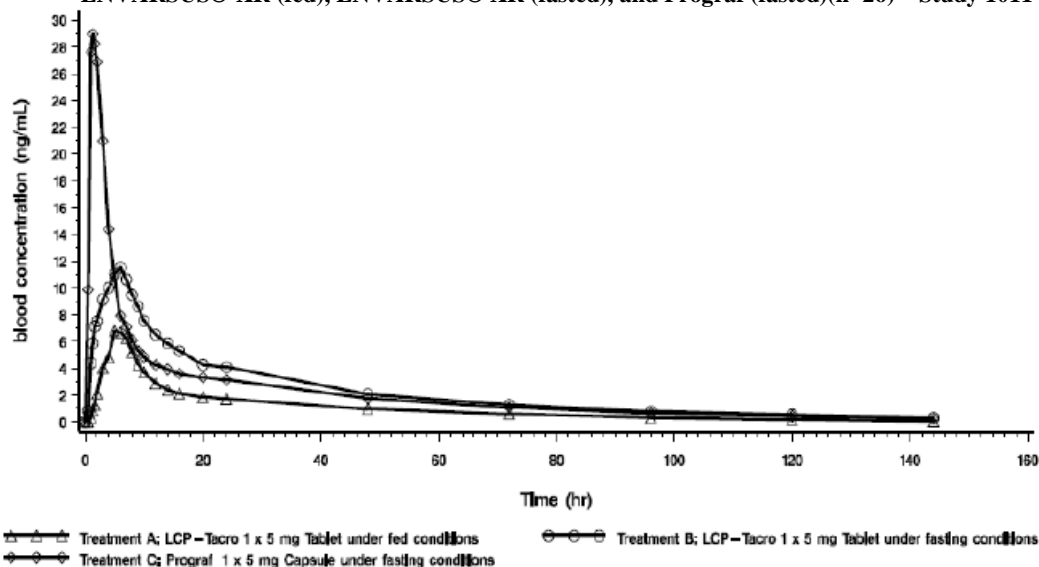
(Source: NDA Study 1011 CSR; Table 11.4.1)

Table 38A. Statistical Comparisons of Tacrolimus PK parameters in Healthy Subjects (Study 1011)

Parameter	Comparison of Treatments A and B:		
	90% C.I.	Ratio of Means	Intra-Subject CV
AUC ₀₋₁₂	44.24% to 52.35%	48.13%	18.19%
AUC ₀₋₂₄	41.83% to 49.82%	45.65%	18.92%
AUC _{0-t}	39.30% to 48.89%	43.83%	23.76%
AUC _{0-inf}	40.31% to 49.14%	44.50%	21.19%
C _{max}	69.92% to 87.96%	78.42%	24.99%
Parameter	Comparison of Treatments B and C:		
	90% C.I.	Ratio of Means	Intra-Subject CV
AUC ₀₋₁₂	68.68% to 81.25%	74.70%	18.19%
AUC ₀₋₂₄	83.36% to 99.29%	90.98%	18.92%
AUC _{0-t}	92.13% to 114.62%	102.76%	23.76%
AUC _{0-inf}	95.99% to 117.02%	105.98%	21.19%
C _{max}	40.34% to 50.75%	45.24%	24.99%

(Source: NDA Study 1011 CSR; Table 11.4.2)

Figure 57. Mean plasma concentrations of tacrolimus in healthy subjects following single doses of ENVARSUS®-XR (fed), ENVARSUS® XR (fasted), and Prograf (fasted)(n=26) – Study 1011



(Source: NDA Study 1011 CSR; Figure 11.4.1.); LCP-Tacro = ENVARSUS® XR

4. When would a fed BE study be appropriate and was one conducted?

A fed BE study was not conducted between ENVARSUS® XR once daily and Prograf twice daily. To ensure maximum possible (and consistent) exposure to tacrolimus, the labeling will recommend taking ENVARSUS® XR at least 1 hour before or 2 hours after the morning meal.

5. How do the dissolution conditions and specifications assure *in vivo* performance and quality of the product?

See the Biopharmaceutics review of the NDA.

6. If different-strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

There is evidence that in stable kidney transplant *patients*, the average values of measured tacrolimus C_{trough} following 1:0.8 conversion/switch from Prograf to the to-be-marketed ENVARSUS® XR formulation

(Formulation G; Study 3003) are comparable to pre-conversion levels, similar to what was observed in the pivotal Phase 3 study (Study 3001); see Section E.1.c of this NDA review.

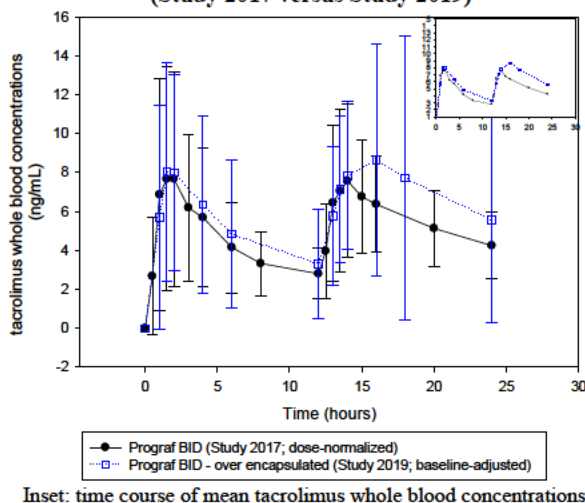
7. If the NDA is for a modified release formulation of an approved immediate product without supportive safety/efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

Not applicable. Clinical efficacy and safety trials were conducted to compare the proposed extended release formulation (ENVARUSUS® XR once daily) to the approved immediate release product (Prograf® twice daily).

8. If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either *in vitro* or *in vivo* data to evaluate BE?

In Phase 3 Study 3002, the double-blind, double-dummy study design required the over-encapsulation of Prograf® (active control) to match the placebo capsules received by the ENVARUSUS® XR group of *de novo* kidney transplant patients. Figure 58 compares the Day 1 tacrolimus concentration time profiles of Prograf BID in two Phase 2 studies involving *de novo* kidney transplant patients, i.e., Study 2019 (double-blind, double dummy) versus Study 2017 (open-label). Based on a cross-study comparison of the dose-normalized, baseline-adjusted tacrolimus concentration profiles of Prograf BID, over-encapsulation of Prograf® capsules to maintain the blind in Study 2019 (and thus, as well as in the pivotal Phase 3 Study 3002) did not appear to have negatively impacted (i.e., reduced) the exposures to tacrolimus. Note that Studies 2017, 2019, and 3002 used the same or similar versions of the validated LC/MS/MS assay for tacrolimus PK.

Figure 58. Time course of Mean $\pm$ SD tacrolimus whole blood concentration in *de novo* kidney transplant patients treated with two doses of Prograf® oral capsules 12 hours apart (Study 2017 versus Study 2019)



9. What other significant, unresolved issues related to *in vitro* dissolution or *in vivo* BA and BE need to be addressed?

See the Biopharmaceutics review of the NDA.

10. What is the effect of alcohol on the bioavailability of ENVARUSUS® XR and what labeling recommendations should be made regarding administration in relation to alcohol consumption?

Alcohol increased the dissolution of but did not induce dose-dumping tacrolimus from the ENVARUSUS® XR tablets. See the Biopharmaceutics review of the NDA. As recommended for other tacrolimus products, alcohol consumption should be avoided by patients taking ENVARUSUS® XR.

F. Analytical Section

1. How are the active moieties identified and measured in the blood in the clinical pharmacology and biopharmaceutics studies and the clinical trials?

In the clinical pharmacology studies, the tacrolimus concentrations in whole blood were measured using one of several versions of a validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) assay. For example, Assay T32 (version 03) was used for the samples of Study 2019. The basic LC/MS/MS method was described as follows:

Blood samples were kept frozen at $-70^{\circ}\text{C} \pm 10^{\circ}\text{C}$ until assayed. Tacrolimus and the internal standard, rapamycin, were extracted by protein precipitation and solid phase extraction from 0.30 mL of human whole blood. An aliquot of this extract was injected into a high performance liquid chromatography system and detected using a tandem mass spectrometer. The analytes were separated by reverse phase chromatography. Evaluation of this LC-MS/MS assay was carried out by the construction of an eight-point calibration curve (excluding zero concentration) which was validated with the concentration range of 0.200 to 25.600 ng/mL $\pm 10\%$ for tacrolimus in human whole blood. The slope and intercept of the calibration curves were determined through weighted linear regression analysis ($1/\text{conc}^2$). Two calibration curves and duplicate quality control (QC) samples (at three or four concentration levels, depending on the study) were analyzed along with each batch of the study samples. Peak area ratios were used to determine the concentration of the standards, QC samples, and the unknown study samples from the calibration curves. The lower limit of quantification (LLOQ) across most of the Phase 1 and Phase 2 studies was 0.200 ng/mL. *[The bioanalytical method was validated for precision and accuracy, linearity of the calibration curves, absolute recovery, selectivity, dilution integrity, carry over and matrix effects. Other validation experiments included the determination of interference with over-the-counter (OTC) drugs (including but not limited to caffeine, ibuprofen, salicylic acid, acetylsalicylic acid, acetaminophen, and nicotine) and oral contraceptives. No interfering peaks were observed with any of the tested analytes.]*

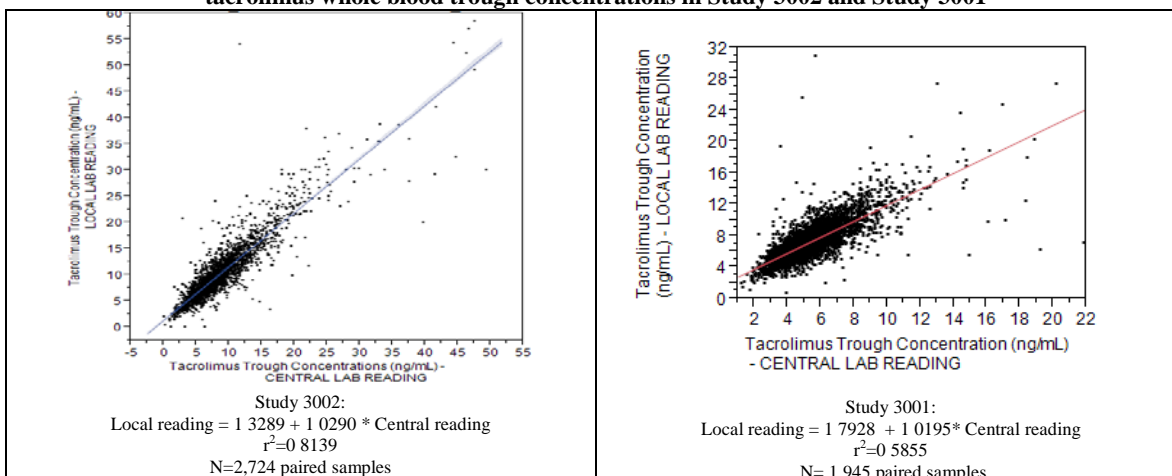
In Phase 3 Studies 3002 and 3001, tacrolimus dosage was titrated to maintain the trough concentrations within the protocol-specified target range based on tacrolimus whole blood trough concentrations measured using the local laboratory assay (i.e., 80% of the samples were assayed for tacrolimus concentrations using an immunoassay-based method). Aliquots of the blood samples were then shipped to the central laboratory ^{(b) (4)} for assay by a validated LC/MS/MS. The summary data of tacrolimus trough levels in the clinical study reports were based on the specimens as assessed by the central laboratory.

In Study 3002 and Study 3001, the tacrolimus trough concentrations measured by the local laboratories were numerically higher than the readings of the same samples by the central laboratory (Table 39); the correlation of the two laboratory readings in ENVARSUS® XR treated patients is described by the linear plots and equations in Figure 59.

Table 39. Tacrolimus Whole Blood Trough Level (ng/ml) – Local versus Central laboratory readings (paired samples in Study 3002) [Mean $\pm$ SD; median (10th – 90th percentile)]

	Number of paired samples	Local Laboratory	Central Laboratory
Study 3002			
ENVARSUS® XR	2724	10.3 $\pm$ 5.6 9.1 (5.1 – 16.4)	8.7 $\pm$ 4.9 7.7 (4.3 – 14.0)
Prograf	2862	8.4 $\pm$ 3.6 8.1 (4.4 – 12.7)	7.1 $\pm$ 3.3 6.6 (3.6 – 10.8)
Study 3001	Number of paired samples	Local Laboratory	Central Laboratory
ENVARSUS® XR	1945	7.31 $\pm$ 2.60 6.9 (4.6 – 10.5)	5.47 $\pm$ 2.02 5.12 (3.35 – 8.0)
Prograf	1913	7.39 $\pm$ 2.31 7 (5 – 10.2)	5.43 $\pm$ 1.7 5.16 (3.64 – 7.49)

Figure 59. Linear relationship between local laboratory readings and central laboratory readings of tacrolimus whole blood trough concentrations in Study 3002 and Study 3001



The performance characteristics of the validated LC/MS/MS assay used by the central laboratory to quantify tacrolimus in the whole blood samples obtained from the patients of Study 3002 and Study 3001 are summarized in the Table 40. The results for each validation parameter passed the pre-established acceptance criteria.

Table 40. Validation parameters of the HPLC/MS/MS assays used for measuring tacrolimus concentrations in the Phase 2 and Phase 3 clinical trials involving kidney transplant patients

Validation Parameter	Studies 3001, 3002, 2019	Study 2017 (revalidation)
Analyte (s)	tacrolimus	tacrolimus
Calibration range (ng/mL)	0.200 to 25.6 ± 10.0%	0.200 to 25.6 ± 10.0%
Accuracy (% RE): intra-assay inter-assay	-6.4 to 20.0 -6.3 to 8.0	-2.9 to 0.5 -4.9 to 0.4
Precision (% CV) intra-assay inter-assay	2.3 to 10.4 2.8 to 15.3	1.2 to 3.1 1.6 to 6.5
Recovery (%) tacrolimus internal standard (rapamycin)	88.4 84.8	88.4 84.8
Determination of Interference by OTC and OC	No significant interference with peak of internal standard nor with commonly used OTC medications (e.g., acetaminophen, ibuprofen, ASA, caffeine, dextromethorphan, loratidine, nicotine) and oral contraceptives	No significant interference with peak of internal standard nor with commonly used OTC medications (e.g., acetaminophen, ibuprofen, ASA, caffeine, dextromethorphan, loratidine, nicotine) and oral contraceptives
Freeze thaw stability	4 cycles at -70°C ± 10°C	4 cycles at -70°C ± 10°C
In Process stability	27.5 hours at room temperature	~ 24 hours at room temperature
Autosampler stability	73 hours at 7°C ± 4°C	69 hours at 4°C ± 4°C
Autosampler re-injection reproducibility	70 hours at 7°C ± 4°C	96 hours at 4°C ± 4°C
Processed sample integrity	76 hours at 4°C ± 4°C	Not available
Whole blood stability □ Without flash freezing □ Withflash freezing	2.5 hours at 4°C ± 4°C 3 hours at 4°C ± 4°C	Not available
Matrix effect Long term stability matrix effect	No significant matrix effect 1003 days at -70°C ± 10°C 154 days at -25°C ± 10°C	No significant matrix effect 277 days at -70°C ± 10°C
Dilution integrity	Concentration diluted up to 8-fold	Concentration diluted up to 8-fold

RE – relative error; CV- coefficient of variation; OTC –over the counter; OC – oral contraceptives

Tacrolimus remained stable when stored for 24 hours at room temperature, in the autosampler extract for 69 hours at $4^{\circ}\text{C} \pm 4^{\circ}\text{C}$, and after three and four freeze-thaw cycles at $-70^{\circ}\text{C} \pm 10^{\circ}\text{C}$. There was no degradation observed after the stock solution was stored for 20 days at $-70^{\circ}\text{C} \pm 10^{\circ}\text{C}$ although there was some degradation (up to $\sim -10\%$) after storage at $-70^{\circ}\text{C} \pm 10^{\circ}\text{C}$ for 87, 109, and 277 days.

III. Detailed Labeling Recommendations

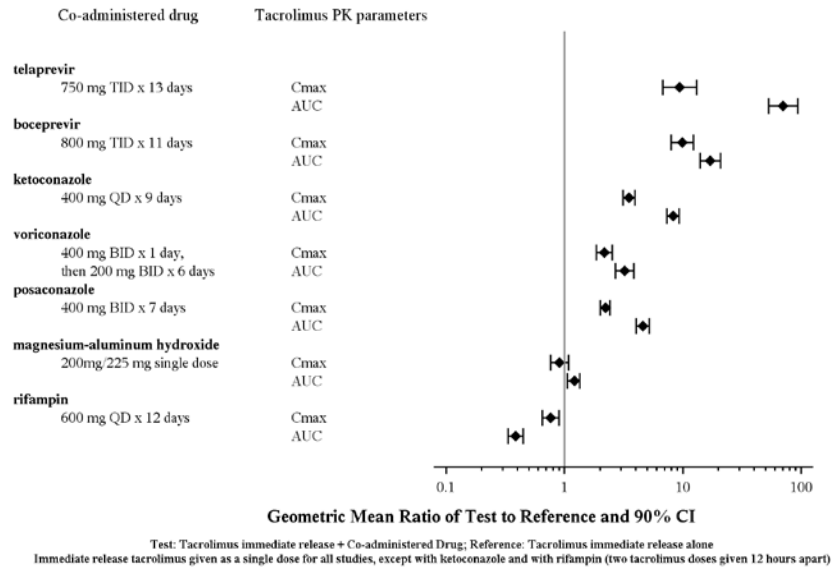
Under Dosage and Administration or Patient Counseling:

1. **Starting Dose for *de novo* kidney transplant patients.** The recommended starting dosage of ENVARSUS® XR is 0.14 mg/kg/day, administered once daily. Titrate dosage based on clinical factors and the attainment of target tacrolimus trough concentration ranges (to be defined in the labeling for different time periods based on the protocol of Phase 3 Study 3002).
2. **Dose for stable kidney transplant patients switched from immediate release oral product.** When switching stable kidney transplant patients from tacrolimus immediate release to ENVARSUS® XR, use a daily dose conversion ratio of 1:0.8. (Upon conversion, the ENVARSUS® XR daily dose should be 80% of the Prograf daily dose prior to conversion.) If needed, titrate the ENVARSUS® XR dosage to achieve tacrolimus C_{trough} within 4-11 ng/mL, preferably similar to the pre-conversion level.
3. **Therapeutic Drug Monitoring.** Based on the protocol of Study 3002, the recommended target tacrolimus whole blood trough concentration ranges are: 6-11 ng/mL during the first 30 days, then 4-11 ng/mL. The time to achieve tacrolimus steady state is usually 7 days. Higher ENVARSUS® XR starting dosages (e.g., ≥ 0.17 mg/kg/day or ≥ 15 mg once daily) may result in attainment of higher than expected initial tacrolimus trough concentrations. Monitoring of tacrolimus trough concentrations should be frequent during the first 7 days after ENVARSUS® XR dosage initiation, after a dosage change, or after introduction or removal of drugs that are CYP3A inhibitors or inducers.
4. **Administration Instructions.**
 - Take the first dose of ENVARSUS® XR within 48 hours following transplantation, or until renal function recovers.
 - To achieve maximal and consistent tacrolimus exposures, ENVARSUS® XR should be taken 1 hour before or 2 hours after breakfast, at approximately the same time every day.
 - Swallow ENVARSUS® tablets whole. Do not split, crush or chew.
 - Avoid consumption of alcohol, grapefruit or grapefruit-containing juice while being treated with ENVARSUS® XR.
5. **Missed Dose.**

If a dose of ENVARSUS® XR is missed, the dose may be taken up to 14 hours after the scheduled time. Beyond the 14-hour time frame, the patient should wait until the usual time the following morning to take the next regular daily dose. It is not recommended to double the dose of ENVARSUS® XR at the time of the next daily dose to make up for any missed doses.

Under Clinical Pharmacology/Drug Interaction:

1. **Pharmacokinetics in *De novo* Kidney Transplant Patients.** The PK parameters of ENVARSUS® XR following a starting dose of 0.17 mg/kg/day and/or 0.14 mg/kg/day in Study 2019 and/or Study 2017 will be summarized. To ensure safe and effective use of ENVARSUS® XR, and to highlight the important differences in tacrolimus PK between ENVARSUS® XR and Prograf, comparative PK may also be included.
2. **Pharmacokinetics in Stable Kidney Transplant Patients (Conversion).** The PK parameters of ENVARSUS® XR following a daily dose conversion ratio of 1:0.8 in Study 2011 will be summarized.
3. **Pharmacokinetics in Healthy Subjects.** The PK parameters of tacrolimus following administration of ENVARSUS® XR in the following studies will be described.
 - a. Food Effect (Study 1011)
 - b. Chronopharmacokinetics (Study 1014).
 - c. Dose-proportionality (Study 1013)
4. **Drug-Drug Interactions.** The following Forest Plot should replace the proposed text under Section 12.3, subsection on Drug-Drug Interaction Studies:



Under Clinical Trials:

- Tacrolimus dosing, tacrolimus trough concentration monitoring, and dosing of concomitant immunosuppressive medications** in Studies 3002 and 3001 will be described.

21 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

B. Individual Study Reviews
(Available upon request)

C. Consult Review

OFFICE OF CLINICAL PHARMACOLOGY

PHARMACOMETRICS REVIEW

Submission	NDA206406
Submission Date	December 30, 2013
Formulation; Strength(s)	Tacrolimus extended release oral tablets (0.75, 1.0, 4.0 mg)
Trade Name	Envarsus® XR
Sponsor	Veloxis Pharmaceuticals, Inc.
Submission Type	505(b)(2) NDA; Standard Review
Pharmacometrics Reviewer	Jeffrey Florian, Ph.D.
Pharmacometrics Team Leader	Yaning Wang, Ph.D.
Clinical Pharmacology Reviewer	Gerlie Gieser, Ph.D.
Clinical Pharmacology Team Leader	Philip Colangelo, Pharm.D., Ph.D.
OCP Division	DCP-4
OND division	OND/ DTOP
Indication	Prevention of acute rejection in adult de novo kidney transplant patients (when used with MMF and steroids)

Key Review Questions

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

Is there evidence of an exposure-response relationship for between treatment efficacy (any failure; biopsy-proven acute rejection) and tacrolimus trough concentration?

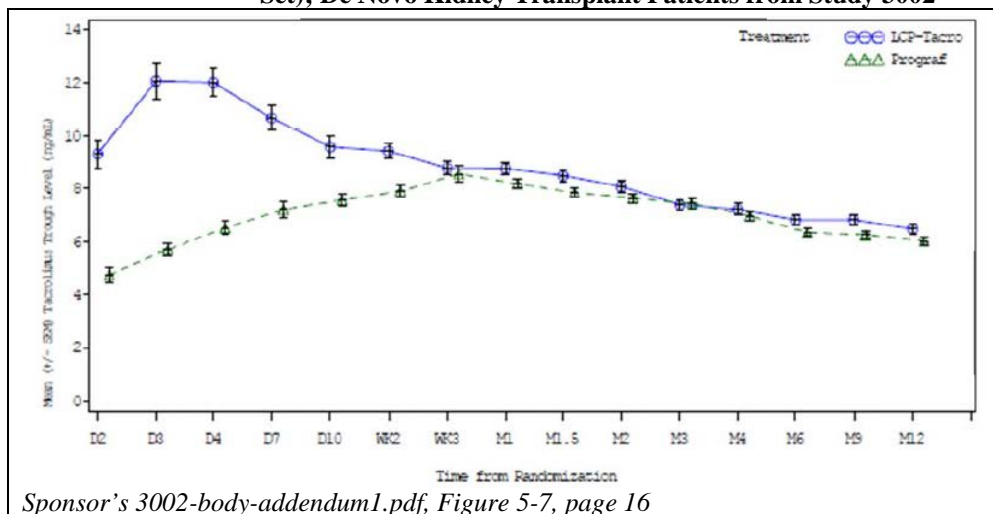
A relationship between tacrolimus C_{trough} and both time to any failure and biopsy-proven acute rejections (BPAR) was identified using a Cox-proportional hazards model based on observations from Study 3002 (*de novo* kidney transplant). Other efficacy measures (all-cause mortality, graft failure, lost to follow-up) were not evaluated individually due to the overall small number of events in each of the categories ($n = 16, 20,$ and $9,$ respectively). Additional patient factors associated with increased likelihood of any failure from this analysis included diabetes status (yes), race (black versus white or other), and region (Asia Pacific or Latin America versus US). These are similar to the factors identified by the Applicant for the same study (see Section 3). Factors associated with an increased likelihood of biopsy-proven graft rejection included region (Latin America or Asia compared to US/Europe). While both analyses identified a relationship between tacrolimus exposures and treatment failure, the available information is not sufficient to suggest an alternative tacrolimus target exposure range from that utilized in Study 3002.

A Cox-proportional hazards model was also attempted for Study 3001 (stable kidney transplant); however, the low overall number of efficacy events ($n=9$ treatment failures; 3 events in Envarsus® XR and 6 events in the Prograf treatment arms total population = 304) as well as patients already being on a stable tacrolimus regimen may have contributed to an inability to identify an exposure-response relationship with respect to tacrolimus C_{trough} in this population.

De Novo Kidney Transplant (Study 3002)

Study 3002 consisted of two treatment arms (Envarsus® XR [n=268] and Prograf [n=275]) with initial total daily dosing of 0.17 mg/kg/day (morning, single dose) and 0.10 mg/kg/day (two doses approximately 12 hours apart). Subsequent doses were adjusted at prespecified visits to maintain trough concentrations between 6 to 11 ng/mL over the first 30 days and between 4 to 11 ng/mL thereafter. A time course plot of tacrolimus C_{trough} concentrations between the two treatments is shown below; note that during the initial 4 weeks of treatment there is a separation in exposure between the treatment arms due to the different initial dosing (see Figure 2; QBR). For more details regarding differences in observed tacrolimus trough concentration over the first 4 weeks of treatment please refer to Question 3.a of the accompanying QBR.

Figure 1. Mean (+/- SEM Tacrolimus Trough Level (ng/mL) Over Time by Treatment Group (ITT Set); De Novo Kidney Transplant Patients from Study 3002



Sponsor's 3002-body-addendum1.pdf, Figure 5-7, page 16

Given that both treatment arms are titrated to a target exposure, as tacrolimus levels vary between initial and maintenance portions of treatment, and as most events occur during the initial month of treatment (see Section 4), it was decided that time-averaged mean tacrolimus trough concentration would not be appropriate for exploring the relationship between tacrolimus exposure and efficacy (i.e., any failure or BPAR). Instead tacrolimus trough concentration was included as a time-varying covariate in a Cox-proportional hazard model analysis along with other baseline covariates of interest including treatment arm, diabetes, body mass index, race, geographic region, age, sex, and CMV or EBV IgG status at baseline. A similar approach was utilized by the Applicant for their exposure-response analysis versus time to any failure event.

Briefly, a univariate analysis was performed for each of the above described covariates as well as tacrolimus trough concentrations. Baseline tacrolimus concentrations were set as the earliest available tacrolimus concentration (day 2, 3, or 4). Subjects without a tacrolimus measurement available prior to event time were not included in the analysis. Covariates which were significant at a Chi-square value of 0.10. All significant covariates were then included and evaluated in a backwards elimination step, where all covariates that were significant at a Chi-square value of 0.05 were retained in the model. A table of model parameters for the time to any failure and time to BPAR are shown below. Identified covariates were similar to those identified by the sponsor for the time to any failure analysis. In both cases, tacrolimus C_{trough} was a significant covariate, with a 1 ng/mL increase in tacrolimus C_{trough} associated with a hazard estimate of 0.90 (95% CI: 0.85; 0.95) and 0.92 (95% CI: 0.86; 0.98) for time to any failure and BPAR, respectively. These observations underscore the importance of therapeutic drug monitoring with tacrolimus but do not suggest that alternative target thresholds are necessary based on the available data.

Table 1. Parameter estimates of the final time to any failure exposure-response model

Parameter	Estimate (SE)	Hazard Ratio (95% CI)	Pr > ChiSq
Tacrolimus C _{tr}	-0.106 (0.027)	0.90 (0.85; 0.95)	9.9e-05
Race (Other vs Black)	-1.361 (0.455)	0.26 (0.11; 0.63)	0.003
Race (White vs Black)	-0.992 (0.379)	0.37 (0.18; 0.78)	0.009
Diabetes (Yes vs No)	0.555 (0.237)	1.74 (1.10; 2.77)	0.02
Region (Europe vs US)	0.448 (0.294)	1.57 (0.88; 2.79)	0.13
Region (Latin America vs US)	0.795 (0.332)	2.21 (1.16; 4.24)	0.02
Region (Asia Pacific vs US)	1.587 (0.390)	4.89 (2.27; 10.51)	4.8e-05

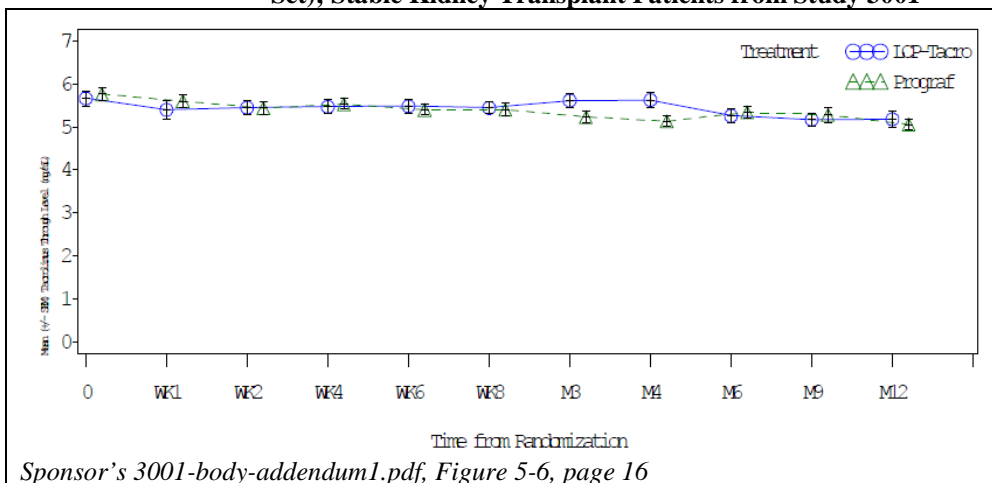
Table 2. Parameter estimates of the final time to BPAR exposure-response model

Parameter	Estimate (SE)	Hazard Ratio (95% CI)	Pr > ChiSq
Tacrolimus C _{trough}	-0.084 (0.031)	0.92 (0.87; 0.98)	0.007
Region (Europe vs US)	-0.176 (0.321)	0.84 (0.45; 1.57)	0.58
Region (Latin America vs US)	0.366 (0.340)	1.44 (0.74; 2.80)	0.28
Region (Asia Pacific vs US)	1.468 (0.383)	4.34 (2.05; 9.19)	0.0001

Stable Kidney Transplant (Study 3001)

Study 3001 consisted of two treatment arms (Envarsus® XR [n=162] and Prograf [n=162]) in stable kidney transplant patients. Patients either continued on the stable Prograf dose or switched to Envarsus® XR total daily dosing of 0.7 times the total daily dose of Prograf being taken (0.85 time for black patients). Overall time course tacrolimus profiles for the two treatment arms are shown below and show no apparent differences in tacrolimus trough concentration between the regimens. An exposure-response relationship between tacrolimus trough concentrations could not be identified based on the data from study 3001, possibly due to the patients already being on a stable tacrolimus regimen maintained within therapeutic thresholds and a low number of treatment failures from the study (n=9 treatment failures; 3 events in Envarsus® XR and 6 events in the Prograf treatment arm)

Figure 2. Mean (+/- SEM) Tacrolimus Trough Level (ng/mL) Over Time by Treatment Group (ITT Set); Stable Kidney Transplant Patients from Study 3001



Is there evidence of exposure-response relationship for safety

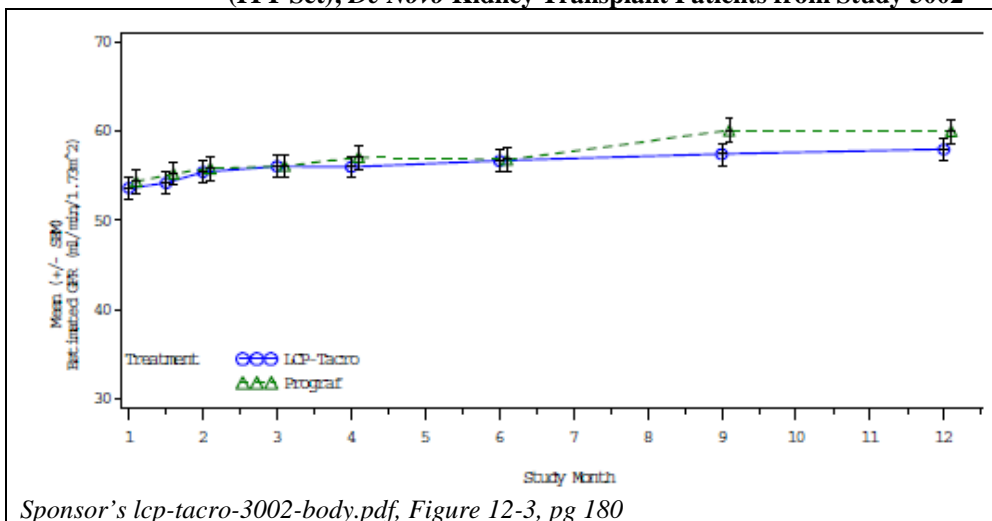
No relationship between tacrolimus C_{trough} exposure and adverse events of interest (i.e., nephrotoxicity) could be identified based on the available data from Study 3002 in *de novo* kidney transplant patients. In addition, estimated glomerular filtration rates were not obtained from patients until week 4 of treatment onward, so no comparison could be performed regarding the impact of higher tacrolimus trough concentrations during the first two weeks in the LCP-Tacro arm on eGFR.

A Cox-proportional hazards analysis was conducted to describe the relationship between nephropathy adverse events and tacrolimus trough concentrations as a time-dependent covariate. A relationship with regards to tacrolimus trough concentrations could not be identified, but that may have been due to the low number of nephropathy events ($n=9$) in the dataset. However, it was noted that there was an imbalance in nephropathy events between the LCP-Tacro ($n=9$) and Prograf ($n=0$) treatment arms. In addition, three of the events in the LCP-Tacro arm occurred during the initial first week of treatment when exposures in the LCP-Tacro arm exceeded those in the Prograf arm. Other safety events of note where there was an imbalance between treatment arms included toxicity to various agents, overdose, and immunosuppressant drug level increased (LCP-Tacro: $n = 10, 9, \text{ and } 5$; Prograf: $n = 3, 1, 0$). These observations suggest that differences in the safety profiles may exist between the studied LCP-Tacro and Prograf regimens, but the available data is not sufficient to determine to the extent to which higher concentrations from the LCP-Tacro treatment arm during the first two weeks may have contributed to these events.

Analyses of the impact of LCP-Tacro exposures on estimated glomerular filtration rate during the initial four weeks of treatment (i.e., time interval when tacrolimus concentrations differ between the two treatment arms) could not be conducted as eGFR measurements were not obtained until week 4 of treatment onward. At this point, concentrations between the two treatment arms were similar and, as expected, no significant differences in eGFR values were observed (Figure 3)

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.

Figure 3. Mean (+/- SEM) Estimated GFR (mL/min/1.73 m²) by Study Visit and Treatment Arm (ITT Set); *De Novo* Kidney Transplant Patients from Study 3002



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.

The current 505(b)(2) submission, LCP-Tacro (Envarsus® XR), is an extended-release formulation of tacrolimus designed for once daily administration for use in the prophylaxis of allograft rejection in recipients of (b) (4) transplants. Specifically, the studies submitted by the Applicant are to support the prophylaxis of organ rejection in kidney transplant patients, either initiating therapy post-transplant (*de novo* kidney transplant) or transitioning from immediate release tacrolimus products to LCP-Tacro. LCP-Tacro extended-release tablets are intended to be marketed at strengths of 0.75 mg, 1 mg and 4 mg drug per tablet.

The current submission consists of 14 Clinical Pharmacology studies; three Phase 2; and two Phase 3 pivotal kidney transplant trials in order to compare the administered tacrolimus doses and the measured tacrolimus trough concentrations, as well as the doses of concomitantly administered immunosuppressive agents in the ENVARUSUS® XR and active comparator (Prograf immediate release) treatment groups. The two Phase 3 studies (3001 and 3002) compared Prograf to LCP-Tacro in stable kidney transplant and *de novo* kidney transplant patients, respectively. The starting regimen of LCP-Tacro for study 3001 was 0.7 times the stable Prograf daily dose (0.85 times in Black patients) while the regimen in 3002 was started at 0.17 mg/kg/day and titrated to a target range of 6 to 11 ng/mL over the first 30 days and 4 to 11 ng/mL over the remainder of the study. In study 3002, the overall percentage of patients with any treatment failure was 18.3% (49/268) on Envarsus® XR and 19.6% (54/275) on Prograf, with a between arm treatment difference of -1.35% (95% CI: -7.94%; 5.27%) favoring the treatment arm. In study 3001 the overall percentage of patients with any treatment failure was 1.9% (3/162) on Envarsus® XR and 3.7% (6/162) on Prograf, with a between arm treatment difference of -1.85% (95% CI: -6.51%; 2.30%) favoring the treatment arm.

Results of sponsor's analysis

Introduction

As part of a pre-NDA communication, the Office of Clinical Pharmacology requested the sponsor to conduct a time to event exposure-response analysis for the primary endpoint (time to any failure) for Study 3002 in *de novo* kidney transplant patients. In addition, the sponsor conducted independent modeling and simulation analyses to support labeling language regarding how to handle missed Envarsus® XR doses.

Exposure-response Analyses (Study 3002) (Addendum 1 to Study 3002 Report)

Methods and Results

A Cox proportional hazards model was constructed using observed data from Study 3002 to evaluate the effect of tacrolimus trough level (TTL) as a time dependent factor on the risk of any treatment failure. Patients that did not have an event by the end of treatment-emergent period were censored at the end of the treatment emergent period. Baseline characteristics predictive of treatment failure were identified and included in the model. A secondary analysis was conducted to assess change from baseline in tacrolimus trough level as the time dependent factor.

The Applicant first identified the most highly predictive baseline characteristics by modeling the time to treatment failure as a function of the treatment and each baseline factor which included age, sex, race group, region, BMI at baseline, diabetes status, donor type at the transplant, and CMV IgG and EBV IgG status. The model estimate indicated that race group, region, BMI at baseline, and diabetes status at the time of transplant are the potential prognostic factors. The forward model was further used for variables selection and the entry significance level was set at 0.15 with treatment effect included. The final model

contains treatment effect, race group, region, and diabetes status at the time of transplant. Treatment was not a significant effect for time to treatment failure after adjusting for these 3 baseline characteristics.

Table 2. Parameter Estimates and P-values from Cox Regression Model with Treatment Effect and Baseline Characteristics; *De Novo* Kidney Transplant Patients from Study 3002

Parameter	Class	Parameter Estimate	Hazard Ratio	Pr > ChiSq
Sex	F vs M	-0.15134	0.86	0.4773
Pooled Age	>=65 vs <65	-0.21984	0.803	0.5752
Age		-0.0049	0.995	0.4873
Race Group	Other vs Black	-0.78809	0.455	0.0542
Race Group	White vs Black	-0.75628	0.469	0.0322
Baseline BMI Group	>= 30 vs <30	0.37072	1.449	0.0961
BMI (kg/m ²) at Baseline		0.02547	1.026	0.2131
Diabetes History?	Y vs N	0.40354	1.497	0.0718
Region	Asia Pacific vs USA	1.09461	2.988	0.0023
Region	Europe vs USA	0.05708	1.059	0.827
Region	Latin America vs USA	0.3387	1.403	0.2468
Donor type	Deceased vs Living	0.21214	1.236	0.2861
Antibody Status CMV IgG	Indeterminate vs Positive	-11.93896	0	0.9847
Antibody Status CMV IgG	Negative vs Positive	0.08172	1.085	0.6946
Antibody Status CMV IgG	Unknown/Not Done vs Positive	-11.93896	0	0.9892
EBV IgG	Indeterminate vs Positive	-0.54884	0.578	0.4433
EBV IgG	Negative vs Positive	-0.40922	0.664	0.2207
EBV IgG	Unknown/Not Done vs Positive	-0.29235	0.747	0.5256

Sponsor's 3002-body-addendum1.pdf, Table 6-1, page 33

For the Applicant's next model building step, the baseline polychotomous variable (race group and region) were converted into dummy numeric variables. Then, tacrolimus trough level was introduced into the model as a time dependent covariate. The forward method was used for variables selection with treatment and TTL included in the model regardless of significance. The significance level of the Chi-square score for entering an effect into the model was specified as 0.15. Similar to the model before introducing the time-dependent variable, the baseline characteristics of race group, region and diabetes status were selected. There were 22 treatment failure events excluded because the TTL measurement was not available prior to event time.

The relationship between treatment failure and the treatment effect using the change in TTL from the first scheduled TTL measurement level as the time-dependent covariate was also evaluated by the Applicant. The first scheduled TTL measurement was on Study Day 2 or Study Day 3 per protocol. A similar variable selection method was used with treatment and change in TTL included in the model regardless of significance. As for the preceding model, the same three baseline characteristics were selected. There were four additional events excluded from modeling with the change in TTL variable.

After exploring and identifying predictive baseline characteristics, factors included in the final model were: treatment, race group, region, and diabetes status at the time of transplant.

Output from the model using tacrolimus trough level as the time-dependent covariate is shown below in Table 1. Output for the model using tacrolimus trough level change from baseline is shown below in Table 2. Tacrolimus trough level, whether introduced into the model as the absolute level or as the change from baseline, was a significant predictor with lower trough levels predicting greater risk of failure.

Table 1. Cox Regression Model with Tacrolimus Trough Level as a Time Dependent Covariate; De Novo Kidney Transplant Patients from Study 3002

Effect	Level	Hazard Ratio		
		Estimate	95% CI	Pr > ChiSq
Treatment	LCP-Tacro vs. Prograf	1.299	(0.825, 2.045)	0.259
Tacrolimus Trough Level*		0.855	(0.824, 0.951)	<0.001
Diabetes	Yes vs. No	2.222	(1.341, 3.684)	0.002
Race	White vs. Black	0.310	(0.133, 0.723)	0.007
	Other vs. Black	0.187	(0.069, 0.508)	0.001
Geographic Region	Asia Pacific vs. USA	7.537	(3.106, 18.294)	<0.001
	Europe vs. USA	1.928	(0.958, 3.880)	0.066
	Latin America vs. USA	3.175	(1.443, 6.989)	0.004

Note: The forward method was used for variables selection; baseline characteristics having significant (at alpha=0.15) effects were added to the model, with treatment and tacrolimus trough level remaining in the model regardless of significance.

* Tacrolimus trough level is the time-dependent covariate. The first scheduled TTL measurement was on Study Day 2 or Study Day 3 depending on the first dose date.

Sponsor's 3002-body-addendum1.pdf, Table 5-3, page 29

Table 2. Cox Regression Model with Tacrolimus Trough Level Change from Baseline as a Time Dependent Covariate; De Novo Kidney Transplant Patients from Study 3002

Effect	Level	Hazard Ratio		
		Estimate	95% CI	Pr > ChiSq
Treatment	LCP-Tacro vs. Prograf	0.848	(0.527, 1.365)	0.498
Change in Tacrolimus Trough Level*		0.951	(0.921, 0.982)	0.002
Diabetes	Yes vs. No	1.995	(1.197, 3.324)	0.008
Race	White vs. Black	0.282	(0.121, 0.657)	0.003
	Other vs. Black	0.192	(0.071, 0.517)	0.001
Geographic Region	Asia Pacific vs. USA	7.143	(2.881, 17.708)	<0.001
	Europe vs. USA	1.975	(0.984, 3.967)	0.056
	Latin America vs. USA	3.514	(1.589, 7.769)	0.002

Note: The forward method was used for variables selection; baseline characteristics having significant (at alpha=0.15) effects were added to the model, with treatment and tacrolimus trough level remaining in the model regardless of significance.

* Change in tacrolimus trough level from the first scheduled measurement after dosing is the time-dependent covariate. The first scheduled TTL measurement was on Study Day 2 or Study Day 3 depending on the first dose date.

Sponsor's 3002-body-addendum1.pdf, Table 5-3, page 30

Reviewer's Comments: One potential caveat for the analysis conducted by the sponsor, and also repeated by the reviewer, is the assumption of a linear relationship between tacrolimus exposure and the log-hazard or log-odds for the event.

Simulations to Inform Handling of Missed Dosing (LCP-Tacro-2011-Missed-Dose-Rpt.pdf)

The objective of this report was to inform recommendations in the label regarding the handling of missed LCP-Tacro doses. To address this item the Applicant developed a physiologically based pharmacokinetic model based on observed Prograf and LCP-Tacro exposure data from LCP-Tacro 2011. The model developed by the Applicant included compartments for unreleased, released, dissolved, absorbed, and metabolized tacrolimus in the stomach, intestine, other organs, and plasma, Model calibration was achieved by altering transit compartment values and comparing model predictions with observations from Study 2011.

LCP-Tacro Study 2011 consisted of PK data of Prograf and LCP-Tacro treatments from 47 patients. In this study, adult stable kidney transplant patients on tacrolimus capsules (Prograf) twice-daily were converted to tacrolimus tablets (LCP-Tacro) once-daily; patients continued on LCP-Tacro once-daily for days 8-21; trough levels were to be maintained between 5-15 ng/mL; 24-hour pharmacokinetic (PK) assessments were done on days 7 (baseline pre-switch), 14, and 21. A summary figure of tacrolimus concentrations from the study is shown below in Figure 4 with model fits to the observed data shown in Figure 5.

Figure 4. Mean Tacrolimus Trough Concentrations from Patients on Days 7, 14, and 21 versus Time; Stable Kidney Transplant Patients from Study 2011

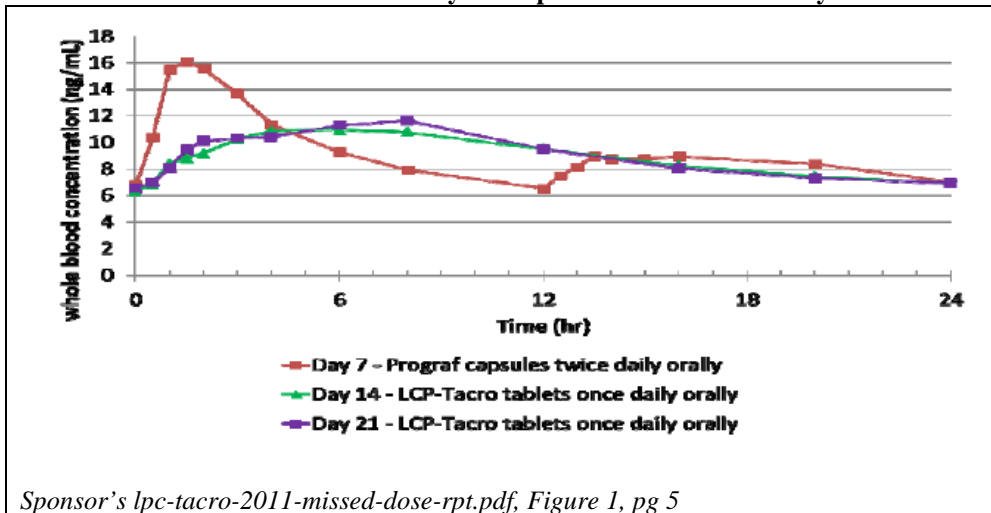
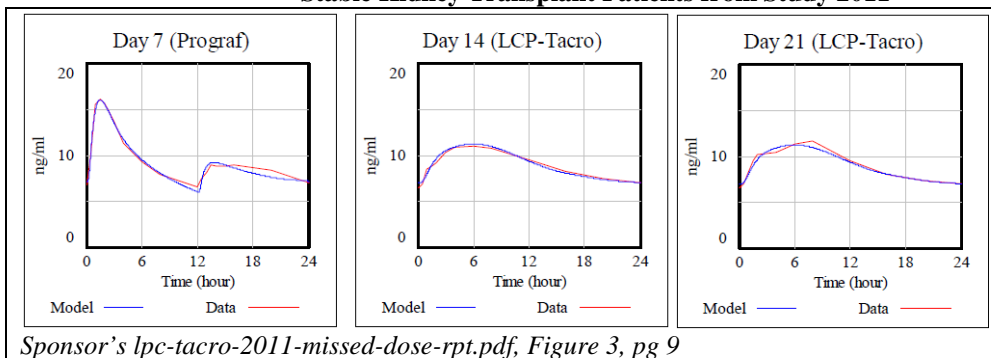


Figure 5. Comparison of 2011 Study Data and Model Using Estimated Patient and Drug Parameters; Stable Kidney Transplant Patients from Study 2011



The Applicant evaluated exposure scenarios assuming a steady state trough level ranging between 12 ng/mL to 6 ng/mL in 2 ng/mL increments. The Applicant considered the following scenarios ((a)-(f)) for handling missed dosing:

- (a) Perfect compliance of Prograf (blue curve, dose taken every 12 hours) and LCP-Tacro (red curve, dose taken every 24 hours).
- (b) A missed LCP-Tacro dose at $t=0$ with no make-up dose.
- (c) A missed dose at $t=0$ with a double taken at $t=24$ hours and a single dose taken at $t=48$.
- (d) A missed dose at $t=0$, a make-up dose taken at 21 hours and normal doses taken at $t=24$ hours and $t=48$.
- (e) A missed dose at $t=0$, a make-up dose taken at 18 hours and normal doses taken at $t=24$ hours and $t=48$.
- (f) A missed dose at $t=0$, a make-up dose taken at 15 hours and normal doses taken at $t=24$ hours and $t=48$.

In all figures, the Prograf and LCP-Tacro regular doses have been adjusted to obtain a target value of $C_{min} = 12$ ng/mL, 10 ng/mL, 8 ng/mL and 6 ng/mL. Each of the figures contains six panels. Each panel compares the tacrolimus concentration as a function of time over a 72 hour period for Prograf and LCP-Tacro formulations, for the same sequence of dose administration. In each panel, the red curve shows the tacrolimus concentration for perfect compliance of LCP-Tacro. Results are shown for the simulations where C_{min} was 12 (Figure 6) or 6 (Figure 7) ng/mL as these evaluations represent the cases which would result in the highest or lowest tacrolimus exposures. From these analyses the applicant observed that

doubling the dose at 24 hours after a missed dose (scenario (c)) result in prolonged elevation of tacrolimus concentrations over the following day. Missing a dose (scenario (b)) completely results in under exposure over an 8-12 hour window following the missed dose. Taking the missed dose at 15, 18, or 21 hours (scenarios (f), (e), and (d)) reduce the window over which tacrolimus exposures may be less than the therapeutic window, but subsequently result in following day C_{max} and AUC values that exceed that of the scenario where the dose is doubled. From these analyses the Applicant concluded and proposed that subjects who miss a dose may take the dose as soon as they remember it and that it is not prudent to recommend a doubling of a dose as a means of handling missed dosing.

Figure 6. Simulation of non-compliance and make-up dose scenarios for a normal trough of 12 ng/mL

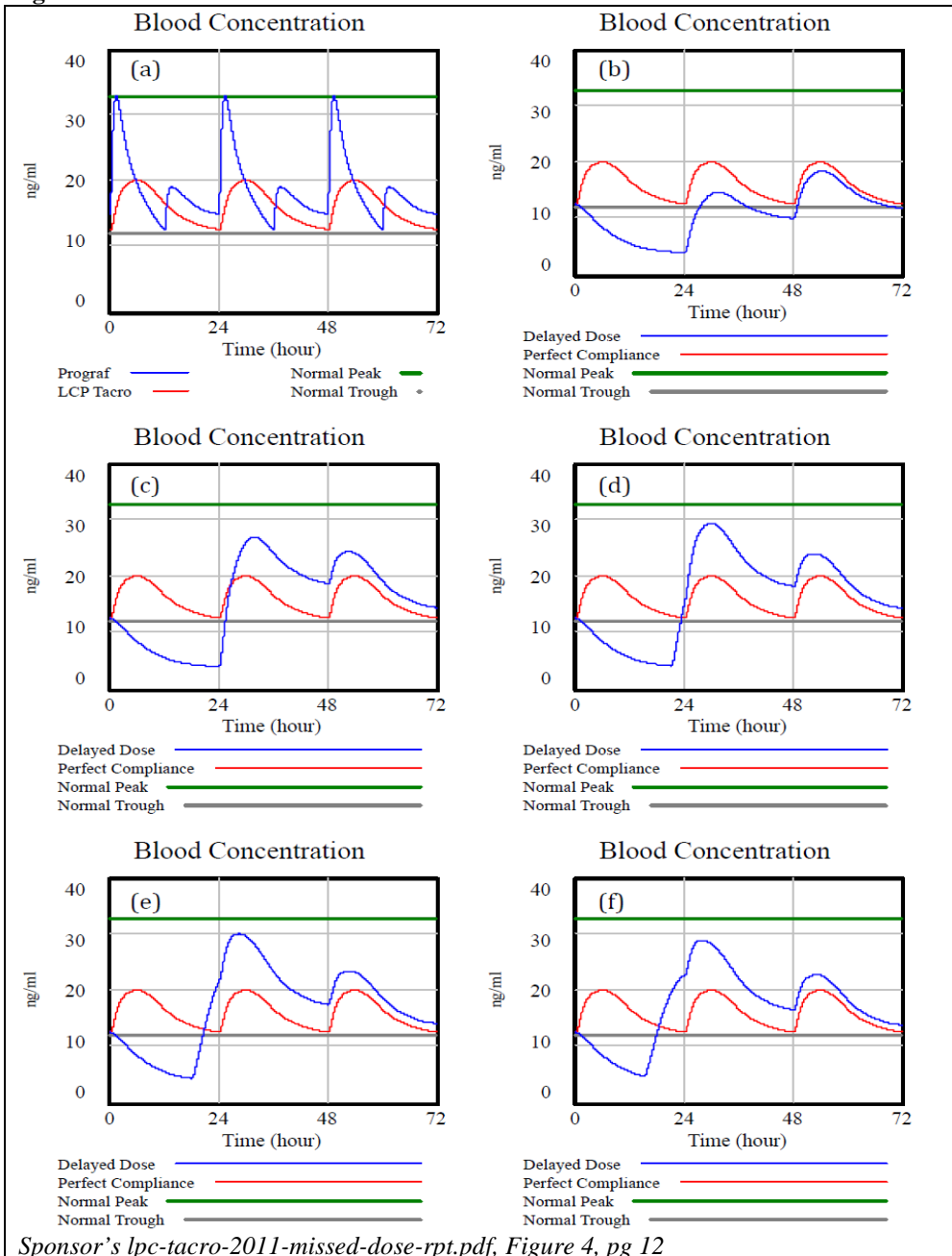
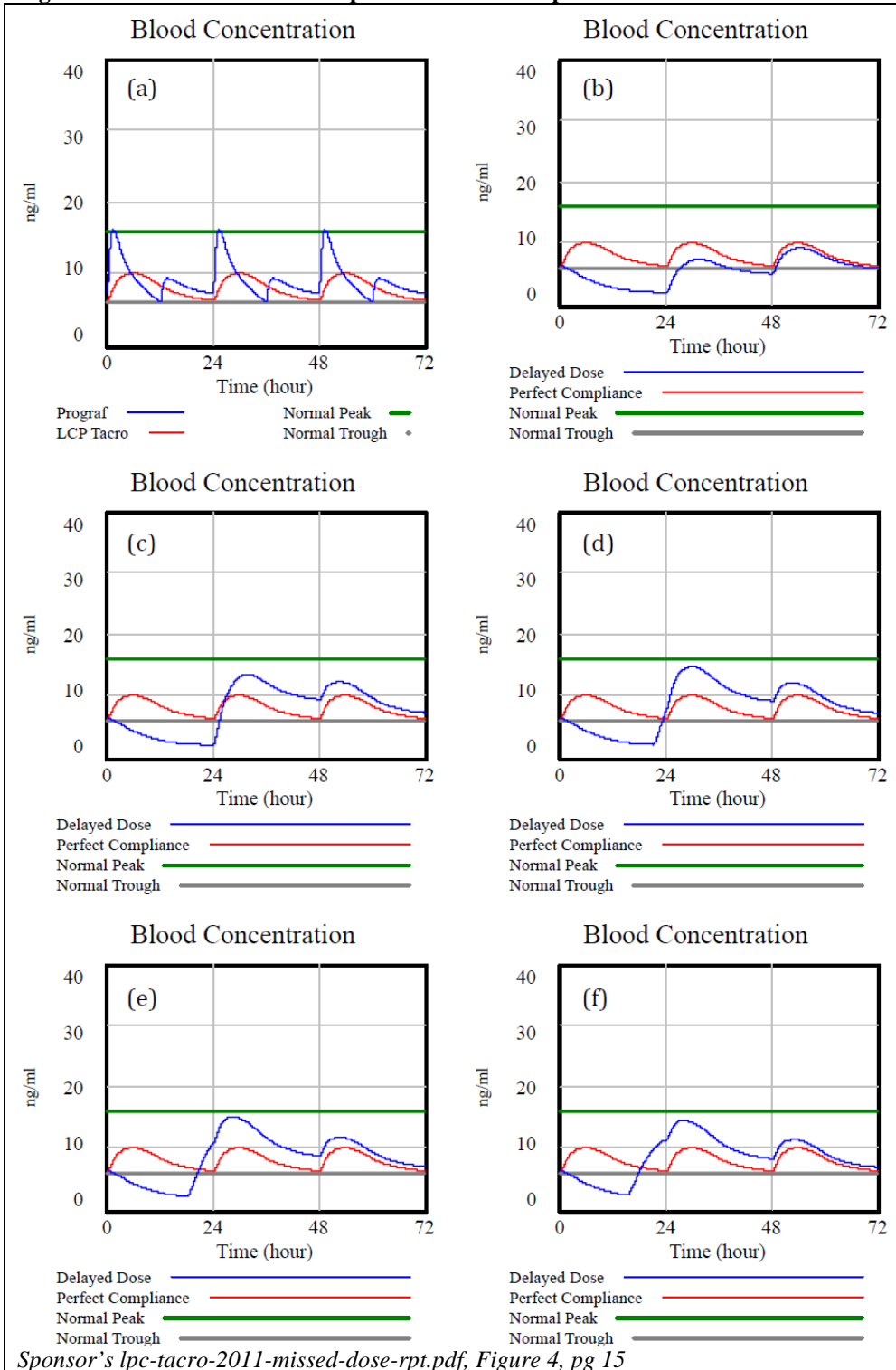


Figure 7. Simulation of non-compliance and make-up dose scenarios for a normal trough of 6 ng/mL



Sponsor's lpc-tacro-2011-missed-dose-rpt.pdf, Figure 4, pg 15

Review comments: The Applicant's provided simulations suggest that failing to address a missed dose will result in a period of time where tacrolimus C_{trough} concentrations may fall below therapeutic levels. Similarly, taking the missed dose between 15 hours to 21 hours after the missed dose or doubling the dose at the next time interval would result in tacrolimus exposures (AUC and C_{max}) which may have an impact on safety. As such, none of the proposed approaches will simultaneously maintain a patient within the

therapeutic range. As the benefit risk of low tacrolimus exposures versus high tacrolimus exposures for a short period of time is unknown, it is not possible to evaluate the trade-off between these scenarios.

The reviewer evaluated alternative scenarios involving a half-dose of tacrolimus between the 15-24 hour window following a missed dose as a means of maintaining tacrolimus levels within the therapeutic range, with a full dose administered at the subsequent dosing interval. While such an approach offers a mathematical solution to maintaining tacrolimus levels within the therapeutic range, the solution was rejected as: i) half-dose increments of tacrolimus may not be available to a patient based on the available formulation strengths; ii) labeling of half-dosing may lead to confusion in usage and further impact maintaining tacrolimus levels within the therapeutic range; iii) the proposed morning dosing would imply that 15-24 hours post-missed dose are during hours when patients are likely to be sleeping and wouldn't note that a tacrolimus dose has been missed.

Given the provided simulations, simulations evaluated by the reviewer, and proposed labeling for other tacrolimus products, the reviewer recommends the dosing for a missed dose should be to take the dose as normal if it is noted within 14 hours of when the dose should have been administered. Otherwise, wait until the next dosing interval and take that dose as normally. In addition, doubling of the tacrolimus at the next dosing time as a means of managing the missed dose should not be recommended. These dosing recommendations are similar to those determined by Dr. Gieser in the clinical pharmacology review for NDA 204096 (6/13/2013).

Reviewer's Analysis

Introduction

The sponsor conducted exposure-response analyses for time to event of any failure based on data from Study 3002. The reviewer sought to evaluate this model as well as develop a similar model for biopsy-proven acute rejection (BPAR).

Objectives

Analysis objectives are:

1. To conduct exposure-response analyses for time-to-event for any failure and biopsy-proven acute rejection (BPAR) based on tacrolimus drug concentrations and other relevant demographic variables for Study 3002

Methods

Multivariate Cox-proportional hazards models were evaluated for time to event for any failure and BPAR in patients from Study 3002. Tacrolimus trough concentrations were included in the model analysis as a time-dependent covariate similar to the approach utilized by the sponsor and described in Section 3. Other covariates evaluated during the model development included treatment arm, diabetes, body mass index, race, geographic region, age, sex, and CMV or EBV IgG status at baseline.

A univariate analysis was performed for each of the above described covariates as well as tacrolimus trough concentrations. Baseline tacrolimus concentrations were set as the earliest available tacrolimus concentration (day 2, 3, or 4). Subjects without a tacrolimus measurement available prior to event time were not included in the analysis. Covariates which were significant at a Chi-square value of 0.10. All significant covariates were then included and evaluated in a backwards elimination step, where all covariates that were significant at a Chi-square value of 0.05 were retained in the model.

Data sets

The analysis was performed for Study 3002 and 3001. However, as the number of events from Study 3001 was low, an exposure-response analysis for Study 3001 did not identify any association with tacrolimus exposure.

Table 1. Analysis Data Sets

Study Number	Name	Link to EDR
LCP-Tacro 3002	adtte.xpt adtac.xpt adsl.xpt adae.xpt adegfr.xpt adeff.xpt	\\cdsesub1\evsprod\NDA206406\0000\m5\datasets\lcp-tacro-3002\analysis\adam\dataset
LCP-Tacro 3001	Adsl.xpt Adctac.xpt Adeff.xpt	\\cdsesub1\evsprod\NDA206406\0000\m5\datasets\lcp-tacro-3001\analysis\adam\dataset

Software

Graphical, statistical analyses were performed with R (version 2.15).

Results**Time-to-event for any failure and BPARacute rejection**

Please refer to the discussion under Key Question 1.1.

Relationships between trough concentrations and AEs

Visual assessments on the mean trough concentration profiles of tacrolimus for patients with nephropathy to patients without the adverse event were conducted. This analysis was performed as an imbalance in the incidence rate of nephropathy events between the LCP-Tacro (n=9 events) and Prograf (n=0 events) was observed, with the notable differences between treatment being difference C_{trough} exposures over the first 2 weeks of treatment, once daily dosing with LCP-Tacro, and a lower total daily dose of LCP-Tacro due to its increased bioavailability relative to Prograf.

As seen in Figure 37 (QBR), there were no significant differences in mean concentration profiles between patients with AE and patients without AE for nephropathy events. Also, attempts to construct an exposure-response safety analysis for nephropathy events from Study 3002 did not identify tacrolimus C_{trough} as a predictor of events. However, given the small number of patients with the relevant safety events, this observation should be interpreted with caution.

Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
NDA206406_ER_Efficacy_Safety.R	Exposure-response analyses with data from Study 3002 and 3001	Reviews\Ongoing PM Reviews\Tacrolimus_NDA206406_JAF \ER Analyses

D. Cover Sheet and OCP Filing Review Form



Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Attention: Renata Albrecht, MD, Director
Division of Transplant and Ophthalmology Products

December 30, 2013

Re: ENVARSUS; LCP-Tacro™ Tablets (Tacrolimus)
NDA No.: 206-406; Sequence 0000
Initial New Drug Application

Dear Dr. Albrecht:

In accordance with Section 505(b)(2) of the Federal Food Drug and Cosmetic Act, Veloxis Pharmaceuticals is submitting a New Drug Application, NDA 206-406, for Envarsus extended-release tablets 0.75 mg, 1.0 mg and 4.0 mg. The proposed indication is for the prophylaxis of organ rejection in patients receiving a kidney transplant.

The safety and efficacy of tacrolimus has been studied extensively. In 1994, the US Food and Drug Administration (FDA) approved the originator tacrolimus product, Prograf® (Astellas), for the prophylaxis of organ rejection in liver transplant patients. Subsequently, the indication has expanded and now includes prophylaxis of organ rejection in kidney transplant patients and heart transplant patients. Tacrolimus has received similar approvals from European regulatory authorities for use in organ transplantation and Astagraf XL was also recently approved for an extended release formulation of tacrolimus in the US.

Veloxis Pharmaceuticals has developed a new extended-release formulation of tacrolimus, LCP-Tacro tablets, using its proprietary MeltDose® drug-delivery technology, which was designed to improve the bioavailability of (b) (4). This extended-release formulation of tacrolimus allows once daily (q.d.) administration, with the aim of improving treatment compliance in adult kidney (b) (4) transplant recipients.

The regulatory correspondence is located in Section 1.6.3. The regulatory correspondence includes the Pre-NDA meeting minutes, as well as other pertinent regulatory correspondence.

On August 7, 2013, two Type B pre-NDA meetings were held to discuss the planned NDA submission. From these meetings, the Agency requested additional information. Located in 1.11.4, please find the List of Questions and the location of the responses. A Reviewer's Guide, which provides an overview and location of key information in the NDA is also included.

Veloxis has requested, and received, Orphan Drug Designation (Designation Reference Number 13-4017) from the Office of Orphan Products Development. The correspondence of December 20, 2013 from OOPD is included in Section 1.6.3.

This NDA is submitted as an electronic Common Technical Document (eCTD) (see attached Electronic Submission Specifications) and is organized in accordance with the Agency's Guidance for Industry, "Providing Regulatory Submissions Using eCTD Specifications (June 2008)."

The confidentiality of this submission, and all information contained herein, is claimed by Veloxis Pharmaceuticals under all applicable laws and regulations. Disclosure of any such information is not authorized without the prior written authorization of Veloxis.

Should you have any question or comment, please do not hesitate to immediately contact me at the contacts noted below.

Yours Sincerely,



Ronald Guido
Sr. Vice-President, Quality and Regulatory Affairs, Veloxis Pharmaceuticals
Phone: 732-321-3211
Fax: 732-906-7943
Mobile: (b) (6)
rgu@veloxis.com

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	NDA 206-406	Brand Name	ENVARUSUS® XR
OCP Division (I, II, III, IV, V)	DCP IV	Generic Name	tacrolimus
Medical Division	DTOP	Drug Class	Immunosuppressive drug
OCP Reviewer	Gerlie Gieser, PhD	Indication(s)	prophylaxis of organ rejection in patients receiving a kidney transplant
OCP Team Leader	Philip Colangelo, PharmD, PhD	Dosage Form	extended release oral tablets
Pharmacometrics Reviewer	Jeffry Florian, PhD	Dosing Regimen	For <i>de novo</i> kidney transplant patients: (b) (4) For <i>conversion</i> from tacrolimus immediate-release in stable kidney transplant patients: use (b) (4) then adjust subsequent doses to achieve target tacrolimus whole blood C _{trough}
Date of Submission	30 December 2013		
Estimated Due Date of OCP Review		Route of Administration	oral
Medical Division Due Date		Sponsor	Veloxis Pharmaceuticals, Inc.
PDUFA Due Date	30 October 2014	Priority Classification	Standard – 505(b)(2) NDA

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	20		9 Phase 1 & 8 Phase 2/3
Healthy Volunteers-				
single dose:	X	4		

	multiple dose:	X	7		
Patients-	single dose:				
	multiple dose:	X	9		5 kidney (b) (4)
Dose proportionality -	fasting / non-fasting single dose:	X	1		
	fasting / non-fasting multiple dose:				
Drug-drug interaction studies -	In-vivo effects on primary drug:				
	In-vivo effects of primary drug:				
	In-vitro:				
Subpopulation studies -	ethnicity:				
	gender:				
	pediatrics:				
	geriatrics:				
	renal impairment:				
	hepatic impairment:				
PD -	Phase 2:	X			
	Phase 3:	X			
PK/PD -	Phase 1 and/or 2, proof of concept:				
	Phase 3 clinical trial:	X			Cox proportional hazards modeling report for 3002; missed dose simulation report
Population Analyses -	Data rich:				
	Data sparse:				
II. Biopharmaceutics	Absolute bioavailability				
	Relative bioavailability -				
	solution as reference:				
	alternate formulation as reference:	X			
Bioequivalence studies -	traditional design; single / multi dose:				
	replicate design; single / multi dose:				
Food-drug interaction studies		X			
Bio-waiver request based on BCS	BCS class				
	Dissolution study to evaluate alcohol induced dose-dumping	X	1		
III. Other CPB Studies	Genotype/phenotype studies				
	Chronopharmacokinetics	X	1		
	Pediatric development plan				(b) (4)
	Literature References	X	45		
	Total Number of Studies		17		excluding literature references

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			Two Phase 2 <u>1</u> studies; to-be-marketed Formulation G also evaluated in Study 3003

2	Has the applicant provided metabolism and drug-drug interaction information?		X		505(b)(2)
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			A population PK analysis was requested (b) (4) at the preNDA meeting.
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			Ph2 and Ph 3 trials are concentration –controlled (TDM)
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			Sponsor provided the requested missed dose and time-to-event efficacy/safety analyses. No datasets for the analyses were provided.
14	Is there an adequate attempt by the applicant to use exposure-response	X			

	relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?				
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	(b) (4)			
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?				
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.

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

Clinical Pharmacology/Pharmacometrics information request (for inclusion in the 74-day letter):

Please provide the datasets and analysis scripts used to generate the information provided in the addendum to ENVARUSUS® XR 3002 (titled: Addendum CSR ENVARUSUS® XR 3002) which was requested by the Agency at the preNDA meeting. Specifically, we are requesting these materials for the dose/concentration time course assessments for major demographic subgroups, immunosuppressant use by treatment group analysis, and time-to-event analysis. Alternatively, if the datasets and scripts were already included in the submission, we request information from the applicant regarding the location of those materials.

Internal Comment (not for inclusion in the 74-day letter):

This is a 505(b)(2) NDA of ENVARUSUS® (tacrolimus extended release oral tablets) submitted by Veloxis Pharmaceuticals. The review will determine which sections of the ENVARUSUS® USPI could be copied/derived from the information presented in the Prograf USPI (tacrolimus immediate release oral capsules manufactured by Astellas) including but not limited to PK in renal impairment, PK in hepatic impairment, drug interactions, ADME.

Gerlie C. Gieser, PhD

Reviewing Clinical Pharmacologist

Date

Jeffry Florian, PhD

Reviewing Pharmacometrician

Date

Philip M. Colangelo, PharmD, PhD

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
09/24/2014

JEFFRY FLORIAN
09/24/2014

YANING WANG
09/25/2014

PHILIP M COLANGELO
09/25/2014

**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 206-406	Brand Name	ENVARUSUS®
OCP Division (I, II, III, IV, V)	DCP IV	Generic Name	tacrolimus
Medical Division	DTOP	Drug Class	Immunosuppressive drug
OCP Reviewer	Gerlie Gieser, PhD	Indication(s)	prophylaxis of organ rejection in patients receiving a kidney transplant
OCP Team Leader	Philip Colangelo, PharmD, PhD	Dosage Form	extended release oral tablets
Pharmacometrics Reviewer	Jeffry Florian, PhD	Dosing Regimen	For <i>de novo</i> kidney transplant patients: (b) (4)  For <i>conversion</i> from tacrolimus immediate-release in stable kidney transplant patients use (b) (4)  then adjust subsequent doses to achieve target tacrolimus whole blood C _{trough}
Date of Submission	30 December 2013		
Estimated Due Date of OCP Review		Route of Administration	oral
Medical Division Due Date		Sponsor	Veloxis Pharmaceuticals, Inc.
PDUFA Due Date	30 October 2014	Priority Classification	Standard – 505(b)(2) NDA

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:				

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

Pharmacokinetics (e.g., Phase I) -	X	20		9 Phase 1 & 8 Phase 2/3
Healthy Volunteers-				
single dose:	X	4		
multiple dose:	X	7		
Patients-				
single dose:				
multiple dose:	X	9		5 kidney + (b) (4)
Dose proportionality -				
fasting / non-fasting single dose:	X	1		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:	X			
Phase 3:	X			
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X			Cox proportional hazards modeling report for 3002; missed dose simulation report
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X			
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	X			
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping	X	1		
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics	X	1		
Pediatric development plan				(b) (4)
Literature References	X	45		
Total Number of Studies		17		excluding literature references

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

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			Two Phase 2 studies; to-be-marketed Formulation G also evaluated in Study 3003
2	Has the applicant provided metabolism and drug-drug interaction information?		X		505(b)(2)
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			A population PK analysis was requested (b) (4) at the preNDA meeting.
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			Ph2 and Ph 3 trials are concentration –controlled (TDM)
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			Sponsor provided the requested missed dose and time-to-event efficacy/safety analyses. No datasets for the analyses were provided.
14	Is there an adequate attempt by the applicant to	X			

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

	use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?				
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	(b) (4)			
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?				
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.

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

Clinical Pharmacology/Pharmacometrics information request (for inclusion in the 74-day letter):
Please provide the datasets and analysis scripts used to generate the information provided in the addendum to LCP-Tacro 3002 (titled: Addendum CSR LCP-Tacro 3002) which was requested by the Agency at the preNDA meeting. Specifically, we are requesting these materials for the dose/concentration time course assessments for major demographic subgroups, immunosuppressant use by treatment group analysis, and time-to-event analysis. Alternatively, if the datasets and scripts were already included in the submission, we request information from the applicant regarding the location of those materials.

Internal Comment (not for inclusion in the 74-day letter):

This is a 505(b)(2) NDA of ENVARSUS® (tacrolimus extended release oral tablets) submitted by Veloxis Pharmaceuticals. The review will determine which sections of the ENVARSUS® USPI could be copied/derived from the information presented in the Prograf USPI (tacrolimus immediate release oral capsules manufactured by Astellas) including but not limited to PK in renal impairment, PK in hepatic impairment, drug interactions, ADME.

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

Gerlie C. Gieser, PhD

Reviewing Clinical Pharmacologist

Date

Jeffry Florian, PhD

Reviewing Pharmacometrician

Date

Philip M. Colangelo, PharmD, PhD

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
01/31/2014

PHILIP M COLANGELO
01/31/2014