CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206406Orig1s000

MEDICAL REVIEW(S)

DIVISION OF TRANSPLANT AND OPHTHALMOLOGY PRODUCTS

Clinical Review of Envarsus XR®

(tacrolimus extended-release tablets) Labeling

NDA 206-406/S-046 SDN 49
Class 1 Resubmission

Name of Drug:	Envarsus XR® (tacrolimus extended-release tablets) 0.75 mg, 1 mg, 4 mg
Applicant:	Veloxis
Initial FDA Approval:	October 30, 2014 (Tentative Approval)
Submission Date:	June 12, 2015 (Class 1 resubmission) July 2, 2015, SDN 55 (MedGuide) July 7, 2015, SDN 57 (Package Insert)
Goal Date:	August 12, 2015
Date of Review Completion:	July 8, 2015
Clinical Reviewer:	Ergun Velidedeoglu, M.D.
Project Manager:	Lois Almoza
Deputy Director for Safety:	Ozlem Belen, MD, MPH
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1. Summary of the Regulatory History:

Envarsus XR is an extended release tablet formulation of tacrolimus which is a calcineurin (CNI) type of immunosuppressant forming one of the main components of most immunosuppressive treatment regimens utilized in the clinical practice of transplantation.

Currently there is an immediate release formulation of tacrolimus (Prograf capsules and generics) and another extended release formulation (Astagraf XL) lawfully marketed in US.

NDA 206406 was originally submitted on December 30, 2013 with a PDUFA goal date of October 30, 2014. NDA 206406 for Envarsus XR is a 505(b)(2)

application and the listed drug product on which the applicant is relying for nonclinical information is Prograf. The Applicant originally sought approval of the Envarsus XR extended release tablets for the prophylaxis of rejection in both the de novo and stable kidney transplant recipients (as conversion from Prograf or generics) and submitted the results of two Phase 3 randomized controlled studies in addition to Phase 2 and Phase 1 studies in support of this indication.

The Phase 3 studies, LCP-Tacro 3002 (de novo) and LCP-Tacro 3001 (conversion), along with the Phase 2 study, LCP-Tacro 2017 (de novo), reviewed in support of the proposed indication demonstrate that the Envarsus XR has comparable safety and efficacy to the active comparator Prograf.

On October 30, 2014, FDA issued a tentative approval (TA) for NDA 206406 because FDA determined that approval of the drug product was blocked by the three-year exclusivity of Astagraf XL (NDA 204096).

As communicated in the October 30, 2014 TA Letter, final approval of NDA 206406, is contingent on submission of an amendment titled “Request for Final Approval” by the Sponsor (Veloxis) two to six months prior to the:1) expiration of the exclusivity protection or 2) date the Sponsor believes that NDA 206406 will be eligible for final approval.

During the course of subsequent communications between the FDA and the Applicant (Veloxis), in the January 12, 2015 letter, FDA stated that:

> *“… FDA concludes that the Envarsus XR NDA is a once-daily, ER dosage form of tacrolimus for prophylaxis of organ rejection that is blocked from approval for de novo kidney transplant patients by Astagraf XL’s exclusivity until that exclusivity expires on July 19, 2016. FDA also concludes, however, that the Envarsus XR NDA can be approved now for conversion of stable kidney transplant patients from tacrolimus immediate-release (IR) products to Envarsus XR (the conversion use), pending Veloxis’ submission and FDA approval of an appropriate labeling amendment deleting reference to the de novo population and seeking approval for the conversion use only.* ”

The applicant chose to seek resolution of the issue through litigation. This review does not include the details of the litigation. Relevant FDA documents related to the review of Envarsus XR and Astagraf XL have been checked into DARRTS.

On June 12, 2015, U.S. District Court ruled in favor of the FDA in the lawsuit filed by Veloxis against FDA. The Court's ruling leaves intact FDA's October 30, 2014 tentative approval of Envarsus XR (tacrolimus extended-release tablets), which delays full approval for use in de novo kidney transplanted recipients ("de novo" patients). On the same date (June 12, 2015) Veloxis submitted revised labeling to FDA as a Class 1 resubmission for the “conversion use indication” only,

requesting approval of Envarsus XR in stable kidney transplant patients who wish to convert from twice-daily immediate release tacrolimus products to once-daily Envarsus XR.

In the revised labeling submitted on June 12, 2015, Veloxis removed sections and statements dealing with the "de novo indication" (since this indication is still protected by the exclusivity granted to Astagraf XL).. The Division made a few additional edits, removing remaining statements of results in de novo kidney transplant patients.

The revised labeling for the PI and MG was sent to Veloxis, and the final agreed upon PI was submitted July 7, 2015 and the MG was submitted on July 2, 2015.

In addition, the CMC reviewer noted that the container, overwrap and carton labels submitted to the NDA on September 26, October 9, and October 16, 2014, respectively, were considered acceptable. Clinical agrees with the CMC recommendations. The package insert and the Medication Guide attached at the end of this review are the final agreed upon versions by the FDA and the applicant.

The major changes pertaining to the clinical discipline in the currently agreed upon labeling compared to the labeling communicated to the applicant in the October 30, 2014 TA Letter are below. For changes pertaining to other disciplines including Clinical Pharmacology, refer to respective reviews in DARRTS.

- **1 INDICATIONS AND USAGE**

  The indication has been changed

  from:

  "*ENVARSUS XR is indicated for the prophylaxis of organ rejection in kidney transplant patients in* (b) (4)

  to:

  "*ENVARSUS XR is indicated for the prophylaxis of organ rejection in kidney transplant patients converted from tacrolimus immediate-release formulations, in combination with other immunosuppressants.*"

- **2 DOSAGE AND ADMINISTRATION**

  - Subsection (b) (4) has been deleted.

- Subsection 2.1 Administration Instructions have been revised based on the applicant's modeling of missed doses of Envarsus XR using data from LCP-Tacro Study 2011.

Changed from:

(b) (4)

to:

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.

For more information about the changes under DOSAGE AND ADMINISTRATION see Clinical Pharmacology review dated July 9, 2015 in DARRTS.

- **6 ADVERSE REACTIONS**

Subsection *6.1 Clinical Studies Experience* has been modified by removing (b) (4) and adding more detailed information and tables pertaining to the conversion Study LCP-Tacro 3001.

- **14 CLINICAL STUDIES**

Subsection (b) (4) has been removed.

Clinical Reviewer's Comment:
By removing (b) (4) has also been removed from this section.

However, to prevent any loss of important safety information from the labeling, the current final agreed upon labeling contains this warning in section 12.2 Pharmacokinetics as a footnote under Table 5:

"*g) Starting ENVARSUS XR dose = 0.17 mg/kg/day. In de novo kidney transplant patients who received ENVARSUS XR starting dose of 0.17 mg/kg/day achieved higher than recommended target tacrolimus trough concentrations, as high as 57 ng/mL during the first 1 to 2 weeks posttransplant*."

Information on this pharmacokinetic measurement following specific doses is considered important safety information.

2. Clinical Reviewer's Recommendation:

I recommend approval of the final agreed upon Package Insert (PI), Medication Guide (MG) and Carton and Container Labeling. The text of the PI and MG are included in the following section of this review.

3. Final Agreed upon Labeling and MG

Envarsus XR® (tacrolimus extended-release tablets)

FULL PRESCRIBING INFORMATION

WARNING: MALIGNANCIES AND SERIOUS INFECTIONS

Increased risk for developing serious infections and malignancies with ENVARSUS XR or other immunosuppressants that may lead to hospitalization or death *[see Warnings and Precautions (5.1, 5.2)]*

1 INDICATIONS AND USAGE

ENVARSUS XR is indicated for the prophylaxis of organ rejection in kidney transplant patients converted from tacrolimus immediate-release formulations, in combination with other immunosuppressants.

Limitation of Use

ENVARSUS XR extended-release tablets are not interchangeable or substitutable with other tacrolimus extended-release or immediate-release products *[see **Warnings and Precautions (5.3)**]*.

2 DOSAGE AND ADMINISTRATION

2.1 Administration Instructions

- Take ENVARSUS XR on an empty stomach at the same time of the day, preferably in the morning (to ensure consistent and maximum possible drug exposure) *[see **Clinical Pharmacology (12.2)**]*.
- Swallow ENVARSUS XR whole with fluid (preferably water); do not chew, divide, or crush the tablets.
- 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..
- Avoid eating grapefruit or drinking grapefruit juice or alcoholic beverage while taking ENVARSUS XR *[see **Drug Interactions (7.2)**]*.
- African-American patients, compared to Caucasian patients, may need to be titrated to higher ENVARSUS XR dosages to attain comparable trough concentrations *[see **Use in Specific Populations (8.8)** and **Clinical Pharmacology (12.2)**]*.

2.2 Conversion from Tacrolimus Immediate-Release Formulations

To convert from a tacrolimus immediate-release product to ENVARSUS XR, administer an ENVARSUS XR once daily dose that is 80% of the total daily dose of the tacrolimus immediate-release product. Monitor tacrolimus whole blood trough concentrations and titrate ENVARSUS XR dosage to achieve target whole blood trough concentration ranges of 4 to 11 ng/mL.

2.3 Therapeutic Drug Monitoring

Measure tacrolimus whole blood trough concentrations at least two times on separate days during the first week after initiation of dosing and after any change in dosage, after a change in co-administration of CYP3A inducers and/or inhibitors, or after a change in renal or hepatic function. When interpreting measured concentrations, consider that the time to achieve tacrolimus steady state is approximately 7 days after initiating or changing the ENVARSUS XR dose.

Monitor tacrolimus whole blood trough concentrations using a validated assay [e.g., immunoassays or high-performance liquid chromatography with tandem mass spectrometric detection (HPLC/MS/MS)]. The immunosuppressive activity of tacrolimus is mainly due to the parent drug rather than to its metabolites. Immunoassays may react with metabolites as well as the parent drug. Therefore, whole blood tacrolimus trough concentrations obtained with immunoassays may be numerically higher than concentrations obtained with an assay using HPLC/MS/MS. Comparison of the whole blood tacrolimus trough concentrations of patients to those described in the prescribing information and other published literature must be made with knowledge of the assay method(s) employed.

3 DOSAGE FORMS AND STRENGTHS

Oval, white to off-white uncoated extended-release tablets debossed with “TCS” on one side:

- 0.75 mg extended-release tablet: debossed with “0.75” on the other side.

- 1 mg extended-release tablet: debossed with "1" on the other side.
- 4 mg extended-release tablet: debossed with "4" on the other side.

4 CONTRAINDICATIONS

ENVARSUS XR is contraindicated in patients with known hypersensitivity to tacrolimus.

5 WARNINGS AND PRECAUTIONS

5.1 Lymphoma and Other Malignancies

Immunosuppressants, including ENVARSUS XR, increase the risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. Examine patients for skin changes and advise to avoid or limit exposure to sunlight and UV light.

Post-transplant lymphoproliferative disorder (PTLD), associated with Epstein-Barr Virus (EBV), has been reported in immunosuppressed organ transplant patients. The risk of PTLD appears greatest in those individuals who are EBV seronegative. Monitor EBV serology during treatment.

5.2 Serious Infections

Immunosuppressants, including ENVARSUS XR, increase the risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections. These infections may lead to serious, including fatal, outcomes. Serious viral infections reported include:

- Polyomavirus-associated nephropathy (especially due to BK virus infection),
- JC virus-associated progressive multifocal leukoencephalopathy (PML), and
- Cytomegalovirus (CMV) infections: CMV seronegative transplant patients who receive an organ from a CMV seropositive donor are at highest risk of CMV viremia and CMV disease.

Monitor for the development of infection and adjust the immunosuppressive regimen to balance the risk of rejection with the risk of infection *[see **Adverse Reactions (6.1)**]*.

5.3 Graft Rejection and Other Serious Adverse Reactions due to Medication Errors

Medication errors, including substitution and dispensing errors, between tacrolimus immediate-release products and tacrolimus extended-release products were reported outside the U.S. This led to serious adverse reactions, including graft rejection, or other adverse reactions due to under- or over-exposure to tacrolimus. ENVARSUS XR is not interchangeable or substitutable with tacrolimus immediate-release products or other tacrolimus extended-release products. Instruct patients and caregivers to recognize the appearance of ENVARSUS XR tablet [*see **Dosage Forms and Strengths (3)***].

5.4 New Onset Diabetes After Transplant

ENVARSUS XR caused new onset diabetes after transplant (NODAT) in kidney transplant patients, which may be reversible in some patients. African-American and Hispanic kidney

transplant patients are at an increased risk. Monitor blood glucose concentrations and treat appropriately [*see **Adverse Reactions (6.1)** and **Use in Specific Populations (8.8)***].

5.5 Nephrotoxicity due to ENVARSUS XR and Drug Interactions

ENVARSUS XR, like other calcineurin-inhibitors, can cause acute or chronic nephrotoxicity. Consider dosage reduction in patients with elevated serum creatinine and tacrolimus whole blood trough concentrations greater than the recommended range. The risk for nephrotoxicity may increase when ENVARSUS XR is concomitantly administered with CYP3A inhibitors (by increasing tacrolimus whole blood concentrations) or drugs associated with nephrotoxicity (e.g., aminoglycosides, ganciclovir, amphotericin B, cisplatin, nucleotide reverse transcriptase inhibitors, protease inhibitors) *[see **Drug Interactions (7.2)**]*. Monitor renal function and consider dosage reduction if nephrotoxicity occurs.

5.6 Neurotoxicity

ENVARSUS XR may cause a spectrum of neurotoxicities. The most severe neurotoxicities include posterior reversible encephalopathy syndrome (PRES), delirium, seizure, and coma; others include tremors, paresthesias, headache, mental status changes, and changes in motor and sensory functions *[see **Adverse Reactions (6.1, 6.2)**]*. As symptoms may be associated with tacrolimus whole blood trough concentrations at or above the recommended range, monitor for neurologic symptoms and consider dosage reduction or discontinuation of ENVARSUS XR if neurotoxicity occurs.

5.7 Hyperkalemia

Mild to severe hyperkalemia, which may require treatment, has been reported with tacrolimus including ENVARSUS XR. Concomitant use of agents associated with hyperkalemia (e.g., potassium-sparing diuretics, ACE inhibitors, angiotensin receptor blockers) may increase the risk for hyperkalemia *[see **Adverse Reactions (6.1)**]*. Monitor serum potassium levels periodically during treatment.

5.8 Hypertension

Hypertension is a common adverse reaction of ENVARSUS XR therapy and may require antihypertensive therapy *[see **Adverse Reactions (6.1)**]*. Some antihypertensive drugs can increase the risk for hyperkalemia *[see **Warnings and Precautions (5.7)**]*. Calcium-channel blocking agents may increase tacrolimus blood concentrations and require dosage reduction of ENVARSUS XR *[see **Drug Interactions (7.2)**]*.

5.9 Risk of Rejection with Strong CYP3A Inducers and Risk of Serious Adverse Reactions with Strong CYP3A Inhibitors

The concomitant use of strong CYP3A inducers may increase the metabolism of tacrolimus, leading to lower whole blood trough concentrations and greater risk of rejection. In contrast, the concomitant use of strong CYP3A inhibitors may decrease the metabolism of tacrolimus, leading to higher whole blood trough concentrations and greater risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see **Warnings and Precautions (5.6, 5.10)**]* Therefore, adjust ENVARSUS XR dose and monitor tacrolimus whole blood trough concentrations when coadministering ENVARSUS XR with strong CYP3A inhibitors (e.g., telaprevir, boceprevir,

ritonavir, ketoconazole, itraconazole, voriconazole, clarithromycin) or strong CYP3A inducers (e.g., rifampin, rifabutin) *[see **Dosage and Administration (2.3)** and **Drug Interactions (7.2)**]*.

5.10 QT Prolongation

ENVARSUS XR may prolong the QT/QTc interval and cause Torsade de Pointes. Avoid ENVARSUS XR in patients with congenital long QT syndrome. Consider obtaining electrocardiograms and monitoring electrolytes (magnesium, potassium, calcium) periodically during treatment in patients with congestive heart failure, bradyarrhythmias, those taking certain antiarrhythmic medications or other products that lead to QT prolongation, and those with electrolyte disturbances (e.g., hypokalemia, hypocalcemia, or hypomagnesemia).

When coadministering ENVARSUS XR with other substrates and/or inhibitors of CYP3A, a reduction in ENVARSUS XR dosage, monitoring of tacrolimus whole blood concentrations, and monitoring for QT prolongation is recommended *[see **Drug Interactions (7.2)**]*.

5.11 Immunizations

Whenever possible, administer the complete complement of vaccines before transplantation and treatment with ENVARSUS XR.

Avoid the use of live attenuated vaccines during treatment with ENVARSUS XR (e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines).

Inactivated vaccines noted to be safe for administration after transplantation may not be sufficiently immunogenic during treatment with ENVARSUS XR.

5.12 Pure Red Cell Aplasia

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with tacrolimus. All of these patients reported risk factors for PRCA such as parvovirus B19 infection, underlying disease, or concomitant medications associated with PRCA. A mechanism for tacrolimus-induced PRCA has not been elucidated. If PRCA is diagnosed, consider discontinuation of ENVARSUS XR.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

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

In an open label, randomized, multinational conversion study, stable kidney transplant patients on a tacrolimus immediate-release product and concomitant immunosuppressants were randomized to treatment with ENVARSUS XR (N=162) or to continued treatment on the tacrolimus immediate-release product (N=162) and treated for a duration of 12 months *[see **Clinical Studies (14)**]*.

The proportion of patients who discontinued treatment due to adverse reactions was 7.4% and 1.2% in the ENVARSUS XR and tacrolimus immediate-release treatment groups, respectively, through 12 months of treatment. The most common adverse reactions leading to discontinuation of study drug in the ENVARSUS XR treatment group was cardiac arrest (2 events).

Infections

The overall incidence of infections, serious infections, and infections with identified etiology reported in stable kidney transplant recipients treated with ENVARSUS XR or tacrolimus immediate-release product are shown in **Table 1**.

Table 1. Percentage of Stable Patients with Infections Through One Year Post- Treatment in the Conversion Study [a]

	ENVARSUS XR ± steroids, MMF/MPS or AZA **N=162**	**Tacrolimus immediate-release product ± steroids, MMF/MPS or AZA** **N=162**
All infections	46%	48%
Respiratory Infections	26%	28%
Urinary Tract Infections	10%	14%
Bacterial Infections	7%	5%
Fungal Infections	4%	4%
Gastrointestinal Infections	4%	5%
BK virus [b]	2%	2%
Cytomegalovirus Infections	2%	1%
Serious Infections	8%	9%

[a] The stable kidney transplant study was not designed to support comparative claims of ENVARSUS XR compared to tacrolimus immediate-release product for the adverse reactions reported in this table.

[b] BK virus associated nephropathy (BKVAN) occurred in 1.2% (2/162) and 0.6% (1/162) in the ENVARSUS XR and tacrolimus immediate-release treatment groups, respectively.

New Onset Diabetes After Transplantation (NODAT)

New onset diabetes after transplantation (NODAT) was defined by the composite occurrence of fasting plasma glucose values ≥126 mg/dL, 2-hour postprandial plasma glucose of at least 200 mg/dL (in oral glucose tolerance test) on 2 or more consecutive occasions post baseline, insulin requirement for ≥31 days, an oral hypoglycemic agent use ≥31 days, or HbA_{1c} ≥6.5% (at least 3 months after randomization) among kidney transplant patients with no medical history of diabetes. The incidence of NODAT for the stable kidney transplant study through one year post-transplant is summarized in **Table 2** below *[see **Warnings and Precautions (5.4)**]*.

Table 2. Percentage of Stable Patients with NODAT Through 1 Year Post- Treatment in the Conversion Study [a]

	ENVARSUS XR ± steroids , MMF/MPS or AZA (N=90)	Tacrolimus immediate-release product ± steroids, MMF/MPS or AZA (N=95)
Composite NODAT [b]	10%	11%
HbA_{1c} ≥6.5%	3%	7%
Fasting Plasma Glucose Values ≥126 mg/dL on 2 consecutive occurrences	8%	6%
Oral hypoglycemic use	1%	1%
Insulin Use ≥31 days	1%	0%

[a] The stable kidney transplant study was not designed to support comparative claims of ENVARSUS XR compared to tacrolimus immediate-release product for the adverse reactions reported in this table.

[b] Analyses restricted to patients at risk for NODAT

Common Adverse Reactions

The incidence of adverse reactions that occurred in ≥5% of ENVARSUS XR-treated patients compared to tacrolimus immediate-release product through one year of treatment in the conversion study is shown by treatment group in **Table 3**.

Table 3. Adverse Reactions (≥ 5%) in Stable Kidney Transplant Patients Through 1 Year Post- Treatment in the Conversion Study[a]

Adverse Reaction	ENVARSUS XR N=162	Tacrolimus immediate-release product N=162
Diarrhea	14%	9%
Blood Creatinine Increased	12%	9%
Urinary Tract Infection	9%	14%
Nasopharyngitis	9%	11%
Headache	9%	7%
Upper Respiratory Tract Infection	7%	9%
Peripheral Edema	7%	6%
Hypertension	4%	6%

[a]The stable kidney transplant study was not designed to support comparative claims of ENVARSUS XR compared to tacrolimus immediate-release for the adverse reactions reported in this table.

6.2 Postmarketing Experience

The following adverse reactions have been reported from marketing experience with tacrolimus in the U.S. and outside the U.S. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: Agranulocytosis, decreased blood fibrinogen, disseminated intravascular coagulation, hemolytic anemia, hemolytic uremic syndrome, pancytopenia, prolonged activated partial thromboplastin time, pure red cell aplasia [*see **Warnings and Precaution (5.12)***], thrombocytopenic purpura, thrombotic thrombocytopenic purpura

Cardiac Disorders: Atrial fibrillation, atrial flutter, cardiac arrhythmia, cardiac arrest, electrocardiogram T wave abnormal, flushing, myocardial hypertrophy, myocardial infarction, myocardial ischaemia, pericardial effusion, QT prolongation, supraventricular extrasystoles, supraventricular tachycardia, Torsade de Pointes, deep limb venous thrombosis, ventricular fibrillation

Ear Disorders: Hearing loss including deafness

Eye Disorders: Blindness, photophobia, optic atrophy

Gastrointestinal Disorders: Colitis, dysphagia, gastrointestinal perforation, impaired gastric emptying, intestinal obstruction, mouth ulceration, peritonitis, stomach ulcer

Hepatobiliary Disorders: Bile duct stenosis, cholangitis, cirrhosis, fatty liver, hepatic cytolysis, hepatic failure, hepatic necrosis, hepatic steatosis, jaundice, hemorrhagic pancreatitis, necrotizing pancreatitis, venoocclusive liver disease

Hypersensitivity Reactions: Hypersensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria

Immune System Disorders: Graft versus host disease (acute and chronic)

Metabolism and Nutrition Disorders: Glycosuria, increased amylase, pancreatitis

Musculoskeletal and Connective Tissue Disorders: Myalgia, polyarthritis, rhabdomyolysis

Neoplasms: Lymphoma including EBV-associated lymphoproliferative disorder, PTLD [*see **Warnings and Precautions (5.1)***]; leukemia

Nervous System Disorders: Carpal tunnel syndrome, cerebral infarction, coma, dysarthria, flaccid paralysis, hemiparesis, mental disorder, mutism, nerve compression, posterior reversible encephalopathy syndrome (PRES) [*see **Warnings and Precautions (5.6)***], progressive multifocal leukoencephalopathy (PML) sometimes fatal [*see **Warnings and Precautions (5.2)***], quadriplegia, speech disorder, status epilepticus, syncope

Renal and Urinary Disorder: Acute renal failure, hemorrhagic cystitis, hemolytic uremic syndrome, micturition disorder

Respiratory, Thoracic and Mediastinal Disorders: Acute respiratory distress syndrome, interstitial lung disease, lung infiltration, pulmonary hypertension, respiratory distress, respiratory failure

Skin and Subcutaneous Tissue Disorders: Hyperpigmentation, photosensitivity

7 DRUG INTERACTIONS

7.1 Mycophenolic Acid

When ENVARSUS XR is prescribed with a given dose of mycophenolic acid (MPA) product, exposure to MPA is higher with ENVARSUS XR coadministration than with cyclosporine coadministration because cyclosporine interrupts the enterohepatic recirculation of MPA while tacrolimus does not. Monitor for MPA associated adverse reactions and reduce the dose of concomitantly administered mycophenolic acid products as needed.

7.2 Effects of Other Drugs/Substances on ENVARSUS XR

Table 4. Effects of Other Drugs/Substances on ENVARSUS XR[a]

Drug/Substance Class or Name	Drug Interaction Effect	Recommendations
Grapefruit or grapefruit juice[b]	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see **Warnings and Precautions (5.6, 5.10)**]*	Avoid grapefruit or grapefruit juice
Alcohol	May modify the rate of tacrolimus release	Avoid alcoholic beverages
Strong CYP3A Inducers[c] such as: Antimycobacterials (e.g., rifampin, rifabutin), anticonvulsants (e.g., phenytoin, carbamazepine and phenobarbital), St John's Wort	May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection *[see **Warnings and Precautions (5.9)**]*	Increase ENVARSUS XR dose and monitor tacrolimus whole blood trough concentrations *[see **Dosage and Administration (2.3)** and **Clinical Pharmacology (12.2)**]*
Strong CYP3A Inhibitors[c], such as: Protease inhibitors (e.g., nelfinavir, telaprevir, boceprevir, ritonavir), azole antifungals (e.g., voriconazole, posaconazole, itraconazole, ketoconazole), antibiotics (e.g., clarithromycin, troleandomycin, chloramphenicol), nefazodone	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see **Warnings and Precautions (5.6, 5.9, 5.10)**]*	Reduce ENVARSUS XR dose (for voriconazole and posaconazole, give one-third of the original dose) and adjust dose based on tacrolimus whole blood trough concentrations *[see **Dosage and Administration (2.3)** and **Clinical Pharmacology (12.2)**]*

Mild or Moderate CYP3A Inhibitors, such as: antibiotics (e.g., erythromycin), calcium channel blockers (e.g., verapamil, diltiazem, nifedipine, nicardipine), amiodarone, danazol, ethinyl estradiol, cimetidine, lansoprazole and omeprazole, azole antifungals (e.g., clotrimazole, fluconazole)	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see **Warnings and Precautions (5.6, 5.10)**]*	Monitor tacrolimus whole blood trough concentrations and reduce ENVARSUS XR dose if needed *[see **Dosage and Administration (2.3), Clinical Pharmacology (12.2)**]*
Other drugs, such as: Magnesium and aluminum hydroxide antacids Metoclopramide	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see **Warnings and Precautions (5.6, 5.10)**]*	Monitor tacrolimus whole blood trough concentrations and reduce ENVARSUS XR dose if needed *[see **Dosage and Administration (2.3), Clinical Pharmacology (12.2)**]*
Mild or Moderate CYP3A Inducers, such as: Methylprednisolone, prednisone	May decrease tacrolimus concentrations	Monitor tacrolimus whole blood trough concentrations and adjust ENVARSUS XR dose if needed [*see **Dosage and Administration (2.3)**]*

[a] ENVARSUS XR dosage adjustment recommendation based on observed effect of coadministered drug on tacrolimus exposures *[see **Clinical Pharmacology (12.2)**]*, literature reports of altered tacrolimus exposures, or the other drug's known CYP3A inhibitor/inducer status
[b] High dose or double strength grapefruit juice is a *strong* CYP3A inhibitor; low dose or single strength grapefruit juice is a *moderate* CYP3A inhibitor
[c] Strong CYP3A inhibitor/inducer, based on reported effect on exposures to tacrolimus along with supporting *in vitro* CYP3A inhibitor/inducer data, or based on drug-drug interaction studies with midazolam (sensitive CYP3A probe substrate)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C
There are no adequate and well-controlled studies in pregnant women. Tacrolimus is transferred across the placenta. The use of tacrolimus during pregnancy in humans has been associated with neonatal hyperkalemia and renal dysfunction.

Tacrolimus given orally to pregnant rabbits at 0.7 times the maximum clinical dose and pregnant rats at 1.1 times the maximum clinical dose was associated with an increased incidence of fetal death *in utero*, fetal malformations (cardiovascular, skeletal, omphalocele, and gallbladder agenesis) and maternal toxicity. ENVARSUS XR should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

In pregnant rabbits, tacrolimus at oral doses of 0.32 and 1.0 mg/kg (0.7 and 2.3 times the maximum clinical dose based on body surface area, respectively) was associated with maternal toxicity as well as an increased incidence of abortions. At the 1 mg/kg dose, fetal rabbits showed an increased incidence of malformations (ventricular hypoplasia, interventricular septal defect, bulbous aortic arch, stenosis of ductus arteriosis, interrupted ossification of vertebral arch, vertebral and rib malformations, omphalocele, and gallbladder agenesis) and developmental variations. In pregnant rats, tacrolimus at oral doses of 3.2 mg/kg (3.7 times the maximum clinical dose) was associated with maternal toxicity, an increase in late resorptions, decreased numbers of live births, and decreased pup weight and viability. Tacrolimus, given orally to pregnant rats after organogenesis and during lactation at 1.0 and 3.2 mg/kg (1.2 and 3.7 times the maximum recommended clinical dose, respectively) was associated with reduced pup weights and pup viability (3.2 mg/kg only); among the high dose pups that died early, an increased incidence of kidney hydronephrosis was observed.

8.3 Nursing Mothers

Tacrolimus is present in breast milk. Because of the potential for serious adverse drug reactions in nursing infants from ENVARSUS XR, a decision should be made whether to discontinue nursing or to discontinue ENVARSUS XR, taking into account the importance of drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of ENVARSUS XR in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of ENVARSUS XR did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In the stable kidney transplant study, there were 17 patients 65 years of age and older, and no patients were over 75 years *[see **Clinical Studies (14)**]*. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Impairment

The pharmacokinetics of tacrolimus in patients with renal impairment was similar to that in healthy subjects with normal renal function. However, due to its potential for nephrotoxicity, monitoring of renal function in patients with renal impairment is recommended; tacrolimus dosage should be reduced if indicated [*see **Warnings and Precautions (5.5), Clinical Pharmacology (12.2)***].

8.7 Hepatic Impairment

The mean clearance of tacrolimus was substantially lower in patients with severe hepatic impairment (mean Child-Pugh score: >10) compared to healthy subjects with normal hepatic function [*see **Clinical Pharmacology (12.2)***]. With greater tacrolimus whole blood trough concentrations in patients with severe hepatic impairment, there is a greater risk of adverse reactions and dosage reduction is recommended *[see **Dosage and Administration (2.2)**]*. For

patients with moderate hepatic impairment, monitor tacrolimus whole blood trough concentrations. For patients with mild hepatic impairment, no dosage adjustments are needed.

8.8 Race

African-American patients may need to be titrated to higher ENVARSUS XR dosages to attain comparable trough concentrations compared to Caucasian patients [*see **Dosage and Administration (2.1), Clinical Pharmacology (12.2))***]

10 OVERDOSAGE

Postmarketing cases of overdose with tacrolimus have been reported. Overdosage adverse reactions included:

- nervous system disorders (tremor, headache, confusional state, balance disorders, encephalopathy, lethargy and somnolence)
- gastrointestinal disturbances (nausea, vomiting, and diarrhea)
- abnormal renal function (increased blood urea nitrogen and elevated serum creatinine)
- urticaria
- hypertension
- peripheral edema, and
- infections [one fatal postmarketing case of bilateral pneumopathy and CMV infection was attributed to tacrolimus (extended-release capsules) overdose].

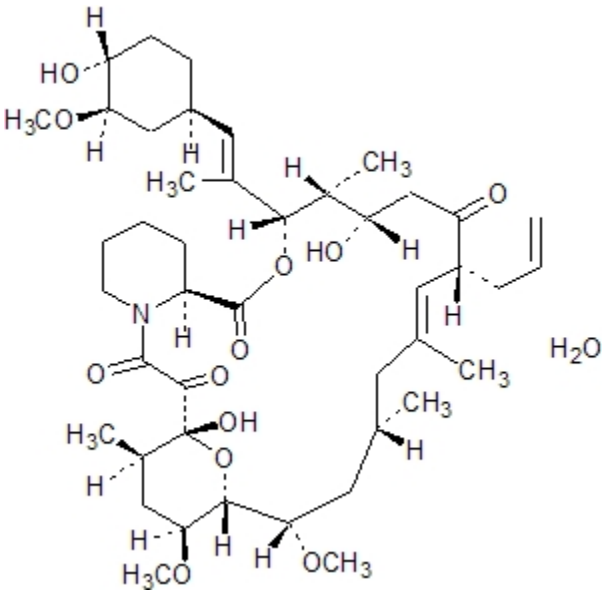
Based on the poor aqueous solubility and extensive erythrocyte and plasma protein binding, it is anticipated that tacrolimus is not dialyzable to any significant extent; there is no experience with charcoal hemoperfusion. The oral use of activated charcoal has been reported in treating acute overdoses, but experience has not been sufficient to warrant recommending its use. General supportive measures and treatment of specific symptoms should be followed in all cases of overdosage.

11 DESCRIPTION

ENVARSUS XR, a calcineurin-inhibitor immunosuppressant, is available for oral administration as extended-release tablets containing the equivalent of 0.75 mg, 1 mg, or 4 mg of anhydrous tacrolimus USP. Inactive ingredients include hypromellose USP, lactose monohydrate NF, polyethylene glycol NF, poloxamer NF, magnesium stearate NF, tartaric acid NF, butylated hydroxytoluene NF, and dimethicone NF.

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

The chemical structure of tacrolimus is:



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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin (an ubiquitous mammalian intracellular enzyme) is then formed and the phosphatase activity of calcineurin inhibited. Such inhibition prevents the dephosphorylation and translocation of various factors such as the nuclear factor of activated T-cells (NF-AT) and nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB).

Tacrolimus inhibits the expression and/or production of several cytokines that include interleukin (IL)-1 beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, gamma interferon, tumor necrosis factor-alpha, and granulocyte macrophage colony stimulating factor. Tacrolimus also inhibits IL-2 receptor expression and nitric oxide release, induces apoptosis and production of transforming growth factor-beta that can lead to immunosuppressive activity. The net result is the inhibition of T-lymphocyte activation and proliferation as well as T-helper-cell-dependent B-cell response (i.e., immunosuppression).

12.2 Pharmacokinetics

Table 5 summarizes the pharmacokinetic (PK) parameters of tacrolimus following oral administration of once-daily ENVARSUS XR in healthy subjects and in kidney transplant patients, under fasted conditions. Whole blood tacrolimus concentrations in the pharmacokinetic studies were measured using validated HPLC/MS/MS assays.

Table 5. Pharmacokinetic Parameters of ENVARSUS XR by Study Day in Healthy Subjects and Kidney Transplant Patients Under Fasted Conditions

Population	ENVARSUS	Day[b]	Pharmacokinetic Parameters of ENVARSUS XR

	XR Dose[a]		C_{max}[c] (ng/mL)	T_{max}[d] (hr)	AUC_{24}[c] (ng•hr/mL)	C_{24}[h] (ng/mL)
Healthy Subjects (n=19)	2 mg 2 mg	Day 1 Day 10	11.9 ± 3.8 8.3 ± 2.9	14.0 [6 - 28] 8.0 [1.0-12.0]	50 ± 14 140 ± 50	1.8 ± 0.6 4.6 ± 1.7
Adult Kidney *De novo*[e] (n=21)	11.8 mg[f] 10 mg 9.5mg	Day 1 Day 7 Day 14	11.8 ± 7.2 25.1 ± 16.3 27.1 ± 13.4	8.0 [4-24] 6.0 [2-12] 4.0 [1-8]	138 ± 80 335 ± 129 371 ± 104	5.2 ± 2.7 9.9 ± 4.4 11.4 ± 4.1[j]
Adult Kidney *De novo* (n=10)	15.5 mg[g] 11.4 mg 11.1 mg	Day 1 Day 14 Day 28	33.6 ± 21.8 31.1 ± 14.6 35.9± 18.7	6.0 [4-24] 4.0 [1-18] 4.0 [1-14]	377 ± 257 376 ± 140 396 ± 150	11.0 ± 6.1 9.1 ± 3.0 10.5 ± 3.2
Adult Kidney (≥ 6 months post-transplant) (n=47)	5.3 mg	Day 7[i]	13.5 ± 4.8	6.0 [1 - 16]	216 ± 63	7.0 ± 2.3

Healthy adult subjects (administered mg/day dose); Adult *de novo* kidney transplant patients (group average of administered mg/day dose); Adult kidney ≥ 6 months post-transplant (group average of administered mg/day dose of ENVARSUS XR, following conversion to 67% to 80% of the daily tacrolimus immediate-release capsules dose)
Day of ENVARSUS XR dosing and PK profiling
Arithmetic means ± S.D.
Median [range]
"*De novo*" refers to immunosuppression starting at the time of transplantation
Starting ENVARSUS XR dose = 0.14 mg/kg/day
Starting ENVARSUS XR dose = 0.17 mg/kg/day. In *de novo* kidney transplant patients who received ENVARSUS XR starting dose of 0.17 mg/kg/day achieved higher than recommended target tacrolimus trough concentrations, as high as 57 ng/mL during the first 1 to 2 weeks post-transplant
Tacrolimus trough concentration before the next dose
After 7 days of stable dosing with ENVARSUS XR
AUC_{0-24} –to- C_{24} correlation coefficient (r) at steady state was 0.80 or higher

In adult kidney transplant patients ≥ 6 months post-transplant switched to ENVARSUS® XR at 67% to 80% of the daily dose of tacrolimus immediate-release capsules, the steady state tacrolimus exposures (AUC_{24}) and tacrolimus trough concentrations (C_{24}) were comparable to the AUC_{24} and C_{24} measured prior to the switch. However, the mean C_{max} estimate was 30% lower and the median T_{max} was more prolonged (6 hours versus 2 hours) following administration of Envarsus XR as compared to that of tacrolimus immediate-release capsules.

Absorption

Absorption of tacrolimus from the gastrointestinal tract after oral administration is incomplete and variable. 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 C_{24} of tacrolimus increased linearly and the elimination half-life did not change with increasing doses.

Food Effects

The presence of a meal affects the absorption of tacrolimus; the rate and extent of absorption is greatest under fasted conditions. In 26 healthy subjects, administration of ENVARSUS XR following a high-fat breakfast reduced the systemic exposure (AUC) to tacrolimus by

approximately 55% and the peak plasma concentration of tacrolimus (C_{max}) by 22%, with no effect on the time to reach maximum plasma concentration (T_{max}), compared to when ENVARSUS XR was administered under fasted conditions.

Chronopharmacokinetic Effect

In 26 healthy subjects, administration of ENVARSUS XR tablets in the evening resulted in a 15% lower $AUC_{0\text{-}inf}$, and a 20% lower C_{24}, as compared to morning dosing.

Distribution

The plasma protein binding of tacrolimus is approximately 99% and is independent of concentration over a range of 5-50 ng/mL. Tacrolimus is bound mainly to albumin and alpha-1-acid glycoprotein, and has a high level of association with erythrocytes. The distribution of tacrolimus between whole blood and plasma depends on several factors, such as hematocrit, temperature at the time of plasma separation, drug concentration, and plasma protein concentration. In a U.S. trial in which tacrolimus was administered as immediate-release formulation, the ratio of whole blood concentration to plasma concentration averaged 35 (range 12 to 67).

Metabolism

The desired pharmacological activity of tacrolimus is primarily due to the parent drug. Tacrolimus is extensively metabolized by the mixed-function oxidase system, primarily the cytochrome P-450 system 3A (CYP3A). A metabolic pathway leading to the formation of 8 possible metabolites has been proposed. Demethylation and hydroxylation were identified as the primary mechanisms of biotransformation *in vitro*. The major metabolite identified in incubations with human liver microsomes is 13-demethyl tacrolimus. In *in vitro* studies, a 31-demethyl metabolite has been reported to have the same activity as tacrolimus.

Excretion

In a mass balance study of orally administered radiolabeled tacrolimus to 6 healthy subjects, the mean recovery of the radiolabel was 94.9 ± 30.7%. Fecal elimination accounted for 92.6 ± 30.7% and urinary elimination accounted for 2.3 ± 1.1% of the total radiolabel administered. The elimination half-life based on radioactivity was 31.9 ± 10.5 hours, whereas it was 48.4 ± 12.3 hours based on tacrolimus concentrations. The mean clearance of radiolabel was 0.226 ± 0.116 L/hr/kg and the mean clearance of tacrolimus was 0.172 ± 0.088 L/hr/kg.

The elimination half-life of tacrolimus after oral administration of 2 mg ENVARSUS XR once-daily for 10 days was 31.0 ± 8.1 hours (mean ± SD) in 25 healthy subjects.

Specific Populations

No dedicated pharmacokinetic studies in specific populations were conducted with ENVARSUS XR.

Renal Impairment

Tacrolimus pharmacokinetics following a single administration of tacrolimus (administered as a continuous IV infusion) were determined in 12 patients (7 not on dialysis and 5 on dialysis, serum creatinine of 3.9±1.6 and 12.0±2.4 mg/dL, respectively) prior to their kidney transplant. The mean clearance of tacrolimus in patients with renal dysfunction given IV tacrolimus was similar to that in healthy subjects given tacrolimus IV and in healthy subjects given oral tacrolimus immediate-release [*see **Use in Specific Populations (8.6)***].

Hepatic Impairment

Tacrolimus pharmacokinetics have been determined in 6 patients with mild hepatic impairment (mean Pugh score: 6.2) following single oral administration of tacrolimus immediate-release. The mean clearance of tacrolimus in patients with mild hepatic impairment was not substantially different from that in healthy subjects. Tacrolimus pharmacokinetics were studied in 6 patients with severe hepatic impairment (mean Pugh score: >10). The mean clearance was substantially lower in patients with severe hepatic impairment [*see **Dosage and Administration (2.2), Use in Specific Populations (8.7)***].

Race

The pharmacokinetics of tacrolimus was studied following single oral administration of tacrolimus immediate-release (5 mg) in 10 African-American, 12 Latino-American, and 12 Caucasian healthy subjects:

- The mean (±SD) tacrolimus C_{max} in African-Americans (23.6±12.1 ng/mL) was lower than in Caucasians (40.2±12.6 ng/mL) and Latino-Americans (36.2±15.8 ng/mL).
- Mean $AUC_{0\text{-}inf}$ tended to be lower in African-Americans (203±115 ng·hr/mL) than Caucasians (344±186 ng·hr/mL) and Latino-Americans (274±150 ng·hr/mL).
- The mean (±SD) absolute oral bioavailability (F) in African-Americans (12±4.5%) and Latino-Americans (14±7.4%) was lower than in Caucasians (19±5.8%).
- There was no significant difference in mean terminal half-life among the three ethnic groups (range from approximately 25 to 30 hours) [*see **Dosage and Administration (2.1), Use in Specific Populations (8.8)***].

Gender

A formal trial to evaluate the effect of gender on tacrolimus pharmacokinetics has not been conducted. In a sub-group analysis from two combined Phase 3 studies in kidney transplant recipients performed with ENVARSUS XR over one year of treatment, no gender-dependent differences in tacrolimus systemic exposures were observed.

Drug Interaction Studies

No drug-drug interaction studies were conducted specifically with ENVARSUS XR.

Because tacrolimus is metabolized mainly by CYP3A enzymes, drugs or substances known to inhibit these enzymes and/or are known CYP3A substrates may increase tacrolimus whole blood concentrations. Drugs known to induce CYP3A enzymes may decrease tacrolimus whole blood concentrations *[see **Warnings and Precautions (5.9), Drug Interactions (7.2)**]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in male and female rats and mice. In the 80-week mouse oral study and in the 104-week rat oral study, no relationship of tumor incidence to tacrolimus dosage was found. The highest dose used in the mouse was 3.0 mg/kg/day (0.84 times the AUC at

the maximum clinical dose of 0.14 mg/kg/day) and in the rat was 5.0 mg/kg/day (0.24 times the AUC at the maximum clinical dose of 0.14 mg/kg/day) [*see **Boxed Warning, Warnings and Precautions (5.1)***].

A 104-week dermal carcinogenicity study was performed in mice with tacrolimus ointment (0.03%-3%), equivalent to tacrolimus doses of 1.1-118 mg/kg/day or 3.3-354 mg/m^2/day. In the study, the incidence of skin tumors was minimal and the topical application of tacrolimus was not associated with skin tumor formation under ambient room lighting. However, a statistically significant elevation in the incidence of pleomorphic lymphoma in high-dose male (25/50) and female animals (27/50) and in the incidence of undifferentiated lymphoma in high-dose female animals (13/50) was noted in the mouse dermal carcinogenicity study. Lymphomas were noted in the mouse dermal carcinogenicity study at a daily dose of 3.5 mg/kg (0.1% tacrolimus ointment; 2.5-fold the human exposure in stable adult renal transplant patients converted from tacrolimus immediate-release product to ENVARSUS XR). No drug-related tumors were noted in the mouse dermal carcinogenicity study at a daily dose of 1.1 mg/kg (0.03% tacrolimus ointment). The relevance of topical administration of tacrolimus in the setting of systemic tacrolimus use is unknown.

The implications of these carcinogenicity studies are limited; doses of tacrolimus were administered that likely induced immunosuppression in these animals, impairing their immune system's ability to inhibit unrelated carcinogenesis.

Mutagenesis

No evidence of genotoxicity was seen in bacterial (*Salmonella* and *E. coli*) or mammalian (Chinese hamster lung-derived cells) *in vitro* assays of mutagenicity, the *in vitro* CHO/HGPRT assay of mutagenicity, or *in vivo* clastogenicity assays performed in mice; tacrolimus did not cause unscheduled DNA synthesis in rodent hepatocytes.

Impairment of Fertility

Tacrolimus given orally at 1.0 mg/kg (1.2 times the maximum clinical dose based on body surface area) to male and female rats, prior to and during mating, as well as to dams during gestation and lactation, was associated with embryolethality and adverse effects on female reproduction. Effects on female reproductive function (parturition) and embryolethal effects were indicated by a higher rate of pre-implantation loss and increased numbers of undelivered and nonviable pups. When given at 3.2 mg/kg (3.7 times the maximum clinical dose based on body surface area), tacrolimus was associated with maternal and paternal toxicity as well as reproductive toxicity including marked adverse effects on estrus cycles, parturition, pup viability, and pup malformations.

14 CLINICAL STUDIES

Conversion Study from Tacrolimus Immediate-Release in Stable Kidney Transplant Recipients

The conversion study was a randomized, open-label, multinational study evaluating once daily ENVARSUS XR when used to replace tacrolimus immediate-release administered twice daily for maintenance immunosuppression to prevent acute allograft rejection in stable adult kidney transplant patients. Patients who received a kidney transplant 3 months to 5 years before study entry and on a stable dose of tacrolimus immediate-release of at least 2 mg per day and tacrolimus whole blood trough concentrations between 4 and 15 ng/mL were randomized to 1)

switch from twice daily tacrolimus immediate-release to once daily ENVARSUS XR (N=163) or 2) continue tacrolimus immediate-release twice daily (N=163). MMF or mycophenolate sodium (MPS), or azathioprine (AZA) and/or corticosteroids were allowed as concomitant immunosuppressants during the study period according to the standard of care at the participating site.

The mean age of study population was 50 years; 67% were male; 73% were Caucasian, 22% were African-American, 2% were Asian and 3% were categorized as other races. Living donors provided 35% of the organs and 65% of patients received a kidney transplant from a deceased donor. Premature discontinuation from treatment at the end of one year occurred in 13% of ENVARSUS XR patients and 6% of tacrolimus immediate-release patients.

Study Drug: Tacrolimus

In the conversion study, stable kidney transplant patients converted to ENVARSUS XR at an average daily dose that was 80% of their tacrolimus immediate-release daily dose prior to conversion. Mean tacrolimus whole blood trough concentrations were maintained within a relatively narrow range throughout the duration of the study for both the ENVARSUS XR conversion group and the tacrolimus immediate-release continuation group. At Week 1 (after 7 days of stable dosing), the mean ± SD tacrolimus trough concentrations were 7.2 ± 3.1 ng/mL for the ENVARSUS XR conversion group and 7.7 ± 2.5 for the tacrolimus immediate-release continuation group; the baseline values were 7.8 ± 2.3, and 8.0 ± 2.3, respectively.

Study Drug: MMF

In the conversion study, the average daily mycophenolate equivalent doses were comparable between the ENVARSUS XR and tacrolimus immediate-release treatment groups.

Efficacy Results

The efficacy failure rates including patients who developed BPAR, graft failure, death, and/or lost to follow-up at 12 months, as well as the rates of the individual events, are shown by treatment group in **Table 6** for the modified intent-to-treat population.

Table 6. Incidence of BPAR, Graft Loss, Death or Lost to Follow-up at 12 Months in Stable Kidney Transplant Patients

	ENVARSUS XR ± Steroids ± MMF, MPS, or AZA N=162	**Tacrolimus Immediate-Release ± Steroids ± MMF, MPS, or AZA N=162**
Overall Treatment Difference of efficacy failure compared to tacrolimus immediate-release (95% CI)[a]	0% (-4.2%, 4.2%)	
Treatment Failure	4 (2.5%)	4 (2.5%)
Biopsy Proven Acute Rejection	2 (1.2%)	2 (1.2%)
Graft Failure	0%	0%

Death	2 (1.2%)	1 (0.6%)
Lost to Follow-up	0%	1 (0.6%)

[a] 95% CI was calculated using an exact method that is based on the standardized statistic and inverting a 2-sided test

Glomerular Filtration Rates

The mean estimated glomerular filtration rates (eGFR), using the Modification of Diet in Renal Disease 7 (MDRD7) formula, were 61.5 ml/min/1.73 m^2 and 60.0 ml/min/1.73 m2 at baseline (Day 0) and 62.0 ml/min/1.73 m^2 and 61.4 ml/min/1.73 m^2 at 12 months in the ENVARSUS XR and tacrolimus immediate-release treatment groups, respectively.

16 HOW SUPPLIED/STORAGE AND HANDLING

ENVARSUS XR is supplied in round bottles (see Table 7); the statement 'ONCE-DAILY' appears on its label.

Table 7. Strengths of ENVARSUS XR

0.75 mg	Oval, white to off-white uncoated extended-release tablet, debossed with "0.75" on one side and "TCS" on the other side. The tablets are supplied in 30-count (NDC 68992-3075-3) and 100-count (NDC 68992-3075-1) 40 ml HDPE bottles with twist off caps.
1 mg	Oval, white to off-white uncoated extended-release tablet, debossed with "1" on one side and "TCS" on the other side. The tablets are supplied in 30-count (NDC 68992-3010-3 and 100-count (NDC 68992-3010-1) 40 ml HDPE bottles with twist off caps.
4 mg	Oval, white to off-white uncoated extended-release tablet, debossed with "4" on one side and "TCS" on the other side. The tablets are supplied in 30-count 40 ml HDPE bottles (NDC 68992-3040-3) and 100-count 75 ml HDPE bottles (NDC 68992-3040-1) with twist off caps.

Store and Dispense

Store at 25 °C (77 °F); excursions permitted to 15 °C-30 °C (59 °F-86 °F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Administration

Advise patients to:

- Inspect their ENVARSUS XR medicine when they receive a new prescription and before taking it. If the appearance of the tablet is not the same as usual, or if dosage instructions have changed, advise patients to contact their healthcare provider as soon as possible to

make sure that you have the right medicine. Other tacrolimus products cannot be substituted for ENVARSUS XR [*see **Warnings and Precautions (5.3)***].

- Take once-daily ENVARSUS XR at the same time every day (preferably in the morning) on an empty stomach to ensure consistent and maximum possible drug concentrations in the blood.
- Swallow tablet whole with liquid, preferably water. Do not chew, divide or crush tablet.
- Avoid alcohol, grapefruit, and grapefruit juice while on ENVARSUS XR [*see **Dosage and Administration (2.1), Drug Interactions (7.2)***].
- Take a missed dose as soon as possible but not more than (b)(4) hours after the scheduled time. Beyond the (b)(4)-hour timeframe, instruct the patient to wait until the usual scheduled time the following morning to take the next regularly scheduled dose. Do not take two doses at the same time. [*see **Dosage and Administration (2.1)***].

Development of Lymphoma and Other Malignancies

Inform patients that they are at an increased risk of developing lymphomas and other malignancies, particularly of the skin, due to immunosuppression. Advise patients to limit exposure to sunlight and ultraviolet (UV) light by wearing protective clothing and use a sunscreen with a high protection factor [*see **Boxed Warning, Warnings and Precautions (5.1)***].

Increased Risk of Infection

Inform patients that they are at an increased risk of developing a variety of infections, including opportunistic infections, due to immunosuppression and to contact their physician if they develop any symptoms of infection [*see **Boxed Warning, Warnings and Precautions (5.2)***].

New Onset Diabetes After Transplant

Inform patients that ENVARSUS XR can cause diabetes mellitus and should be advised to contact their physician if they develop frequent urination, increased thirst or hunger [*see **Warnings and Precautions (5.4)***].

Nephrotoxicity

Inform patients that ENVARSUS XR can have toxic effects on the kidney that should be monitored. Advise patients to attend all visits and complete all blood tests ordered by their medical team [*see **Warnings and Precautions (5.5)***].

Neurotoxicity

Inform patients that they are at risk of developing adverse neurologic effects including seizure, altered mental status, and tremor. Advise patients to contact their physician should they develop vision changes, delirium, or tremors [*see **Warnings and Precautions (5.6)***].

Hyperkalemia

Inform patients that ENVARSUS XR can cause hyperkalemia. Monitoring of potassium levels may be necessary, especially with concomitant use of other drugs known to cause hyperkalemia [*see **Warnings and Precautions (5.7)***].

Hypertension

Inform patients that ENVARSUS XR can cause high blood pressure which may require treatment with anti-hypertensive therapy [*see **Warnings and Precautions (5.8)***].

Drug Interactions

Instruct patients to tell their health care providers when they start or stop taking any concomitant medications, including prescription and non-prescription medicines, herbal and dietary supplements. Some medications could alter tacrolimus concentrations in the blood and thus may require the adjustment of the dosage of ENVARSUS XR [*see **Warnings and Precautions (5.9), Drug Interactions (7)***].

Immunizations

Inform patients that ENVARSUS XR can interfere with the usual response to immunizations and that they should avoid live vaccines [*see **Warnings and Precautions (5.11)***].

Product of Germany

Manufactured by:
Rottendorf Pharma GmbH
59320 Ennigerloh
North Rhine-Westphalia
Germany

Manufactured for:
Veloxis Pharmaceuticals, Inc.
499 Thornall Street, 3rd floor,
Edison, New Jersey 08837
United States

MEDICATION GUIDE
ENVARSUS XR® (En var' sus XR**)**
(tacrolimus extended-release tablets)

Read this Medication Guide before you start taking ENVARSUS XR and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about ENVARSUS XR, ask your doctor or pharmacist.

What is the most important information I should know about ENVARSUS XR?
ENVARSUS XR can cause serious side effects, including:

1. **Increased risk of cancer.** People who take ENVARSUS XR have an increased risk of getting some kinds of cancer, including skin and lymph gland cancer (lymphoma).

2. **Increased risk of infection.** ENVARSUS XR is a medicine that affects your immune system. ENVARSUS XR can lower the ability of your immune system to fight infections. Serious infections can happen in people receiving ENVARSUS XR that can cause death.

Call your doctor right away if you have symptoms of an infection such as:

- fever
- muscle aches
- cough or flu-like symptoms
- sweats or chills
- warm, red, or painful areas on your skin

What is ENVARSUS XR?

- ENVARSUS XR is a prescription medicine used with other medicines to help prevent organ

rejection in people who have had a kidney transplant.

- ENVARSUS XR is an extended-release tablet and is not the same as tacrolimus extended-release capsules or tacrolimus immediate-release capsules. Your doctor should decide what medicine is right for you.

Who should not take ENVARSUS XR?
Do not take ENVARSUS XR if you are allergic to tacrolimus or any of the ingredients in ENVARSUS XR. See the end of this leaflet for a complete list of ingredients in ENVARSUS XR.

What should I tell my doctor before taking ENVARSUS XR?
Before you take ENVARSUS XR, tell your doctor if you:

- plan to receive any live vaccines. Ask your doctor if you are not sure if your vaccine is a live vaccine.
- have or have had liver, kidney or heart problems.
- have any other medical conditions.
- are pregnant or plan to become pregnant. ENVARSUS XR may harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. ENVARSUS XR can pass into your breast milk. You and your doctor should decide if you will take ENVARSUS XR or breastfeed. You should not do both.

. **Tell your doctor about all the medicines you take,** including prescription and over-the-counter medicines, vitamins, and herbal supplements.

ENVARSUS XR may affect the way other medicines work, and other medicines may affect how ENVARSUS XR works.

How should I take ENVARSUS XR?

- Take ENVARSUS XR exactly as your doctor tells you to take it.
- Your doctor may change your dose of ENVARSUS XR if needed. **Do not** stop taking or change your dose of ENVARSUS XR without talking to your doctor.
- Take ENVARSUS XR once daily with fluid (preferably water) on an empty stomach at the same time each day (preferably in the morning).
- Take ENVARSUS XR tablets whole. **Do not** chew, divide or crush ENVARSUS XR tablets before swallowing. If you cannot swallow ENVARSUS XR tablets whole, tell your doctor.
- If you miss your dose of ENVARSUS XR, it should be taken as soon as possible, but no longer than (b) (4) hours, the missed dose should be skipped and the next dose should be taken the following morning at your regularly scheduled time. **Do not** take 2 doses at the same time.
- If you take too much ENVARSUS XR, call your doctor or go to the nearest hospital emergency room right away.

What should I avoid while taking ENVARSUS XR?

- Live vaccines such as flu vaccine through your nose, measles, mumps, rubella, polio by mouth, BCG (TB vaccine), yellow fever, chicken pox (varicella), or typhoid.
- Exposure to sunlight and UV light such as tanning machines. Wear protective clothing and use a

sunscreen.

- You should not eat grapefruit or drink grapefruit juice while taking ENVARSUS XR.
- You should not drink alcohol while taking ENVARSUS XR.

What are the possible side effects of ENVARSUS XR?
ENVARSUS XR may cause serious side effects, including:

- **See "What the most important information I should know about ENVARSUS XR?"**
- **graft rejection and other serious reactions.** People who take ENVARSUS XR have sometimes been given the wrong medicine because some medicines have the same ingredient (tacrolimus) as ENVARSUS XR. **Check your ENVARSUS XR when you get a new prescription to make sure you have received the right medicine**.
  - Call your doctor right away if you think you were given the wrong medicine.
  - Ask your doctor or pharmacist if you are not sure what ENVARSUS XR should look like.
- **high blood sugar (diabetes)**. Your doctor may do certain tests to check for diabetes while you take ENVARSUS XR. Call your doctor right away if you have:
  - frequent urination
  - increased thirst or hunger
  - blurred vision
  - confusion
  - drowsiness
  - loss of appetite
  - fruity smell on your breath
  - nausea, vomiting, or stomach pain
- **kidney problems**. Your doctor may do certain tests to check for kidney function while you take ENVARSUS XR.
- **nervous system problems**. Call your doctor right away if you get any of these symptoms while taking ENVARSUS XR. These could be signs of a serious nervous system problem:
  - confusion
  - coma
  - seizures
  - numbness and tingling
  - headache
  - vision changes
  - muscle tremors
- **high levels of potassium in your blood**. Your doctor may do certain tests to check your potassium level while you take ENVARSUS XR.
- **high blood pressure**. Your doctor will monitor your blood pressure while you take ENVARSUS XR.
- **changes in the electrical activity of your heart (QT prolongation).**

The most common side effects of ENVARSUS XR include, diarrhea, urinary tract infection, low red blood cell count (anemia), high blood pressure, and constipation.
These are not all the possible side effects of ENVARSUS XR. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ENVARSUS XR?

- Store ENVARSUS XR at room temperature between 68 ºF to 77 ºF (20 °C to 25 ºC).
- Safely throw away medicine that is out of date or no longer needed.

Keep ENVARSUS XR and all medicines out of reach of children.

General information about the safe and effective use of ENVARSUS XR.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ENVARSUS XR for a condition for which it was not prescribed. Do not give ENVARSUS XR to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about ENVARSUS XR. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about ENVARSUS XR that is written for health professionals. For more information, go to www.ENVARSUSXR.com or call 1-844-Veloxis (1-844-835-6947).

What are the ingredients in ENVARSUS XR?
Active ingredient: tacrolimus USP
Inactive ingredients: hypromellose USP, lactose monohydrate NF, polyethylene glycol NF, poloxamer NF, magnesium stearate NF, tartaric acid NF, butylated hydroxytoluene NF, and dimethicone NF
Manufactured by: **Rottendorf Pharma GmbH**, 59320 Ennigerloh, North Rhine-Westphalia, Germany Marketed by: **Veloxis Pharmaceuticals Inc.** 499 Thornall Street, 3rd floor Edison, New Jersey 08837, United States

This Medication Guide has been approved by the U.S. Food and Drug Administration.
Approved: Month/Year

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

/s/

HUSEYIN E VELIDEDEOGLU
07/09/2015
CLINICAL REVIEW OF ENVARSUS XR LABELING - CLASS 1 RESUBMISSION

OZLEM A BELEN
07/10/2015

RENATA ALBRECHT
07/10/2015

CLINICAL REVIEW

Application Type	NDA, 505(b)(2)
Application Number(s)	206-406
Priority or Standard	Standard
Submit Date(s)	December 28, 2013
Received Date(s)	December 30, 2013
PDUFA Goal Date	October 30, 2014
Division / Office	DTOP/OND
Reviewer Name(s)	Ergun Velidedeoglu
Review Completion Date	September 25, 2014
Established Name	Tacrolimus extended-release tablets
(Proposed) Trade Name	Envarsus XR
Therapeutic Class	Immunosuppressant/calcineurin inhibitor (CNI)
Applicant	Veloxis
Formulation(s)	Extended release tablet
Dosage Strength(s)	0.75 mg, 1 mg and 4 mg
Dosing Regimen	QD
Indication(s)	Prophylaxis of rejection in kidney transplant recipients
Intended Population(s)	De novo and stable kidney transplant recipients

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend the approval of Envarsus® XR ((tacrolimus extended release tablets)[1] for the prophylaxis of organ rejection in kidney transplant patients. I also recommend that a lower starting dose (or starting dose range) below the Applicant proposed (b) (4) mg/kg/day starting dose for de novo kidney transplant recipients be considered for labeling. For concerns and reviewer recommendations about the proposed starting dose see Section 1.2 and other relevant sections of this review.

LCP-Tacrolimus is an extended release formulation of tacrolimus, a macrolide immunosuppressant belonging to the calcineurin inhibitor (CNI) group of immunosuppressants produced by *Streptomyces tsukubaensis*. Tacrolimus was originally approved as an immediate-release formulation under the name Prograf ®. It was first approved by the FDA in 1994 for the prophylaxis of rejection in liver transplant recipients which was followed by the approval in kidney transplant recipients in 1997 and heart transplant recipients in 2006. In addition to Prograf, currently there are multiple generic tacrolimus immediate release formulations lawfully marketed in US.

The first extended release formulation of tacrolimus (Astagraf XL) was approved by the FDA for the prophylaxis of rejection in de novo kidney transplant recipients on July 19, 2013.

As evident from the regulatory history, the active moiety (tacrolimus) has been on the market for 20 years and has been used as the mainstay of the immunosuppressive regimens in the majority of transplant recipients not only for the approved indications but off-label in other types of organ and tissue transplantations.

NDA 206406 is a 505(b)(2) application and the listed drug product on which the applicant is relying for preclinical information is Prograf. The Applicant is seeking approval of the LCP-Tacrolimus extended release tablets for the prophylaxis of rejection in both the de novo and stable kidney transplant recipients (as conversion from Prograf) and submitted the results of two Phase 3 randomized controlled studies in addition to Phase 2 and Phase 1 studies in support of this indication. The Phase 3 studies LCP-Tacro 3002 and LCP-Tacro 3001, along with the Phase 2 study, LCP-Tacro 2017, were reviewed in support of the proposed indication demonstrate that the LCP-tacrolimus extended release tablets have comparable safety and efficacy to the active comparator Prograf immediate release capsules. These studies will be referred as 3002, 3001 and 2017, respectively, in the review.

[1] During drug development, this product was referred to as LCP-Tacrolimus or LCP-Tacro; therefore this name is used interchangeably in this review to refer to Envarsus XR (tacrolimus extended-release tablets).

1.2 Risk Benefit Assessment

In the risk/benefit analysis, the efficacy and safety of LCP-Tacrolimus extended release tablets were compared to the control, Prograf®. In the two Phase 3 randomized controlled studies 3002 and 3001 and the Phase 2 randomized controlled Study 2017. As detailed in the Efficacy section of this review, in the pivotal Study 3002, LCP-Tacro was shown to be non-inferior to Prograf within a 10% justified NI margin as agreed upon in the special protocol assessment (SPA) and there were no statistically significant differences between the efficacy rates of LCP-Tacro and Prograf in the other two studies 3001 and 2017.

As presented in the Safety section of this review, LCP-Tacrolimus based regimens used in de novo kidney transplant recipients (Phase 3 Study 3002 and the Phase 2 Study 2017) and used in stable kidney transplant recipients converted from Prograf (Phase 3 Study 3001) displayed a safety profile which is not much different from the safety profile of the Prograf based regimens. As expected, both the extended release formulation (LCP-Tacro) and the immediate release formulation (Prograf) share similar risks arising from the active moiety (tacrolimus) . These risks such as increased risk of opportunistic infections, malignancies which are common to all immunosuppressants and the risk of neurotoxicity which is specific to calcineurin inhibitors (CNI) including tacrolimus are well described in the Prograf package insert.

In all three studies no imbalances were observed between the LCP-Tacro groups and the Prograf groups with regards to deaths, graft loses, serious adverse events (SAEs), AEs, opportunistic infections, malignancies and other adverse events of interest, except for a higher number of patients with tacrolimus toxicity and BK virus associated nephropathy (BKVAN) events in the LCP-Tacro group of Study 3002, but not the other two studies..

The high number of tacrolimus toxicity cases (26 LCP-Tacro vs. 3 Prograf) and relatively higher number of BKVAN cases (6 LCP-Tacro vs. 3 Prograf) reported in the pivotal Phase 3 Study 3002 are most likely related to the Applicant's method of calculation of the LCP-Tacro daily doses based on the prescribed Prograf doses. While a patient randomized to Prograf would receive the actual dose prescribed, the patient who was randomized to Prograf would have that dose multiplied by a conversion factor of 1.7 to arrive at the LCP-Tacro dose. This approach resulted in unnecessary high dosing in the LCP-Tacro group especially early in the trial, and was spontaneously corrected later since the daily doses prescribed as Prograf doses for all patients in the study were titrated according to the observed trough levels. The calculation of the daily LCP-Tacro doses based on the prescribed Prograf doses was done to maintain blinding of the study and is not expected to occur in real clinical practice. The reason for this initial high LCP-Tacro dosing is explained in detail in Section 6.1.1.7 (Treatments administered in Study 3002).

This higher number of tacrolimus toxicity and BKVAN cases did not result in any deaths or graft loses and did not impact the overall safety profile of LCP-Tacro in Study 3002. Similar numerical imbalances with regards to the same safety events were not reported in the other two studies 3001 and 2017.

As explained in Section 6.1.1.4 of this review, The Study 3002 population is a highly select low cardiac risk patient population due to stringent exclusion criteria. Therefore the possibility of a different safety profile of LCP-Tacro tablets when used in a typical US de novo transplant patient population involving high cardiac risk patients cannot be ruled out especially if LCP-Tacro is used with the same high starting dose of 0.17 mg/kg/day as performed in Study 3002. Therefore it is prudent to recommend a lower starting dose such as 0.14 mg/kg/day evaluated in Study 2017 or alternatively a starting 'dose range' between 0.14 mg/kg/day and 0.17 mg/kg/day in the labeling. Subtherapeutic tacrolimus blood levels within the first few days after transplantation should not be a concern because almost all kidney transplant patients receive induction treatment and other concomitant immunosuppressives in current clinical practice.

Even if it is hypothesized that there may be a small increase in the risk of rejection due to subtherapeutic tacrolimus levels within the initial days after transplantation as a consequence of a suboptimal starting dose; this risk is probably of miniscule importance compared to the risk of a possible tacrolimus induced arrhythmia such as torsade de pointes in susceptible patients induced or perpetrated by supratherapeutic tacrolimus levels. Susceptible patients such as patients with long QT syndrome may even be more susceptible to arrhythmias during the immediate posttransplant period due to electrolyte imbalances and other factors.[2] As explained in Section 7.3.5 (Submission Specific Primary Safety Concerns) QTc prolongation is a common and independent predictor of mortality in end stage renal disease (ESRD) patients being evaluated for renal transplantation. I recommend that a lower starting dose or alternatively a starting dose range instead of the proposed (b) (4) mg/kg/day for LCP-Tacro in de novo kidney transplant recipients be considered for labeling and further discussed with the Clinical Pharmacology Team.

Therefore LCP-Tacrolimus extended release tablets have a favorable risk/benefit profile for the proposed indication of prophylaxis of rejection in de novo and stable kidney transplant recipients with the caveat about the starting dose explained above.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

LCP-Tacrolimus extended-release tablets are not interchangeable or substitutable with other tacrolimus products. The most important postmarketing concern is medication

2 Choi et al Torsades de pointes observed in the early postoperative period in a patient with long QT syndrome. Korean J Anesthesiol 2013 64(1): 89-90

errors due to potential confusion with tacrolimus immediate release formulation (Prograf and generics) and the other recently approved tacrolimus extended release formulation, Astagraf XL especially due to overlap in 1 mg strength for all three products. See Labeling Review by the Division of Medication Error Prevention and Analysis (DMEPA) dated August 26, 2014 and the table created by the DMEPA Reviewer (Table 1).

Table 1. Tacrolimus products
(Table created by the DMEPA Reviewer)

	Envarsus XR[***] (under review)	**Prograf** Approved 4/8/94	**Astagraf XL** Approved 7/19/13
NDA number	206406	050708	204096
Active Ingredient	Tacrolimus	Tacrolimus	Tacrolimus
Interchangeability	Not interchangeable with Prograf or Astagraf XL	Not interchangeable with Envarsus XR or Astagraf XL	Not interchangeable with Envarsus XR or Prograf
Indication of Use	Prophylaxis of organ rejection in patients receiving a kidney transplant	Prophylaxis of organ rejection in patients receiving a kidney, liver, or heart transplant	Prophylaxis of organ rejection in patients receiving a kidney transplant
Route of Administration	Oral	Oral	Oral
Dosage Form	Extended-release tablets	Immediate-release capsules	Extended-release capsules
Formulation Differences	LCP-Tacro tablets (MeltDose® drug-delivery technology)	Immediate Release product	Extended release hard gelatin capsules
Strengths	0.75 mg 1 mg 4 mg	0.5 mg 1 mg 5 mg	0.5 mg 1 mg 5 mg
Dose and Frequency	(b) (4) mg/kg once daily at the same time	0.1 to 0.2 mg/kg/day in two divided doses	0.15 mg/kg once daily at the same time

As a consequence of these potential medication errors serious tacrolimus underdosing or overdosing can occur. Underdosing may result in graft rejection and overdosing may result in opportunistic infections and malignancies in the long term if not recognized early by observing the trough concentrations.

At the pre-NDA meeting, held on August 7, 2013, the Division requested the Applicant provide a plan, including planned communications (e.g., (b) (4)

*** This document contains proprietary and confidential information that should not be released to the public.

(b) (4)) and a Medication Guide to address possible medication errors due to lack of interchangeability of LCP-Tacrolimus extended release tablets with any other tacrolimus formulation. As part of the current NDA submission the Applicant provided a draft (b) (4) and a Medication Guide in addition to other measures implemented to prevent confusion such as the physical features of the carton/container labeling (e.g., shape, size, dress, color).

DMEPA found the medication error reducing strategies proposed by the Applicant acceptable. The proposed strategies are the same as those were used for Astagraf XL in US and the European Union and no medication errors have been identified so far. To be consistent with Astagraf XL program, DMEPA recommended that the Applicant also develop Dear Pharmacist and Dear Professional Society letters to ensure further communication and reinforce the information that the three formulations are different and are not interchangeable and warn of the potential for confusion among these products. I agree with these recommendations and the request for developing Dear Pharmacist and Dear Professional Society letters has been communicated to the Applicant. Comments for these "Dear" letters will also be sent pending the result of Office of Prescription Drug Promotion (OPDP) consultative review and recommendations.

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

2.1 Product Information

The subject of this 505(b)(2) NDA is Envarsus® XR (tacrolimus extended release tablets, once daily for the indication of prophylaxis of organ rejection in patients receiving kidney transplants. Immediate-release capsules of tacrolimus (Prograf® and generics) are approved in the United States for prophylaxis of organ rejection in patients receiving allogeneic liver, kidney, or heart transplants and recommend twice daily oral dosing.

LCP-Tacrolimus, a new extended-release formulation of tacrolimus, was prepared using the MeltDose® drug-delivery technology; according to the applicant this should enhance bioavailability and may reduce the intra-individual variability in tacrolimus absorption.

Patent Information

United States Patent Number: 7,994,214
Name of Patent Owner: Veloxis Pharmaceuticals A/S
Orphan Designation and Exclusivity Request

Upon the request of the Applicant, tacrolimus has been granted orphan-drug designation for prophylaxis of organ rejection in patients receiving allogeneic kidney transplantation by the Office of Orphan Products Development on December 20, 2013. The Applicant was advised that it is the active moiety or principal molecular structural features of the drug and not the formulation of the drug that is designated as orphan. The designation was based on a plausible hypothesis that the Applicant's drug may be clinically superior to the same drug that is already approved for the same orphan indication. Failure to demonstrate clinical superiority over the already approved same drug(s) will result in LCP-Tacrolimus extended release tablets not receiving orphan-drug exclusivity.

Reviewer's note: See Section 7.4.5 (Special Safety Studies/Clinical Trials) for information about the specific clinical study (Study LCP-Tacro 3003) that the Applicant conducted to demonstrate clinical superiority in stable kidney transplant recipients on Prograf converted to LCP-Tacro and the effect this conversion had on hand tremors.

The Applicant claims (b) (4) seven year period of orphan drug exclusivity pursuant to section 526 of the FDC Act (21 U.S.C. 36bb), for LCP-Tacro extended release tablets with the supportive information summarized below:

(b) (4)

(b) (4)

Aspects of the LCP-Tacro product which differentiate it from other tacrolimus formulations are:

- An increase in oral absorption from LCP-Tacro resulting in a clinical necessity to administer lower doses to achieve the same target blood levels.

- Study LCP-Tacro 3003, STRATO demonstrated a highly statistically significant reduction in tremors resulting from the altered profile when switching from traditional tacrolimus therapy to LCP-Tacro therapy.

3. Studies have been conducted by the Applicant
The Applicant (Veloxis) was the Sponsor named in FDA Form 1571 for the new clinical investigations submitted under IND 75,250.

(b) (4)

Clinical Reviewer's Comment
As explained in the FDA guidance document entitled "How to Comply with the Pediatric Research Equity Act (PREA)"[3] submission of a pediatric assessment is not required for an application to market a product for an orphan-designated indication, and waivers are not needed. The Applicant will be notified that the PREA requirements do not apply to their applications because of the orphan designation.

2.2 Tables of Currently Available Treatments for Proposed Indications

The following products for use in kidney transplant recipients as induction, prevention, or treatment of acute rejection have been approved. The wording from the Indications and Usage sections of the package insert is provided below.

2.2.1 Induction

Simulect® (basiliximab)

3 http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077855.pdf

Simulect® is indicated for the prophylaxis of acute organ rejection in patients receiving renal transplantation when used as part of an immunosuppressive regimen that includes cyclosporine, USP (MODIFIED) and corticosteroids. The efficacy of Simulect® for the prophylaxis of acute rejection in recipients of other solid organ allografts has not been demonstrated.

Zenapax® (daclizumab)

ZENAPAX is indicated for the prophylaxis of acute organ rejection in patients receiving renal transplants. It is used as part of an immunosuppressive regimen that includes cyclosporine and corticosteroids. The efficacy of ZENAPAX for the prophylaxis of acute rejection in recipients of other solid organ allografts has not been demonstrated.

Drugs used off-label for induction treatment

Thymoglobulin® (rabbit-derived antithymocyte globulin), Campath® (alemtuzumab), Atgam® (anti-thymocyte globulin, Orthoclone OKT3® (muromomab-CD3) are used off-label as induction agents; all are indicated for the treatment of rejection (see below), except Campath® which is approved only for treatment of B-cell chronic lymphocytic leukemia (B-CLL).

2.2.2 Prevention of Rejection

Nulojix® (belatacept)

NULOJIX is a selective T-cell costimulation blocker indicated for prophylaxis of organ rejection in adult patients receiving a kidney transplant.

- Use in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids

Zortress® (everolimus)

Zortress is indicated for the prophylaxis of organ rejection in adult patients:

- Kidney transplant: at low-moderate immunologic risk. Use in combination with basiliximab, cyclosporine (reduced doses) and corticosteroids. (1.1)
- Liver transplant: Administer no earlier than 30 days post-transplant. Use in combination with tacrolimus (reduced doses) and corticosteroids.

Astagraf XL® (tacrolimus extended release capsules)

ASTAGRAF XL is a calcineurin-inhibitor immunosuppressant indicated for the prophylaxis of organ rejection in patients receiving a kidney transplant with mycophenolate mofetil (MMF) and corticosteroids, with or without basiliximab induction

Prograf® (tacrolimus) and generics for Prograf

Prograf is a calcineurin-inhibitor immunosuppressant indicated for

- Prophylaxis of organ rejection in patients receiving allogeneic liver, kidney or heart transplants

Neoral® (cyclosporine) and generics for Neoral

Neoral® is indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants. Neoral® has been used in combination with azathioprine and corticosteroids.

Myfortic® (mycophenolic acid)

Myfortic® (mycophenolic acid) delayed-release tablets are indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants, administered in combination with cyclosporine and corticosteroids.

CellCept® (mycophenolate mofetil) and generics for Cellcept

CellCept is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac or hepatic transplants. CellCept should be used concomitantly with cyclosporine and corticosteroids.

Rapamune® (sirolimus)

Rapamune (sirolimus) is indicated for the prophylaxis of organ rejection in patients aged 13 years or older receiving renal transplants. Therapeutic drug monitoring is recommended for all patients receiving Rapamune.

Imuran® (azathioprine) and generics for Imuran

IMURAN is indicated as an adjunct for the prevention of rejection in renal homotransplantation. It is also indicated for the management of active rheumatoid arthritis to reduce signs and symptoms. Renal Homotransplantation: IMURAN is indicated as an adjunct for the prevention of rejection in renal homotransplantation. Experience with over 16,000 transplants shows a 5-year patient survival of 35% to 55%, but this is dependent on donor, match for HLA antigens, anti-donor or anti-B-cell alloantigen antibody, and other variables. The effect of IMURAN on these variables has not been tested in controlled trials.

Corticosteroids

No specific labeling regarding use in transplantation

2.2.3 Treatment of Rejection

ATGAM®

Lymphocyte immune globulin, anti-thymocyte globulin [equine] sterile solution (Atgam®) ATGAM Sterile Solution is indicated for the management of allograft rejection in renal transplant patients. When administered with conventional therapy at the time of rejection, it increases the frequency of resolution of the acute rejection episode. The drug has also been administered as an adjunct to other immunosuppressive therapy to delay the onset of the first rejection episode.

Orthoclone OKT3 (muromonab-CD3) Sterile Solution – murine monoclonal antibody

ORTHOCLONE OKT3 is indicated for the treatment of acute allograft rejection in renal transplant patients.

ORTHOCLONE OKT3 is indicated for the treatment of steroid-resistant acute allograft rejection in cardiac and hepatic transplant patients.

) Thymoglobulin® (Anti-Thymocyte Globulin (Rabbit))
Thymoglobulin is indicated for the treatment of renal transplant acute rejection in conjunction with concomitant immunosuppression.

2.3 Availability of Proposed Active Ingredient in the United States

As stated in Section 1.1 (Recommendation on Regulatory Action) the active ingredient tacrolimus has been available on the market since 1994 as Prograf and since 2013 as Astagraf XL.

2.4 Important Safety Issues with Consideration to Related Drugs

All immunosuppressants including CNIs (tacrolimus, cyclosporine) increase the risk of opportunistic infections and malignancies. Most immunosuppressants including CNIs increase the risk of new onset diabetes after transplantation. As a specific adverse effect of this drug class, CNIs decrease the glomerular filtration rate due to their vasoconstrictive properties; this effect is generally reversible. CNIs may also cause neurotoxicity, hypertension and hyperkalemia.

As included under Warnings and Precautions in the package inserts of Prograf and Astagraf XL, tacrolimus may prolong the QT/QTc interval and may cause Torsade de Pointes. Tacrolimus has also been associated with myocardial hypertrophy which has been observed in animal toxicology studies and reported in humans.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On May 30, 2006, Life Cycle Pharma (LCP) which is the former name for the current Applicant (Veloxis) based in Copenhagen, Denmark requested a Pre-IND meeting to

discuss the development plan for their extended release formulation of tacrolimus (LCP-Tacro) as an immunosuppressant drug for (b) (4) transplantation. The Division provided preliminary comments on July 27, 2006 and the pre-IND meeting was held on August 2, 2006. During the meeting the development plan for the LCP-tacrolimus extended release tablets and the appropriateness of submitting the application under Section 505(b)(2) of the Food, Drug and Cosmetic Act were discussed. The Division agreed with the 505(b)(2) route and provided advice on the Phase 1, Phase 2 and Phase 3 development. CMC issues were also discussed. The Applicant completed the Phase 1 and Phase 2 studies and requested an End-of-Phase 2 (EOP2) meeting which was held on May 20, 2008.

End-of-Phase 2 meeting on May 20, 2008 and draft Phase 3 protocols

The purpose the May 20, 2008 meeting was to discuss results of the completed Phase 2 kidney (conversion) study (LCP-Tacro study 2011) and the proposed Phase 3 development plans for indications in kidney (b) (4) transplantation. The May 20, 2008 meeting package also contained two draft Phase 3 protocols; protocol LCP-Tacro 3001 in stable kidney transplant recipients and protocol LCP-Tacro 3002 in de novo kidney transplant recipients.

The primary objective of Study LCP-Tacro 2011 was to evaluate the steady state of tacrolimus exposure (AUC0-24) and trough levels (C24) in stable kidney transplant patients converted from Prograf capsules twice-daily to LCP-Tacro tablets once-daily in a three sequence study design; the study period was 52 days.

A total of 60 patients were enrolled of which 47 were available for per protocol PK analyses. The mean dose conversion ratio for switching the 47 patients from Prograf to LCP-Tacro was 0.71+/- 0.05 (median 0.70, range 0.67-0.80). The Applicant reported no significant differences between the AUC and Cmin obtained at the end of the first week (Prograf) and at the end of the second week (LCP-Tacro). The overall increase in bioavailability for tacrolimus was approximately 40% when patients were switched to LCP-Tacro; however the increase in African American patients was only about half as large. The sponsor concluded that results from this study show that following conversion from Prograf to LCP-Tacro , a significantly higher systemic exposure and a lower degree of fluctuation in tacrolimus trough concentrations are seen with LCP-Tacro at steady state compared to Prograf in stable kidney transplant recipients.

Study 2011 provided the PK data in stable kidney transplant patients. The Sponsor did not have PK data from de novo kidney transplant patients at the time of the meeting. During the meeting the Division recommended that the PK data in de novo kidney transplant patients be obtained and also included as part of the labeling.

The Division indicated that determining the AUC/Ctrough ratio for LCP-Tacro in de novo kidney transplant patients would help assess the initial dosing requirement of LCP-Tacro in these patients and the AUC/Ctrough ratio in de novo kidney transplant patients

may not be comparable to that of stable kidney transplant patients. The Division suggested that the Applicant conduct a Phase 2 PK study (including subgroup analyses by gender and race) in de novo kidney transplant patients in order to ascertain appropriate initial dosing regimen(s) of LCP-Tacro prior to the initiation of the de novo Phase 3 Study 3002.

The Applicant proposed to include a PK sub-study in the planned de novo Phase 3 Study 3002. Additionally, they proposed to conduct an interim analysis of the first 30-50 patients to assess the AUC and Ctrough relationship; if indicated, an adjustment to initial dosing would apply to the remaining study patients. The Division stated that they would be willing to review a detailed proposal pertaining to the planned interim analysis, which should take into account the statistical issues associated with interim analyses and subsequent adaptations. The Division further cautioned the Applicant that patient data assessed at the interim analysis may not be eligible for inclusion in the primary efficacy and safety analyses depending on changes made following the interim analysis. The Sponsor agreed to submit a detailed proposal.

The next discussion point concerned the selection of the comparator for the Phase 3 Study 3002. The Division emphasized that a non-inferiority study requires an approved active control. Since the combination of tacrolimus plus mycophenolate mofetil (MMF) was not an FDA approved regimen at the time, the Division stated that this regimen is not considered an acceptable comparator regimen in the planned Phase 3 de novo kidney trial. The Division recommended that the sponsor specify and justify the proposed active-control regimen in the planned trial. The Sponsor agreed to provide the requested information.

The last discussion point concerned the Phase 3 study design (open-label vs. double-blind). The Sponsor suggested that scientific integrity may be undermined by blinding the study. The Sponsor also explained that executing dose adjustments through blinded central labs would result in delays of 3-5 days and compromise patient care. The Division responded that a double-blind study is superior to an open-label study as it reduces the potential for bias that may ensue if the patient and/or investigator are aware of treatment assignment; further, the Division did not concur that a blinded study would compromise the study integrity. The Division suggested that the Applicant submit a justification of an open-label study to which the Applicant agreed.

FDA July 30, 2008 Letter

In a communication to the Applicant dated July 30, 2008, the Division stated that the findings from the planned conversion study LCP-Tacro 3001 of which a draft protocol had been submitted will be considered as supportive to findings from the de novo Phase 3 trial LCP-Tacro 3002 in kidney transplantation. In the July 30, 2008 letter it was also emphasized that the priority in the randomized clinical trial in de novo patients should be to obtain the best estimate of efficacy of the LCP-Tacro formulation and this could be best done in a blinded trial.

Some of the important comments on Protocol 3002 included in the FDA July 30, 2008 letter:

- You state that centralized monitoring of tacrolimus drug levels will result in significant delays in implementing dosing changes; however, we believe that therapeutic drug monitoring (TDM) could still be performed on-site, provided the study includes a pharmacist (or other study personnel) who are unblinded to make the dosing adjustments necessary based upon the lab results. Since tacrolimus levels are being measured in both arms, it is not necessary to blind the investigator to the drug levels.

- You state that a blinded design will place the burden of an increased pill count on patients and that this will increase the risk of non-adherence to the study protocol and increase the number of dropouts. While we acknowledge the higher pill burden, we do not believe that this is a significant risk factor for non-adherence and dropouts. Transplant patients are experienced in taking multiple medications and understand the importance of adherence to their immunuosuppressants. Patients should be informed of the pill burden prior to consenting to participate in the study.

Submission of the Protocol LCP-Tacro 2017

The sponsor had already conducted a Phase 2 pharmacokinetic (PK) study in stable kidney transplant patient (Study 2011) but as included in the summary of the May 20, 2008 meeting with the Applicant, the Division requested that the PK of LCP-Tacrolimus tablets be evaluated in de novo kidney transplant recipients in addition to stable kidney transplant recipients. In response to this request, Protocol LCP-Tacro 2017 titled "A phase II, open-label, multi-center, randomized, trial to demonstrate the pharmacokinetics of LCP-Tacro tables once daily and Prograf® capsules twice daily in adult de novo kidney transplant patients" was submitted on August 13, 2008. The study objective was to compare the PK and safety of LCP-Tacro tablets versus Prograf® capsules in the first two weeks following kidney transplantation. In addition, safety and efficacy would be assessed for an additional 50 weeks after transplantation.

(b) (4)

Resubmission of Protocol 3002 on October 24, 2008

The Applicant agreed to the blinded design recommended by the Division for the de novo Study 3002 and submitted a revised protocol on October 24, 2008. Study 3002 was planned as a non-inferiority study comparing a regimen containing LCP-Tacro and MMF with one containing Prograf and MMF and the October 24, 2008 submission contained a justification for the proposed NI margin of 10%.

In a letter dated December 18, 2008, the Division expressed concerns about the proposed comparator regimen, Prograf and [mycophenolate mofetil (MMF) or (b) (4) in studies 3002 and 3001 since this was not an FDA approved regimen at the time.

Submission of the Protocol LCP-Tacro 3001

Revised Protocol LCP-Tacro 3001 titled, "A phase 3, open-label, multi-center, prospective, randomized study of the efficacy and safety of conversion from Prograf capsules twice-a-day to LCP-Tacro tablets once a- day for the prevention of acute allograft rejection in stable kidney transplant patients" was submitted on October 27, 2008. The Applicant could not provide a justification for the non-inferiority margin specified at (b) (4) for this conversion trial in stable kidney transplant recipients. The Applicant revised the Protocol 3001 further and resubmitted on December 23, 2008.

Initiation of Study 3001 in stable kidney transplant recipients

The Applicant initiated the Study 3001 in stable kidney transplant recipients on December 23, 2008 but discussions on the design of the de novo Phase 3 Study 3002 and NI margin justifications for both the ongoing Study 3001 and the planned Study 3002 continued as discussed later in this review.

Prograf Labeling Change: FDA Approval of the Tacrolimus + MMF regimen in kidney transplantation on May 19, 2009 and the following FDA letter to the Applicant dated July 15, 2009

Since the FDA approved revised labeling for Prograf capsules on May 19, 2009 to add the use of tacrolimus in combination with mycophenolate mofetil (MMF) in the setting of induction with an IL-2 receptor antagonist for the prophylaxis of acute rejection in kidney transplantation, the Division agreed that the data which supported that labeling may also support the use of tacrolimus/MMF as a comparator regimen in trials of de novo kidney transplant patients, such as the LCP-Tacro 3002 trial and this was communicated to the Applicant on July 15, 2009.

The Division stated that original version of Protocol LCP-Tacro 3002 describes target tacrolimus trough levels of 7-20 ng/mL until the end of Month 3 and 5-15 ng/mL for the remainder of the study and If the Applicant chose to use tacrolimus/MMF as a

comparator regimen, the use of tacrolimus with MMF should be modified as described in the new Prograf labeling.

Study 3001 had already started but the Division also included comments on Protocol 3001 and recommended that the dose of LCP-Tacro be adjusted if post-conversion LCP-Tacro trough concentrations of tacrolimus are >25% of pre-conversion trough concentrations obtained with Prograf.

Additionally the Division also requested that the Applicant resubmit revised protocols for Studies 3001 and 3002 including a detailed justification for the proposed non-inferiority margins.

In a letter dated July 28, 2009, the Applicant agreed to the FDA comments in the July 15, 2009 letter and submitted revised protocol for LCP-Tacro 3002.

Second End-of-Phase 2 (EOP2) meeting, February 16, 2010

On December 2, 2009, the Applicant requested a second EOP2 (Type B) meeting to continue discussing their clinical development program for LCP-Tacro. Background information and questions were submitted in a meeting package dated December 22, 2009. This meeting package also included an updated Investigator Brochure and two amended Phase 3 Protocols entitled "A Phase 3, Open-label, Multicenter, Prospective, Randomized Study of the Efficacy and Safety of Conversion from Prograf Capsules Twice Daily to LCP-Tacro Tablets Once Daily for the Prevention of Acute Allograft Rejection in Stable Kidney Transplant Patients (Protocol LCP-Tacro 3001)" and "A Phase 3, Open-Label, Multicenter, Prospective, Randomized Study of the Efficacy and Safety of LCP-Tacro Tablets Once Daily Compared to Prograf Capsules Twice Daily in Combination with Mycophenolate mofetil for the Prevention of Acute Allograft Rejection in *de novo* Adult Kidney Transplant Recipients (Protocol LCP-Tacro 3002)."

On February 5, 2010, the Division provided preliminary responses in preparation for the meeting and the meeting was held on February 16, 2010. During this second EOP2 meeting the following were among the discussed issues:

- Introduction of the new dose strengths (LCP-Tacro 0.75 mg, 1.5 mg and 4 mg tablets), whose compositions are dose-proportional to existing strengths(LCP-Tacro 1 mg, 2 mg and 5 mg tablets), directly into Study LCP-Tacro 3002 without the need for a pharmacokinetic dose-equivalence study:

  The Division stated that an in vivo bioavailability waiver for the new 4 mg and 0.75 mg strengths could be granted if similarity is shown in the dissolution profiles between the 4 mg and 5 mg strengths and the 0.75 mg and 1 mg strengths in all three media tested (0.1 N HCl, and phosphate buffer pH 4.5 and 6.8).

- Evaluation of which strength scenario is least error-prone to medication errors (1 mg, 1.5 mg and 4 mg versus 0.75 mg, 2 mg and 4 mg) by the proposed FMEA study:

  The Division agreed.

- Acceptability of the proposed (b) (4) NI margin for the ongoing Study 3001 in stable kidney transplant recipients:

  The Division stated that based on the information provided in the briefing package, using only the acute rejection rates, the FDA biostatisticians calculated the lower bound to be approximately (b) (4) which would support a margin no larger than (b) (4)

- Determination of the appropriate initial dosing regimen(s) in de novo kidney transplant patients based on the results from study LCP-Tacro 2017:

  The Division stated that in Study LCP-Tacro 2017, the tacrolimus AUC on Day 1 after the first dose of LCP-Tacro (0.14 mg/kg/day) was approximately 50% lower than after the first day dose of Prograf (0.2 mg/kg/day) which was in contradiction to the previous studies in healthy volunteers and stable kidney transplant patients which suggested that a 30% lower daily dose of LCP-Tacro should provide a comparable tacrolimus AUC to Prograf.

  The Division continued by stating that the PK results from Study LCP-Tacro 2017 provided in the meeting package did not appear to be sufficient to adequately demonstrate that an appropriate initial dose regimen of LCP-Tacro has been established. The Division requested the Applicant to submit detailed, patient-level pharmacokinetic data from their initial PK studies to provide sufficient information to justify their selection of 0.14 mg/kg as the appropriate dose in Study 3002 and the Applicant agreed.

- Division's opinion on the acceptability of conducting the Phase 3 study in de novo kidney transplant patients (Study 3002) as an open-label study:

  The Division responded that they acknowledge the high pill burden in a double-blind, double-dummy design, but they do not believe that this is a significant risk factor for non-adherence and drop-outs. The Division strongly recommended that Study 3002 should be double-blinded to minimize bias and increase data quality, particularly given the importance placed on the outcome of this study, as the only controlled clinical trial for which a non-inferiority margin can be justified.

The Division also recommended working toward a practical blinding process that will mitigate potential bias and is consistent with clinical practice. The Applicant agreed to consider blinding the Study 3002 and to address this issue in their planned future special protocol assessment (SPA) request.

- Study 3002 sample size and the non-inferiority (NI) margin of 10%:

  The Division requested that a robust, formal statistical justification for the proposed sample size and the NI margin be submitted.

- The Applicant's proposal to submit the protocol for Special Protocol Assessment (SPA) as Study LCP-Tacro 3002 will form the primary basis for an efficacy claim:

  The Division agreed.

Applicant's March 31, 2010 request, for a special protocol assessment (SPA) of Protocol LCP-Tacro 3002

The Applicant requested a special protocol assessment (SPA) of the protocol titled "A Phase 3, Double-Blind, Double-Dummy, Multicenter, Prospective, Randomized Study of the Safety and Efficacy of LCP-Tacro Tablets Once-Daily Compared to Prograf Capsules Twice-Daily in Combination with MPA for the Prevention of Acute Allograft Rejection in De Novo Adult Kidney Transplant Recipients (Protocol LCP-Tacro 3002)" on March 31, 2010. The Division reviewed the protocol and issued a "SPA No Agreement" letter on May 14, 2010. The Division also responded to the Applicant's questions in the submission.

SPA No Agreement Letter dated May 14, 2010 (LCP-Tacro 3002)

Important points of disagreement on the SPA of the Protocol 3002 included:

- Proposed indication: The Applicant proposed that Protocol LCP-Tacro 3002 in de novo kidney transplant recipients serve as the basis for (b) (4)

- Randomization: Details of the randomization procedure was missing in the protocol.

- Concomitant therapy: The protocol allowed for the use of mycophenolate mofetil (MMF) or mycophenolic sodium (MPS) in combination with Prograf or LCP-Tacro. The Division recommended excluding the use of MPS in this protocol.

- Primary efficacy endpoint and main secondary endpoint: The Division agreed with the proposed primary efficacy endpoint of treatment failure defined as death, graft failure, BPAR (Banff Grade >=1A based on central laboratory assessment), or loss to follow-up at 12-months but also wanted the incidence of death, graft loss or loss to follow-up at 12-months post-transplant be included as a main secondary endpoint.

- Exclusion criteria: The Applicant proposed to randomize only the patients who exhibit a urine output within the first 24 hours of transplantation of greater than (b) (4) in the 2 hours immediately prior to randomization as an enrollment criterion. The Division did not agree with this criterion since restriction would limit the study population to patients with excellent kidney function which would not be representative of the general kidney recipient patient population. The Division added that the subgroup of patients who exhibit excellent renal function immediately post-operatively are likely to have good outcomes and given that this is a non-inferiority design, selecting a patient population predisposed to good outcomes inherently would lead to a trial more likely to meet its NI margin. The Division requested the Applicant to modify this randomization criterion of early post-transplant good kidney function.

- Starting doses of LCP-Tacrolimus and Prograf: In Study 3002, the proposed initial dose of LCP-Tacro was 0.17 mg/k/day and the proposed initial dose of Prograf was 0.1 mg/kg/day. Subsequent doses of both drugs would be adjusted to maintain the trough concentrations of tacrolimus at 6 to 11 ng/mL for the first 30 days and 4 to 11 ng/mL thereafter.

  The Division was concerned that the initial dose of LCP-Tacro (0.17 mg/kg/day) might result in a higher exposure to tacrolimus compared to the Prograf active-control arm (0.1 mg/kg/day). Higher exposure to tacrolimus in the LCP-Tacro arm could result in fewer rejection episodes, which may favor the investigational arm; however, it could also increase the adverse events associated with over-immunosuppression.

- Target tacrolimus trough concentrations: The Division expressed doubts as to whether targeting the same trough concentration range in both arms would result in similar AUCs, particularly when used in de novo renal transplant recipients.

Division's recommendation for a PK substudy in Protocol 3002

In light of these concerns, the Division strongly recommended that the Applicant conduct a PK substudy in Study 3002 in order to compare AUC and trough

concentrations of LCP-Tacro to Prograf at the proposed dose regimens and requested the Applicant evaluate the PK of LCP-Tacro and Prograf at Day 1, 7, 14 and 28.

SPA Agreement Reached, August 5, 2010 (Protocol LCP-Tacro 3002)

The Applicant modified the protocol and submitted for a second time SPA assessment on June 18, 2010. The Division reviewed the protocol and noted that the revised protocol included the revisions requested in the May 14, 2010 SPA No Agreement letter. The Division agreed with the Applicant's justification for a 10% non-inferiority margin with some comments. The Division also recommended that the Applicant conduct a relative bioavailability study between the 4 mg strength, and the lower dose strengths in order to demonstrate that the two formulations result in similar systemic exposure of tacrolimus and pointed that until the Applicant is able to confirm this assumption, they should not allow use of the 4 mg strength tablets in this study.
An SPA Agreement Letter was issued for the LCP-Tacro 3002 protocol on August 5, 2010.

Consequent to the SPA agreement, Study LCP-Tacro 3002 was initiated by the Applicant on October 13, 2010.

Submission of the Tremor Study (LCP-Tacro 3003) Protocol, September 19, 2011:

On September 16, 2011, the Applicant submitted a clinical protocol (LCP-Tacro 3003) entitled "Switching Study of Kidney Transplant Patients with Tremor to LCP- Tacro (STRATO)". Their hypothesis was that there would be a beneficial effect of switching to LCP-Tacro from the immediate-release tacrolimus, in stable kidney transplant patients with tremor. For more information about this study and the results see Section 7.4.5 of this NDA review (Special Safety Studies/Clinical Trials).

Orphan Drug Designation:

The Applicant received, Orphan Drug Designation on December 20, 2013 (Designation Reference Number 13-4017) from the Office of Orphan Products Development (OOPD). OOPD stated that it is the active moiety or principal molecular structural features of the drug and not the formulation of the drug that is designated. Orphan designation was based on a plausible hypothesis that LCP-Tacrolimus may be clinically superior to the same drug that is already approved for the same orphan indication. In order to obtain orphan-drug exclusivity upon approval, the Applicant needs to demonstrate that LCP-Tacrolimus is clinically superior to the already approved same drug (and any other versions of the same drug approved for the same orphan indication before it is approved). Failure to demonstrate clinical superiority over the already approved same drug(s) will result in not receiving orphan-drug exclusivity. See Section 7.4.5 for the assessment of the clinical study that the Applicant conducted to demonstrate clinical superiority of LCP-Tacrolimus.

December 30, 2011 Meeting Request (b) (4)

On December 30, 2011, the Applicant requested a Type (b) (4)

(b) (4)

Submission of the PK Study Protocol (LCP-Tacro 2019) on August 10, 2012:

On August 10, 2012, the Applicant submitted a new protocol for a PK study in de novo kidney transplant recipients, Study LCP-Tacro 2019 "A Phase 2 Double-blind, Double-dummy, Multicenter, Prospective, Randomized Study of the Pharmacokinetics of LCP-Tacro™ Tablets, Once-daily, Compared to Prograf® Capsules, Twice-daily, for the Prevention of Acute Allograft Rejection in De Novo Adult Kidney Transplant Recipients". The design, tacrolimus starting doses and the target trough levels in this PK study were similar to the ongoing Phase 3 Study LCP-Tacro 3002 which had been started two years ago. Instead of conducting this PK study as a substudy of the ongoing Phase 3 Study 3002, the Applicant chose to conduct it as a separate PK study (2019). The Division provided comments on this protocol.

November 14, 2012 Meeting Request:

On November 14, 2012, the Applicant submitted a request for a meeting to discuss:

- The methodology of data collection in the blinded, central assessment of kidney biopsy specimens for the primary endpoint in LCP-Tacro Study 3002.

- FDA's required standard for submission of 12 months of treatment data from a pivotal efficacy study in transplant as mandatory to support approval.

The Division responded to the Applicant's questions on December 12, 2012 and stated that the clinical and laboratory information conveyed to the evaluating pathologist will not interfere with the blinded nature of the double blind Study 3002 as suggested by the Applicant. In response to the second question, the Division stated that at least one adequate and well-controlled study of 12 months duration using the primary endpoint of biopsy proven acute rejection (BPAR) where death, graft loss and lost to follow-up are imputed as failures is required to support a new product application for a kidney transplant indication.

Subsequent to the Division's responses to the Applicant's questions, the Applicant requested cancellation of the meeting and the meeting was cancelled.

Pre-NDA Meeting

The Applicant made a request for a pre-NDA meeting on May 24, 2013 to discuss the content and format of the NDA submission. The meeting was held on August 7, 2013. In general the Division agreed with the proposed content and format of the NDA and referred the Applicant to the "Comprehensive Table of Contents Headings and Hierarchy" published by the FDA (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM315023.pdf) for the missing items.

The Division also asked the Applicant to provide a plan to address possible medication errors due to the lack of interchangeability of LCP-tacrolimus extended release tablets with the other tacrolimus formulations.

Additional Clinical Pharmacology requests were also communicated to the Applicant as part of the Divisions responses to the Applicant's questions. The Applicant requested clarification on how to approach exposure– response analyses. The Division stated that the exposure-response analyses could be done with exposure metrics such as daily tacrolimus trough concentrations for time-to-event analyses for efficacy and safety endpoints and pointed that tacrolimus trough concentrations should be treated as a time-dependent covariate and be imputed for days when measurement did not occur. The sponsor agreed to the requested additional analyses.

Given that in vivo bioequivalence appears to have been demonstrated between Formulations F and G at the 4 mg dose, it has been deemed by the ONDQA Biopharmaceutics and Clinical Pharmacology reviewers that no additional in vivo BA/BE studies are needed between these two formulations, unless during the NDA review, the bioequivalence claim could not be confirmed.

NDA Submission

NDA 206406 was submitted electronically on December 28, 2013. The Applicant is seeking approval of Envarsus XR (tacrolimus extended release tablets) for the prophylaxis of organ rejection in both de novo and stable kidney transplant patients. The current NDA contains the results of two randomized controlled Phase 3 studies (3002 and 3001) and one Phase 2 study (2017) with sufficient duration of follow-up in addition to other clinical studies to assess the efficacy and safety of LCP-Tacro tablets in support of the proposed indication.

2.6 Other Relevant Background Information

There is no other relevant background information.

3 Ethics and Good Clinical Practices

Inspections were performed at one domestic site (UCLA Medical Center) and two international sites (Poland and Germany) by the Office of Scientific Investigations (OSI). No issues were identified in any of these three sites and NAI letters will be issued.

3.1 Submission Quality and Integrity

NDA 206406 is well organized and contains the required sections and elements.

3.2 Compliance with Good Clinical Practices

The studies and any amendments were reviewed by the Independent Ethics Committee or Institutional Review Board for each center. The studies were conducted according to the ethical principles of:

- International Conference on Harmonisation (ICH) harmonised tripartite guideline E6(R1): GCP
- Directive 2001/20/EC of the European Parliament for the implementation of GCP on the conduct of clinical trials on medicinal products for human use
- United States (US) Title 21 Code of Federal Regulations (CFR) Parts 50 and 56
- Food and Drug Administration (FDA) 21 CFR Part 312

3.3 Financial Disclosures

As part of the NDA submission the Applicant included the FDA Form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) and the FDA Form 3455 (Disclosure Statement). According to the information provided in these two forms the Applicant obtained certification from each investigator and sub-investigator in the clinical development program and there was no disclosable financial information reported except for two investigators for whom the FDA Form 3455 was submitted. Clinical

Investigator Financial Disclosure forms for the three main studies (3002, 3001 and 2017) are attached to the end of this review. (Section 9, Appendices)

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

At the time of the writing of this review the CMC Review was pending.

4.2 Clinical Microbiology/Immunology

See Clinical Microbiology Review dated July 24, 2014 by Shukal Bala, PhD.

Mechanism of Action of Tacrolimus excerpted from Dr. Bala's review:

> The mechanism of action section for Prograf® labeling is based on review of studies in 1993 – 1994 before the initial FDA approval. No new nonclinical studies were performed by the applicant; however, some of the publications supporting activity of tacrolimus in vitro and/or in vivo, included in the NDA submission and obtained by an independent literature search were reviewed. Some of the studies were in various animal models of transplantation and support activity of tacrolimus in improving animal and graft survival. As most of these studies have now been superseded by clinical data, this review focuses only on those studies supporting additional information for mechanism of action than currently described in the Prograf® labeling.
>
> Tacrolimus may exhibit its immunosuppressive activity by a variety of different mechanisms. The primary event appears to be formation of a complex between tacrolimus and the FK-506 binding protein (FKBP) 12 that binds to calcineurin, inhibiting its phosphatase activity. Inhibition of calcineurin activity leads to prevention of dephosphorylation and translocation of various nuclear factors such as the cytosolic subunit of NF-AT and NF-κB to the nucleus. NF-κB, a group of dimeric transcription factors, exerts both positive and negative effects on gene transcription and has a large impact on the development, homeostasis, survival, and function of T-cells.
>
> Calcineurin is widely distributed in mammalian tissues and it is possible that inhibition of calcineurin may be responsible for some of the well-established effects including nephrotoxic, diabetogenic, neurological and cardiovascular effects where several cellular and immunological mechanisms are potentially involved.

4.3 Preclinical Pharmacology/Toxicology

The toxicity of tacrolimus has been previously well established. This is a 505(b)(2) application: no new toxicity studies were conducted by the Applicant with the current extended-release formulation of tacrolimus.

4.4 Clinical Pharmacology

For detailed information on Clinical Pharmacology see the Clinical Pharmacology NDA Review dated September 25, 2014 by Gerlie Gieser, PhD and Jeffry Florian, PhD. All the information, tables and figures in the current Section 4.4 are copied from the Clinical Pharmacology Review:

> Tacrolimus is a poorly water soluble drug. To develop ENVARSUS® 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, adjustments related to (b) (4) 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 (G and F) is (b) (4) Formulation G tablets resulting in a minor change in tablet shape without altering the surface to volume ratio.
>
> Two bioequivalence studies 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 Formulations D, F, and C, respectively. Two BE studies were conducted between Formulations D and F; one BE study between Formulations C and D.
>
> 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 ENVARSUS® XR tablet strengths were evaluated during drug product development. In consideration of the proposed 'lower than 1.0' daily dose conversion ratio of

ENVARSUS® XR when switched from immediate release tacrolimus oral dosage forms in stable kidney transplant recipients, the Applicant intends to market ENVARSUS® 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.

4.4.1 Mechanism of Action

Described in Section 4.2

4.4.2 Pharmacodynamics

As excerpted from the Clinical Pharmacology NDA Review:

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).

4.4.3 Pharmacokinetics

The Executive Summary of the Clinical Pharmacology NDA Review by Gerlie Gieser, PhD and Jeffry Florian, PhD is copied below in smaller font size for differentiation from the rest of the review. To preserve the integrity of the Clinical Pharmacology Executive Summary, table and figure numbers are kept in their original form; therefore may duplicate other table and figure numbers in the rest of this review.

I. Executive Summary of the Clinical Pharmacology NDA Review

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

During the IND stage, ENVARSUS® XR was known as LCP-Tacro. The pharmacokinetics of tacrolimus following single dose and/or multiple dose administration of ENVARSUS® 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) were not reviewed. 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.

<u>ENVARSUS® XR Starting Dosage and Dosage Titration</u>

- *De novo kidney transplant patients receiving* (b) (4)
  (b) (4)
- *Stable kidney transplant patients*
  When switching from tacrolimus immediate release 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.

<u>Administration:</u>

- 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).

<u>Therapeutic Drug Monitoring:</u>

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 immediate attainment of steady state.

B. Phase IV Commitments

None.

C. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

1. *De novo* Kidney Transplant

Recommended Dosing Regimen for *de novo* kidney transplant patients when ENVARSUS® XR is given (b) (4)

[redacted]

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 that 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}/Cmax/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 immediate tacrolimus PK steady state, when approximately 7 days would typically be needed to achieve steady state for Prograf given at a starting dose of 0.1 mg/kg/day. On Day 1, ENVARSUS® XR patients in Study 2019 received an average tacrolimus dose of 15.5 mg, which exceeds the dose range for linear PK of tacrolimus (i.e., up to 10 mg in healthy subjects; Study 1013).

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

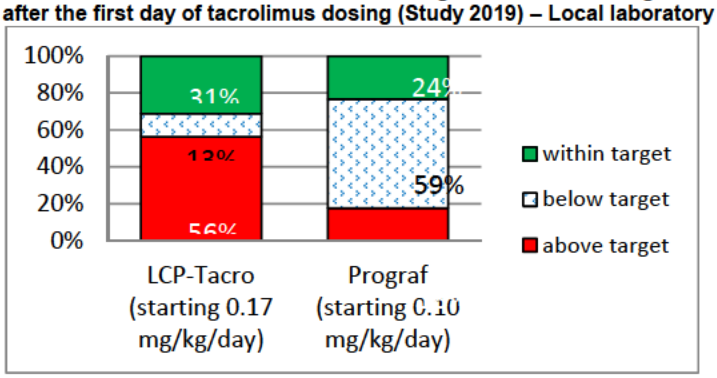
	ENVARSUS® XR Once Daily Starting dose: 0.17 mg/kg/day (n=10)			Prograf Twice Daily Starting dose: 0.1 mg/kg/day (n=11)		
	Day 1	Day 14	Day 28	Day 1	Day 14	Day 28

AUC_{0-24} (ng·hr/mL)	376.66 ± 256.83	375.64 ± 10	396.23 ± 149.93	149.16 ± 89.34	243.13 ± 69.97	205.79 ± 36.25
Cmax (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
Tmax[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

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).

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



LCP-Tacro = ENVARSUS® XR

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 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} *approaching* steady state by Day 1. [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) low incidence of tacrolimus nephrotoxicity (n=1 ENVARSUS® XR ; n=0 Prograf), b) no reported cases of malignancy (e.g., PTLD), c) 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 (2 ENVARSUS® XR ; 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
Cmax	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
Tmax[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 than 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.

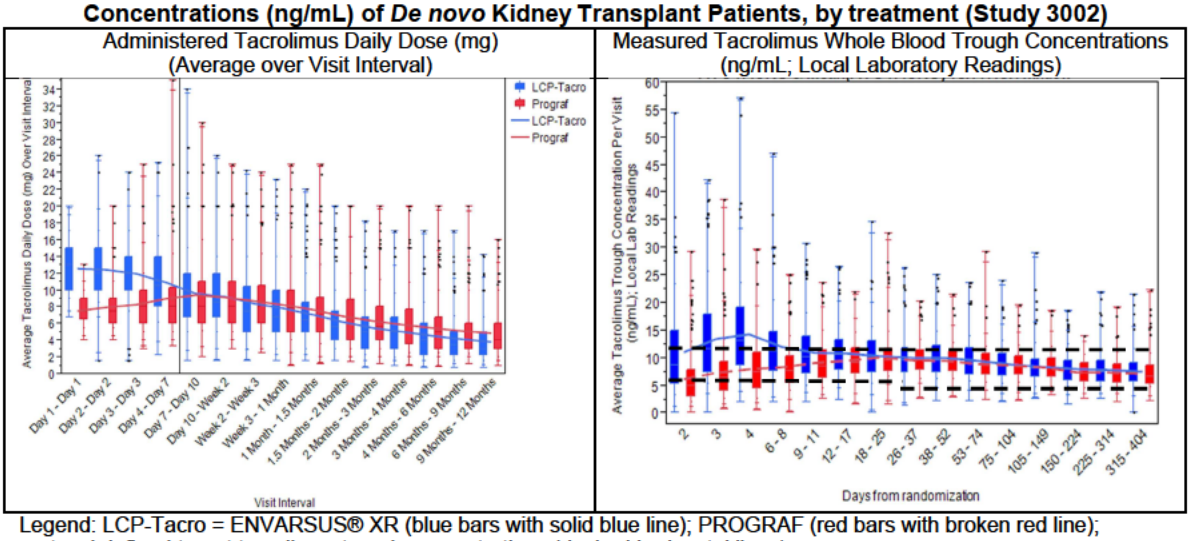
Tacrolimus and Concomitant Immunosuppressive Exposures in 12-month clinical trials (*de novo* kidney)

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 appear 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. Box plots of 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

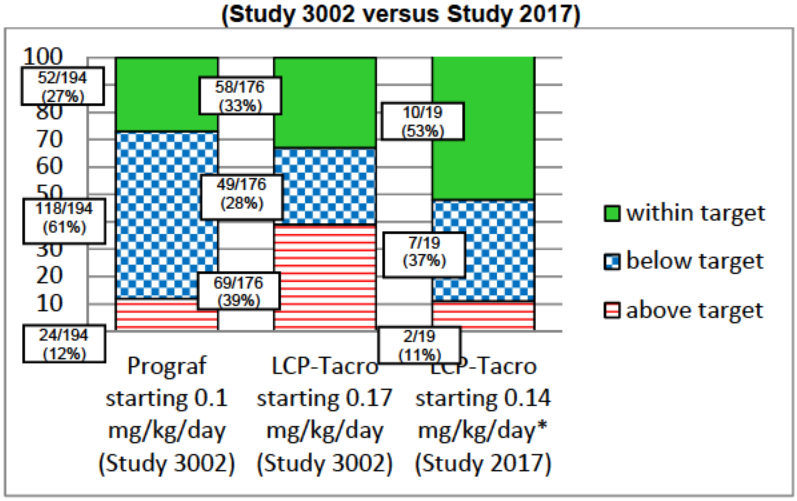
Based on the reviewer's confirmatory analyses, majority of the patients (96% ENVARSUS® XR and 99% Prograf) received two 20 mg doses of basiliximab for antibody induction. Additionally, the average daily doses of concomitant MMF and corticosteroids were comparable between the two tacrolimus treatment 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; the mean/median daily MMF equivalent doses were comparable between the two treatment arms. Likewise, the mean/median daily doses of corticosteroids (as prednisone equivalent) and antibody induction agents (mainly antithymocyte immunoglobulin) 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 Pharmacometrics reviewer to describe the relationship between nephropathy adverse events and tacrolimus trough concentrations as a time-dependent covariate from Study 3002. 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 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 Recipients 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 (twice daily) should receive a daily dose of ENVARSUS® XR (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 recipients

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).

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)

	Geometric Mean (%CV) Arithmetic Mean ± SD		
	Prograf Capsules	ENVARSUS® XR Tablets	
Parameter	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
Cmax (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
Cava (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
Tmax (hr)"	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
Cmax/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

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 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)

	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**	
Parameter	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
Cmax (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
Cavg (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
Tmax (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 F1uctuation (%)	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)
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 recipients

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 the same as that used in Phase 2 Study 2011, i.e., 1:0.85 for Blacks/African Americans,

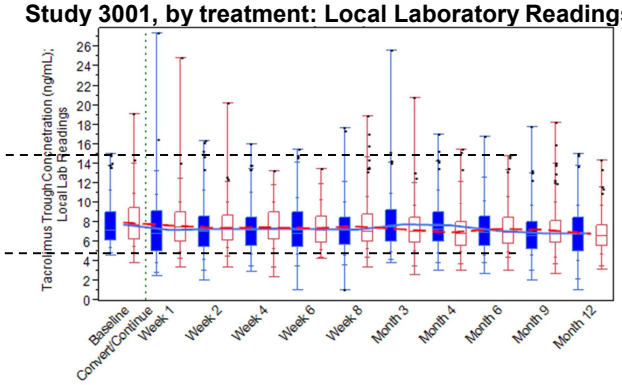
or 1:0.7 for non-African Americans/non-Blacks. ENVARSUS® XR dosage adjustment was not allowed during the first week post-conversion but was considered afterwards if tacrolimus trough concentration measured on Day 7 post-conversion deviated from the pre-conversion value by more than 25%. All subsequent 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.

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 TAC C_{trough} measurement.

- Chronopharmacokinetic effect (diurnal variation)
  - In healthy subjects, evening dosing of ENVARSUS® XR produced a 15% lower $AUC_{0\text{-}inf}$ 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:
  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 $AUC_{0\text{-}inf}$ and Cmax (Study 1013).
  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 were higher than anticipated, and appear to have reached steady state levels by Day 1, suggesting the possible attainment of nonlinear PK 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.

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 ± 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-AAs. 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.

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.

Missed dosing
The applicant proposed that missed dosing with ENVARSUS® XR could be mitigated by [redacted] (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 Astragraf 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.

Clinical Reviewer's Comment
As explained in Sections 1.2, 6.1.1.4 and 7.3.5 of this review I believe a starting dose lower than the Applicant proposed [redacted] (b) (4) mg/kg/day for de novo kidney transplant recipients will be a safer approach in clinical practice without losing any efficacy in the presence of induction and concomitant immunosuppression.

Therefore I agree with the Clinical Pharmacology Reviewer's recommendations on the starting dose of ENVARSUS® XR (0.14 mg/kg/day once daily) and the target trough levels (6-11 ng/mL during the first month, and 4-11 ng/mL thereafter) for de novo kidney transplant patients receiving antibody induction and concomitant MMF/corticosteroids. I also agree with the recommendation to use a daily dose conversion ratio of 1:0.80 when stable kidney transplant patients are switched from tacrolimus immediate release to ENVARSUS® XR, and to titrate the dose to keep the trough concentrations within a 4 to 11 ng/mL range, and preferably similar to the pre-conversion level.

5 Sources of Clinical Data

NDA 206406 has been submitted electronically in ECTD format.

EDR location:
\\CDSESUB1\evsprod\NDA206406\0000 and
\\CDSESUB1\evsprod\NDA206406\206406.enx

5.1 Tables of Studies/Clinical Trials

The LCP-Tacro clinical development program comprises 27 clinical studies involving over 1000 subjects including healthy volunteers, adult kidney transplant patients (b) (4) . The current NDA submission is intended to support the approval of LCP-Tacrolimus extended release tablets for the indication of prophylaxis of rejection in kidney transplant recipients. (b) (4)

The efficacy and safety of LCP-Tacrolimus tablets in kidney transplant patients has been evaluated in three controlled, randomized 12-month studies (the first 3 studies in Table 2). Two of these trials are Phase 3 studies (3002 and 3001) and one is a Phase 2 study (2017).

An additional Phase 3b study (LCP-Tacro 3003) was conducted in stable kidney transplant recipients on Prograf and with hand tremor. These patients were converted to LCP-Tacro treatment for 1-week (to assess changes in tacrolimus-induced tremor) with an optional 2-year extension phase. This study did not have any efficacy endpoints and did not collect efficacy information. For more information about Study 3003, see Section 7.4.5, Special Safety Studies/Clinical Trials.

A table of all the clinical efficacy and safety studies is provided below (Table 2) but only the Phase 3 studies (3002 and 3001) and the Phase 2 Study 2017 which form the basis of the efficacy and safety evaluation of the current NDA will be described in detail in the following sections.

Table 2. Overview of Phase 3 and Phase 2 Clinical Efficacy Studies in Kidney [redacted] (b) (4) Transplant Patients

(Source: Table 1, page 11 of Summary of Clinical Efficacy)

Study	Design	Patient Population	Treatments	No. Patients Randomized / Completed	Study Duration
Phase 3 Studies					
LCP-Tacro 3001	Open-label, multicenter, prospective, randomized, conversion	Adult (≥18 years) stable kidney transplant patients on Prograf (b.i.d.)	Patients were randomized 1:1 to: LCP-Tacro tablets (dose conversion ratio 0.7 [0.85 for AA patients]) or Prograf capsules (continue existing dose) Target tacrolimus trough levels: 4 -15 ng/mL.	326 / 296	12 months
LCP-Tacro 3002	Double-blind, double-dummy, multicenter, prospective, randomized	Adult (18–70 years) de novo kidney transplant patients	Patients are randomized 1:1 to: LCP-Tacro tablets Starting dose 0.17 mg/kg/day **or** Prograf capsules (b.i.d.) Starting dose 0.1 mg/kg/day Target tacrolimus trough levels: 6 - 11 ng/mL for the first 30 days and 4 - 11 ng/mL for the remainder of the study. All patients: interleukin-2 receptor antagonist induction therapy, MMF, corticosteroids	543 / 517	12 months
Phase 2 Studies					
LCP-Tacro 2017	Open-label, multicenter, randomized	Adult (≥18 years) de novo kidney transplant patients	Patients randomized 1:1 to: LCP-Tacro tablets Starting dose 0.14 mg/kg/day (0.17 mg/kg/day AA patients) or Prograf capsules Starting dose 0.2 mg/kg/day Target tacrolimus trough levels: 7 - 20 ng/mL	63 / 49	12 months

LCP-Tacro 2011	Open-label, multicenter, prospective, conversion	Adult (18-65 years) stable kidney transplant patients on Prograf (b.i.d.)	On Day 8, patients were converted to: LCP-Tacro tablets (q.d.) (dose conversion ratio ranging from 0.66-0.80) On Day 22, patients were converted back to pre-study Prograf dose (b.i.d.) Study drug doses were adjusted to maintain target tacrolimus trough levels between 7 and 12 ng/mL. oral administration	60*/48 * number enrolled rather than randomized (all patients received the same treatment)	52 days
LCP-Tacro 2019	Double-blind, double-dummy, multicenter, prospective, randomized study	De novo kidney transplant patients	Patients randomized to: LCP-Tacro tablets starting dose: 0.17 mg/kg or Prograf capsules starting dose: 0.1 mg/kg day Target tacrolimus trough levels: 6 - 11 ng/mL. Administered with MMF/MPS and corticosteroids (and interleukin-2 receptor antagonist or other induction therapy at the investigator's discretion)	36 / 31	30 days treatment and 30 days safety follow-up
(b) (4)					

5.2 Review Strategy

The efficacy and safety of LCP-Tacrolimus tablets in kidney transplant patients has been evaluated in three active controlled, randomized 12-month studies to support the indication of prevention of rejection in kidney transplant recipients. These are the two Phase 3 studies, 3002 in de novo kidney transplant recipients and 3001 in stable kidney transplant recipients and one Phase 2 study, 2017 in de novo kidney transplant recipients. All three studies are summarized in Section 5.3.

The Applicant is seeking the proposed indication both in de novo and stable (conversion setting) kidney transplant recipients. The results of Study 3002 will be reviewed in support of the de novo indication and the results of the Study 3001 will be reviewed in support of the conversion indication. The Applicant was able to justify a non-inferiority (NI) margin of 10% for Study 3002. There is no justified NI margin for the conversion Study 3001.

Both the Phase 2 Study 2017 and the Phase 3 Study 3002 conducted in de novo kidney transplant recipients have similar designs and the results of the Phase 2 Study 2017 informed the design of Phase 3 Study 3002 but the starting doses and target trough levels both for LCP-Tacrolimus and the comparator Prograf are different in each study. As included in Table 2 in Section 5.1 the starting dose for Prograf was decreased from 0.2 mg/kg/day to 0.1 mg/kg/day whereas LCP-Tacrolimus starting dose was increased from 0.14 to 0.17 mg/kg/day when moving from the Phase 2 Study 2017 to the Phase 3 Study 3002. See SPA No Agreement Letter dated May 14, 2010 (LCP-Tacro 3002) subsection under Section 2.5 for related regulatory history.

As discussed in more detail later in this review, the higher starting dose and the Applicant's daily dose calculation method for LCP-Tacrolimus tablets in the double blind Study 3002 resulted in higher than expected tacrolimus exposure within the first 7-10

days after transplantation in the LCP-Tacro group. Although the trough levels became similar after the initial 10 days in both treatment groups the possibility of over exposure in the LCP-Tacro group still exists since the AUC/Cmin ratio at steady state may be higher with LCP-Tacrolimus compared to Prograf.

Due to concerns related to a possible tacrolimus overexposure in the LCP-Tacrolimus group of Study 3002 at least early on it became necessary to review the Phase 2 Study 2017 results which used a lower starting dose for LCP-Tacrolimus (0.14 mg/kg/day instead of the 0.17 mg/kg/day) as part of the assessment of the safety and efficacy of using a lower starting dose for LCP-tacrolimus in de novo kidney transplant recipients.

Therefore all three studies (3002, 3001 and 2017) will be reviewed for the assessment of the proposed indication and other Phase 1 and Phase 2 study results included in the NDA submission will be referred to as needed.

5.3 Discussion of Individual Studies/Clinical Trials

The order of discussion of the three main studies (3002, 3001 and 2017) for the assessment of efficacy and safety in the upcoming sections of this review is as follows:

1. Phase 3 Study 3002 in de novo kidney transplant recipients
2. Phase 3 Study 3001 in stable kidney transplant recipients
3. Phase 2 Study 2017 in de novo kidney transplant recipients

A different order of discussion is followed in the current Section 5.3 and Phase 2 Study 2017 is discussed ahead of the Phase 3 Study 3002 since it formed the foundation for Study 3002.Overview of the three main studies and some particular issues pertaining to each study are presented below.

Phase 2 Study LCP-Tacro 2017 in De Novo Kidney Transplant Recipients:

Title: A Phase 2, Open-Label, Multi-Center, Randomized Trial to Demonstrate the Pharmacokinetics of LCP-Tacro™ Tablets Once Daily and Prograf® Capsules Twice Daily in Adult de novo Kidney Transplant Patients

The study was conducted at 9 sites in the United States.

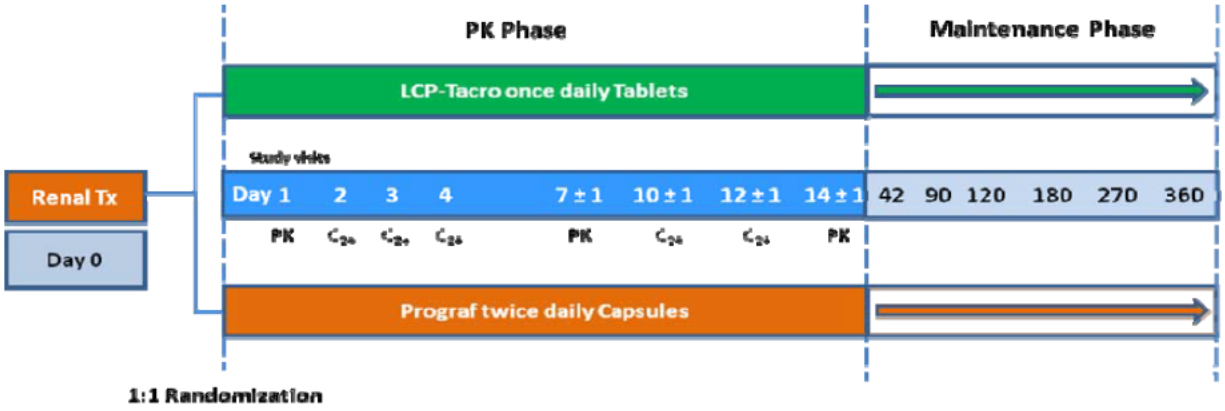
Study Initiation Date: September 22, 2008
Study Completion Date: February 15, 2010

This study was a multi-center study designed to demonstrate the pharmacokinetics and safety of LCP-Tacro tablets compared to Prograf capsules in the first 2 weeks after kidney transplantation. In addition the study compared the efficacy and safety of LCP-Tacro and Prograf over an additional 50 weeks after kidney transplantation (Figure 1). The primary evaluation was an assessment of tacrolimus pharmacokinetics on Days 1,

7, and 14 and the proportion of patients in each treatment arm achieving therapeutic tacrolimus whole blood trough levels within the therapeutic range of 7 to 20 ng/mL on Days 1, 2, 3, 4, 7, 10, 12, and 14.

Secondary endpoints were incidence of death or graft failure, biopsy proven acute rejection (BPAR) (Banff Grade ≥1A), severity of BPAR episodes (Banff Grade), time to first BPAR, incidence of clinically suspected and treated rejection episodes, new onset diabetes mellitus, opportunistic infections and/or malignancies in the first 6 and 12 months post transplantation.

Figure 1. Study 2017 Design
(Source: Figure 4.1, page 24 of Protocol 2017)



Study 2017 was a descriptive study and formal sample size calculations were not performed for efficacy. In the Applicant's assessment of previous Phase 2 studies in stable kidney (b) (4) recipients, a per protocol (PP) analysis of 47 patients (LCP-Tacro 2011) and (b) (4) Study 2017 was designed for the assessment of PK in de novo kidney transplant patients.

A total of 63 patients were randomized in Study 2017; 32 received LCP-Tacro and 31 received Prograf. Overall, 58 patients completed the pharmacokinetics portion of the study and 24 patients in the LCP-Tacro group and 25 patients in the Prograf group completed the one year study period.

Concomitant therapy with either mycophenolate mofetil or mycophenolic acid sodium, or azathioprine was permitted. Corticosteroid therapy was permitted at the discretion of the investigator. Antibody induction according to standard practice at each center was permitted. Alemtuzumab, sirolimus or everolimus was not permitted.

Eligible patients were randomized 1:1 within 12 hours after transplantation to receive either LCP-Tacro tablets once daily in the morning, starting at 0.14 mg/kg/day (the

starting daily dose for African-American patients was 0.17 mg/kg/day), or Prograf capsules in two equally divided doses, starting at 0.2 mg/kg/day which is the labeled starting dose for tacrolimus immediate release formulations (Prograf and generics) when used in combination with azathioprine and in the absence of induction treatment. Subsequent doses of both Prograf and LCP-Tacro in Study 2017 were adjusted to maintain a target trough level of 7 to 20 ng/mL.

The Applicant utilized the label recommended starting dose of 0.2 mg/kg/day for Prograf (0.14 mg/kg/day for LCP-Tacro) and the label recommended target trough range of 7-20 ng/mL for both Prograf and LCP-Tacro when Prograf is used in combination with azathioprine and in the absence of induction treatment:

Study 2017 starting doses:

LCP-Tac: 0.14 mg/kg/day in Caucasian patients
0.17 mg/kg/day in African-American patients

Prograf: 0.2 mg/kg/day in all patients

Study 2017 target trough concentrations for both groups: 7-20 ng/mL

Clinical Reviewer's Comment
At the time when Study 2017 was designed the new reduced starting dose of 0.1 mg/kg/day and reduced target trough concentration range of 4-11 ng/mL for Prograf when used in combination with MMF (Mycophenolate Mofetil) and induction with IL-2 receptor antagonists (similar to the regimens in Study 2017) had not been approved yet (see Section 2.5, Summary of Presubmission Regulatory Activity Related to Submission).

Applicant's conclusion after Study 2017:

According to the applicant's analysis, the proportion of patients achieving therapeutic trough tacrolimus levels (7 to 20 ng/mL) in the LCP-Tacro group was lower than the Prograf group on Day 1, similar to the Prograf group on Day 7, and higher than the Prograf group on Day 14 (Tables 3 and 4).

The Applicant concluded that although there was no difference in efficacy outcomes, the PK results suggest the optimal starting dose of LCP-Tacro on Day 1 might be higher than what was used in this study to more rapidly achieve therapeutic blood levels (7-20 ng/mL) and the pharmacokinetic results indicated that LCP-Tacro regimens can be improved by incorporating a slightly higher Day 1 dose in the de novo setting.

Table 3. Tacrolimus Whole Blood Trough Levels (ng/mL) - Study 2017
(Source: Table 13, page 50 of CSR)

Visit	Statistic	LCP-Tacro (N=32)	Prograf (N=31)
Day 2	Mean	7.3	13.1
	Median (Min-Max)	6.4 (1.5 - 16.6)	11.2 (4.5-33.0)
Day 3	Mean	10.2	12.8
	Median (Min-Max)	9.0 (3.0 - 22.6)	12.7 (3.9 - 29.0)
Day 7	Mean	11.3	12.1
	Median (Min-Max)	11.2 (4.2 - 20.4)	11.1 (3.5 - 23.0)
Day 14	Mean	12.9	11.3
	Median (Min-Max)	12.9 (6.5 - 20.4)	11.3 (3.4 - 23.5)

Table 4 Number and Percentage of Patients Achieving Therapeutic Trough Tacrolimus Levels (7-20 ng/mL) - Study 2017
(Source: Table 14, page 51 of CSR)

	Treatment	
Day	**LCP-Tacro**	**Progra**
1	6/30 (20%)	19/29 (65.5%)
7	18/27 (66.7%)	21/28 (7%)
14	22/28 (78.6%)	16/28 (57.1%)

Clinical Reviewer's Comment
Based on the Applicant's conclusion stated above, the starting dose for LCP-Tacro was chosen to be 0.17 mg/day in the Phase 3 Study 3002 instead of the 0.14 mg/day utilized in the Phase 2 Study 2017. This decision was based on the ratio of patients who met the target trough range of 7-20 ng/mL in Study 2017. This is the range recommended in the absence of induction and when Prograf is used in combination with azathioprine.

Prograf label was subsequently updated with the new recommended reduced starting dose and new reduced target trough range when it is used in combination MMF and in the presence of induction treatment before the commencement of Study 3002. Instead of the old range of 7-20 ng/mL, the Applicant should have used the new reduced target trough range of 4-11 ng/mL which is recommended when Prograf is used in combination with MMF and in the presence of induction treatment when calculating the percentage of patients who reached therapeutic trough concentrations.

If the Applicant had used the new range of 4-11 ng/mL in their analysis, then even on Day 2, a higher percentage of LCP-Tacro patients (20% in the Applicant's analysis, Table 4) would be within the new reduced target range and probably the majority of the Prograf patients would be above the target range as suggested by the median value of 11.2 in Table 3.

Therefore I do not agree with the Applicant's rationale for increasing the starting dose of LCP-tacrolimus from 0.14 mg/kg/day to 0.17 mg/kg/day from Study 2017 to Study 3002 since this rationale is not based on the newly approved target trough range of 4-11 ng/mL but the old range of 7-20 ng/mL. (See Clinical Pharmacology Review for further information)

In Study 3002, while increasing the starting dose of LCP-tacrolimus, the Applicant followed the recommendation in the updated label for Prograf and reduced the starting dose of Prograf to 0.1 mg/kg/day (from the 0.2 mg/kg/day used in Study 2017) and targeted the newly recommended reduced trough levels of 4-11 ng/mL in both treatment groups. Therefore in general Study 3002 was designed utilizing the new reduced starting dose and the new reduced target trough range in the Prograf package insert except for the fact that the opposite was done for LCP-Tacro tablets and the starting dose was increased instead of a reduction.

Phase 3 Study LCP-Tacro 3002 in De Novo Kidney Transplant Recipients:

Title: A Phase 3, Double-Blind, Double-Dummy, Multi-Center, Prospective, Randomized Study of the Efficacy and Safety of LCP-Tacro™ Tablets, Once Daily, Compared to Prograf® Capsules, Twice Daily, in Combination With Mycophenolate Mofetil for the Prevention of Acute Allograft Rejection in De Novo Adult Kidney Transplant Recipients

Study LCP-Tacro 3002 is a 2-arm parallel group, prospective, randomized, double-blind, double-dummy, multicenter12-month study with additional 12 month extension period to evaluate the efficacy and safety of LCP-Tacro tablets compared with immediate-release tacrolimus (Prograf) capsules for the prevention of acute allograft rejection in de novo kidney transplant patients. (Figure 2) In this multinational, multicenter study, 68 sites enrolled patients, 31 in the United States, 13 in Latin America, 15 in Europe, and 9 in Asia Pacific. Current NDA submission contains the initial 12 month results.

Study Initiation Date: October 13, 2010
12-Month Study Completion Date: March 20, 2013

In this non-inferiority study the primary efficacy endpoint is the incidence of treatment failures within 12 months, defined as a composite endpoint that included death, graft

failure, biopsy-proven acute rejection, or lost to follow-up. The non-inferiority of LCP-Tacro to Prograf with respect to treatment failure within 12 months was assessed using a two-sided 95% CI based on the difference in treatment failure rates between the treatment groups at 12 months. The Applicant provided justification for a 10% NI margin.

Sample Size

Assuming that both treatment groups will have a 15% 12-month treatment failure rate, the study required 270 patients per group to have 90% power to reject the null hypothesis that the investigational drug (LCP-Tacro) was inferior to the reference drug (Prograf). In Study 3002, 543 recipients of a primary or secondary kidney transplant from a live or a deceased donor were randomized 1:1, 268 patients to the LCP-Tacro group and 275 patients to the Prograf group.

The database was locked and analyzed after all randomized patients completed the 12-month treatment period; a second, extension analysis will be performed after all patients entering the 12-month extension period have completed the End of Study Visit (Visit 22).

As discussed earlier the results of the Phase 2 Study 2017 and the Prograf labeling update on May 19, 2009 which occurred while the Study 2017 was still ongoing helped in the determination of the starting doses and target trough levels. The starting doses and target trough ranges in Study 3002 are as follows:

Study 3002 starting doses:

LCP-Tac: 0.17 mg/kg/day
Prograf: 0.1 mg/kg/day

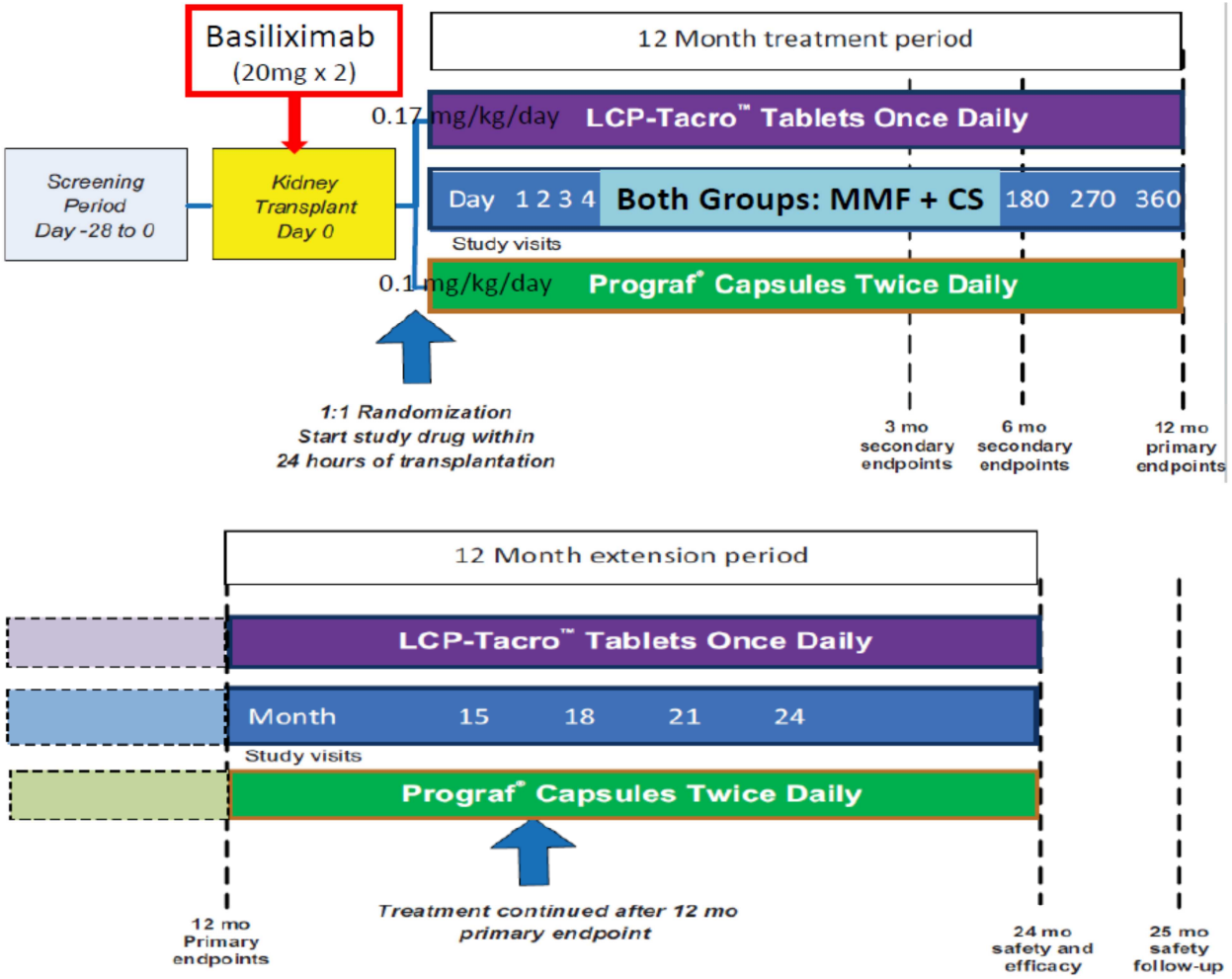
Study 3002 target trough concentrations for both groups:

6-11 ng/mL (first 30 days)
4-11 ng/mL (after the first 30 days)

All patients also received mycophenolate mofetil (MMF), corticosteroids, and IL-2 receptor antagonist (basiliximab) per the standard of care.

As will be discussed later, stringent exclusion criteria based on echocardiographic (ejection fraction) and ECG findings (QT prolongation) were utilized in Study 3002. Due to the international nature of this study there is underrepresentation of African Americans and diabetics compared to a US transplant patient population. Patients were randomly assigned post-transplant to study treatment in a 1:1 ratio, using an interactive, automated system. Randomization was stratified by site and race (African American vs non-African American).

Figure 2 Study 3002 Design
(Source: Figure 6-1, page 36 of Protocol 3002)



Study Entry Assessments and Randomization

Entry assessments included medical history, physical examination, vital sign measurements, ECG, and review/recording of concomitant medications. Patient entry criteria were reviewed following transplantation. Only those patients meeting all of the inclusion criteria and none of the exclusion criteria and who could fulfill the randomization criteria were randomly assigned to study drug according to the protocol. All available laboratory data were reviewed in making the determination for study eligibility. However, investigators did not need to await the results of posttransplantation laboratory data in making this determination if timing did not allow; the pre-transplantation/screening results may have been used for this purpose. Upon determination that a patient was eligible for randomization, the interactive, automated system was accessed to assign the correct blinded treatment (LCP-Tacro or Prograf) for the patient and the study site dispensed blinded study drug.

Clinical Reviewer's Comment
In Study 3002 randomization was done after the transplantation. In my impression from reading the Clinical Study Report (CSR) and reviewing the observed DGF rates (as will be discussed later) that some of the screened patients were not randomized due to inadequate initial graft function.

On page 91 of the CSR, among the reasons for the second protocol amendment, the Applicant states that "*The time period that study drug must be started in was revised from within 24 hours to within 48 hours after transplantation to permit enrollment of patients with marginally delayed graft function who were otherwise good candidates or who were unable to take study drug within 24 hours after transplant due to local site medical practices or postoperative effects*." which suggests that although the Division objected to enrollment of only the patients with initial good kidney function, this enrollment criterion was still followed at least in some cases. This enrollment criterion in addition to the stringent cardiac exclusion criteria probably resulted in selecting, a relatively healthier study population which may not be fully representative of the actual transplant patient population in US.

Blinding and Calculation of the LCP-Tacrolimus Daily Doses

A double-blind, double-dummy study design was used to mask the placebo and active formulations. Consequently, both the investigator and patient did not know the treatment group to which the patient was assigned, thus reducing bias. To maintain blinding of both the investigator and the patient, all patients took tablets (LCP-Tacro/matching placebo) in the morning and capsules (over encapsulated Prograf /matching placebo) twice daily.

For patients in the Prograf group the prescribed Prograf dose and the actual Prograf dose received by the patients were the same. For patients in the LCP-Tacro group, the patients were prescribed a Prograf dose as if the patient were receiving Prograf and this prescribed Prograf dose was converted to LCP-Tacrolimus equivalent by preserving the initial 1.7/1.0 ratio between the LCP-Tacro and Prograf and rounding to the nearest digit throughout the 12 month study period. As an example if the patient was prescribed a Prograf daily dose of 5.5 mg, he/she received a daily dose of 9 mg (5.5 mg x 1.7 = 9.3) LCP-tacrolimus.

Clinical Reviewer's Comment
The initial higher starting dose for LCP-Tacro compared to Prograf (0.17 mg/kg/day vs 0.1 mg/kg/day) and the method of calculation of the daily LCP-Tacro dose based on the prescribed daily dose of Prograf as described above resulted in higher than expected trough levels in some LCP-Tacro patients especially early on in the study as will be discussed later.

Phase 3 Study LCP-Tacro 3001 in Stable Kidney Transplant Recipients

(Conversion Study):

Title: A Phase 3, Open-label, Multicenter, Prospective, Randomized Study of the Efficacy and Safety of Conversion From Prograf® Capsules Twice Daily to LCP-Tacro Tablets Once Daily for the Prevention of Acute Allograft Rejection in Stable Kidney Transplant Patients

Study Initiation Date: December 23, 2008
Study Completion Date: February 07, 2011

Study LCP-Tacro 3001 is a two-armed, parallel-group, prospective, randomized, open-label, multicenter Phase 3 controlled12-month study to evaluate the efficacy and safety of LCP-Tacro tablets when used to replace immediate-release tacrolimus (Prograf) capsules for maintenance immunosuppression in stable renal transplant patients (conversion setting). Thirty-three sites in US, 3 sites in United Kingdom, 3 sites in France, 3 sites in Poland, 2 sites in Germany, and 3 sites in Spain participated in the study. Recipients of a kidney transplant 3 months to 5 years before screening and on a stable dose of Prograf of at least 2 mg per day were randomly assigned to be converted from Prograf twice daily to LCP-Tacro once daily or to remain on maintenance therapy with Prograf twice daily. (Figure 3)

The primary objective of the study was to evaluate the efficacy and safety of LCP-Tacro tablets administered once daily when used to replace Prograf capsules administered twice daily for prevention of acute rejection in adult renal transplant patients.

A composite primary endpoint for non-inferiority was used for efficacy failure at 12 months consisting of death, graft failure, biopsy-proven acute rejection (BPAR), or loss to follow-up.

Clinical Reviewer's Comment
As discussed in the Regulatory History section of this review, the Applicant has not been able to justify an NI margin for this conversion study but was able to justify an NI margin of 10% for the de novo Study 3002. Therefore Study 3002 will be reviewed as the primary study in support of the efficacy and safety of LCP-Tacro tablets in kidney transplant recipients and Study 3001 will provide supportive evidence. See Biostatistics Review by Hongling Zhou for details.

Sample Size

The Applicant predicted the efficacy failure rate at 1 year for stable kidney transplant patients, to be approximately 6%, which is based on 25% of the event rate for de novo patients and chose a non-inferiority margin of (b) (4) by (b) (4) . A (b) (4) efficacy failure rate and a (b) (4) non-inferiority margin with (b) (4) % power at the 1-sided significance level (b) (4) ,

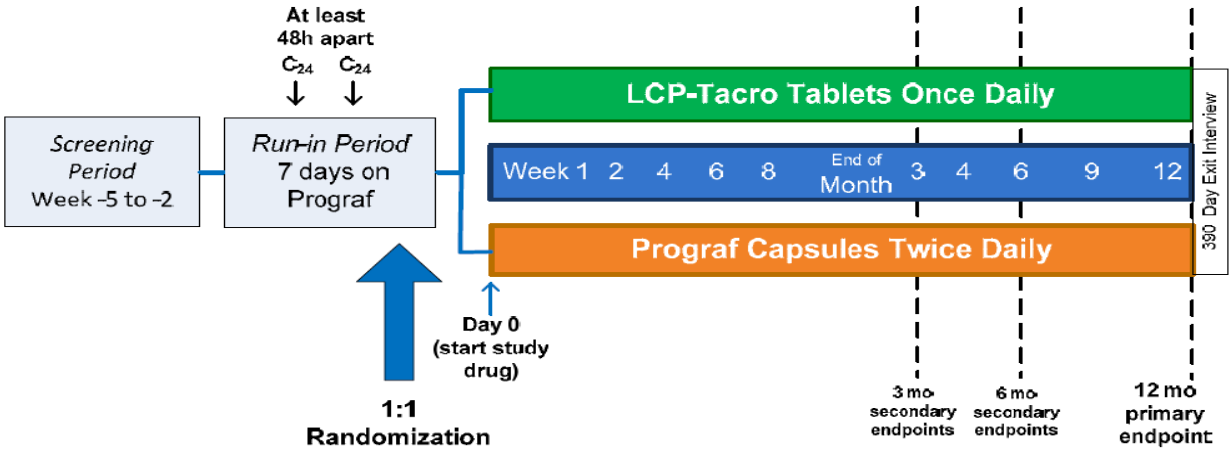
required 136 patients per treatment arm. Considering a (b) (4)% dropout rate, the revised total sample size was 151 patients per group or 302 patients overall.

Three hundred and twenty-six patients were randomized 1:1,163 patients to each treatment group and 296 patients completed the 12-month treatment period, 142 patients in the LCP-Tacro group and 154 patients in the Prograf group.

Screening and Run-in Period

Patients were screened within the 4 weeks (Week –5 to Week –2) before the Run-in Period. All patients considered for study enrollment were required to be maintained on Prograf as part of their maintenance immunosuppression therapy. Candidates with an eGFR <30 mL/min at Screening were not eligible for the study. After successful screening, eligible patients entered a 7-day Run-in Period during which they continued on their current dose of Prograf. Patients were required to have 2 successive tacrolimus trough levels within the range of 4 to 15 ng/m, taken at least 48 hours apart during the Run-in Period, to be eligible for randomization.

Figure 3 Study 3001 Design
(Source: Figure 1, page 31 of Protocol 3001)



On the basis of findings in the preceding Phase 2 PK Study 2011, for patients randomly assigned to LCP-Tacro initial dosing was 0.7 times the total daily dose of Prograf being taken by the patient just before conversion. Due to decreased bioavailability of LCP-Tacro, African American patients were converted using a 0.85 conversion multiplier. All subsequent study drug dose adjustments were based on clinical assessment of the patient and maintenance of target whole blood trough levels within the range of 4 to15 ng/mL in both groups.

6 Review of Efficacy

Efficacy Summary

The efficacy of LCP-tacrolimus extended release tablets were evaluated in two Phase 3 randomized controlled trials, studies 3002 and 3001. Additionally the Phase 2 randomized controlled PK Study 2017 with one year follow-up is included in the review of efficacy and safety in support of a possible lower starting dose consideration for LCP-Tacro than (b) (4) mg/kg/day proposed by the Applicant for de novo kidney transplant recipients since Study 2017 utilized a lower starting dose (0.14 mg/kg/day) which is being considered for labeling as an alternative. Studies 3002 and 2017 were conducted in de novo kidney transplant recipients and Study 3001 was conducted in stable kidney transplant recipients who were converted from a stable dose of Prograf to LCP-Tacro. The efficacy analysis of the NDA was conducted by Hongling Zhou, Ph.D., Biostatistics. See the Biostatistics review of NDA 206-406 dated September 24, 2014 for detailed information.

Phase 3 studies 3002 and 3001 were designed as non-inferiority trials but the Applicant was able to justify an NI margin (10%) only for the de novo Study 3002.The Applicant proposed an NI margin of (b) (4) for the conversion Study 3001 but was not able to justify it which is a common issue in conversion trials due to scarcity of published transplantation studies in the conversion setting. Phase 2 Study 2017 is a relatively smaller study and is not powered to demonstrate efficacy.

Therefore among these three studies the only study with a justified NI margin and powered to show efficacy is the Study 3002 conducted in de novo kidney transplant recipients. Given that tacrolimus is already approved in other formulations, one adequate and well controlled trial with the additional information is sufficient to support a regulatory decision. The other two studies 3001 and 2017 are reviewed as supportive studies. In all three studies the same efficacy composite endpoint consisting of death, graft failure, biopsy proven acute rejection (BPAR), or lost to follow-up has been used.

In the de novo Study 3002, the incidence rate for the composite efficacy failure was slightly lower for the LCP-Tacro group (18.7%) than the incidence rate for the Prograf group (19.6%), with a difference between the two groups (LCP-Tacro – Prograf) of -0.9% and 95% confidence interval of (-7.6%, 5.6%). The upper bound of this CI is smaller than the pre-specified NI margin of 10%. LCP-Tacro was therefore shown to be non-inferior to Prograf based on a 10% NI margin. The BPAR rates were 13.4% in the LCP-Tacro group and 13.5% in the

Prograf group.

In the conversion Study 3001 of stable kidney transplant patients there were very few events. The incidence rate for the composite efficacy failure was the same (2.5%) in both the LCP-Tacro and the Prograf groups with a 95% confidence interval of the difference between the two groups as (-4.2%, 4.2%). There was no statistically significant difference of the efficacy failure rates between the two groups. The incidence rate of BPAR was 1.2% in both groups.

In Study 2017 no patient died or experienced graft failure. The incidence rate of BPAR was 3.1% in the LCP-Tacro group and 6.5% in the Prograf group. There was no statistically significant difference between treatment groups in the cumulative incidence of freedom from BPAR.

In conclusion, LCP-Tacro was shown to be non-inferior to Prograf within a 10% justified NI margin in the pivotal Study 3002 as agreed upon in the SPA and there were no statistically significant differences between the efficacy failure rates of LCP-Tacro and Prograf in the other two studies 3001 and 2017.

6.1 Indication

Prophylaxis of rejection in de novo and stable kidney transplant recipients

6.1.1 Methods

The overview of the three main studies 3002, 3001 and 2017 is presented in Section 5.3. The aspects that are not discussed or discussed but not detailed in Section 5.3 (mainly the endpoints, inclusion/exclusion criteria, treatments and the study assessments) will be discussed in the current section. See Biostatistics Review by Hongling Zhou for a discussion of statistical methods and NI margin justification.

6.1.1.1. Endpoints in Study 3002

Primary Efficacy Endpoint

The primary efficacy endpoint was the incidence of treatment failures within 12 months, up to and including Day 365, after the randomization date. Treatment failure was a composite endpoint that included any of the following events: death, graft failure, BPAR (Banff Grade ≥1A), or lost to follow-up.

Secondary Efficacy Endpoints

Twelve-month all-cause mortality rate

- Twelve-month graft failure rate
- Twelve-month BPAR rate
- Twelve-month incidence of death or graft failure

Important Safety Endpoints

- Incidence of AEs, SAEs, and discontinuations due to AEs
- New-onset diabetes mellitus within 12 months
- Incidence of posttransplant lymphoproliferative disorder
- Mean dose of study drug and mean tacrolimus whole blood trough level at each visit
- Mean change from baseline (Day 30) in HbA1c at Days 90, 180, and 360
- Incidence of opportunistic infections

6.1.1.2 Endpoints in Study 3001

Primary Efficacy Endpoint

Efficacy failure at 12 months defined as: death, graft failure, biopsy-proven acute rejection (BPAR) (Banff grade ≥1A), or loss to follow-up.

Important Secondary Efficacy Endpoints

- Incidence of efficacy failure in the mITT and in the PP populations within 6 months after first dose of study drug
- Incidences of death or graft failure within 6 months and 12 months after first dose of study drug
- Incidences of BPAR (Banff grade ≥1A) within 6 months and 12 months after first dose of study drug
- Proportion of severity grades of the first episode of BPAR (by Banff grade) occurring within 6 months and 12 months after first dose of study drug

Safety Endpoints

The safety endpoints were the differences between treatment groups at Month 12 (Day 360) with respect to AEs and the incidence of predefined potentially clinically significant laboratory measures.

6.1.1.3 Endpoints in Study 2017

Primary Endpoint:

The primary evaluation was an assessment of tacrolimus pharmacokinetics on Days 1, 7, and 14 and the proportion of patients in each treatment arm achieving therapeutic tacrolimus whole blood trough levels within the therapeutic range of 7 to 20 ng/mL on Days 1, 2, 3, 4, 7, 10, 12, and 14.

Secondary Endpoints

The following secondary efficacy endpoints were evaluated at Day 180 and Day 360 post-transplantation, using the mITT dataset.

- Graft survival
- Patient survival
- Incidence of BPAR
- Time to first BPAR
- Severity of BPAR episodes (Banff Grade)
- Incidence of clinically suspected and treated rejection episodes
- Incidence of steroid-resistant acute rejection

Safety Endpoints

Standard summary and/or analysis techniques were used for the evaluation of AEs, SAEs, vital sign measurements, clinical laboratory results, physical examinations, and ECGs.

Clinical Reviewer's Comment
All endpoints used in studies 3002, 3001 and 2017 are standard endpoints used in clinical trials of transplantation and compatible with the study objectives.

6.1.1.4 Inclusion/Exclusion Criteria in Study 3002

Important Inclusion Criteria

1. Patient was receiving a primary or secondary renal allograft from a deceased donor or non-HLA identical living donor
2. Patient had a negative cross match test, and compatible (A, B, AB, or O) blood type
3. Patient was able to swallow tablets and capsules

Important Exclusion Criteria

1. Patient was a recipient of any non-renal transplant
2. Patient had a panel reactive antibody (PRA) >30%
3. Patient had a 12-lead ECG at Screening demonstrating clinically relevant abnormalities (including QTc prolongation, reversible ischemia, and clinically symptomatic congestive heart failure or documented ejection fraction of less than 45%)
4. Patients with malignancies or with a history of malignancies (within the last 5 years) with the exception of local, noninvasive, fully excised: cutaneous basal cell carcinoma, cutaneous squamous cell carcinoma, or cervical carcinoma in situ
5. Patients who received or expected to receive sirolimus, everolimus, azathioprine, or cyclophosphamide within 3 months before enrollment

6. Patient with reversible ischemia (history of untreated reversible ischemia upon stress test)
7. Patients with significant chronic obstructive pulmonary disease, pulmonary restrictive disease, or significant pulmonary hypertension
8. Patients with positive results of any of the following serological tests: human immunodeficiency virus (HIV)-1 antibody, hepatitis B surface antigen, anti-hepatitis B core antibody (HBcAb), and anti-hepatitis C virus (HCV) antibody (HCV Ab).
9. Patients who were receiving concomitant drugs that may have affected concentrations of tacrolimus in whole blood, as listed in the protocol
10. Cold ischemia time >30 hours
11. Non-heart-beating donor

Clinical Reviewer's Comment
Patients with QTc prolongation, reversible ischemia, and clinically symptomatic congestive heart failure or documented ejection fraction of less than 45% are excluded from this trial. Exclusion of patients with reversible ischemia, and clinically symptomatic congestive heart failure are commonly employed in transplantation trials but exclusion of patients with QTc prolongation or with documented ejection fraction of less than 45% represent stringent cardiac exclusion criteria and are not commonly employed. Similar criteria were not used in Study 2017.

These restrictive cardiac exclusion criteria possibly resulted in a highly select and relatively healthy study population in Study 3002 as discussed in the safety section of this review.

6.1.1.5 Inclusion/Exclusion Criteria in Study 3001

Important Inclusion Criteria

To be eligible to participate in this study, patients must have met the following criteria:

1. Men and women at least 18 years of age who were recipients of a kidney transplant between 3 months and 5 years before the screening date.
2. Patients taking a stable dose of oral Prograf capsules twice daily, at least 2 mg total dose per day, as part of their maintenance immunosuppression therapy, with tacrolimus trough levels within the range of 4 to 15 ng/mL.
3. Patients must have maintained tacrolimus trough levels in this range during the 7-day Run-in Period to have been eligible for randomization (based on 2 consecutive trough level measurements at least 48 hours apart). A stable dose of Prograf was defined as a dose that has been unchanged for at least 30 days.

Important Exclusion Criteria

1. Recipients of any transplanted organ other than kidney

2. Patients with an estimated glomerular filtration rate (eGFR) (with MDRD7 formula) <30 mL/min
3. Patients who had taken sirolimus or everolimus within 3 months
4. Patients on concurrent immunosuppression with MMF or mycophenolate sodium (MPS) delayed-release tablets who had not been on stable doses for at least 4 weeks before screening
5. Patients withdrawn from corticosteroids less than 30 days before screening
6. Patients with an episode of acute rejection requiring antibody therapy within 3 months before screening
7. Patients treated for acute rejection within 30 days before screening
8. Patients seropositive for human immunodeficiency virus
9. Patients with a current malignancy or a history of malignancy (within the past 5 years), except basal or non-metastatic squamous cell carcinoma of the skin that had been treated successfully

6.1.1.6 Inclusion/Exclusion Criteria in Study 2017

Inclusion Criteria

Adult men and women at least 18 years of age who were recipients of a kidney transplant from a deceased donor or a live donor and who received their first oral dose of randomized study medication within 48 hours of the transplant surgery

Important Exclusion Criteria

1. Recipients of any transplanted organ other than a kidney
2. Recipients of a kidney from a non-heart beating donor
3. Recipients of a kidney from an ABO incompatible donor
4. Recipients of a kidney with a cold ischemia time of ≥36 hours
5. Patients who were seropositive for human immunodeficiency virus
6. Patients who had a current malignancy or a history of malignancy (within the past 5 years), except basal or non-metastatic squamous cell carcinoma of the skin that had been treated successfully

6.1.1.7 Treatments administered in Study 3002

Patients were randomly assigned to receive 1 of 2 formulations of tacrolimus (LCP-Tacro or Prograf) as follows:

> Test treatment: LCP-Tacro tablets, once daily, orally; provided in 0.75-mg, 1.0-mg, and 4.0-mg dosage strengths.
>
> Reference treatment: Prograf capsules, twice daily, orally; provided in 0.5-mg, 1-mg, and 5-mg dosage strengths.

All patients also received matching double-dummy placebo to maintain the blind. The double-blind, double-dummy daily doses for the two treatment groups are shown in Table 5.

Table 5. Treatment Group Daily Doses - Study 3002
(Source: Table 9-1, CSR page 42)

Treatment Group	Morning Dose	Evening Dose
LCP-Tacro tablets	LCP-Tacro tablets (≥1) Placebo capsules (≥1)	Placebo capsules (≥1)[a]
Prograf capsules	Placebo tablets (≥1) Prograf capsules (≥1)[a]	Prograf capsules (≥1)[a]

Note: Number of tablets and capsules depended on dose level.
[a] Does not apply to the Prograf 0.5-mg daily dose.

LCP-Tacro tablets were administered orally once daily in the morning at an initial dose of 0.17 mg/kg/day. Prograf capsules were administered orally at a starting total daily dose of 0.1 mg/kg/day delivered in 2 equally divided doses 12 hours apart (1 in the morning before noon and 1 in the evening). The first study drug dose was to be given in the morning (before noon) no later than 24 hours (for patients enrolled under Version 3.0 of the protocol) or 48 hours (for patients enrolled under Version 4.0 of the protocol) following transplantation.

Whole blood tacrolimus levels were to be measured 24 hours after the initial dose and dose titration was permitted at this time point if clinically indicated. Study drug was to be adjusted to maintain the whole blood trough level of tacrolimus in the target range of 6 to 11 ng/mL for the first 30 days, then 4 to 11 ng/mL for the remainder of the study. The initial dosage was calculated and indicated via an interactive, automated system and subsequent doses were determined by the investigator. Dose changes were to be based on measurements of whole blood trough levels at intervals specified in the schedule of study activities

Calculation of the Equivalent Daily Dose of LCP-Tacro

To achieve blinding, every Investigator treated every patient as if that patient were receiving Prograf at a "Prograf dose" specified by the Investigator (starting at a protocol-specified "Prograf dose" of 0.10 mg/kg/day dose on Day 1). The order was written in terms of the “Prograf” dose whether the patient was receiving Prograf or LCP-Tacro. For patients who were randomized to LCP-Tacro, In order to convert the dose from the “Prograf dose” to the LCP-dose, a ratio of 1.7/1 was used, the a patient prescribed 10 mg “Prograf” would receive 17 mg LCP-Tacro.

In order to titrate any subsequent doses, the IRT system adjusted the dose based on the proportionate change to the presumed Prograf dose as requested by the physician.

As an example, if a hypothetical "Patient X" was randomized to receive LCP-Tacro at a total daily "Prograf dose" of 10 mg on Day 1 (because she/he weighed approximately 100 kg), the patient actually received an LCP-Tacro 17 mg daily dose. If a few days later the Investigator wanted to reduce the "Prograf dose" to 5 mg (50%) by submitting the dose request in the IRT (Interactive Response Technology) system, the new, actual LCP-Tacro dose allocated would be 8.5 mg (50% of the 17 mg preceding dose level).

Clinical Reviewer's Comment
The initial higher starting dose for LCP-Tacro compared to Prograf (0.17 mg/kg/day vs 0.1 mg/kg/day) and the method of calculation of the daily LCP-Tacro dose based on the prescribed daily dose of Prograf as described above resulted in maintaining the initial 1.7:1 daily dose ratio between LCP-Tacro and Prograf and resulted in higher daily doses of LCP-Tacro compared to the prescribed Prograf dose for that patient till the end of the study period. Maintenance of this conversion ratio resulted in higher than expected trough levels in some LCP-Tacro patients especially early on in the study as discussed further later in the review. This 1.7:1 ratio between LCP-Tacro and Prograf in Study 3002 also is not in agreement with the 0.7:1 conversion ratio utilized in the conversion Study 3001.

Concomitant Immunosuppression

Interleukin-2 receptor antagonist (basiliximab) was administered as per the approved product labeling. The first 20 mg dose was given within 2 hours before transplantation surgery. The recommended second 20 mg dose was given 4 days after transplantation. Use of polyclonal or monoclonal T-cell depleting antibodies for induction was not permitted.

In this study all patients were to receive mycophenolate mofetil (MMF) (1 g twice daily). All patients were to be maintained for the first month on a minimum of 10mg daily oral dose of corticosteroids and, thereafter, on a minimum of 5mg daily oral dose for the remainder of the 12-month treatment period. During the 12-month extension period, the corticosteroid treatment was based on the standard of care at the participating site. Use of sirolimus, everolimus and investigational agents was not permitted.

6.1.1.8 Treatments administered in Study 3001

In this study, patients on a stable dose of oral Prograf of at least 2 mg per day were randomly assigned to be converted from Prograf twice daily to oral LCP-Tacro once daily or to remain on maintenance therapy with oral Prograf twice daily. After successful screening, eligible patients entered a 7-day Run-in Period during which they continued on their current dose of Prograf using their regularly prescribed medication. Patients must have had 2 successive tacrolimus trough levels within the therapeutic range of 4 to

15 ng/mL checked at least 48 hours apart during the Run-in Period for randomization eligibility.

For patients randomly assigned to LCP-Tacro, initial dosing was 0.7 times the total daily dose of Prograf being taken by the patient just before conversion. Because of decreased bioavailability of LCP-Tacro, black patients were converted using a 0.85 conversion multiplier. 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 range of 4 to 15 ng/mL. LCP-Tacro tablets were to be administered orally once daily in the morning, with an interval of 24 hours (±1 hour) between doses. Prograf was to be administrated twice daily in 2 equally divided doses (or as close to equally divided as feasible).

Concomitant Immunosuppression

Patients were maintained on their usual doses of azathioprine, MMF, or MPS (mycophenolic acid sodium) with or without corticosteroids. Only MMF or MPS or azathioprine and/or corticosteroids were allowed; choice of treatment and dose was according to the standard of care at the participating site. The use of sirolimus or everolimus was not allowed.

6.1.1.9 Treatments administered in Study 2017

In this PK study two formulations of tacrolimus were used:

- Test formulation: LCP-Tacro tablets QD orally
- Reference formulation: Prograf capsules BID orally

LCP-Tacro tablets were administered orally in the morning, with an interval of 24±1 hours between daily doses. The initial dose was 0.17 mg/kg/day in African-American patients and 0.14 mg/kg in all other patients. Subsequent doses were to be adjusted at the discretion of the investigator to maintain the target whole blood trough level of tacrolimus between 7 to 20 ng/mL. Prograf was administered twice daily with an interval of 12±1 hours between the morning and evening doses. The initial dose of Prograf was 0.2 mg/kg/day administered in 2 equally divided doses. Subsequent doses were to be adjusted by the investigator to maintain the target whole blood trough level at 7 to 20 ng/mL.

Concomitant Immunosuppression

Concomitant therapy with either MMF or MPS or azathioprine was permitted. Corticosteroid therapy was permitted at the discretion of the investigator. Antibody induction according to standard practice at each center was permitted. All prophylactic and other medications were permitted according to the standard of care in each of the participating sites. Alemtuzumab, sirolimus and everolimus were not permitted.

6.1.1.10 Assessments in Study 3002

Patients underwent the procedures at the time points specified in the schedule of study activities as shown in Table 6. Specimens from all hematology, chemistry, hepatic function and lipid profiles, and urinalysis were sent to and analyzed by the central laboratory. Central laboratory results were used for assessment of the study outcomes.

For tacrolimus trough levels, blood was drawn within 30 minutes before the morning dose of LCP-Tacro tablets or Prograf capsules at each study visit, beginning 24 hours after the first dose of study drug. Dose adjustments to maintain tacrolimus whole blood trough levels within the predefined therapeutic ranges were based on local laboratory determinations. However, an aliquot was also collected and stored for later shipment to a central laboratory for archival storage and/or possible re-assay of tacrolimus level. The results from the central laboratory were used for the analysis and summary of tacrolimus trough levels.

The diagnosis of biopsy-proven acute rejection (BPAR), Banff grade ≥1A, was based on histological grading using the Banff 2007 criteria for renal allograft pathology. Treatment decisions were based on the local readings and interpretation. All biopsies were also read by a single, blinded central reader and the central reading was considered the definitive reading for endpoint purposes of the study protocol. Serum creatinine was measured beginning at Day 30, at each study visit.

Renal function was assessed as change from Day 30 (baseline for renal function evaluation) in eGFR calculated using the MDRD7 equation.

New-onset diabetes mellitus was defined as a fasting plasma glucose (FPG) level of at least 126 mg/dL, or 2-hour postprandial plasma glucose of at least 200 mg/dL (in oral glucose tolerance test) on 2 or more consecutive occasions post-baseline, or hemoglobin A1c (HbA1c) at least 6.5% (at least 3 months after randomization), or new-onset hypoglycemic agent use, or new-onset insulin use greater than 30 days at any time during the study among those patients without baseline diabetes defined as with baseline FPG and HbA1c levels not meeting the respective threshold values and with no prior medical history of diabetes as assessed during the screening period.

A treatment-emergent AE (TEAE) was defined as any untoward sign, symptom, or medical condition occurring at any time after the patient received his/her first dose and within 30 days after the last dose of study drug. Any AEs experienced by patients who were randomly assigned to study drug but did not receive at least 1 dose were not considered as treatment emergent.

Table 6. Schedule of Activities in Study 3002

(Source: 9-2 of the study report, page 51 of CSR)

Phase	Screen-ing[a]	Trans-plantation	Entry	Treatment																Treatment Extension & Follow-up				
Visit number	S	T	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Day	-28 to 0	0[b]	1[b]	1[b]	2	3	4	7 ± 1	10 ± 1	14 ± 2	21 ± 3	30 ± 3	45 ± 3	60 ± 4	90 ± 5	120 ± 5	180 ± 7	270 ± 7	360 ± 7	450 ± 10	540 ± 10	630 ± 10	720 ± 10	750 ± 10
End of week								1		2	3													
End of month												1		2	3	4	6	9	12	15	18	21	24	25
Study Activity																								
Informed consent	X																							Assess AEs and any un-resolved safety issues by phone call (or visit)
Medical history	X	X																						
Inclusion/ exclusion criteria	X		X																					
Kidney transplantation		X																						
Randomization			X[c]																					
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination	X		X									X			X		X		X		X		X	
12-lead electrocardiogram	X		X														X		X		X		X	
Serum creatinine (eGFR calculated[d])	X		X						X	X	X	X	X	X	X	X	X	X	X		X		X	
Hematology profile	X		X					X	X	X	X	X	X	X	X	X	X	X	X		X		X	
Fasting chemistry profile	X[e]		X[e]					X	X	X	X	X[e]	X	X	X	X	X[e]	X	X[e]		X[e]		X[e]	
Fasting lipid profile			X														X		X		X		X	
Urinalysis	X							X	X	X	X	X	X	X	X	X	X	X	X		X		X	

Phase	Screen-ing[a]	Trans-plantation	Entry	Treatment																Treatment Extension & Follow-up				
Visit number	S	T	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Day	-28 to 0	0[b]	1[b]	1[b]	2	3	4	7 ± 1	10 ± 1	14 ± 2	21 ± 3	30 ± 3	45 ± 3	60 ± 4	90 ± 5	120 ± 5	180 ± 7	270 ± 7	360 ± 7	450 ± 10	540 ± 10	630 ± 10	720 ± 10	750 ± 10
End of week								1		2	3													
End of month												1		2	3	4	6	9	12	15	18	21	24	25
Study Activity																								
Spot protein: creatinine ratio	X							X	X	X	X	X	X	X	X	X	X	X	X		X		X	Assess AEs and any un-resolved safety issues by phone call (or visit)
HbA_{1c}	X		X								X	X	X	X	X	X	X	X	X		X		X	
Cytomegalovirus	X															X	X	X	X		X		X	
BK virus	X									X		X		X	X	X	X	X	X		X		X	
EBV	X																							
Anti-HLA antibody	X																		X					
Pregnancy test (urine or serum)	X	(X)[f]	(X)[f]																					
Tacrolimus trough samples					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant drugs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense study drug (as needed)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
AE assessment			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Allograft rejection assessment			<---------- As necessary ---------->																					
Renal biopsy			<---------- As necessary ---------->																					

S, screening; T, transplantation.

[a] Patients must have been screened and consented up to 28 days before transplant surgery and before patients received any pre-medication (before surgery). Patients could not be consented after surgery.

[b] Day 0 and Day 1 may have been combined, if transplantation and randomization occurred on the same calendar day; Day 1 randomization and first dose of study drug may have occurred on the same calendar day.
[c] Randomization must have occurred after transplantation and study drug dosing must have begun within 48 hours following transplantation for patients enrolled under Version 4.0 of the protocol and within 24 hours for patients enrolled under Versions 2.0 and 3.0 of the protocol.
[d] The estimated glomerular filtration rate will be calculated from serum creatinine concentration; baseline is at Day 30.
[e] Including hepatic function profile.
[f] Pregnancy test should have been repeated if not previously done within the past 7 days.

Data Safety Monitoring Board

Accumulating safety data from the ongoing study were reviewed periodically by a Data Safety Monitoring Board (DSMB) consisting of medical experts not participating as investigators in the study and a nonvoting statistician. The DSMB operated according to a charter that described its duties and responsibilities and the mechanisms in place to preserve the blinding of the ongoing study. The DSMB members met in closed session on 3 occasions to review semi-unblinded DSMB-specific interim safety data, including summaries of AEs and clinical laboratory data. These reviews were conducted when 50% of target enrollment reached Day 30 on study treatment, and when 100% of the patients had reached 3 months, and 9 months of follow-up. In each instance, the DSMB recommended that the sponsor continue the study as planned. After completion of the 12-month treatment period, unblinded data for all patients was presented to the DSMB. A review of DSMB-specific study data is planned for when 100% of the patients reach 18 months of follow-up.

6.1.1.11 Assessments in Study 3001

Patients underwent the procedures at the time points specified in the schedule of study activities as shown in Table 7. All hematology, chemistry, fasting lipid profile, hepatic profile, hemoglobin A1c (HbA1c) and urinalysis testing were performed by the central laboratory. Blood samples to measure HbA1c (%) were collected at Baseline and at Days 90, 180 and 360.

Dose adjustments to maintain tacrolimus whole blood trough levels within the predefined therapeutic range of 4 to15 ng/mL were based on local laboratory determinations. However, an aliquot was also collected and stored for later shipment to a central laboratory. Summary data of tacrolimus levels collected during the study were based on the specimens assessed by a central laboratory.

The diagnosis of BPAR (Banff grade ≥1A) was based on histological grading using the 1997 Banff criteria for renal allograft pathology. Biopsies were read locally at each site by a pathologist blinded to treatment assignment and treatment decisions were based on the local interpretation. All biopsies were reviewed at the end of the study by a blinded central pathologist. Patients with treated, suspected acute rejection were not considered to have BPAR and were not counted as efficacy failures if the biopsy did not

confirm rejection but were counted as having a “clinically suspected and treated acute rejection episode,” which is a secondary endpoint.

Initially, new onset diabetes mellitus (NODM) was defined as a fasting plasma glucose level of at least 126 mg/dL, insulin requirement for at least 30 days, or need for an oral hypoglycemic agent at any time during the Treatment Period among those patients who had no medical history of diabetes as assessed during the Screening Period. Based upon more recent literature, the criteria for diagnosis of NODM was revised after database lock to include a fasting plasma glucose >126 mg/dL confirmed by repeat testing, or a HgbA1c >6.5% at least 3 months after randomization, or insulin requirement for at least 30 days, or need for an oral hypoglycemic agent at any time during the Treatment Period among those patients who had no medical history consistent with diabetes as assessed during the Screening Period (a HgbA1c<6.5% at baseline, fasting plasma glucose<126 mg/dL at screening and baseline , and who were not on any diabetes medications at or prior to baseline).

Table 7. Schedule of Activities in Study 3001
(Source: 8-2 of the study report, page 48 of CSR)

Assessment	Screening Period		7-day Run-in	Treatment Period											Exit Safety Interview [a]
	Visit	1	2, 3[b]	4	5	6[c]	7	8[c]	9	10	11	12	13	14	15
	Day			0	7±2	14±2	28±3	42±3	56±4	90±4	120±5	180±5	270±5	360±5	390±5
	Week	–5 to –2	–1		1	2	4	6	8						
	End of Month									3	4	6	9	12	
Informed consent		X													
Medical history		X													
Inclusion/Exclusion criteria		X		X											
Vital signs		X		X	X		X		X	X	X	X	X	X	
Height		X													
Physical examination and weight		X		X			X		X	X		X		X	
12-lead electrocardiogram		X		X								X		X	
Hematology profile[b]		X		X			X		X	X	X	X	X	X	
Chemistry profile		X[d]		X[d]	X		X[d]		X	X[d]	X	X[d]	X	X[d]	
Hemoglobin A_{1c}[b]				X						X		X		X	
Estimated glomerular filtration rate		X													
Spot urine protein:creatinine ratio				X						X		X		X	
Fasting lipid profile[b]				X								X		X	
Urinalysis		X		X			X		X	X	X	X	X	X	
Pregnancy test (serum or urine)			X											X	
Tacrolimus dose and trough		X	X[b]	X	X	X[c]	X	X[c]	X	X	X	X	X	X	
Study drug dispensation (as				X	X		X		X	X	X	X	X		
Concomitant medications		X		X	X		X		X	X	X	X	X	X	
AE assessment		X	X	X	X		X		X	X	X	X	X	X	

AE=adverse event.

[a] Interview could have been conducted as a phone interview unless safety issues warranted a study visit.

[b] Patients must have had at least 2 consecutive tacrolimus whole blood trough levels measuring within 4 to 15 ng/mL and obtained at least 48 hours apart during the Run-in Period to qualify for entry into the study.

[c] Tacrolimus trough levels on Visits 6 and 8 may have been done at the site laboratory and duplicates for the central laboratory were not required. A visit to the transplant clinic was not required for additional evaluation or testing. The patient may have needed to come to the transplant center if a dose change was required and if study drug needed to be dispensed there.

[d] Included hepatic profile (albumin, total and indirect bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma glutamyl transferase).
[e] Tacrolimus whole blood trough levels obtained from local laboratories were used for dosage adjustment but a duplicate specimen was sent to a central laboratory

Safety was assessed by monitoring physical examinations, vital signs, ECGs, chemistry and hematology clinical laboratory tests, hemoglobin A1c, fasting lipids, urinalysis, urine protein:creatinine ratio, eGFR, creatinine clearance, tacrolimus trough concentrations, concomitant medications, plasma glucose and AEs. AE monitoring and reporting were to continue until 30 days after the last dose of study drug (LCP-Tacro or Prograf), until the AE became chronic, or until the patient was deemed "lost to follow-up" by the investigator or subinvestigator. Study personnel were required to follow up with the patient via telephone 30 days after the patient received their last dose of study drug for the purposes of AE monitoring and reporting of new events that may have occurred within the 30-day post-study drug period.

Data Safety Monitoring Board

A data safety monitoring board (DSMB) consisting of medical experts not participating as investigators in the study and a non-voting statistician was chartered to monitor this study. The DSMB members met to review interim safety data when 50% of the patients to be enrolled reached 4 weeks on study treatment and when 100% of the patients reached 3 months on study treatment.

6.1.1.12 Assessments in Study 2017

Patients underwent the procedures at the time points specified in the schedule of study activities as shown in Table 8. Blood specimens were collected on Days 1, 7, and 14 at specified time points after the morning dose of study medication for pharmacokinetic analyses. Pharmacokinetic blood samples were to be processed and shipped on dry ice to a central laboratory ((b) (4)) for standardized evaluation using a validated method. Dose adjustments to maintain tacrolimus whole blood trough levels within the predefined therapeutic ranges and the statistical analysis of tacrolimus trough levels were based on local laboratory data.

Biopsy-proven acute rejection (BPAR) was defined as an episode of acute rejection that was diagnosed based on histological grading using the Banff Classification criteria Grade 1A or greater. Clinically suspected acute rejection was defined as a suspected episode of acute rejection that was treated but not confirmed with a biopsy.

Baseline renal function (estimated glomerular filtration rate, eGFR) was determined at the Day 42 follow-up visit and compared to renal function at Day 180 and Day 360.

A 12-lead ECG was to be obtained from all patients on Days 1, 14, 180, and 360. ECGs were to be evaluated according to local procedures.

Table 8. Schedule of Study Activities in Study LCP-Tacro 2017
(Source: Section 7.1 of the Protocol 2017)

		Screening	Entry	Pharmacokinetic Phase								Maintenance Phase					
	Visit	S	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
	Study Day*	-14 to 0	0	1	2	3	4	7±1	10±1	12±1	14±1	42±3	90±7	120±7	180±10	270±10	360±10
Assessment	Month												3	4	6	8	12
Informed consent		X															
Medical history		X															
Inclusion/exclusion criteria		X	X														
Vital signs		X	X	X			X	X			X	X	X	X	X	X	X
Physical examination		X	X								X		X		X	X	X
12-lead electrocardiogram			X								X				X		X
Hematology profile		X	X	X			X	X			X	X	X	X	X	X	X
Chemistry profile		X[a]	X[a]	X			X	X			X[a]	X[a]	X	X	X[a]	X[a]	X[a]
Urinalysis											X	X	X	X	X	X	X
Pregnancy test		X[b]															
Tacrolimus trough samples					X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study medication[c]			X	X	X	X	X	X					X		X		X
Concomitant medications		X	X				X	X			X	X	X	X	X	X	X
Drug screen		X															
Adverse events				X	X	X	X	X	X	X	X	X	X	X	X	X	X
24-hour pharmacokinetic profile				X[d]				X[d]			X[d]						

a Including hepatic profile.
b Within 7 days prior to receiving study medication.
c Study drug was dispensed daily from the hospital pharmacy until discharge, then in amounts at least sufficient to last to the next study visit but not to exceed 90 days
of treatment. The schedule shown assumed that after the first week, a 90-day supply was issued. More frequent dispensing was allowed.
d Including a predose concentration sample (tacrolimus trough).

6.1.2 Demographics

6.1.2.1 Demographics in Study 3002

Recipient demographic characteristics and baseline transplant information are summarized in Table 9 below. The two groups were generally balanced with respect to demographic and background characteristics. LCP-Tacro group was on average slightly younger (mean=44.8 years) than the Prograf group (mean=46.9 years). Across the groups, about 65% of patients were males, and the majority of patients were Caucasian (76.8%). African Americans are underrepresented in both groups compared to a US transplant patient population. The LCP-Tacro group had slightly higher proportion of living donor than the Prograf group (50.4% vs 46.9%). The majority of patients had not received a prior transplant (95.8%). The majority patients had 2 or less

HLA mismatches. Approximately half of all patients had 1 mismatch in HLA-A, HLA-B, and HLA-DR.

Table 9. Demographic and Baseline Characteristics – Study 3002 (ITT)
(Source: Tables 11-1and 11-2 of the CSR)

Characteristic		LCP-Tacro N=268	Prograf N=275
Age (years)	Mean±SD	44.8±13.3	46.9±14.3
	Range	18-70	18-70
	Median	46	50
	<65 years	252 (94.0)	247 (89.8)
	≥65 years	16 (6.0)	28 (10.2)
Sex- n(%)	Male	174 (64.9)	181 (65.8)
	Female	94 (35.1)	94 (34.2)
Race –n(%)	White	203 (75.7)	214 (77.8)
	African American	10 (3.7)	15 (5.5)
	Asian	10 (3.7)	10 (3.6)
	American Indian or Alaska native	0	1 (0.4)
	Pacific Islander	1 (0.4)	1 (0.4)
	Other	44 (16.4)	34 (12.4)
Ethnicity	Hispanic/Latino	74 (27.6)	79 (28.7)
	Non-Hispanic/Latino	194 (72.4)	196 (71.3)
Baseline BMI (kg/m^2)	Mean±SD	25.7±4.6	26.7±4.9
	Range	16.6 - 38.2	15.6 – 42.1
	Median	25.2	26.5
Donor Type n(%)	Living	135 (50.4)	129 (46.9)
	Deceased	133 (49.6)	145 (52.7)
	missing	0	1 (0.4)
Previous Transplant n(%)	Yes	11 (4.1)	11 (4.0)
	No	257 (95.9)	263 (95.6)
	missing	0	1 (0.4)
HLA mismatches - n(%)	0	31 (11.6)	37 (13.5)
HLA-A	1	129 (48.1)	135 (49.1)
	2	91 (34.0)	83 (30.2)
	0	32 (11.9)	21 (7.6)
HLA-B	1	127 (47.4)	136 (49.5)
	2	91 (34.0)	97 (35.3)
	0	45 (16.8)	51 (18.5)
HLA-DR	1	136 (50.7)	141 (51.3)
	2	67 (25.0)	62 (22.5)

6.1.2.2 Demographics in Study 3001

Overall, demographic characteristics were similar across both treatment groups. The patient population was predominately Caucasian (72.7%), male (67.2%), and middle aged (mean age of 50.3 years) (Table 10). The number of days from transplant to informed consent was the only parameter with a statistically significant difference between treatment groups, with a median of 643 days for the LCP-Tacro treatment group and 569 days for the Prograf treatment group (P=0.025).

Table 10. Demographic and Baseline Characteristics – Study 3001 (Randomized Set)
(Source: Table 10–2, page 85 of CSR)

Characteristic	LCP-Tacro n=163	Prograf n=163
Mean Age (SD)	50.4 (11.71)	50.2 (13.49)
Age categories (years)		
<65	146 (89.6%)	137 (84.0%)
≥65	17 (10.4%)	26 (16.0%)
Male	117 (71.8%)	102 (62.6%)
Female	46 (28.2%)	61 (37.4)
White	120 (73.6%)	117 (71.8%)
Black	36 (22.1%)	34 (20.9%)
Asian	3 (1.8%)	3 (1.8%)
American Indian or Alaska Native	0	1 (0.6%)
Native Hawaiian or other Pacific Islander	0	1 (0.6%)
Other	4 (2.5%)	7 (4.3%)
Mean (SD) Body mass index (kg/m^2)d	29.01 (5.420)	28.73 (6.124)
Diabetes history (both insulin dependent and non-insulin dependent)	61 (37.4%)	53 (32.5%)
Previous rejection for the current graft	20 (12.3%)	23 (14.1%)
Living Donor	62 (38.0%)	51 (31.3%)
Deceased Donor	101 (62.0%)	112 (68.7%)
Number of human leukocyte antigen (HLA) mismatches		
0	16 (9.8%)	15 (9.2%)
1	10 (6.1%)	8 (4.9%)
2	18 (11.0%)	11 (6.7%)
≥3	119 (73.0%)	129 (79.1%)
Subjects who had a previous transplant other than the current transplant	22 (13.5%)	20 (12.3%)
Panel reactive antibody (%)		
<20	120 (73.6%)	117 (71.8%)

≥20	21 (12.9%)	21 (12.9%)
Missing	22 (13.5%)	25 (15.3%)
Days from transplant to informed consent		
Median	643.0	569.0
Minimum, maximum	115, 2005	82, 1821
Baseline Prograf dose (mg/day)		
Mean (SD)	6.09 (3.903)	5.34 (3.347)
Median	5.00	4.00
Minimum, maximum	2.0, 24.0	2.0, 24.0
Baseline weight-adjusted Prograf dose (mg/kg/day)		
Mean (SD)	0.07 (0.052)	0.07 (0.040)
Median	0.06	0.06
Minimum, maximum	0.0, 0.3	0.0, 0.2

6.1.2.3 Demographics in Study 2017

The majority of patients were Caucasian (74.6%). There were 43 (68.3%) males and 20 (31.7%) females with a mean (SD) age of 47.7 (12.94) years. Baseline characteristics were balanced across the two treatment groups in general (Table 11).

Table 11. Demographic Characteristics – Study 2017 (mITT Population)
(Source: Table 8, page 44 of CSR)

Characteristics	**LCP-Tacro (N=32)**	**Prograf (N=31)**
Gender n (%)		
Male	21 (65.6%)	22 (71.0%)
Female	11 (34.4%)	9 (29.0%)
Age		
Mean (SD)	49.3 (12.00)	46.1 (13.87)
Race n (%)		
Asian	1 (3.1%)	2 (6.5%)
African -American	5 (15.6%)	8 (25.8%)
Caucasian	26 (81.3%)	21 (67.7%)
Ethnicity n (%)		
Hispanic or Latino	6 (18.8%)	3 (9.7%)
Not Hispanic or Latino	26 (81.3%)	28 (90.3%)

6.1.3 Subject Disposition

6.1.3.1 Subject Disposition in Study 3002

A summary of overall disposition for all enrolled patients in Study 3002 is presented in Table 12. A total of 601 patients were enrolled into the study and 58 of these patients (9.7%) were not randomly assigned to any treatment due to screening failures. Of the 543 patients randomly assigned to study drug, 268 patients were in the LCP-Tacro group and 275 were in the Prograf group. Two patients in the LCP-Tacro group and 4 patients in the Prograf group were randomized but not dosed.

A greater proportion of patients in the LCP-Tacro group discontinued study drug before Month 12 (22.4%) compared with the Prograf group (18.9%). The most common reasons for early discontinuation of study drug were adverse events in both groups (23 patients, 8.6% in the LCP-Tacro group and 27 patients, 9.8% in the Prograf group).

Overall, 517 patients (95.2%) completed the 12-month study period. Twelve patients (4.5%) in the LCP-Tacro group and 14 patients (5.1%) in the Prograf group withdrew from the study early. The most common reason for early withdrawal from the study on or before day 365 was death (8 patients in each group).

Table 12. Overall Disposition in Study 3002
(Source: Table 14.1.1, page 204 of CSR)

Parameter	**Total Enrolled**	**Not Randomized**	**LCP-Tacro (N=268)**	**Prograf (N=275)**
Patients enrolled	**601**	**58 (9.7)[a]**	**n (%)**	**n (%)**
Patients randomized			268 (100.0)	275 (100.0)
Patients who received at least 1 dose of study drug[b]			266 (99.3)	271 (98.5)
Patients who completed 12-month study drug treatment			206 (76.9)	219 (79.6)
Patients discontinued from study drug prior to Month 12			**60 (22.4)**	**52 (18.9)**
Reasons for early discontinuation of study drug prior to Month 12				
Graft failure			3 (1.1)	1 (0.4)
Rejection			0	0
Adverse event			23 (8.6)	27 (9.8)
Unsatisfactory therapeutic effect			1 (0.4)	2 (0.7)
Patient voluntarily discontinued			22 (8.2)	18 (6.5)
Physician decision			4 (1.5)	2 (0.7)
Sponsor decision			0	0
Noncompliance			2 (0.7)	0
Other			5 (1.9)	2 (0.7)
Patients who completed the 12-month study period			256 (95.5)	261 (94.9)
Patients withdrawn from study prior to Month 12			**12 (4.5)**	**14 (5.1)**
Reasons for early termination from study				

Death	8 (3.0)	8 (2.9)
Adverse event	1 (0.4)	2 (0.7)
Lost to follow-up	0	2 (0.7)
Patient voluntarily discontinued	3 (1.1)	2 (0.7)

a Number of patients enrolled but not randomized, as a percentage of total enrolled. All other percentages are based on the total number of patients randomized to each treatment group.
b Includes the patients who received 1 dose of either drug (study drug or active control).

Clinical Reviewer's Comment
A greater proportion of patients in the LCP-Tacro group discontinued study drug (22.4%) compared with the Prograf group (18.9%) but the rates of treatment discontinuations due to adverse events are similar in both the LCP-Tacro and Prograf treatment groups (8.6% and 9.8% respectively) in this blinded trial.

6.1.3.2 Subject Disposition in Study 3001

A total of 409 patients were enrolled into the Study 3001, 83 of these patients were not randomized (Table 13). Overall, 326 patients were randomly assigned to the study, 163 patients in each treatment group, and 296 patients completed the 12-month treatment period, 142 patients in the LCP-Tacro group and 154 patients in the Prograf group. One patient in each treatment group was randomized but not dosed; thus, a total of 324 patients (99.4%) were included in the (mITT) set, 162 (99.4%) in each treatment group.

Thirty patients (9.2%) discontinued from the study; of these, more patients in the LCP-Tacro treatment group (n=21, 12.9%) discontinued from the study than in the Prograf treatment group (n=9, 5.5%).

Table 13. Overall Disposition in Study 3001 (Randomized Set)
(Source: Table 9-1, page 82 of CSR)

	LCP-Tacro n=163 (%)	**Prograf n=163 (%)**
Total number of patients		
Modified intent-to-treat set	162 (99.4)	162 (99.4)
Per-protocol set within 12 months	142 (87.1)	154 (94.5)
Discontinued study drug	**21 (12.9)**	**9 (5.5)**
Primary reason for discontinuation of study drug		
AE	12 (7.4)	2 (1.2)
Patient voluntarily discontinued	6 (3.7)	3 (1.8)
Physician decision	2 (1.2)	0
Sponsor decision	0	2 (1.2)
Rejection	1 (0.6)	0
Other	0	2 (1.2)

Discontinued the study	**21 (12.9)**	**9 (5.5)**
Reasons for discontinuation from the Study		
AE	10 (6.1)	3 (1.8)
Protocol violation	0	2 (1.2)
Lost to follow-up	0	1 (0.6)
Patient died	2 (1.2)	0
Patient voluntarily discontinued	7 (4.3)	3 (1.8)
Physician decision	2 (1.2)	0

Clinical Reviewer's Comment
Unlike in the double blind de novo Study 3002 where the rates of study and treatment discontinuations were more similar across the treatment groups, in the open label conversion Study 3001 there are higher rates of treatment and study discontinuations in the LCP-Tacro group compared to the Prograf group (12.9% vs. 5.5% for both). This may at least partially be due to the open label nature of the Study 3001. Most of the treatment discontinuations in the LCP-Tacro group were due to adverse events without a preponderance of any SOC (7.4% and 1.2% respectively in the LCP and Prograf groups). For a list of AEs leading to treatment discontinuations in Study 3001 see Section 7.3.3.2.

6.1.3.3 Subject Disposition in Study 2017

A total of 63 patients were randomized (32 received LCP-Tacro and 31 received Prograf). Twenty-four (75.0%) patients in the LCP-Tacro group and 25 (80.6%) patients In the Prograf group completed the study through the Day 360 visit (Table 14).

Table 14. Overall Disposition in Study 2017
(Source: Table 6, page 42 of CSR)

Patient Disposition	**LCP-Tacro n=32 (%)**	**Prograf n=31 (%)**
Number of Patients who Completed the Pharmacokinetic Portion of the Study - n (%)		
Yes	29 (90.6%)	29 (93.5%)
No	3 (9.4%)	2 (6.5%)
Reason for Early Withdrawal - n (%)		
Withdrew consent	3 (9.4%)	1 (3.2%)
Request for termination by sponsor or regulatory authorities	0.0%	1 (3.2%)
Number of Patients who Completed the Study Through Day 360 - n (%)		

Yes	24 (75.0%)	25 (80.6%)
No	8 (25.0%)	5[a] (16.1%)
Reason for Early Withdrawal - n (%)		
Adverse event	2 (6.3%)	2 (6.5%)
Withdrew consent	4 (12.5%)	1 (3.2%)
Lost to follow up	1 (3.1%)	1 (3.2%)
Request for termination by sponsor or regulatory authorities	0 (0.0%)	2 (6.5%)
Administrative/other reason	1 (3.1%)	0 (0.0%)

[a] Due to a discrepancy not discovered until after database lock, there were 6 patients in the Prograf treatment group (not 5) who did not complete the study through the Day 360 visit.

Clinical Reviewer's Comment
Similar to the Phase 3 de novo Study 3002, in the Phase 2 de novo Study 2017 the rates of study discontinuations are balanced across the treatment groups.

6.1.4 Analysis of Primary Endpoint(s)

The efficacy analysis of the NDA was conducted by Hongling Zhou, Ph.D., Biostatistics. See Biostatistics review of NDA 206-406 dated September 24, 2014 for detailed information.

6.1.4.1 Analysis of the Primary Endpoint(s) for Study 3002

Study 3002 was designed as a non-inferiority (NI) study with a justified NI margin of 10%. The primary efficacy endpoint is the incidence of treatment failures defined as a composite consisting of death, graft failure, biopsy-proven acute rejection (BPAR, Banff Grade ≥ 1A) or loss to follow-up within 12 months after randomization. Based on the protocol, central laboratory results were used for assessment of the study outcomes.

The null hypothesis for the primary efficacy analysis is LCP-Tacro was inferior to Prograf with respect to the proportion of treatment failures 12 months after randomization. The non-inferiority of LCP-Tacro with respect to treatment failure within 12 months was assessed using a 2-sided 95% CI based on the difference in treatment failure rates between the treatment groups at 12 months, i.e., LCP-Tacro minus Prograf. If the upper bound of the 95% CI for the difference in treatment failure rates was less than 0.10, then LCP-Tacro is considered non-inferior to Prograf. See Biostatistics review of NDA 206406 by Hongling Zhou, Ph.D. for NI margin justification.

An inspection of Rejection Analysis dataset by the Biostatistics Reviewer revealed that Patient 034154017 in the LCP-Tacro arm was randomized on March 4 2012 and had a biopsy on March 4 2013 that resulted in the confirmation of an acute rejection event. Because the biopsy date was Day 366 after randomization, this acute rejection event

was not included as a BPAR event by the Applicant and therefore was not an efficacy failure in the Efficacy Analysis dataset. However, further inspection of the eCRF revealed that this rejection event occurred on Feb 25 2013 and the biopsy was performed 8 days later on March 4 2013 which happened to be Study Day 366, one day past the cut-off date for 12 month primary analysis.

It was decided to include the rejection in patient 034154017 as an event since the rejection occurred within the 12 month study period, although the biopsy was performed 8 days later. Table 15 below is updated with inclusion of patient 034154017 as a BPAR event therefore as an efficacy failure. Thirty six patients in the LCP-Tacro group had BPAR events compared to 37 patients in the Prograf group.
The incidence rate for efficacy failure for the LCP-Tacro group (18.7%) and for the Prograf group (19.6%), yielded a difference between the two groups (LCP-Tacro – Prograf) of -0.9% and 95% confidence interval of (-7.6%, 5.6%). The upper bound of this CI is smaller than the pre-specified NI margin of 10%. LCP-Tacro was therefore shown to be non-inferior to Prograf based on a 10% NI margin (Table 15).

The incidence rate for the endpoint of graft loss/death/lost to follow-up was also numerically lower for the test drug LCP-Tacro (7.1%) compared with the control Prograf (8.4%). For the individual components of the efficacy endpoint, incidence rate of BPAR, graft loss and rate of lost to follow-up were slightly lower in the LCP-Tacro arm than the Prograf arm.

Table 15. Efficacy Results by Treatment Group at 12 Months (ITT Population) – Study 3002
(Source: Biostatistics Review by Hongling Zhou, PhD)

Endpoints	LCP-Tacro N=268 n(%)	Prograf N=275 n(%)
Efficacy Failure Endpoint	50 (18.7)	54 (19.6)
	95% CI of LCP-Tacro - Prograf: -1.0% (-7.6%, 5.6%)[(a)]	
Biopsy Proven Acute Rejection	36 (13.4)	37 (13.5)
Death	8 (3.0)	8 (2.9)
Graft Loss	9 (3.4)	11 (4.0)
Lost to Follow-up	4 (1.5)	5 (1.8)
Graft Loss or Death or Lost to Follow-up	19 (7.1)	23 (8.4)
	95% CI of LCP-Tacro – Prograf: -1.3%(-5.8%, 3.2%)	
Graft Loss or Death	15 (5.6)	18 (6.6)

Lost to Follow-up	4 (1.5)	5 (1.8)
95% CI for difference in efficacy failure rate compared to Prograf group calculated using exact method(b)	(-7.7%, 5.7%)	
95% CI for difference in efficacy failure rate compared to Prograf group calculated using the Newcombe-Wilson score method(c)	(-7.6%, 5.6%)	

(a) CI calculated using normal approximation
(b) The method specified in the protocol
(c) The method specified in the SAP version 6.

Table 16 presents the distribution of the number of BPARs and the severity distribution of central biopsy assessments for first episode of BPAR occurred within 12 months after randomization. The numbers of patients with 1-4 BPAR episodes were similar between the two groups. Severity of first BPAR episode was also similarly distributed between the two groups.

Table 16. Number of BPAR and First BPAR Episode Severity Assessment* within 12 Months by Treatment Group (ITT set) – Study 3002
(Source: Biostatistics Review by Hongling Zhou, PhD)

	LCP-Tacro N=268	Prograf N=275
No. of Patients who had BPAR	36 (13.4)	37 (13.5)
Number of BPAR		
No. of Patients with 1 BPAR episode	27 (10.1)	29 (10.5)
No. of Patients with 2 BPAR episodes	6 (2.2)	6 (2.2)
No. of Patients with 3 BPAR episodes	2 (0.7)	2 (0.7)
No. of Patients with 4 BPAR episodes	1 (0.4)	0 (0)
Severity Assessment* of first BPAR		
Mild	29 (10.8)	29 (10.5)
Moderate	6 (2.2)	8 (2.9)
Severe	1 (0.4)	0 (0)

*Mild is acute T-cell-mediated rejection Grade IA or IB, Moderate is acute T-cell-mediated rejection Grade IIA or Grade IIB, and Severe is acute T-cell-mediated rejection Grade III using Banff 2007 criteria.

The primary endpoint is defined using the central biopsy readings in this trial but acute rejection episodes were treated according to the local readings. Table 17 shows comparison of local and central biopsy assessments for the BPAR events confirmed by central reading as treatment failures. In this trial, BPAR is defined as Banff Grade ≥1A. In Table 17 below the severity of the rejection episodes are categorized using Banff 2007 criteria as follows:

Mild: Grade IA or IB,
Moderate: Grade IIA or Grade IIB,
Severe: Grade III.

Among the biopsies that were confirmed as AR by central reading, 19 (52.8% of 36) in LCP-Tacro arm and 22 (59.5% of 37) in Prograf arm were not considered as AR events by local readings. While the central review identified 1 severe rejection in LCP-Tacro group, the local review identified 1 severe rejection in the Prograf control arm. Overall, local lab readings appear to be more conservative compared with central readings which generally is not the case in transplantation trials since usually local readings result in higher rejection rates compared to the central readings.

Table 17. Local Biopsy Assessments for Central BPAR Events – Study 3002
(Source: Biostatistics Review by Hongling Zhou, PhD)

	Central Assessment		**Local Assessment**	
	LCP-Tacro	Prograf	LCP-Tacro	Prograf
Number of biopsies confirmed as BPAR by central reading	36	37	36	37
non-specific/borderline change	0	0	19	22
mild	29	29	10	9
moderate	6	8	5	5
severe	1	0	0	1
missing	0	0	2	0

Table 18 below shows the efficacy results at 12 Months (ITT Population) by local BPAR readings as calculated and tabulated by the Biostatistics Reviewer Dr. Hongling Zhou. The local BPAR results were based on dataset ADREJ.xpt. Using locally read BPAR results, the conclusion on efficacy outcome would stay the same as using the results from central readings.

Table 18. Efficacy Results at 12 Months (ITT Population) by Locally Read BPAR – Study 3002
(Source: Biostatistics Review by Hongling Zhou, PhD)

Endpoints	**LCP-Tacro** N=268 N (%)	**Prograf** N=275 N (%)
Efficacy Failure Endpoint	42 (15.7)	45 (16.4)
	95% CI of LCP-Tacro - Prograf: -0.7%(-6.9%, 5.5%) [(a)]	
Biopsy Proven Acute Rejection	25 (9.3)	23 (8.4)

Death	8 (3.0)	8 (2.9)
Graft Loss	9 (3.4)	11 (4.0)
Lost to Follow-up	4 (1.5)	5 (1.8)
Graft Loss or Death or Lost to Follow-up	19 (7.1)	23 (8.4)
	95% CI of LCP-Tacro – Prograf: -1.3%(-5.8%, 3.2%)	
Graft Loss or Death	15 (5.6)	18 (6.6)
Lost to Follow-up	4 (1.5)	5 (1.8)
95% CI for difference in efficacy failure rate compared to Prograf group calculated using exact method(b)	(-6.9%, 5.5%)	
95% CI for difference in efficacy failure rate compared to Prograf group calculated using the Newcombe-Wilson score method(c)	(-6.9%, 5.5%)	

(a) CI calculated using normal approximation
(b) The method specified in the protocol
(c) The method specified in the SAP version 6.

6.1.4.2 Analysis of the Primary Endpoint(s) for Study 3001

Study 3001 is a conversion study in stable kidney transplant recipients. The Applicant designed Study 3001 as a non-inferiority study and proposed an NI margin of (b) (4) but was not able to justify this NI margin in the conversion setting as discussed earlier. Similar to the de novo Study 3002, the primary efficacy endpoint is the incidence of efficacy failure defined as a composite consisting of death, graft failure, biopsy-proven acute rejection (BPAR, Banff Grade ≥ 1A) or loss to follow-up within 12 months after randomization. The diagnosis of BPAR (Banff grade ≥1A) was based on local histological grading using the Banff criteria.

Comparisons between treatment groups on efficacy failure endpoint and each component of this endpoint are summarized in Table 19. There were very few events in this conversion study of stable kidney transplant patients. There were 4 efficacy failures in each treatment group, with a 95% confidence interval of the difference of the efficacy failure rates between the two groups as (-4.2%, 4.2%). There was no statistically significant difference of the efficacy failure rates between the two groups (p=1.0000, Fisher's exact test).

For the individual components of the efficacy failure endpoint, the two groups were comparable as well. The incidence rate of BPAR was the same for the two groups. There were 2 deaths in the LCP-Tacro group and 1 death in the Prograf group. No graft losses occurred within the 12 month study period. One patient in the Prograf arm was lost to follow-up and no patients in the Prograf arm were lost to follow-up.

Table 19. Efficacy Results by Locally Read BPAR at 12 Months (mITT Population) – Study 3001

(Source: Biostatistics Review by Hongling Zhou, PhD)

Endpoints	**LCP-Tacro** N=162 n(%)	**Prograf** N=162 n(%)
Efficacy Failure Endpoint	4 (2.5)	4 (2.5)
	95% CI of LCP-Tacro - Prograf: 0% (-4.2%, 4.2%)	
Biopsy Proven Acute Rejection	2 (1.2)	2(1.2)
Death	2 (1.2)	1 (0.6)
Graft Loss	0	0
Lost to Follow-up	0	1(0.6)
Graft Loss or Death or Lost to Follow-up	2 (1.2)	2 (1.2)
	95% CI of LCP-Tacro - Prograf: 0%(-3.4%, 3.4%)	
Graft Loss or Death	2 (1.2)	1(0.6)
Lost to Follow-up	0	1(0.6)

Table 20 below presents the efficacy results using the central biopsy readings. The confidence intervals in Table 20 were calculated using the exact method. The incidence of efficacy failure in the LCP-Tacro arm (3/162=1.9%) was slightly lower compared with the Prograf control (6/162=3.7%). The difference of the efficacy failure rates between the two groups (LCP-Tacro – Prograf) was -1.9% with a 95% C.I. of (-6.5%, 2.3%). There was no statistically significant difference of the efficacy failure rates between the two groups (p=0.3389, Fisher's exact test). The numbers for graft loss, death and lost to follow-up are the same as in local reading (Table 19). There was a slight advantage to the LCP-Tacro test arm using the central biopsy readings as opposed to the local readings.

Table 20. Efficacy Results by Centrally Read BPAR at 12 Months (mITT Population) – Study 3001

(Source: Biostatistics Review by Hongling Zhou, PhD)

Endpoints	**LCP-Tacro** N=162 n(%)	**Prograf** N=162 n(%)
Efficacy Failure Endpoint	3 (1.9)	6 (3.7)
	95% CI of LCP-Tacro - Prograf: -1.9%(-6.5%, 2.3%)	

Biopsy Proven Acute Rejection	1(0.6)	4(2.5)
Death	2 (1.2)	1 (0.6)
Graft Loss	0	0
Lost to Follow-up	0	1(0.6)
Graft Loss or Death or Lost to Follow-up	2 (1.2)	2 (1.2)
	95% CI of LCP-Tacro - Prograf: 0%(-3.4%, 3.4%)	
Graft Loss or Death	2 (1.2)	1(0.6)
Lost to Follow-up	0	1(0.6)

6.1.4.3 Analysis of the Primary Endpoint(s) for Study 2017

Study 2017 was designed as a PK study with one year follow-up. It was not designed to evaluate efficacy. Treatment failure at Month 6 was defined as a composite of death, graft loss, BPAR, or loss to follow-up.

In Study 2017 no patient died or experienced graft failure. A total of 3 patients experienced BPAR (1 LCP-Tacro, 2 Prograf) and 2 patients were lost to follow-up (1 LCP-Tacro and 1 Prograf).

Treatment failure therefore included 2 patients in the LCP-Tacro treatment group and 3 patients in the Prograf group. There was no statistically significant difference between treatment groups in the cumulative incidence of freedom from BPAR and no statistically significant difference in the severity of BPAR episodes in LCP-Tacro patients compared to Prograf patients at Day 180 or Day 365. Table 21 below gives the results of treatment failures.

Table 21. Treatment Failures at 6 Months – Study 2017
(Source: Biostatistics Review by Hongling Zhou, PhD)

Event	**LCP-Tacro N = 32**	**Prograf N = 31**
BPAR/D/GL/LTFU	2 (6.3)	3 (9.7)
	95% exact C.I. of LCP-Tacro – Prograf (-20.7%, 12.6%) P=0.7082	
BPAR/D/GL	1 (3.1)	2 (6.5)
BPAR	1 (3.1)	2 (6.5)
Death	0 (0)	0 (0)
Graft loss	0 (0)	0 (0)
Lost to follow-up	1 (3.1)	1 (3.2)
Death/Graft Loss	0 (0)	0 (0)

6.1.5 Analysis of Secondary Endpoints(s)

In all three main clinical studies most of the secondary efficacy endpoints represent the individual components of the composite primary efficacy endpoint such as the mortality rate, graft failure rate and the acute rejection rate. Most of these secondary endpoints are already covered and discussed in the previous section (6.1.4) as part of the assessment of the primary efficacy endpoints; therefore are not repeated in the current section. Safety endpoints for each study are assessed in Section 7 of this review.

6.1.6 Other Endpoints

None

6.1.7 Subpopulations

The subpopulation analyses summary and tables in this section are from the Biostatistics review by Hongling Zhou, PhD. See the Biostatistics NDA review for more information.

The subgroup analyses in this section will focus on the De Novo Study 3002. There were very few events in Study 3001 to allow any meaningful subgroup analyses.

6.1.7.1 Subpopulations in Study 3002

In the subgroup analyses based on gender, race, age, geographic region and donor type none of the differences between the LCP-Tacro and Prograf groups reached statistical significance.

In the analysis by gender (Table 22), the most conspicuous difference is the lower efficacy failure rate in the females of the LCP-Tacro arm (13.8%) compared to the failure rate in the females of the Prograf arm (20.2%). (p=0.2443)

Table 22. Efficacy Outcome by Gender-Study 3002
(Source: Biostatistics Review by Hongling Zhou, PhD)

Number of Patients (%)	**Males N=355**		**Females N=188**	
	LCP-Tacro N=174	Prograf N=181	LCP-Tacro N=94	Prograf N=94
Efficacy Failure	37 (21.3)	35 (19.3)	13 (13.8)	19 (20.2)
GL/D/LTFU	12 (6.9)	12 (6.6)	7 (7.4)	11 (11.7)
GL/D	10 (5.7)	10 (5.5)	5 (5.3)	8 (8.5)
BPAR	27 (15.5)	25 (13.8)	9 (9.6)	12 (12.8)
Death	5 (2.9)	5 (2.8)	3 (3.2)	3 (3.2)
Graft loss	5 (2.9)	6 (3.3)	4 (4.3)	5 (5.3)
LTFU	2 (1.2)	2 (1.1)	2 (2.1)	3 (3.2)

95% CI* of Efficacy Failure (LCP-Tacro - Prograf) p-value**	(-6.4%, 10.3%) 0.6517	(-17.1%, 4.3%) 0.2443
95% CI* of GL/D/LTFU (LCP-Tacro - Prograf) p-value**	(-5.0%, 5.5%) 0.9203	(-12.6%, 4.1%) 0.3215

*Confidence intervals constructed using a normal approximation.
**P-value based on Chi-square test.

Among older (> 65) patients, the efficacy failure rate was lower in the LCP-Tacro arm (1/16=6.3%) than in the Prograf arm (6/28=21.4%). (p=0.2263, Table 23)

Table 23. Efficacy Outcome by Age Category Study 3002
(Source: Biostatistics Review by Hongling Zhou, PhD)

Number of Patients (%)	**Age (<65) N=499**		**Age (≥ 65) N=44**	
	LCP-Tacro N=252	Prograf N=247	LCP-Tacro N=16	Prograf N=28
Efficacy Failure	49 (19.4)	48 (19.4)	1 (6.3)	6 (21.4)
GL/D/LTFU	18 (7.1)	19 (7.7)	1 (6.3)	4 (14.3)
GL/D	14 (5.6)	15 (6.1)	1 (6.3)	3 (10.7)
BPAR	35 (13.9)	34 (13.8)	1 (6.3)	3 (10.7)
Death	7 (2.8)	5 (2.0)	1 (6.3)	3 (10.7)
Graft loss	8 (3.2)	10 (4.1)	1 (6.3)	1 (3.6)
LTFU	4 (1.6)	4 (1.6)	0 (0)	1 (3.6)
95% CI of Efficacy Failure (LCP-Tacro - Prograf) p-value	(-6.9%, 7.0%)* 0.9975**		(-35.5%, 10.8%)# 0.2263##	
95% CI of GL/D/LTFU (LCP-Tacro - Prograf) p-value	(-5.1%, 4.0%)* 0.8148**		(-27.5%, 16.6%)# 0.4533##	

*Confidence intervals constructed using a normal approximation.
**P-value based on Chi-square test.
Confidence interval constructed using the exact method.
P-value based on Fisher's exact test.

In the analysis of the efficacy endpoints by race (Table 24), the results between the two treatment groups appear to be similar for Caucasian and other groups of patients. For African American patients, the failure rate was lower (3/10=30%) in the LCP-Tacro arm than in the Prograf arm (6/15=40%). The difference was not statistically significant (p=0.6426).

Table 24. Efficacy Outcome by Race Study 3002
(Source: Biostatistics Review by Hongling Zhou, PhD)

Number of Patients (%)	White N=417		Black N=25		Other N=101	
	LCP-Tacro N=203	Prograf N=214	LCP-Tacro N=10	Prograf N=15	LCP-Tacro N=55	Prograf N=46
Efficacy Failure	37 (18.2)	40 (18.7)	3(30.0)	6 (40.0)	10 (18.2)	8 (17.4)
GL/D/LTFU	15 (7.4)	17 (7.9)	2 (20.0)	3 (20.0)	2 (3.6)	3 (6.5)
GL/D	11 (5.4)	14 (6.5)	2 (20.0)	1 (6.7)	2 (3.6)	3 (6.5)
BPAR	25 (12.3)	27 (12.6)	2 (20.0)	3 (20.0)	9 (16.4)	7 (15.2)
Death	6 (3.0)	6 (2.8)	2 (20.0)	0 (0)	0 (0)	2 (4.4)
Graft loss	6 (3.0)	8 (3.7)	1 (10.0)	1 (6.7)	2 (3.6)	2 (4.4)
LTFU	4 (2.0)	3 (1.4)	0 (0)	2 (13.3)	0 (0)	0 (0)
95% CI of Efficacy Failure (LCP-Tacro - Prograf)	(-7.9%, 7.0%)*		(-46.1%, 30.0%)#		(-14.2%, 15.8%)*	
p-value**	0.9026**		0.6426##		0.9177**	
95% CI* of GL/D/LTFU (LCP-Tacro - Prograf)	(-5.7%, 4.6%)*		(-31.8%, 37.8%)#		(-15.2%, 7.3%)#	
p-value**	0.8315**		1.000##		0.6055##	

*Confidence intervals constructed using a normal approximation.
**P-value based on Chi-square test.
Confidence interval constructed using exact method.
P-value based on Fisher's exact test.

The efficacy failure rates among US patients were slightly higher (17.9%) in the LCP-Tacro group than in the Prograf group (14.3%) (Table 25). Among non-US patients, the failure rate for LCP-Tacro arm was lower 18.9%) compared with failure rate for Prograf arm (21.5%).

Table 25. Efficacy Outcome by Region (US vs non-US) Study 3002
(Source: Biostatistics Review by Hongling Zhou, PhD)

Number of Patients (%)	US N=137		Non-US N=406	
	LCP-Tacro N=67	Prograf N=70	LCP-Tacro N=201	Prograf N=205
Efficacy Failure	12 (17.9)	10 (14.3)	38 (18.9)	44 (21.5)
GL/D/LTFU	4 (6.0)	4 (5.7)	15 (7.5)	19 (9.3)
GL/D	4 (6.0)	3 (4.3)	11 (5.5)	15 (7.3)
BPAR	9 (13.4)	7 (10.0)	27 (13.4)	30 (14.6)
Death	4 (6.0)	1 (1.4)	4 (2.0)	7 (3.4)
Graft loss	1 (1.5)	2 (2.9)	8 (4.0)	9 (4.4)
LTFU	0 (0)	1 (1.4)	4 (2.0)	4 (2.0)
95% CI of Efficacy Failure	(-8.7%, 15.9%)*		(-10.4%, 5.2%)*	

(LCP-Tacro - Prograf) p-value	 0.5635**	 0.5210**
95% CI of GL/D/LTFU (LCP-Tacro - Prograf) p-value	(-9.0%, 9.6%)# 0.9998##	(-7.2%, 3.6%)* 0.5114**

*Confidence intervals constructed using a normal approximation.
**P-value based on Chi-square test.
Confidence interval constructed using exact method.
P-value based on Fisher's exact test.

6.1.7.2 Subpopulations in Study 3001

There were very few events in Study 3001 to allow any meaningful subgroup analyses.

6.1.8 Analysis of Clinical Information Relevant to Dosing

Recommendations

Tacrolimus immediate release formulation (Prograf ®) was approved by the FDA for the prevention of rejection in kidney transplant recipients in 1997. The starting dose labeled in 1997 in de novo kidney transplant recipients when Prograf is used in combination with azathioprine and in the absence of induction treatment is 0.2 mg/kg/day later to be titrated to meet the target trough levels of 7-20 ng/mL for the first three months and 5-15 ng/mL thereafter.

Since the time of initial FDA approval, tacrolimus immediate release formulation has been extensively used in kidney and other organ transplantations and clinical practice has evolved which is reflected in the May 19, 2009 Prograf labeling update. The May 19, 2009 update added new reduced starting dose and reduced target trough levels to the label when Prograf is used in combination with MMF and in the presence of IL-2 receptor blocker induction treatment. As discussed in sections 2.5 and 5.3 of this review, this 2009 Prograf labeling update affected the determination of the starting doses and target trough levels in the pivotal Phase 3 Study 3002.

In Study 3002 the starting dose of Prograf is 0.1 mg/kg/day and the starting dose of LCP-Tacro is 0.17 mg/kg/day. Both tacrolimus formulations were later titrated to the same trough range of 6-11 ng/mL for the first 30 days and to 4-11 ng/mL thereafter. Study 3002 met its efficacy endpoints and the safety of the LCP-Tacro regimen proved to be similar to the safety of the Prograf regimen in the control arm without any major safety issues.

Despite the overall acceptability of the safety of the LCP-Tacro regimen in Study 3002, a higher than expected tacrolimus toxicity events and BKVAN events are reported with the LCP-Tacro regimen compared to the Prograf regimen as discussed in sections 7.3.4.2 and 7.3.4.3. BKVAN is generally associated with over-immunosuppression. This

higher number of tacrolimus toxicity and BKVAN events did not result in an imbalance with regard to deaths, graft loses or SAEs in LCP-Tacro group of Study 3002 with one caveat. This caveat is the highly select relatively healthy nature of the Study 3002 patient population compared to a US transplant candidate patient population because of the stringent selection criteria employed as discussed in Section 6.1.

Clinical Reviewer's Comment
In my opinion the relatively higher starting dose of LCP-Tacro (0.17 mg/kg/day) compared to the starting dose of Prograf (0.1 mg/kg/day) is not the only factor which resulted in higher number of tacrolimus toxicity events and BKVAN events in the LCP-Tacro group but other factors related to the design of this double-blind trial also significantly contributed to higher tacrolimus exposure especially early on after transplantation as explained in Section 6.1.1.7 (Treatments administered in Study 3002). The dosing recommendations in the proposed Envarsus XR Label are reviewed with consideration of these observations from Study 3002 and the other Phase 3 Study 3001. See also Clinical Pharmacology Review of the current NDA.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable

6.1.10 Additional Efficacy Issues/Analyses

HLA Antibodies in Study 3002

In Study 3002, blood samples for measuring HLA antibodies were obtained on days 21, 30, 45, 60, 90, 120, 180, 270 and 360 as per the protocol. The measurements were performed at the central laboratory. The Applicant's analysis results of the HLA antibodies during the 12 month study period are presented below.

At Baseline, the percentage of patients with positive results for HLA antibodies (Class I or Class II) was higher in the LCP-Tacro group compared with the Prograf group (16.5% vs 12.8%), but the difference was not statistically significant (Table 26).

Table 26. HLA Antibodies by Visit -Study 3002

(Source: CSR, page 185)

Visit	Parameter	LCP-Tacro (N=268) n (%)	Prograf (N=275) n (%)	Difference (LCP-Tacro – Prograf 95% CI	P value
Baseline	n	260	265	–	–
	HLA Antibody Positive (Class I or Class II)	43 (16.5)	34 (12.8)	3.71% (-2.38%, 9.81%)	0.267

	Class I Positive	27 (10.4)	28 (10.6)	–	–
	Class II Positive	25 (9.6)	10 (3.8)	–	–
	Both Class I and II Positive	9 (3.5)	4 (1.5)	–	–
Month 12	n	171	169	–	–
	HLA Antibody Positive (Class I or Class II)	40 (23.4)	25 (14.8)	8.60% (0.21%, 16.86%)	0.053
	Class I Positive	25 (14.6)	18 (10.7)	–	–
	Class II Positive	21 (12.3)	9 (5.3)	–	–
	Both Class I and II Positive	6 (3.5)	2 (1.2)	–	–
Month 12	n	166	166	–	–
	De novo HLA Antibody Positive (Class I or Class II)a	26 (15.7)	21 (12.7)	3.01% (-4.57%, 10.60%)	0.529
	Class I Positive	13 (7.8)	13 (7.8)	–	–
	Class II Positive	15 (9.0)	8 (4.8)	–	–
	Both Class I and II Positive	2 (1.2)	0 (0)	–	–

At Month 12, the percentage of patients with positive results for HLA antibodies (Class I or Class II) was higher for the LCP-Tacro group compared with the Prograf group (23.4% vs 14.8%), but the difference did not reach statistical significance ($P = 0.053$).

For patients with de novo HLA antibody formation (those who became positive for a specific epitope after Baseline), the percentage who had positive results for HLA antibodies (Class I or Class II) at Month 12 was higher for the LCP-Tacro group compared with the Prograf group (15.7% vs 12.7%), but the difference was not statistically significant ($P = 0.529$). The percentage of de novo patients who tested positive for HLA Class I antibodies was the same for both treatment groups (7.8%) but the percentage of de novo patients who tested positive for HLA Class II antibodies was higher for the LCP-Tacro group compared with the Prograf group (9.0% vs 4.8%).

Clinical Reviewer's Comment
Patients undergoing renal transplantation frequently have non-donor-specific HLA antibodies (NDSA) which is reflected by their panel reactive antibody (PRA) status. In Study 3002 patients PRA >30% were excluded as commonly performed in kidney transplantation trials and patients with HLA antibodies at baseline are low in both treatment groups (16.5% and 12.8%),

NDSA levels slowly fall in the first month after transplantation, but in some patients their levels initially rise during a rejection episode with increased synthesis of DSA.[4] Published clinical studies suggest that that de novo production of anti-HLA antibodies in patients receiving kidney transplantation is a useful and noninvasive tool to identify the onset of an immune response towards the graft before any clinical manifestation of antibody-mediated graft injury.[5]

In Study 3002 at 12 months, the percentage of patients with positive results for HLA antibodies (Class I or Class II) was higher for the LCP-Tacro group compared with the Prograf group (23.4% vs 14.8%) but this difference did not reach statistical significance. The percentage of de novo patients who tested positive for HLA Class I antibodies was the same for both treatment groups (7.8%) but the percentage of de novo patients who tested positive for HLA Class II antibodies was higher for the LCP-Tacro group compared with the Prograf group (9.0% vs 4.8%).

De novo HLA antibody formation has been associated with decreased graft survival in the published literature but the significance of this small difference between the two treatment groups with regard to de novo Class II HLA antibody formation is not currently known and may need to be assessed in future clinical trials.

7 Review of Safety

Summary of Safety:

LCP-Tacrolimus extended release tablets contain tacrolimus as the active ingredient. The immediate release formulation of tacrolimus (Prograf) has been lawfully marketed in US since 1994; hence the safety profile of tacrolimus is well characterized and it has been the immunosuppressant of choice in the great majority of kidney and other solid organ transplant recipients.

In the current NDA, in all three major studies reviewed (3002, 3001 and 2017) LCP-Tacro has been compared to the immediate release formulation, Prograf. Since the active moiety is the same in both the experimental and the control groups, any safety (and efficacy) differences if observed would be the result of the differences in tacrolimus exposure and the different PK characteristics of the two formulations.

4 Briggs, D., Zehnder, Daniel and Higgins, R. M.. (2009) Development of non-donor-specific HLA antibodies after kidney transplantation : frequency and clinical implications. Contributions to Nephrology, Vol.162 . pp. 107-116.
5 Piazza A, Poggi E, Ozzella G, Borrelli L, Scornajenghi A, Iaria G, Tisone G, Adorno D. Post-transplant donor-specific antibody production and graft outcome in kidney transplantation: results of sixteen-year monitoring by flow cytometry. Clin Transpl. 2006:323-36.

LCP-Tacrolimus based regimens when used in de novo kidney transplant recipients as demonstrated by the Phase 3 Study 3002 and the Phase 2 Study 2017 and when used in stable kidney transplant recipients who are converted from Prograf as demonstrated by the Phase 3 Study 3001 displayed a favorable safety profile which is not much different than the safety profile of the Prograf based regimens. (Table 27)

Table 27. Major Safety Events within 12 Months in LCP-Tacro Clinical Studies
(Generated by the Clinical Reviewer)

	LCP-Tacro Group N (%)	**Prograf Group N (%)**
Study 3002	**N=268**	**N=275**
Deaths	8 (2.9%)	8 (2.9%)
Graft Loses	9 (3.3%)	11 (4.0%)
SAEs	143 (53.4%)	162 (58.9%)
Treat. Discontinuation due to AEs	23 (8.6%)	27 (9.8%)
Study 3001	**N=162**	**N=162**
Deaths	2 (1.2%)	1 (0.6%)
Graft Loses	0	0
SAEs	36 (22.2%)	26 (16.0%)
Treat. Discontinuation due to AEs	13 (8.0%)	2 (1.2%)
Study 2017	**N=32**	**N=31**
Deaths	0	0
Graft Loses	0	0
SAEs	15 (46.9%)	21 (67.7%)
Treat. Discontinuation due to AEs	2 (6.3%)	2 (6.5%)

In Study 3001 there seems to be an imbalance in favor of the Prograf group with regards to discontinuations due to adverse events (8.0% vs. 1.2%) which is not observed in Study 3002 and 2017. This higher treatment discontinuation rate due to AEs may be partly related to the open label design of Study 3001 among other possible reasons.

Also as discussed in in Section 7.3.4.2, in Study 3002 tacrolimus toxicity cases related to observed high trough levels were almost exclusively reported in the LCP-Tacro group. As explained in more detail in the relevant sections of this review these events are probably related to the higher starting dose and the method of calculation of LCP-Tacro doses (converted from the investigator prescribed Prograf equivalents) in Study 3002 which had a double blind design. These tacrolimus toxicity cases occurring under blinded study conditions are not expected to occur in clinical practice.

In summary, LCP-Tacrolimus based regimens displayed acceptable safety profiles both in de novo and in stable kidney transplant recipients in all three main studies reviewed.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Two randomized controlled Phase 3 studies, Study 3002 in de novo kidney transplant recipients and the conversion Study 3001 in stable kidney transplant recipients and the randomized controlled Phase 2 Study 2017 were reviewed to evaluate the safety of LCP-Tacrolimus extended release tablets. In the following sub-sections of the current section the results from the de novo Study 3002 is included first followed by the results from the conversion Study 3001 and the Phase 2 Study 2017. More emphasis is given to the safety findings from the de novo Study 3002 since early posttransplant period is the most vulnerable period of the transplant patients and the overall level of immunosuppression is highest in the early post-transplant period. Most of the rejection events occur during the first six months after transplantation and treatment of rejection may also impact the safety findings. Comparisons in-between the studies are made where appropriate.

7.1.2 Categorization of Adverse Events

The Applicant used the MedDRA version 14.0 in Study 3002 and MedDRA version 12.0 in Study 3001 (Study 3001 is an older study) to code the investigator reported terms (AEs) into preferred terms. Each diagnosis or "investigator reported term" was mapped to the lower level term and then to a preferred term (PT), which was then mapped to a system organ class (SOC). The number and percentage of patients with any reported adverse event were summarized for each SOC and PT. For the tables, if the same PT was reported for a patient multiple times, then that PT was counted only once for that patient. Similarly, if multiple PTs within the same system organ class were reported for the same patient, then that SOC was counted only once for that patient in the tables. All AEs were summarized by treatment group and overall using the safety data set.

7.1.3 Pooling of Data across Clinical Trials

Clinical Reviewer's Comment
The Applicant submitted safety analyses of pooled data from the Phase 3 studies 3002, 3001 and the Phase 2 Study 2017 as part of the NDA submission but the utility of this pooled data is found to be very limited by this clinical reviewer due to the following reasons:

- Study 3002 was conducted on de novo kidney transplant recipients whereas Study 3001 is a conversion study and was conducted on stable kidney transplant recipients.
- The starting doses and the target trough levels for LCP-tacrolimus and Prograf are not the same across all studies.

- Study 3002 was blinded which also affected the dose calculations of LCP-Tacrolimus throughout the study period whereas the other two studies (3001 and 2017) were open label studies.

Therefore the rates and severity of adverse events are different across these three studies as expected and pooling of data may be misleading and may dilute any possible safety signals pertaining to one particular study.

7.2 Adequacy of Safety Assessments

The safety assessments made by the Applicant are adequate.

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

Adequate number of kidney transplant patients representative of a US transplant patient population, both de novo and stable were exposed to LCP-Tacrolimus extended release tablets at appropriate doses and with sufficient duration to permit an adequate safety analysis. Below is a summary of the extent of exposure in the Phase 3 (3002 and 3001) and the Phase 2 (2017) studies as presented by the Applicant. For more information on tacrolimus and concomitant immunosuppressive exposures in all three studies see the Clinical Pharmacology NDA Review Executive Summary by Gerlie Gieser, Pharm D and Jeffry Florian, PhD in Section 4.4 of this review and the full Clinical Pharmacology Review in DARRTS dated September 25, 2014.

7.2.1.1 Extent of Exposure in the de novo Study 3002:

In this two-arm parallel group, prospective, randomized, double-blind, double-dummy, multicenter Phase 3 clinical trial, 543 recipients of a primary or secondary kidney transplant from a live or a deceased donor were randomly assigned 1:1, 268 patients to the LCP-Tacro extended release tablets once a day group and 275 patients to the Prograf capsules twice daily group. All patients also received mycophenolate mofetil (MMF), corticosteroids, and IL-2 receptor antagonist (basiliximab) per the standard of care. All patients were also maintained on daily oral dose of corticosteroids of 10-mg minimum daily for the first month and, 5-mg minimum daily thereafter for the remainder of the 12-month treatment period.

Clinical Reviewer's Comment
Based on the Clinical Pharmacology Reviewer's confirmatory analyses for Study 3002, the 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.

Overall, 425 patients (78.3%) completed the 12-month study drug treatment; 60 patients (22.4%) and 52 patients (18.9%) discontinued study drug before Month 12 in the LCP-Tacro and Prograf groups, respectively.

In the LCP-Tacro group the starting dose was 0.17 mg/kg/day. In the Prograf group, the starting dose was 0.1 mg/kg/day. After the initial dosing, in both treatment groups doses were adjusted to maintain trough levels within the range of 6 to 11 ng/mL for the first 30 days of the study, and 4 to 11 ng/mL for the remainder of the study.

In the first week of dosing, total daily dose levels were higher in patients in the LCP-Tacro group compared with the Prograf group; likely reflecting the higher starting dose of LCP-Tacro (0.17 mg/kg vs 0.10 mg/kg for Prograf) (Figure 4) and due to the method of calculation of the daily LCP-Tacro doses (as explained in Section 6.1.1.7 Treatments administered in Study 3002). Tacrolimus total daily doses were similar in both treatment groups from Day 10 through Week 3. From Month 1 through Month 12, tacrolimus total daily doses were lower in the LCP-Tacro group compared with the Prograf group and the difference increased continually over time. At the final visit on Month 12, mean total daily doses in the LCP-Tacro group were 18.3% lower than in the Prograf group (4.09 mg in the LCP-Tacro group and 5.01 mg in the Prograf group). This observed decrease in the LCP-Tacrolimus total daily doses starting at Month 1 is probably due to the increased bioavailability of LCP-tacrolimus.

Tacrolimus trough level (TTL) over time is displayed graphically in Figure 5. Tacrolimus trough levels were notably greater in the LCP-Tacro group compared with the Prograf group in the first 2 weeks after dosing; thereafter, trough levels in the 2 groups were similar. The mean trough levels from Day 1 through Month 12 were greater in the LCP-Tacro group; when calculated as the average of all trough level records, mean levels were 8.8 ng/mL in the LCP-Tacro group compared with 7.0 ng/mL in the Prograf group. Median values were generally similar or slightly lower than mean values. MMF and corticosteroid mean total daily doses were similar across the two treatment groups throughout the study period.

Figure 4. Mean (±SEM) Tacrolimus Total Daily Dose (mg) Over Time by Treatment Group (ITT Set) - Study 3002
(Source: Figure 12-1, page 124 of CSR)

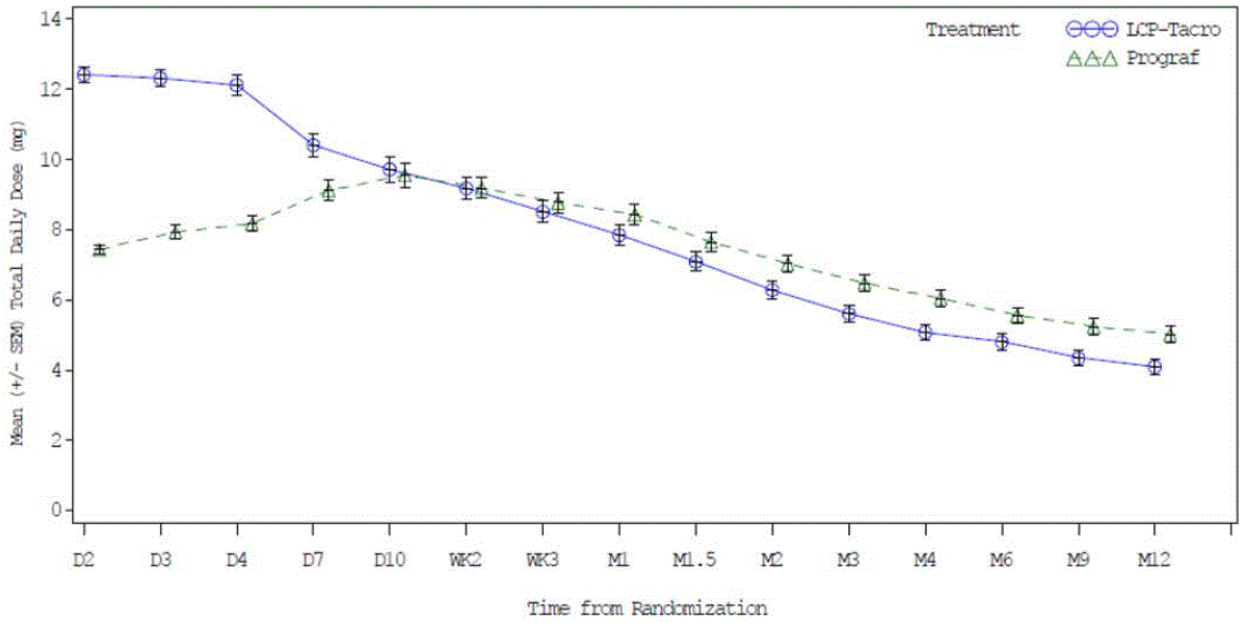
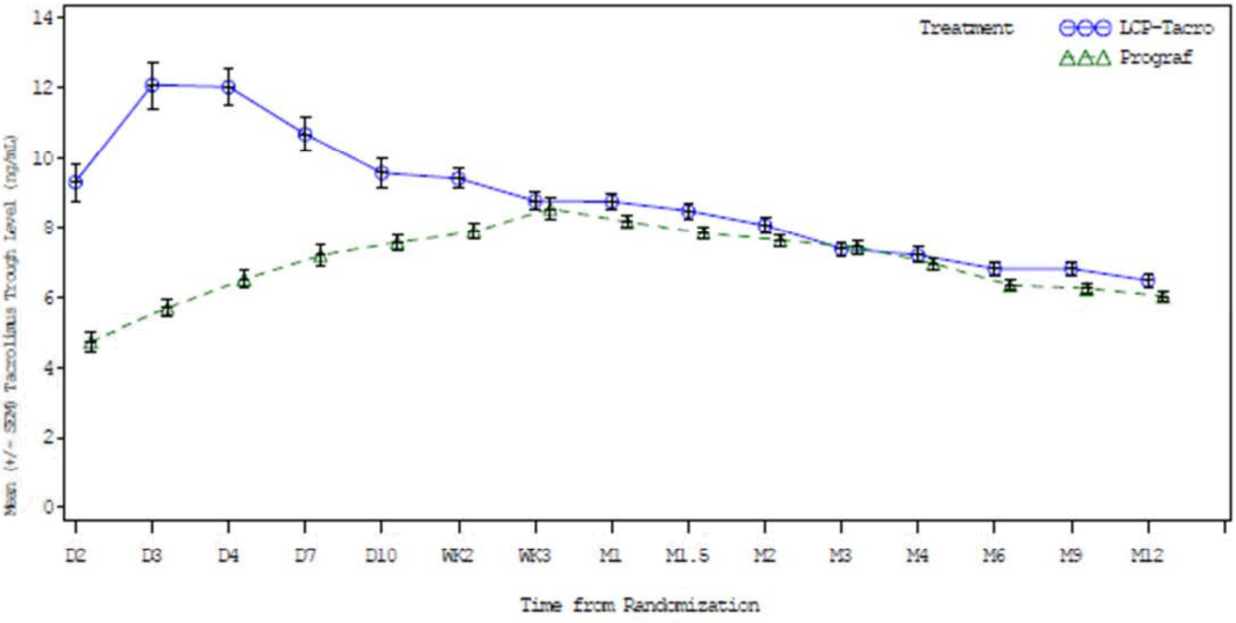


Figure 5. Mean (±SEM) Tacrolimus Trough Level (ng/mL) Over Time by Treatment Group (ITT Set) - Study 3002
(Source: Figure 12-2, page 124 of CSR)



Exposure in African American (AA) Patients:

Figure 6. Mean (±SEM) Tacrolimus Total Daily Dose (mg) Over Time by Treatment Group – AA Patients - Study 3002
(Source: Figure Ad Hoc Figure 1.1, CSR)

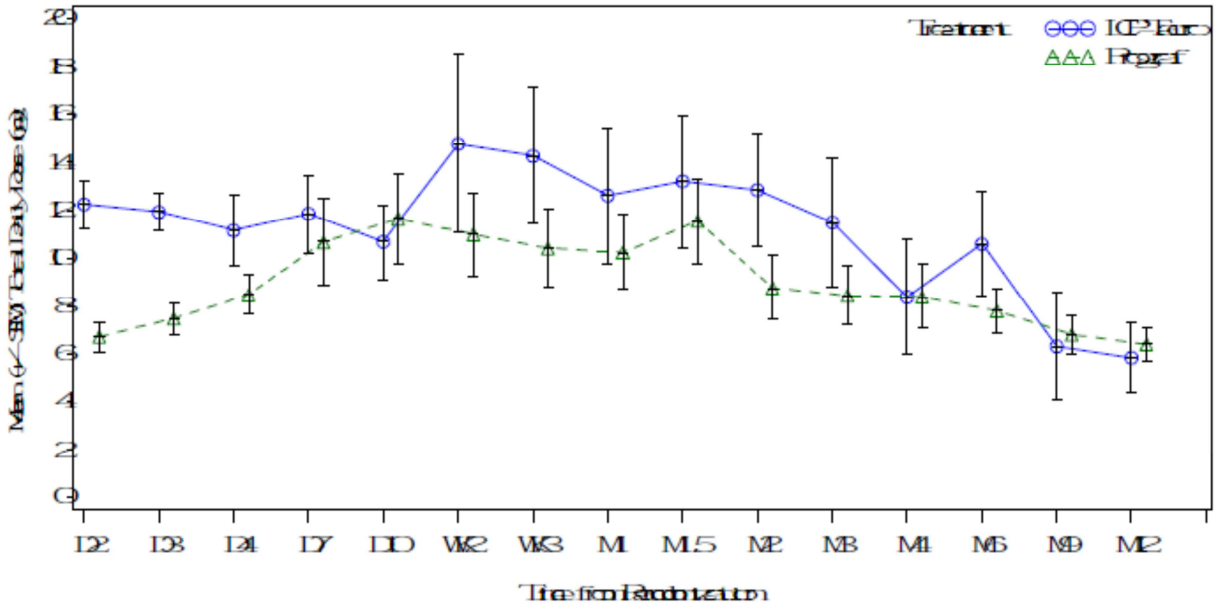
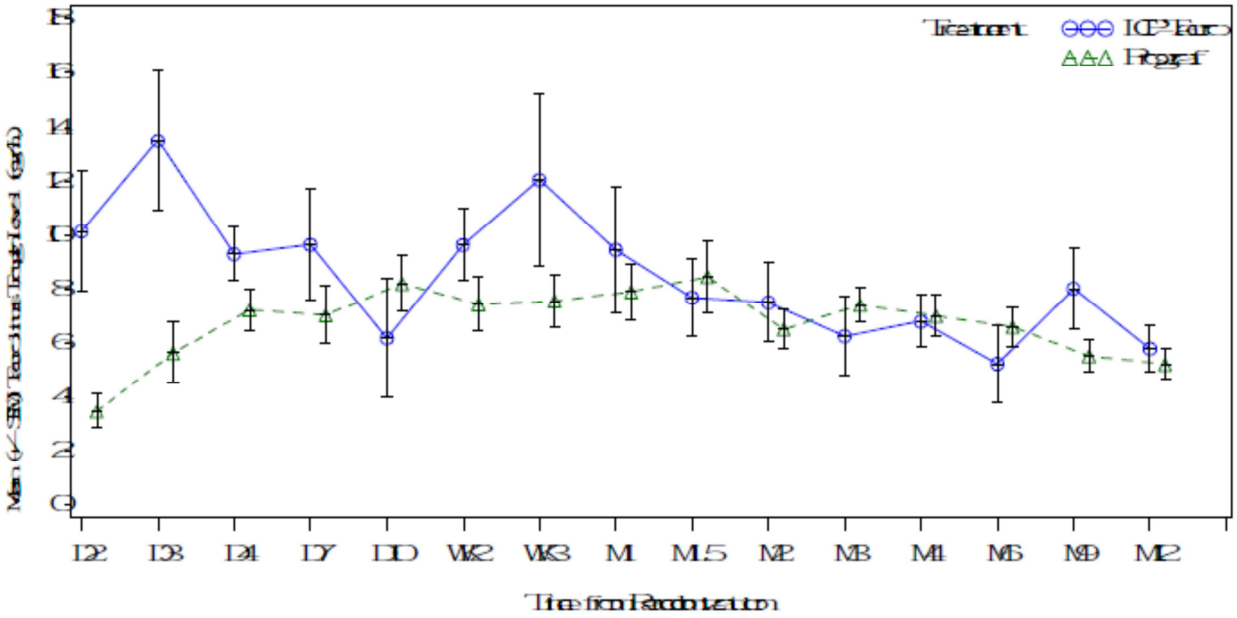


Figure 7. Mean (±SEM) Tacrolimus Trough Level (ng/mL) Over Time by Treatment Group – AA Patients - Study 3002
(Source: Figure Ad Hoc Figure 2.1, CSR)



Clinical Reviewer's Comment
Since the percentage of AA patients was small in Study 3002 it is difficult to make any interpretation of the available exposure data but when compared to Caucasians and other races, AA patients seem to have required higher LCP-Tacrolimus doses compared to Prograf throughout the study period and displayed variable trough concentrations which were generally higher than the AA patients on Prograf (see Clinical Pharmacology review by Gerlie Gieser PhD and Jeffry Florian PhD).

On Day 2, among patients with central pharmacokinetic data, 36.6% of patients in the LCP-Tacro group and 18.5% of patients in the Prograf group were within the target tacrolimus trough range; the majority of Prograf patients (74.7%) had trough levels less than 6 ng/mL compared with 33.5% in the LCP-Tacro group. From Day 2 through Day 7, approximately 30% to 40% of patients were within the target range. Of the patients in the LCP-Tacro group who did not meet the target range in this time period, the majority had levels greater than 11 ng/mL, while the majority of patients in the Prograf group had levels below 6 ng/mL. By Day 10, approximately 50% of patients were within the target range and at Month 1, 57.1% and 70.3% of patients in the LCP-Tacro and Prograf groups, respectively, were within the target range. From Month 1.5 through Month 12, the majority of patients were within the post 30-day target range of 4 to 11 ng/mL and the proportions of patients in each range were similar between the treatment groups.

Clinical Reviewer's Comment
In the Applicant's assessment, on Day 2, the majority of Prograf patients (74.7%) had trough levels less than the lower bound of the target range (6 ng/mL) compared with 33.5% in the LCP-Tacro group (Figure 5). This trend of relatively lower tacrolimus exposure continued until Day 10 after which the mean trough levels in both groups became similar. This initial lower tacrolimus exposure in the Prograf group possibly due to the lower starting dose did not result in higher acute rejection rates in this group later on as discussed in the Efficacy section of this review.

7.2.1.2 Extent of Exposure in the conversion Study LCP-Tacro 3001:

In this two-armed, parallel-group, prospective, randomized, open-label, multicenter Phase 3 controlled trial 326 patients were randomly assigned to the study, 163 patients in each treatment group, and 296 patients completed the 12-month treatment period, 142 patients in the LCP-Tacro group and 154 patients in the Prograf group..

For patients randomly assigned to LCP-Tacro, initial dosing was 0.7 times the total daily dose of Prograf being taken by the patient just before conversion. Because of the

relatively decreased bioavailability of LCP-Tacro, black patients were converted instead using a 0.85 conversion multiplier.

Clinical Reviewer's Comment
Based on the Clinical Pharmacology Reviewer's analyses for Study 3001, the daily MMF equivalent doses and prednisone equivalent doses received by LCP-Tacrolimus and Prograf patients during the 12-month study period were comparable.

After initial dosing, patients in both the LCP-Tacro and the Prograf groups had their doses adjusted to maintain tacrolimus whole blood trough levels within the therapeutic range of 4 to15 ng/mL for the duration of the study, following standards of care at each participating site. Study drug dose adjustments were based on clinical assessment of the patient and maintenance of target tacrolimus whole blood trough levels.

The overall mean (SD) and median daily dose was slightly lower for the LCP- Tacro group, 4.7 (3.2) and 3.5 mg, than for the Prograf group, 4.9 (2.9) and 4.0 mg. The results for the daily study drug dosage (mg/day) at Weeks 4 and 8, and Months 3, 6 and 12 were similar, with a lower mean daily dose for LCP-Tacro at each visit compared with Prograf. The median LCP-Tacro dose was lower than Prograf at Week 4 and at Months 6 and 12.

The mean (SD) trough level for the LCP-Tacro group at baseline was 7.8 (2.3) ng/mL compared with 7.9 (2.3) ng/mL at baseline for the Prograf group. Mean trough levels of tacrolimus were maintained within a relatively narrow range for both the LCP-Tacro and Prograf treatment groups throughout the duration of the study staying between 6.8 ng/mL and 7.8 ng/mL.

7.2.1.3 Extent of Exposure in the Phase 2 Study 2017:

A total of 63 patients were randomized (32 received LCP-Tacro and 31 received Prograf). Overall, 58 (92.1%) of patients completed the pharmacokinetics portion of the study and 24 (75.0%) patients and 25 (80.6%) patients, respectively, completed the study through the Day 360 visit.

The starting dose for LCP-Tacro was 0.14 mg/kg/day for non-African-American patients and 0.17 mg/kg/day for African-American patients. The starting dose of Prograf was 0.2 mg/kg/day for all patients in the Prograf group regardless of race. Subsequent doses for both LCP-Tacro and Prograf were adjusted to maintain a target whole blood tacrolimus trough level of 7 to 20 ng/mL.

Concomitant therapy with either mycophenolate mofetil or mycophenolic acid sodium, or azathioprine was permitted. Corticosteroid therapy was permitted at the discretion of the investigator. Antibody induction according to standard practice at each center was permitted. Alemtuzumab, sirolimus or everolimus was not permitted. Overall, the 4 most

commonly used immunosuppressive medications on Days 1 to 14 were MMF (56/63), prednisone (50/63), antithymocyte globulin (41/63), and methylprednisolone (31/63). The daily doses of these medications were similar between treatment groups.

Clinical Reviewer's Comment
Based on the Clinical Pharmacology Reviewer's analyses for Study 2017, almost all of the tacrolimus treated patients in Study 2017 received concomitant MMF; the mean/median daily MMF equivalent doses were comparable between the two treatment arms. Likewise, the mean/median daily doses of corticosteroids (as prednisone equivalent) and antibody induction agents (mainly antithymocyte immunoglobulin) in this trial were similar between treatment groups.

According to the Applicant's analysis, on day 1, both the overall systemic exposure (AUCt) and Cmax of tacrolimus was approximately 54% lower after administration of LCP-Tacro compared to Prograf. And the trough levels (Cmin) was approximately 41% lower for LCP-Tacro compared to Prograf. The median Tmax of LCP-Tacro was delayed (11.9 hours) compared to Prograf (4.0 hours).

On Day 7, there were no statistically significant differences in AUCt, Cmax , Cmin, or percentage of fluctuation and swing of LCP-Tacro compared to Prograf. The median Tmax of LCP-Tacro was significantly delayed (6.0 hours) compared to Prograf (1.6 hours).

In the Applicant's analysis on Day 14, the AUCt of tacrolimus was approximately 37% higher after administration of LCP-Tacro compared to Prograf ($p<0.05$). Cmax was approximately 34% higher for LCP-Tacro compared to Prograf and Cmin was approximately 28% higher for LCP-Tacro compared to Prograf ($p<0.05$).

The proportion of patients achieving therapeutic trough tacrolimus levels (7-20 ng/mL) in the LCP-Tacro group was lower than the Prograf group on Day 1, was similar to the Prograf group on Day 7, and was higher than the Prograf group on Day 14.

In the Applicant's analysis, after 14 days, LCP-Tacro resulted in significantly greater systemic exposure to tacrolimus compared with Prograf. In the Applicant's assessment this finding may be due to excessive dosing of patients in the LCP-Tacro group by clinicians to compensate for the low exposure observed on Day 1 resulting in higher exposures on Day 14.

7.2.2 Explorations for Dose Response

As included in the Clinical Pharmacology Review of NDA 206,406 by Gerlie Gieser, PhD and Jeffry Florian, PhD:

The Applicant conducted post-hoc exposure-response analyses to evaluate the relationship between tacrolimus trough concentrations and time to event of any failure (biopsy proven graft rejection, death, lost to follow-up, graft rejection) as requested during pre-NDA discussion.

A Cox-proportional hazards analysis was conducted by the Applicant 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 Pharmacometrics reviewer to describe the relationship between nephropathy adverse events and tacrolimus trough concentrations as a time-dependent covariate from Study 3002. 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 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.

Clinical Reviewer's Comment
Generally the results of the exposure-response analyses both for efficacy and safety conducted by the Applicant are as expected and I agree with the Clinical Pharmacology reviewers' assessments.

7.2.3 Special Animal and/or In Vitro Testing

This is a 505(b2) NDA submission and no animal or in vitro testing was performed by the applicant.

7.2.4 Routine Clinical Testing

See sections 6.1.1.10, 6.1.1.11 and 6.1.1.12

7.2.5 Metabolic, Clearance, and Interaction Workup

The active moiety in LCP-Tacrolimus extended release tablets is tacrolimus and the immediate release formulation of tacrolimus (Prograf and generics) are already approved. Since metabolic, clearance, and interaction information for tacrolimus is already known, the Applicant did not perform additional testing other than PK studies.

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

Calcineurin inhibitors including tacrolimus and cyclosporine are immunosuppressants and their package inserts have a boxed warning about the increased risk of infections and malignancies like other immunosuppressants. Other than the known possible adverse consequences associated with immunosuppression in general, CNIs are associated with neurotoxicity, diabetes, hypertension and decrease in GFR due to vasoconstriction. Among the two well-known CNIs, tacrolimus and cyclosporine, tacrolimus has a greater diabetogenic effect. Myocardial hypertrophy has also been reported with tacrolimus use as included in the Prograf package insert.

7.3 Major Safety Results

7.3.1 Deaths

7.3.1.1 Deaths in the de novo Study 3002:

A total of 16 deaths (8 in each group) occurred during the first 12 months of the study. Eleven of the 16 deaths occurred either when the patient was receiving the study drug or within 30 days of last dose of the study drug, hence classified as “treatment emergent” by the Applicant. Remaining five deaths either occurred after 30 days of the last dose or in patients who never received the study drug, hence considered as “non-treatment emergent” by the Applicant. Of the 8 deaths in the LCP-Tacro group 5 are treatment emergent and 3 are non-treatment emergent and of the 8 deaths in the Prograf group 6 are treatment emergent and 2 are non-treatment emergent.

In addition to these 16 deaths, two more deaths in the Prograf group and one more death in the LCP-Tacro group occurred outside the 12 month study period making the total number of deaths in the study 19.

All 19 deaths that occurred in Study 3002 are summarized in Table 28 below generated by the reviewer based on the information included in the electronic case report forms (eCRFs) and patient narratives. The table is separated into two parts; first part for the LCP-Tacro group deaths and the second part for the Prograf group deaths. The lower parts of each group table contains the deaths considered to be "non-treatment emergent" and these are shaded in gray color for ease of distinguishing from the treatment emergent deaths. The two deaths in the Prograf group and one death in the LCP-Tacro group that occurred outside the 12 month study period are included at the very bottom of each group below the red line in *italics*.

Patient column includes patient's subject ID, age, race (C: Caucasian, AA: African American, M: Mestizo and O: other), gender (M or F) and the type of donor (L: living, DD: deceased donor) that the patient received organ from.

The column titled "Relevant History" includes important medical events which may be helpful in making a possible causality assessment of the death. The column titled "Cause of Death (FDA Reviewer)" includes the Reviewer's assessment of the cause of death based on the patient narratives and the eCRFs. The column titled TAC Trough levels includes the tacrolimus C_{min} values at various time points (study days) during the study as obtained from the eCRFs by to clarify any possible associations between the death, other important safety events and the tacrolimus exposure at the time of the event or at the time last measured.

Table 28. All Deaths Reported in Study 3002
(Reviewer Generated)

Deaths in the LCP-Tacro Group							
Patient		**Day of Death**	**Day of D/C Study Medication**	**Relevant History**	**Cause of Death (Sponsor)**	**Cause of Death (FDA Reviewer)**	**TAC Trough Levels (ng/mL)**
1	001001/014 59, C, M, LD	140	140	reported to have died in his sleep	unknown	unknown	D2 30.5 D3 45.4 D4 25.5 D7 12.6 D90 9.3 D110 7.0

2	001011/00149, C, F, DD	179	179	autopsy: cardiorespiratory failure secondary to bilateral thromboemboli of the lungs	cardiorespiratory failure secondary to bilateral thromboemboli	cardiorespiratory failure secondary to bilateral lung thromboembolii	D2 18.9 D3 20.8 D14 13.1 D123 11.5 D180 11.9
3	034157/01560, C, M, DD	173	159 (D/C ed due to bacterial sepsis)	postoperative wound infection, limb abscess, bacterial sepsis	respiratory distress	bacterial sepsis	D1 38.2 D2 52.4 D3 23.9 D6 10.1 D10 5.5 D20 16.9 D28 20.7 D40 9.9 D59 17.8 D84 7 D115 10.9
4	055176/00249, C, M, DD	102	102	cardiac failure congestive, oppressive precordial pain, CMV infection	acute myocardial infarction	acute myocardial infarction	D1 13.1 D3 14.9 D4 16.1 D5 17 D11 5 D20 10.9 D32 18.6 D42 6.7 D90 9.6
5	381140/00632, C, M, DD	217	216	D 195: (R) nephrectomy for circular mass in the right kidney: PTLD (posttransplant lymphoproliferative disorder)	lymphoma B cell	PTLD	D1 17 D3 12.3 D4 18.7 D6 8.7 D10 13.50 D14 8.30 D30 8.7 D45 10.5 D60 13.7 D90 6.7 D120 10.8 D180 9.7
6	001001/01152, AA, M, LD	176	58	D 176: congestive cardiac failure	pulmonary edema	pulmonary edema	D2 13.8 D3 16.4 D8 4.6 D12 10.9 D14 15.4 D21 16.4 D28 10.1 D39 12.3 D51 10.3
7	033134/04460, C, F, DD	284	136	aortic aneurysm D 30: graft	sepsis	sepsis	D2 15.1 D7 9.2 D14 7.2

				failure (Cre: 11 mg/dL) D 284: sepsis			D42 7.1 D60 5.1 D92 6.2
8	001009/01366, AA, F, DD	276	N/A	The patient did not receive study drug D36: Gr. loss	unknown	unknown	
9	*048149/00762, C, M, DD*	*434*	*400*	*D 305 CMV viremia and infection, pneumonia, D 335 UTI*	*ischemic stroke, superior sagittal sinus thrombosis, asystolia*	*recurrent infections?*	*D1 29.3 D2 26.7 D3 26.6 D9 10.9 D30 22.2 D51 8.5 D60 13.4 D85 7.3*

Deaths in the Prograf Group

	Patient	Day of Death	Day of D/C Study Medication	Relevant History	Cause of Death (Sponsor)	Cause of Death (FDA Reviewer)	TAC trough levels (ng/mL)
1	048148/00154, C, M, DD	38	28	D 30: pneumonia	ARDS and sepsis	pneumonia	D5 3.4 D8 5.8 D15 8.0
2	048148/020,64, C, M, DD	20	19	D20: sepsis	sepsis	sepsis	D2 8.6 D3 13.3 D4 11.4 D7 13.8 D13 12.1 D14 5.7
3	052184/009,54, M*, F, LD	29	27	D27: sepsis due to wound infection due to urinary fistula	Sepsis	sepsis due to wound infection	D2 10.8 D3 10.4 D4 10.8 D8 9.6 D10 9.3 D15 10.7 D22 6.6
4	055179/00367, C, M, DD	44	44	D44: cardiorespiratory arrest at home (Glucose: 558, no units)	cardio-respiratory arrest (sudden death)	uncontrolled diabetes	D2 3.7 D3 7.0 D8 4.8 D11 7.2 D14 10.1 D24 7.0 D29 7.3

5	381140/008 51, C, F, DD	210	208	D188:Pneumonia	bilateral pneumonia	bilateral pneumonia	D2 6.0 D3 9.8 D4 8.5 D7 10.7 D10 8.7 D14 7.2 D21 10.2 D30 11.2 D44 9.0 D57 6.7 D90 8.2 D120 7.3 D180 9.7
6	381140/009 33, C, M, LD	209	199	D195: bilateral pneumonia (CMV?)	bilateral pneumonia	bilateral pneumonia	D2 2.3 D3 2.6 D4 3.2 D5 5.6 D10 11.5 D13 10,2 D20 12.9 D31 8.9 D44 10.2 D60 13.2 D90 9.0 D120 11.4 D180 8.0
7	055172/012 66, O**, M, DD	224	107	D106: CMV gastroenteritis, hemolytic anemia, D140: allograft nephrectomy D194: sepsis	sepsis	sepsis	D2 2.5 D3 3.4 D7 4.7 D12 4.9 D14 13.5 D23 6.3 D30 6.6 D60 10.4 D90 13.3
8	001056/004 65, C, F, LD	27	N/A	The patient did not receive study drug D27:Septick shock	septic shock	septic shock	
9	*033134/002* *58, C, F, DD*	*393*	*387*	*suicide attempt*	*suicide*	*suicide*	*D2 6.6* *D3 10.0* *D4 12.9* *D7 17.3* *D12 9.1* *D14 8.2* *D22 8.8* *D27 6.0* *D42 9.6* *D60 10.2* *D90 8.1*

							D120 6.0 *D270 7.3* *D365 7.4*
10	*033134/011* *70, C, M, DD*	*591*	*401*	*D -1 a. flutter, anticoagulation, renal hematoma*	*Multiorgan dissemination of neoplasia of unknown origin*	*Multiorgan dissemination of neoplasia of unknown origin*	*D3 20.0* *D7 18.3* *D9 8.8* *D14 15,3* *D21 10.3* *D30 7.2* *D120 7.0* *D270 8.3* *D360 6.4*

*: Mestizo (Hispanic + American Indian)
** Other race

Reviewer's Assessment of Deaths in Study 3002
During the 12 month study period, the most common cause of death was cardiovascular AEs (3/8) in the LCP-Tacro group compared to infections (7/8) in the Prograf group. There was only one malignancy related death in the study which was in patient 381140/006 in the LCP-Tacro group who died due to PTLD (posttransplant lymphoproliferative disorder).

Interestingly, within the 12 month study period, 4 of the 6 treatment emergent deaths in the Prograf group occurred within the first 45 days after transplantation compared to no deaths in the LCP-Tacro group during the first three months. The earliest death observed in the LCP-Tacro group was on D102 (055176/002).

Of these four early deaths in the Prograf group one was due to diabetic ketoacidosis and the remaining 3 were due to sepsis.

Of the six treatment emergent deaths in the Prograf group, 4 (patients 1, 2, 5 and 6 in the table) were reported from two centers (2 from each center and around the same postoperative time frame). In the LCP-Tacro group, each one of the deaths occurred in a different center.

Overall, the numbers of deaths in the two study groups are balanced and the reported causes of death are compatible with the generally encountered causes of death in this patient population.

Patients who died in the LCP-Tacro group had comparatively more frequent and higher recordings of tacrolimus trough levels above the protocol specified upper range of 11 ng/mL, mainly occurring during the initial two weeks after transplantation which was as high as 52 ng/ml in one patient. Conversely patients who died in the Prograf group experienced less frequent and of smaller magnitude elevations of trough levels above

11 ng/mL throughout the study. This difference is likely due to the higher starting dose in the LCP-Tacro group compared to the Prograf group and the method of calculating the daily doses of LCP-Tacro as discussed earlier in this review. In my assessment higher number and extent of C_{min} level elevations (which serve as a surrogate for higher tacrolimus exposure) in the LCP-Tacro group does not seem to have caused any of the deaths but the contribution of higher tacrolimus exposure to the death event in any patient cannot be ruled out with certainty both in the LCP-Tacro and the Prograf groups.

Due to stringent cardiac exclusion criteria only low cardiac risk patients were enrolled into Study 3002 as discussed earlier. Patients with electrocardiograms (ECG) demonstrating clinically relevant abnormalities (including QTc prolongation, reversible ischemia), clinically symptomatic congestive heart failure or documented ejection fraction of less than 45% were excluded from the trial. Therefore it is not known if the same higher tacrolimus exposure observed in the LCP-Tacro group especially early on in the study would have resulted in a similar or higher rate of mortality in a transplant patient population which includes high cardiac risk patients.

7.3.1.2 Deaths in the conversion Study 3001:

A total of four patients died in Study 3001, three in the LCP-Tacro group and one in the Prograf group. One of the three deaths in the LCP-Tacro group occurred outside the 12 month study period.

All 4 deaths that occurred in the Study 3001 are summarized in Table 29 below generated by the reviewer. Similar to the table for Study 3002, the lower parts of the table containing deaths considered to be “non-treatment emergent” are shaded in gray for ease of distinguishing from the treatment emergent deaths. The death in the LCP-Tacro group that occurred outside the 12 month study period is included at the bottom below the red line in *italics*.

Similar to the table for Study 3002, the column titled “Patient” includes patient’s age, race (C: Caucasian, AA: African America, M: Mestizo and O: other), gender and the type of donor (L: living, DD: deceased donor) that the patient received organ from. The column titled “Cause of Death (FDA Reviewer)” includes the reviewer’s assessment of the cause of death based on the patient narratives and the electronic case report forms (eCRF).

Unlike in the table for Study 3002, tacrolimus trough levels are not included in this table since there were no extreme deviations from the protocol specified range as observed from the recorded values in the eCRFs.

Table 29. All Deaths Reported in Study 3001
(Reviewer Generated)

Deaths in the LCP-Tacro Group

	Patient	Day of Death	Day of D/C Study Medication	Relevant History	Cause of Death (Sponsor)	Cause of Death (FDA Reviewer)
1	0131-009 62, C, M, DD, 160 days post-tx	90	89	Cardiac arrest on D90	Cardiac arrest, cardiac arrhythmia	Hypoglycemia, pneumonia?
2	4882-019 55, C, M, 1 yr post-tx	240	239	Cardiac arrest on D240 (found dead in bed by his wife)	Cardiac arrest	Unknown
3	*0120-013* *58, C, M, DD,* *4 years post-tx*	*385*	*264*	*DVT on D250* *Brain hemorrhage D264,* *Pneumonia D275*	*Not provided*	*Complication of anti-coagulation*

Deaths in the Prograf Group

	Patient	Day of Death	Day of D/C Study Medication	Relevant History	Cause of Death (Sponsor)	Cause of Death (FDA Reviewer)
1	4991-001 77, C, F, DD, 1 yr post-tx	270	90 (switched to everolimus)	Non-small cell lung Cancer on D80	Not provided	Non-small cell lung Cancer

Reviewer's Assessment of Deaths in Study 3001
During the 12 month study period two patients in the LCP-Tacro group and one patient in the Prograf group died. Another patient in the LCP-Tacro group died outside the 12 month study period. In the Clinical Reviewer's assessment none of the four deaths seem to be attributable to the study drugs. Although the number of deaths in each group are too small to make any comparisons there does not seem to be any imbalance between the treatment groups with regard to mortality.

7.3.1.3 Deaths in the Phase 2 de novo Study 2017:

There were no deaths in Study 2017.

7.3.2 Nonfatal Serious Adverse Events

7.3.2.1 Graft Losses in the de novo Study 3002:

During the 12 month study period 9 patients in the LCP-Tacro group and 11 patients in the Prograf group lost their grafts. One patient in each group lost their grafts without ever receiving the study drug (Table 30). Table 30 for graft losses was generated by the Reviewer based on the information provided in the eCRFs and patient narratives. Patient column includes patient's subject ID, age, race (C: Caucasian, AA: African American, M: Mestizo and O: other), gender (M or F) and the type of donor (L: living, DD: deceased donor) that the patient received organ from. The column titled "Reviewer's Cause of Graft Loss" includes the reviewer's assessment of the cause of graft loss based on the patient narratives and the eCRFs.

Table 30. Graft Losses by 12 Month Analysis in Study 3002
(Reviewer Generated)

Graft Losses in the LCP-Tacro Group						
Patient		**Day of graft loss**	**Day of Death**	**Day of last dose of medication**	**Applicant's Cause of Graft Loss**	**Reviewer's Cause of Graft Loss**
1	001009-013 66, AA, F, DD	36	276	never received	acute rejection	acute rejection
2	033134-044 60, C, F, DD	144 (Gr. Nephrectomy)	284	136	primary non function (eCRF)	primary non function (eCRF)
3	381140-004 30, C, M*, DD	171 (Gr. Nephrectomy)	-	180	obstructive uropathy	obstructive uropathy
4	033134/012 54, C, M, DD	4 (Gr. Nephrectomy)	-	5	renal vein thrombosis	renal vein thrombosis
5	034157/003 62, C, F, DD	1 (Gr. Nephrectomy)	-	1	graft thrombosis	graft thrombosis
6	052182-004 36, O**, M, LD	196	-	165	acute rejection	toxic nephropathy? + acute rejection
7	048148/019 30, C, F, DD	98	-	77	other (surgical	other (surgical

					complication)	complication)
8	049139/024 55, C, M,	16	-	16	renal necrosis	renal necrosis
9	052184/007 18, O, M, LD	52	-	51	renal hypoperfusion	acute tubular necrosis (biopsy)

Graft Losses in the Prograf Group

Patient		Day of graft loss	Day of Death	Day of last dose of medication	Investigator's Cause of Graft Loss	FDA's Cause of Graft Loss
1	055172-012 66, C, M, DD	125	194	104	chronic rejection	chronic rejection
2	001009/017 44, C, F, DD	348	-	2	acute rejection	acute rejection
3	001051/001 49, AA, M, DD	185	-	42	Other	ATN + Chronic donor disease
4	033134/018 53, C, F, DD	6	-	5	renal vein thrombosis	renal vein thrombosis
5	033134/020 56, C, M, DD	1	-	never received	renal vein thrombosis	renal vein thrombosis
6	033134/035 34, C, M, LD	2	-	1	renal vein thrombosis	renal vein thrombosis
7	049137/026 60, C, M, LD	2	-	2	renal artery thrombosis	renal artery thrombosis
8	049139/021 62, C, F, DD	5	-	4	renal vein thrombosis	renal vein thrombosis
9	052183/007 29, O, F, LD	8	-	7	graft thrombosis	graft thrombosis
10	055179/001 45, C, F, DD	4	-	4	graft thrombosis	graft thrombosis
11	381140/005 54, C, M, DD	126	-	125	myocardial infraction and infection	myocardial infraction and infection

*: Mestizo (Hispanic + American Indian)
**: Other race

Reviewer's Assessment of Graft Loses
There is not an imbalance in terms of graft losses between the two treatment groups. As in the causality assessment of deaths, it is difficult to make an accurate assessment of the cause of graft failure based on the information provided in the eCRFs and patient narratives but there were more graft thrombosis events in the Prograf group compared to the LCP-Tacro group. Seven patients in the Prograf group compared to two patients in the LCP-Tacro group lost their grafts early on after the transplant surgery due to thrombotic events. This is noteworthy since there were not excessive graft losses in the LCP-Tacro group despite the higher tacrolimus exposure early on in this group as discussed earlier. Overall the Reviewer's assessment of the cause of graft losses was in agreement with the Applicant's assessment and there does not seem to be an imbalance between the groups except for the numerically higher graft thrombotic events in the Prograf group..

7.3.2.2 Graft Losses in the conversion Study 3001:

No graft loses were reported in Study 3001 during the 12 month study period.

7.3.2.3 Graft Losses in the Phase 2 de novo Study 2017:

No patients experienced graft loss during the study**.**

7.3.2.4 Other Serious Adverse Events in the de novo Study 3002:

Treatment-emergent adverse event was defined as any adverse event that started after the first dose and within 30 days after the final dose of study drug. More than half of all patients (53.4% in the LCP-Tacro group and 58.9% in the Prograf group) experienced at least 1 serious treatment-emergent adverse event. Serious treatment emergent adverse events experienced by more than 5% of patients in any treatment group are displayed in Table 31. Toxic nephropathy was exclusively reported in the LCP-Tacro group (5 vs 0 patients).

Table 31. Serious Treatment-Emergent Adverse Events in 2 or More Patients in Any Treatment Group in Study 3002 in Decreasing Frequency (ITT Set) – n (%)
(Source: Table 12-13, page 149 of CSR)
Note: A patient reporting more than 1 adverse event within a preferred term was counted only once at that level of summarization.

Preferred Term	LCP-Tacro (N=268)	Prograf (N=275)
Total number of SAEs	389	415
Number of patients with ≥1 SAE	143 (53.4)	162 (58.9)

Urinary tract infection	25 (9.3)	19 (6.9)
Kidney transplant rejection	14 (5.2)	22 (8.0)
Complications of transplanted kidney	8 (3.0)	18 (6.5)
Cytomegalovirus infection	11 (4.1)	10 (3.6)
Blood creatinine increased	7 (2.6)	13 (4.7)
Diabetes mellitus	8 (3.0)	5 (1.8)
Diarrhoea	8 (3.0)	5 (1.8)
Graft dysfunction	6 (2.2)	7 (2.5)
Renal failure acute	4 (1.5)	9 (3.3)
Lymphocele	3 (1.1)	9 (3.3)
Gastroenteritis	7 (2.6)	3 (1.1)
Renal impairment	4 (1.5)	6 (2.2)
Sepsis	4 (1.5)	6 (2.2)
Pneumonia	2 (0.7)	8 (2.9)
Transplant rejection	5 (1.9)	3 (1.1)
Pyelonephritis	4 (1.5)	3 (1.1)
Anaemia	3 (1.1)	4 (1.5)
Abdominal pain	3 (1.1)	3 (1.1)
Renal artery stenosis	3 (1.1)	3 (1.1)
Ureteric stenosis	3 (1.1)	3 (1.1)
Nephropathy toxic	5 (1.9)	0
Pyrexia	4 (1.5)	1 (0.4)
Urosepsis	4 (1.5)	1 (0.4)
Transplant failure	4 (1.5)	1 (0.4)
Benign prostatic hyperplasia	4 (1.5)	1 (0.4)
Bronchitis	3 (1.1)	2 (0.7)
Hypertension	2 (0.7)	3 (1.1)
Pulmonary embolism	1 (0.4)	4 (1.5)
Urinary retention	3 (1.1)	1 (0.4)
Urinary tract obstruction	3 (1.1)	1 (0.4)
Dehydration	3 (1.1)	1 (0.4)
Arteriovenous fistula thrombosis	2 (0.7)	2 (0.7)
Urinary fistula	2 (0.7)	2 (0.7)
Hyperglycaemia	2 (0.7)	2 (0.7)
Escherichia urinary tract infection	1 (0.4)	3 (1.1)
Respiratory failure	1 (0.4)	3 (1.1)
Neutropenia	3 (1.1)	0
Peripheral ischaemia	3 (1.1)	0
Thrombotic microangiopathy	2 (0.7)	1 (0.4)
Acute coronary syndrome	2 (0.7)	1 (0.4)
Cardiac failure congestive	2 (0.7)	1 (0.4)
Small intestinal obstruction	2 (0.7)	1 (0.4)
Tubulointerstitial nephritis	2 (0.7)	1 (0.4)
Leukopenia	1 (0.4)	2 (0.7)
Acute myocardial infarction	1 (0.4)	2 (0.7)
Atrial fibrillation	1 (0.4)	2 (0.7)
Cardiac failure	1 (0.4)	2 (0.7)
Graft thrombosis	1 (0.4)	2 (0.7)
Haematuria	1 (0.4)	2 (0.7)
Ureteral necrosis	1 (0.4)	2 (0.7)
Gastric ulcer	0	3 (1.1)
Renal artery thrombosis	0	3 (1.1)
Pulmonary oedema	0	3 (1.1)

Deep vein thrombosis	0	3 (1.1)
Enterocolitis	2 (0.7)	0
Retroperitoneal haematoma	2 (0.7)	0
Polyomavirus-associated nephropathy	2 (0.7)	0
Postoperative wound infection	2 (0.7)	0
Pyelonephritis acute	2 (0.7)	0
Toxicity to various agents	2 (0.7)	0
Hypercalcaemia	2 (0.7)	0
Bladder obstruction	2 (0.7)	0
Graft complication	1 (0.4)	1 (0.4)
Intra-abdominal haematoma	1 (0.4)	1 (0.4)
Gangrene	0	2 (0.7)
Urinary tract infection bacterial	0	2 (0.7)
Viral infection	0	2 (0.7)
Colitis	0	2 (0.7)
Liver function test abnormal	0	2 (0.7)
Renal tubular necrosis	0	2 (0.7)
Agranulocytosis	0	2 (0.7)
Febrile neutropenia	0	2 (0.7)
Haemolytic anaemia	0	2 (0.7)

Clinical Reviewer's Comment
There is not a significant imbalance across the two treatment groups with regard to safety events reported as SAEs. This is not surprising considering that the drug substance is the same (tacrolimus) in both groups and the tacrolimus exposures (as measured by trough levels) are similar excluding the initial 10 days of the trial as discussed earlier notwithstanding the Cmin/AUC ratio differences between the two formulations of tacrolimus.

Toxic nephropathy was exclusively reported in the LCP-Tacro group (5 vs 0 patients). Polyomavirus-associated nephropathy (PVAN) as an SAE was also reported only in the LCP-Tacro group (n=2) and resulted in treatment discontinuation in these two patients. For an overall discussion of events reported due to increased tacrolimus blood levels including toxic nephropathy see Section 7.3.4.2.1.It is difficult to make a causality assessment with small number of cases but there is a possibility that the two cases of PVAN reported as an SAE may be associated with the initial higher tacrolimus exposure in the LCP-Tacro group. See Section 7.3.4.3.1 for a discussion of all PVAN events in the study.

7.3.2.5 Other Serious Adverse Events in the conversion Study 3001:

SAEs were reported for 36 (22.2%) patients in the LCP-Tacro group and 26 (16.0%) patients in the Prograf group. The most frequently reported SAE was UTI (2.2% overall), and this event occurred in both treatment groups.

Table 32. Serious Treatment-Emergent Adverse Events Occurring in Two or More Patients in Study 3001 (Safety Set)
(Source: Table 11-5, page 102 of CSR)

	LCP-Tacro n=162	Prograf n=162
Number of patients with at least 1 serious TEAE	36 (22.2%)	26 (16.0%)
Urinary tract infection	3 (1.9%)	4 (2.5%)
Blood creatinine increased	1 (0.6%)	2 (1.2%)
Gastroenteritis	1 (0.6%)	2 (1.2%)
Pneumonia	1 (0.6%)	2 (1.2%)
Cellulitis	2 (1.2%)	0
Diverticulitis	0	2 (1.2%)
Osteomyelitis	2 (1.2%)	0
Renal cancer	2 (1.2%)	0
Angina pectoris	2 (1.2%)	0
Cardiac arrest	2 (1.2%)	0
Diarrhea	2 (1.2%)	0
Deep vein thrombosis	1 (0.6%)	1 (0.6%)

Clinical Reviewer's Comment
Since Study 3001 is a study conducted in stable transplant patients the rates of SAEs in both groups are much lower compared to Study 3002 conducted in de novo transplant recipients. Overall SAEs are balanced across the two treatment groups.

7.3.2.6 Other Serious Adverse Events in the Phase 2 De Novo Study 2017:

SAEs were reported for 15 (46.9%) patients in the LCP-Tacro group and 21 (67.7%) patients in the Prograf group in this de novo Phase 2 study. The most frequently reported SAE were in the Infections and Infestations group (Table 33).

Table 33. Serious Treatment-Emergent Adverse Events in 2 or More Patients in Any Treatment Group in Study 2017 (ITT Set) – n (%)
(Source: Table 14.3.1.3, page 151 of CSR, Section 14)

System Organ Class Preferred Term	LCP-Tacro n=32	Prograf n=31
All Body Systems	15 (46.9%)	21 (67.7%)
Gastrointestinal Disorders	4 (12.5%)	2 (6.5%)
Abdominal pain	2 (6.3%)	1 (3.2%)
Vomiting	2 (6.3%)	0 (0.0%)
Infections and infestations	6 (18.8%)	7 (22.6%)
Urosepsis	2 (6.3%)	1 (3.2%)

Injury poisoning and procedural complications	2 (6.3%)	6 (19.4%)
Complications of transplanted kidney	1 (3.1%)	2 (6.5%)
Metabolism and nutrition disorders	2 (6.3%)	1 (3.2%)
Dehydration	2 (6.3%)	1 (3.2%)
Renal and urinary disorders	1 (3.1%)	5 (16.1%)
Renal failure acute	0 (0.0%)	2 (6.5%)

Clinical Reviewer's Comment
Similar to the studies 3002 and 3001 SAEs are not significantly different across the two treatment groups in Study 2017.

7.3.3 Dropouts and/or Discontinuations

See also Section 6.1.3 (Subject Disposition)

7.3.3.1 Dropouts and/or Discontinuations in the de novo Study 3002

Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug and/or Termination from the Study

The TEAEs leading to discontinuation of study drug and/or withdrawal from study for the ITT set is presented in Table 34. The numbers of patients who experienced TEAEs resulting in discontinuation from study drug and/or withdrawal from the study were similar in the two treatment groups (12.3% and 12.4% in the LCP-Tacro and Prograf groups, respectively).

Table 34. Treatment-Emergent Adverse Events Leading to Discontinuation or Withdrawal in Study 3002
(Source: Table 12-14, page 151 of CSR)

System Organ Class Preferred Term	LCP-Tacro (N=268)	Prograf (N=275)
Number of patients with ≥1 TEAE	33 (12.3)	34 (12.4)
Blood and lymphatic system disorders	1 (0.4)	3 (1.1)
Thrombotic microangiopathy	1 (0.4)	1 (0.4)
Haemolytic anaemia	0	1 (0.4)
Haemolytic uraemic syndrome	0	1 (0.4)
Cardiac disorders	1 (0.4)	3 (1.1)
Acute myocardial infarction	0	1 (0.4)
Cardiac failure	0	1 (0.4)

Cardio-respiratory arrest	0	1 (0.4)
Cardiopulmonary failure	1 (0.4)	0
Gastrointestinal disorders	6 (2.2)	2 (0.7)
Oesophagitis	2 (0.7)	0
Aphthous stomatitis	1 (0.4)	0
Diarrhoea	1 (0.4)	0
Gastrointestinal disorder	0	1 (0.4)
Gastrointestinal haemorrhage	0	1 (0.4)
Gastrooesophageal reflux disease	1 (0.4)	0
Peritonitis	1 (0.4)	0
General disorders and administration site conditions	1 (0.4)	0
Death	1(0.4)	0
Immune system disorders	3 (1.1)	3 (1.1)
Kidney transplant rejection	1 (0.4)	3 (1.1)
Pancreas transplant rejection	1 (0.4)	0
Transplant rejection	1 (0.4)	0
Infections and infestations	3 (1.1)	8 (2.9)
Pneumonia	0	5 (1.8)
BK virus infection	1 (0.4)	2 (0.7)
Sepsis	0	3 (1.1)
Polyomavirus-associated nephropathy	2 (0.7)	0
Viraemia	1 (0.4)	0
Injury, poisoning, and procedural c	6 (2.2)	4 (1.5)
Graft dysfunction	2 (0.7)	1 (0.4)
Graft thrombosis	1 (0.4)	2 (0.7)
Complications of transplanted kidney	2 (0.7)	0
Toxicity to various agents	1 (0.4)	0
Transplant failure	0	1 (0.4)
Vascular graft thrombosis	0	1 (0.4)
Investigations	1 (0.4)	1 (0.4)
Immunosuppressant drug level	1 (0.4)	0
Liver function test abnormal	0	1 (0.4)
Metabolism and nutrition disorders	2 (0.7)	2 (0.7)
Diabetes mellitus	2 (0.7)	2 (0.7)
Neoplasms	1 (0.4)	0
Lymphoma	1 (0.4)	0
Nervous system disorders	1 (0.4)	1 (0.4)
Amnesia	0	1 (0.4)
Complex regional pain syndrome	1 (0.4)	0
Tremor	0	1 (0.4)
Psychiatric disorders	0	1 (0.4)
Suicide attempt	0	1 (0.4)
Renal and urinary disorders	4 (1.5)	8 (2.9)
Renal impairment	0	3 (1.1)
Renal artery thrombosis	0	2 (0.7)
Renal necrosis	1 (0.4)	1 (0.4)
Renal vein thrombosis	1 (0.4)	1 (0.4)
Nephropathy toxic	1 (0.4)	0
Obstructive uropathy	1 (0.4)	0

Renal tubular necrosis	1 (0.4)	0
Respiratory, thoracic, and mediastinal	2 (0.7)	2 (0.7)
Acute respiratory distress syndrome	2 (0.7)	1 (0.4)
Alveolitis allergic	0	1 (0.4)
Respiratory distress	1 (0.4)	0
Respiratory failure	0	1 (0.4)
Skin and subcutaneous tissue disorders	1 (0.4)	0
Pruritus	1 (0.4)	0
Surgical and medical procedures	1 (0.4)	0
Pancreas transplant	1 (0.4)	0

Clinical Reviewer's Comment
The rates of adverse events leading to treatment discontinuation and withdrawal from the study are generally balanced across the LCP-Tacro and Prograf treatment groups. Among the discontinuations due to adverse events which may be directly attributable to immunosuppression pneumonia (n=5) and sepsis (n=3) were exclusively reported in the Prograf treatment group.

7.3.3.2 Dropouts and/or Discontinuations in the conversion Study 3001

The TEAEs leading to discontinuation of study drug and/or withdrawal from study was more frequent in the LCP-Tacro group compared to the Prograf group (8.0% vs. 1.2%) as presented in Table 35.

Table 35.Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation in Study 3001 (Safety Set)
(Source: Table 14.3.1.5, page 285 of CSR)

System Organ Class Preferred Term	LCP-Tacro (N=162)	Prograf (N=162)
Total Number of Treatment-Emergent	13 (8.0%)	2 (1.2%)
Infections and infestations	2 (1.2%)	1 (0.6%)
BK virus infection	2 (1.2%)	1 (0.6%)
PVAN	1 (0.6%)	0
Vulval cellulitis	1 (0.6%)	0
Neoplasms benign, malignant	2 (1.2%)	1 (0.6%)
Hepatic neoplasm	1 (0.6%)	0
Renal cancer	1 (0.6%)	0
Renal cell carcinoma recurrent	0	1 (0.6%)
Cardiac disorders	2 (1.2%)	0
Cardiac arrest	2 (1.2%)	0
Investigations	2 (1.2%)	0
Drug level fluctuating	1 (0.6%)	0
Renal function test abnormal	1 (0.6%)	0
Musculoskeletal and connective tissue disorders	2 (1.2%)	0
Myalgia	1 (0.6%)	0

Pain in extremity	1 (0.6%)	0
Nervous system disorders	1 (0.6%)	0
Brain stem haemorrhage	1 (0.6%)	0
Renal and urinary disorders	1 (0.6%)	0
Nephropathy toxic	1 (0.6%)	0
Respiratory, thoracic and mediastinal	1 (0.6%)	0
Acute respiratory distress syndrome	1 (0.6%)	0

Clinical Reviewer's Comment
In Study 3001 there is a numerical imbalance between the rates of discontinuations due to AEs in favor of the Prograf group. This may be partially explained by the open label design of the study. Of note is the single case of discontinuation due to PVAN reported in the LCP-Tacro group parallel to that observed in Study 3002 in which two patients in the LCP-Tacro group vs. none in the Prograf group discontinued treatment due to the same reason. PVAN generally occurs as a consequence of overimmunosuppression but It is difficult to draw any conclusions since only one case is reported in the LCP-Tacro group of the study. Although the number of cases is too small, this rare complication appeared more often in the LCP-Tacro groups of both Phase 3 studies.

7.3.3.3 Dropouts and/or Discontinuations in the Phase 2 de novo Study 2017

In both the LCP-Tacro and the Prograf groups 2 patients in each group withdrew early from the study due to adverse events.

7.3.4 Significant Adverse Events

Reviewer's Note: Since Study 3001 is in stable kidney transplant patients delayed graft function (DGF) applies only to studies 3002 and 2017 conducted in de novo kidney transplant patients.

7.3.4.1 Delayed Graft Function (Study 3002)

Clinical Reviewer's Comment
In MedDRA there is no preferred term (PT) as "delayed graft function" hence the investigator reported term of "delayed graft function" is generally coded as the preferred term "complications of transplanted kidney" under the SOC of injury, poisoning, and procedural complications. Therefore the same coding procedure was followed in Study 3002 and the investigator reported term of "delayed graft function" was coded as the PT "complications of transplanted kidney".

The overall rates of treatment-emergent renal and urinary disorder events and complications of transplanted kidney are provided in Table 36 below. The rates of treatment-emergent complications of transplanted kidney were 7.1% and 10.9% in the

LCP-Tacro and Prograf groups, respectively and these rates reflect the DGF rates in Study 3002.

Table 36. Renal and Urinary Disorder and Complications of Transplanted Kidney Treatment-Emergent Adverse Events in Study 3002 (ITT Set) – n (%)
(Source: Table 12-22, page 166 of CSR)

System Organ Class Preferred Term	LCP-Tacro (N=268)	Prograf (N=275)
Renal and urinary disorders	113 (42.2%)	115 (41.8%)
Injury, poisoning, and procedural complications		
Complications of transplanted kidney	19 (7.1%)	30 (10.9%)

Clinical Reviewer's Comment
As included in the previous versions of the Study 3002 Protocol before the SPA agreement was reached, good kidney function after transplantation was an enrollment criterion and patients would not be enrolled (even if they passed the screening) into the trial unless they have good kidney function following transplantation. FDA did not agree with this enrollment criterion and this criterion was subsequently removed from the agreed protocol version. The main reason for removing this criterion was, if implemented, this requirement for good kidney function early on would naturally select out the lower quality kidneys hence the less optimum recipients who are generally the recipients of these lower quality kidneys in clinical practice as a result of allocation preferences. Consequently this might have resulted in a highly select relatively healthier recipient population in the study which would not be representative of the general kidney recipient population. This becomes even more important if we consider the other restrictive inclusion criteria in Study 3002 which leave out patients with QT prolongation and LVEF less than 45%.

Although this requirement of good early kidney function was removed from the agreed upon version of the protocol, there are statements made by the Applicant in the CSR of Study 3002 which gives the impression that this removed criterion was still followed at least in some study centers.

This concern is further supported by the fact that the reported DGF rates (7.1% in the LCP-Tacro and 10.9% in the Prograf groups) in Study 3002 are generally lower than the DGF rates reported in similar Phase 3 studies conducted in similar patient populations of kidney transplant recipients reviewed by the FDA recently. In these other recent similar Phase 3 trial populations consisting of both live donor and deceased donor transplant recipients the reported DGF rates were higher than 15%.

This overall low rate of DGF reported in Study 3002 and possible exclusion of patients at some centers due to inadequate early kidney function will be considered in the overall assessment of the study results.

7.3.4.1 Delayed Graft Function in the Phase 2 de novo Study 2017

Only one patient (1033-001) in the Prograf group was reported to experience DGF and the event resolved.

7.3.4.2 Events Reported Due to Increased Tacrolimus Blood Levels

7.3.4.2.1 Events Reported Due to Increased Tacrolimus Blood Levels in Study 3002

Treatment-emergent AEs reported due to increased tacrolimus blood levels are presented in Table 37. There was an imbalance in the incidence of events mapping to the preferred term of toxic nephropathy and overdose associated with high levels of tacrolimus trough values observed in a higher number of patients in the LCP-Tacro group. No actual overdoses (ie, a patient taking significantly more doses of study medication than as prescribed per protocol) were reported during the study.

Table 37. Treatment-Emergent Adverse Events Reported Due to Increased Tacrolimus Blood Levels in Study 3002 (ITT Set) – n (%)
(Source: Table 12–23, page 167 of CSR)

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

Clinical Reviewer's Comment

In Study 3002 datasets, I identified a total of 29 patients reported to have tacrolimus toxicity by the investigators. Twenty-six of these patients were in the LCP-Tacro group and three were in the Prograf group (Table 38). None of these 29 patients died during the 12 month study period. Only one patient reported to have tacrolimus toxicity in the LCP-Tacrolimus group (052182-004) lost his graft on day 196, 30 days after the last dose of study medication and in the Reviewer's assessment tacrolimus toxicity played little role if any in his graft loss.

In my assessment these 29 cases were reported due to observed very high tacrolimus trough levels rather than any clinical symptoms. The three most common investigator reported terms for reporting tacrolimus toxicity were “tacrolimus overdose”, “tacrolimus toxicity” and “nephrotoxicity”.

In the reviewer’s opinion the high number of tacrolimus toxicity cases reported from the LCP-Tacro group is due to the initial high starting dose of 0.17 mg/kg/day and the 1.7x conversion factor for converting the investigator prescribed Prograf daily doses into LCP-Tacrolimus daily doses throughout the study period in this double-blind trial. Because of these two main reasons very high tacrolimus trough concentrations sometimes higher than 50ng/mL were reported from the LCP-Tacro group which was not the case in the Prograf group of the trial. Most of these events related to the high tacrolimus levels were reported early on and did not result in an imbalance with regard to deaths, graft loses and other adverse events including cardiac adverse events across the treatment groups but it is not known if this still would be the case if high cardiac risk patients such as with QT prolongation or LVEF values below 45% had been enrolled into this trial.

Therefore in my opinion this imbalance of tacrolimus toxicity against the LCP-Tacro group reflects the high trough levels observed in this group and is a consequence of the high starting dose and the consequently maintained 1.7 x conversion factor and is not expected to happen in clinical practice if the LCP-Tacrolimus extended release tablets are approved for the proposed indication. The findings from the open-label conversion Study 3001 as explained below are in support of this assessment with the caveat that there are two cases of toxic nephropathy reported exclusively from the LCP-Tacro group of Study 3001 which may be explained by increased bioavailability of the LCP-Tacrolimus formulation compared to the immediate release tacrolimus formulation of Prograf increasing the possibility of unintended higher exposure in patients treated with this extended release formulation even in the absence of a high starting dose.

Table 38. Patients Reported with Tacrolimus Overdose and Toxic Nephropathy in Study 3002
(Generated by the Clinical Reviewer)

	Unique Subject ID	Investigator Reported Term	Coded Dictionary Term (PT)	Treatment Group
1	033131-015	Tacrolimus overdose	Overdose	LCP-Tacro
2	033134-027	Tacrolimus Overdose	Overdose	LCP-Tacro
3	033134-016	Tacrolimus Overdosing	Overdose	LCP-Tacro

4	033134-017	Tacrolimus Overdosing	Overdose	LCP-Tacro
5	033134-024	Tacrolimus Overdosing	Overdose	LCP-Tacro
6	033134-032	Tacrolimus Overdosing	Overdose	LCP-Tacro
7	033134-038	Tacrolimus Overdosing	Overdose	LCP-Tacro
8	033134-045	Tacrolimus Overdosing	Overdose	LCP-Tacro
9	001009-015	Tacrolimus toxicity	Toxicity to various agents	LCP-Tacro
10	034154-013	Tacrolimus toxicity	Toxicity to various agents	LCP-Tacro
11	034154-015	Tacrolimus toxicity	Toxicity to various agents	LCP-Tacro
12	001058-005	Tacrolimus toxicity	Toxicity to various agents	LCP-Tacro
13	055172-005	Tacrolimus toxicity	Toxicity to various agents	LCP-Tacro
14	001050-001	Tacrolimus Toxicity	Toxicity to various agents	LCP-Tacro
15	055176-004	Tacrolinemia	Immunosuppressant drug level increased	LCP-Tacro
16	001009-022	Calcineurin inhibitor toxicity	Nephropathy toxic	LCP-Tacro
19	052182-004	Calcineurina Inhibitor Toxicity	Nephropathy toxic	LCP-Tacro
20	065126-001	FK nephrotoxicity	Nephropathy toxic	LCP-Tacro
21	033134-021	Nephrotoxicity	Nephropathy toxic	LCP-Tacro
22	055176-010	Nephrotoxicity	Nephropathy toxic	LCP-Tacro
23	049139-001	Nephrotoxicity of kidney transplant	Nephropathy toxic	LCP-Tacro
24	034157-013	Nephrotoxicity to tacrolimus	Nephropathy toxic	LCP-Tacro
25	049137-028	Tacrolimus nephrotoxicity	Nephropathy toxic	LCP-Tacro
26	049137-045	Tacrolimus nephrotoxicity	Nephropathy toxic	LCP-Tacro
27	033134-026	Tacrolimus Overdosing	Overdose	Prograf
28	034154-016	Tacrolimus toxicity	Toxicity to various agents	Prograf

29	049137-049	CNI nephropaty	Nephropathy	Prograf

7.3.4.2.2 Events Reported Due to Increased Tacrolimus Blood Levels in Study 3001

Unlike in the de novo Study 3002, very few events of high tacrolimus levels were reported in the conversion Study 3001 with no significant imbalance between the treatment groups (Table 39).

Table 39. Treatment-Emergent Adverse Events Reported Due to Increased Tacrolimus Blood Levels in Study 3001 (ITT Set) – n (%)
(Source: Reviewer generated)

Preferred Term	LCP-Tacro (N=163)	Prograf (N=163)
Nephropathy toxic	2 (1.2)	0
Toxicity to various agents	0	0
Overdose	0	1 (0.6)
Immunosuppressant drug level increased	0	0

Clinical Reviewer's Comment
A similar imbalance of tacrolimus toxicity events as in Study 3002 is not observed in the conversion Study 3001 which is an open label study. In Study 3001 the starting daily doses of LCP-Tacrolimus were calculated using a conversion factor of 0.7 for non-African Americans and 0.85 for African Americans for converting their current Prograf doses. In the Clinical Pharmacology Reviewer's assessment as included in Section 4.4, the tacrolimus daily doses and trough concentrations were stable, and were comparable between patients switched to LCP-Tacro and patients who continued to receive Prograf throughout the 12-month study period, Despite this observation there were still two cases of toxic nephropathy reported exclusively from the LCP-Tacro group which may be explained by the higher bioavailability of the extended release formulation compared to the immediate release formulation of Prograf.

7.3.4.2.3 Events Reported Due to Increased Tacrolimus Blood Levels in Study 2017

Only one patient in the study (1033-005 in the LCP-Tacro group) experienced tacrolimus toxicity. This was a 54-year-old Caucasian female patient. At an outpatient clinic visit on postoperative day 26, the patient's tacrolimus level was 46.7 ng/mL. It was determined that, in addition to her study medication, the patient had also continued

taking her usual maintenance dose of tacrolimus. The patient's LCP-Tacro was interrupted until the concentration came down to normal range and the event resolved without any adverse consequences.

7.3.4.3 Infections and Infestations

7.3.4.3.1 Infections and Infestations in Study 3002

Infections and infestations were assessed as both opportunistic infections (Table 40) and all infections. The overall incidence rates of the SOC infections and infestations TEAEs were 70.1% and 64.7% for the LCP-Tacro and Prograf groups, respectively. The most common events and respective incidence rates were: urinary tract infection (24.6% and 24.4%), BK virus infection (6.0% and 9.1%), and upper respiratory tract infection (8.6% and 5.1%) for the LCP-Tacro and Prograf groups, respectively.

The incidence rates of treatment-emergent infections and infestations resulting in discontinuation of study drug and/or withdrawal from the study were 1.1% and 2.9% for the LCP-Tacro and Prograf groups, respectively. The incidence rates of serious treatment-emergent infections and infestations were 25.7% and 24.4% in the LCP-Tacro and Prograf groups, respectively. There was 1 patient in the LCP-Tacro group, and 5 patients in the Prograf group who died from treatment-emergent infections and infestations.

Table 40. Incidence of Opportunistic Infections in Study 3002
(Source: Table 12-15, page 154 of CSR)

Infection Category	**LCP-Tacro (N=268) No of Patients (%)**	**Prograf** (N=275) No of Patients (%)
Any opportunistic infection	92 (34.3)	84 (30.5)
Any CMV disease event	31 (11.6)	25 (9.1)
Cytomegalovirus gastroenteritis	1 (0.4)	0
Cytomegalovirus gastrointestinal infection	0	1 (0.4)
Cytomegalovirus infection	19 (7.1)	16 (5.8)
Cytomegalovirus test positive	2 (0.7)	1 (0.4)
Cytomegalovirus viraemia	10 (3.7)	7 (2.5)
Pneumonia cytomegaloviral	0	1 (0.4)
Any BK virus disease event	24 (9.0)	26 (9.5)

BK viraemia	7 (2.6)	3 (1.1)
BK virus infection	16 (6.0)	25 (9.1)
Polyomavirus-associated nephropathy (PVAN)	4 (1.5)	2 (0.7)

Cytomegalovirus Infection:

The incidence of CMV-related TEAEs was 11.6% and 9.1% for the LCP-Tacro and Prograf treatment groups, respectively ($p < 0.05$). The 2 most common specific events were CMV infection and CMV viremia. There were no occurrences of either of these events leading to discontinuation of study drug and/or withdrawal from the study. The incidence of serious treatment-emergent CMV infection was 4.1% and 3.6% in the LCP-Tacro and Prograf groups, respectively; for CMV viremia, the incidence rate was 0.4% in both groups. There were no occurrences of deaths related to either of these events.

BK Virus Infection:

The incidence of BK virus-related TEAEs was 9.0% and 9.5% for the LCP-Tacro and Prograf groups, respectively ($p < 0.05$). The 2 most common specific events were BK virus infection and BK viremia. The incidence rates of BK virus infection resulting in discontinuation of study drug and/or withdrawal from the study were 0.4% and 0.7% for the LCP-Tacro and Prograf groups, respectively. There were no occurrences of BK viremia leading to discontinuation of study drug and/or withdrawal from the study. The incidence of serious treatment-emergent BK infection was 0.4% (n=1) in both treatment groups. There were 2 patients (0.7%) in the LCP-Tacro group who discontinued study drug treatment due to serious events of polyomavirus-associated nephropathy (PVAN) and no such events in the Prograf group resulting in either discontinuation and/or seriousness. There were no occurrences of deaths related to either of these events.

Clinical Reviewer's analysis of PVAN cases:

In the general kidney transplant patient population the majority of the cases with PVAN are due to BK virus (BKVAN) and a very small percentage is due to JC virus. Since PVAN is the advanced form of Polyoma virus infection generally following viruria and viremia and may result in graft loss, the Reviewer focused on this advanced complication and reanalyzed the reported cases of PVAN in Study 3002.

As background information, BKVAN currently affects 1–7% of kidney recipients and has been associated with a 10–100% graft loss rate depending on the severity of histological involvement. It is likely that the last stage of an unchecked BKV infection begins as asymptomatic viruria, progresses to sustained viremia, possibly associated with subclinical nephritis, and culminates in overt nephropathy. Thus, sustained BKV

detected in plasma predicts progression to BKV-associated interstitial nephritis, or nephropathy.[6]

I identified 6 patients in the LCP-Tacro group and 3 patients in the Prograf group reported to have PVAN (Table 41). Four of the 6 cases in the LCP-Tacro group and 2 of the 3 cases in the Prograf group were flagged as treatment emergent. Most of the PVAN cases were reported approximately 3-4 months after transplantation. In 5 of the 6 patients in the LCP-Tacro group and in 1 of the 3 patients in the Prograf group, study medication was discontinued although not in all of the discontinuations PVAN was listed as the cause of discontinuation.

As assessed by the Clinical Pharmacology Reviewer Gerlie Gieser, most of the patients with PVAN had tacrolimus trough levels around 20 ng/mL or higher early on after transplantation although a definitive conclusion cannot be reached. (See Clinical Pharmacology Review in DARRTS)

Table 41. PVAN Cases in Study 3002
(Generated by the Clinical reviewer)

LCP-Tacrolimus Group

	Patient ID	Investigator Term	Study Day	Treatment Emergent	Action taken with the Study Drug
1	061101-002	BK nephritis	88	Yes	discontinued
2	001029-001	BK nephropathy	89	Yes	discontinued
3	061104-004	BK nephropathy	126	Yes	discontinued
4	061104-002	BK Nephropathy	90	No	discontinued
5	061103-001	BK Virus Nephritis	330	No	discontinued
6	381142-001	BK virus nephropaty	33	Yes	Not discontinued

Prograf Group

	Patient ID	Investigator Term	Study Day	Treatment Emergent	Action taken with the Study Drug
1	055172-003	BKV Nephropaty	126	Yes	Not discontinued
2	001051-003	BK Nephropathy	122	Yes	Not discontinued

6 Memon et al. Progression from Sustained BK Viruria to Sustained BK Viremia with Immunosuppression Reduction Is Not Associated with Changes in the Noncoding Control Region of the BK Virus Genome. Journal of Transplantation Volume 2012, http://www.hindawi.com/journals/jtrans/2012/761283/

3	061101-001	BK virus nephropathy	328	No	discontinued

Clinical Reviewer's Comment
In general there is not a significant imbalance with regard to the opportunistic infections across the treatment groups but there are more PVAN and CMV disease cases in the LCP-Tacro group compared to the Prograf group which may be due to the possible higher tacrolimus exposure in the LCP-Tacro group especially early after transplantation because of the reasons discussed earlier. Unlike in this blinded trial, this numerical imbalance between the two treatment groups against the LCP-Tacro group with regard to number of cases of PVAN and CMV disease may not occur in real life.

7.3.4.3.2 Infections and Infestations in Study 3001

There was no difference between treatment groups in the incidence of overall infections and infestations and opportunistic infections between the LCP-Tacro and Prograf treatment groups (45.1% vs. 47.5% and 5.6% vs. 6.2%, respectively).

Table 42. Incidence of Opportunistic Infections in Study 3001
(Source: Table 14.3.1.2, page 179 of CSR**)**

Infection Category	LCP-Tacro (N=162) No of Patients (%)	Prograf (N=162) No of Patients (%)
All Infections and infestations	73 (45.1%)	77 (47.5%)
Opportunistic infections	9 (5.6%)	10 (6.2%)
BK virus infection	2 (1.2%)	4 (2.5%)
Oral candidiasis	3 (1.9%)	2 (1.2%)
Candidiasis	3 (1.9%)	1 (0.6%)
Herpes zoster	2 (1.2%)	2 (1.2%)
Polyomavirus-associated nephropathy	2 (1.2%)	1 (0.6%)
Cytomegalovirus infection	1 (0.6%)	1 (0.6%)
Cytomegalovirus viraemia	2 (1.2%)	0
Pneumocystis Jiroveci pneumonia	0	1 (0.6%)

Clinical Reviewer's Comment:
Overall infections and opportunistic infections are balanced across the treatment groups in the open label conversion Study 3001. The trend of increased number of PVAN and CMV disease cases in the LCP-Tacro group observed in Study 3002 is not observed in the open label Study 3001 which supports the possibility that the observed imbalance in Study 3002 may be due to the high starting dose of LCP-Tacrolimus and other study

design related issues such as the 1.7 x conversion factor for calculating the LCP-Tacrolimus dose throughout the study period.

7.3.4.3.3 Infections and Infestations in Study 2017

The incidence of Infections and Infestations were similar in the two treatment groups (65.6% in the LCP-Tacro group and 74.2% in the Prograf group, Table 43). Two patients experienced serious opportunistic infections, pneumonia and mild urinary tract infection, both in the Prograf group. There was only one PVAN case in the study which was in the LCP-Tacro group.

Table 43. Incidence of Opportunistic Infections in Study 2017
(Source: Table 14.3.1.2, page 135 of CSR, Section 14)

Infection Category	LCP-Tacro (N=32) No of Patients (%)	Prograf (N=31) No of Patients (%)
All Infections and infestations	21 (65.6%)	23 (74.2%)
Sepsis	1 (3.1%)	1 (3.2%)
BK virus infection	2 (6.3%)	2 (6.5%)
Pneumonia	1 (3.1%)	1 (3.2%)
Candidiasis	0	2 (6.5%)
Polyomavirus infection	0	2 (6.5%)
Polyomavirus-associated nephropathy	1 (3.1%)	0
Cytomegalovirus infection	1 (3.1%)	1 (3.2%)
Cytomegalovirus viraemia	1 (3.1%)	1 (3.2%)

Clinical Reviewer's Comment
The incidence of overall infections and opportunistic infections are balanced across the two treatment groups.

7.3.4.4 Malignancies

7.3.4.4.1 Malignancies in Study 3002

The incidence rates of malignancy TEAEs were 1.5% and 1.1% for the LCP-Tacro and Prograf groups, respectively (Table 44). Events of individual preferred terms were rare and there was no occurrence of the same cancer occurring in more than 1 patient in either of the treatment groups. The single case of lymphoma (PTLD), occurring in the

LCP-Tacro group, was serious, and resulted in the patient's death. No other malignant event resulted in patient discontinuation. By definition, all malignant events with the exception of the basal cell carcinoma were considered serious. It should be noted that 1 patient in the Prograf group was mistakenly coded as "mycosis fungoides" (cutaneous T-cell lymphoma) when in fact this patient had a nonmalignant fungal skin infection. There were no other occurrences of deaths related to malignancy TEAEs.

Table 44. Incidence of Malignancies in Study 3002
(Source: Table 12–15, page 154 of CSR)

Type of Malignancy	**LCP-Tacro (N=268) No of Patients (%)**	**Prograf** (N=275) No of Patients (%)
Any malignancy	4 (1.5)	3 (1.1)
Basal cell carcinoma	0	1 (0.4)
Bowen's disease	1 (0.4)	0
Lymphoma (PTLD)	1 (0.4)	0
Mycosis fungoides	0	1 (0.4)*
Renal cancer	1 (0.4)	0
Renal cell carcinoma	0	1 (0.4)
Squamous cell carcinoma	1 (0.4)	0

* Patient 055171/011 experienced nonmalignant mycosis (ie, topical skin infection); however, the event was mistakenly coded as mycosis fungoides.

7.3.4.4.2 Malignancies in Study 3001

There was no significant difference between groups in the incidence of malignancies within 12 months between the LCP-Tacro and Prograf treatment groups (4.9% and 5.6%, respectively, *P* >0.999) (Table 45).

Table 45. Incidence of Malignancies in Study 3001
(Source: Generated by the Clinical Reviewer)

Type of Malignancy	**LCP-Tacro (N=162) No of Patients (%)**	**Prograf (N=162) No of Patients (%)**
Any malignancy	8 (4.9)	9 (5.6)
Basal cell carcinoma	0	1 (0.6)
Squamous cell carcinoma	4 (2.4)	6 (3.7)
Vulvar carcinoma	1(0.6)	0
Recurrent renal cell carcinoma	0	1 (0.6)
Renal cancer (native)	2	0
Prostate cancer	1 (0.6)	0

Hepatic neoplasm	1 (0.6)	0
Lung cancer	0	1 (0.6)

Clinical Reviewer's Comment
Neither in Study 3002 nor in Study 3001 there seems to be a numerical imbalance between the treatment groups with regard to malignancies. Overall malignancy rates are higher in the conversion Study 3001 in both treatment groups compared to the de novo Study 3002. This overall higher malignancy rate is primarily driven by the higher occurrence of squamous cell carcinoma in the stable kidney transplant patient population compared to the de novo transplant patient population as expected.

7.3.4.4.3 Malignancies in Study 2017

No patients were diagnosed with a malignancy during the study.

7.3.4.5 Cardiac and Vascular Disorders

7.3.4.5.1 Cardiac and Vascular Disorders in Study 3002

Cardiac Disorders

The overall incidence rates of TEAEs in the SOC of cardiac disorders were 10.8% and 12.7% for the LCP-Tacro and Prograf groups, respectively (Table 46). The most common TEAEs and respective incidence rates were: tachycardia (3.7% and 3.3%), atrial fibrillation (1.5% and 2.2%), and angina pectoris (1.5% and 1.5%) for the LCP-Tacro and Prograf groups, respectively. Ventricular hypertrophy was reported only in one patient who was in the Prograf group.

The incidence rates of treatment-emergent cardiac disorders resulting in discontinuation of study drug and/or withdrawal from the study were 0.4% and 1.1% for the LCP-Tacro and Prograf groups, respectively. The incidence rates of serious treatment-emergent cardiac disorders were 2.6% and 4.7% in the LCP-Tacro and Prograf groups, respectively.

Table 46. Incidence of Cardiac Disorders in Study 3002
(Source: Table 14.3.2.2, page 439 of CSR)

System Organ Class **Preferred Term**	**LCP-Tacro** **(N=268)**	**Prograf** **(N=275)**
CARDIAC DISORDERS	29 (10.8%)	35 (12.7%)
Tachycardia	10 (3.7%)	9 (3.3%)

Atrial fibrillation	4 (1.5%)	6 (2.2%)
Angina pectoris	4 (1.5%)	4 (1.5%)
Sinus tachycardia	4 (1.5%)	3 (1.1%)
Acute myocardial infarction	2 (0.7%)	3 (1.1%)
Cardiac failure congestive	2 (0.7%)	2 (0.7%)
Palpitations	2 (0.7%)	2 (0.7%)
Acute coronary syndrome	2 (0.7%)	1 (0.4%)
Atrial flutter	2 (0.7%)	1 (0.4%)
Cardiac failure	1 (0.4%)	2 (0.7%)
Sinus bradycardia	2 (0.7%)	1 (0.4%)
Arrhythmia supraventricular	1 (0.4%)	1 (0.4%)
Pericarditis	1 (0.4%)	1 (0.4%)
Ventricular extrasystoles	0	2 (0.7%)
Atrioventricular block first degree	0	1 (0.4%)
Bundle branch block right	0	1 (0.4%)
Cardio-respiratory arrest	0	1 (0.4%)
Cardiomyopathy	0	1 (0.4%)
Cardiopulmonary failure	1 (0.4%)	0
Coronary artery disease	0	1 (0.4%)
Diastolic dysfunction	1 (0.4%)	0
Intracardiac thrombus	0	1 (0.4%)
Ischaemic cardiomyopathy	1 (0.4%)	0
Myocardial ischaemia	1 (0.4%)	0
Myocarditis	0	1 (0.4%)
Nodal rhythm	0	1 (0.4%)
Sinus arrhythmia	0	1 (0.4%)
Tachyarrhythmia	0	1 (0.4%)
Ventricular hypertrophy	0	1 (0.4%)

Vascular Disorders

The overall incidence rates of TEAEs in the SOC of vascular disorders were 37.7% and 38.2% for the LCP-Tacro and Prograf groups, respectively. The most common TEAEs and respective incidence rates were: hypertension (23.1% and 22.5%) and hypotension (6.7% and 4.7%), for the LCP-Tacro and Prograf groups, respectively. Venous thrombosis was reported in one patient (1.1%) in the LCP-Tacro group and in 3 patients (1.1%) in the Prograf group. Thrombosis was reported in 2 patients (0.7%) in the LCP-Tacro group and in 1 patient (0.4%) in the Prograf group.

Clinical Reviewer's Comment
In Study 3002 the incidence of cardiac adverse events and vascular adverse events are similar across the two treatment groups (10.8% and 12.7%). These relatively low overall rates are probably due to the fact that selective cardiac exclusion criteria yielded a better prognostic study population. The initial higher tacrolimus exposure in the LCP-Tacro group did not result in higher number of cardiac and vascular adverse events in this low-cardiac risk study population.

7.3.4.5.2 Cardiac and Vascular Disorders in Study 3001

Cardiac Disorders

The overall incidence rates of TEAEs in the SOC of cardiac disorders were 14 (8.6%) and 8 (4.9%) for the LCP-Tacro and Prograf groups, respectively (Table 47).

The incidence rates of treatment-emergent cardiac disorders resulting in discontinuation of study drug and/or withdrawal from the study were 1.2% and 0% for the LCP-Tacro and Prograf groups, respectively. The incidence rates of serious treatment-emergent cardiac disorders were 1.2% and 0% in the LCP-Tacro and Prograf groups, respectively.

Table 47. Incidence of Cardiac Disorders in Study 3001
(Source: Table 14.3.1.2, page 25 of CSR)

Cardiac Disorder	LCP-Tacro (N=162) No of Patients (%)	Prograf (N=162) No of Patients (%)
Any cardiac disorder	14 (8.6%)	8 (4.9%)
Angina pectoris	4 (2.5%)	1 (0.6%)
Atrial fibrillation	2 (1.2%)	1 (0.6%)
Bradycardia	1 (0.6%)	1 (0.6%)
Cardiac arrest	2 (1.2%)	0
Left ventricular hypertrophy	2 (1.2%)	0
Palpitations	1 (0.6%)	1 (0.6%)
Tachycardia	2 (1.2%)	0
Acute myocardial infarction	1 (0.6%)	0
Arrhythmia	0	1 (0.6%)
Bundle branch block left	0	1 (0.6%)
Cardiac discomfort	0	1 (0.6%)
Cardiac failure congestive	1 (0.6%)	0
Cardiomegaly	1 (0.6%)	0
Cardiovascular disorder	1 (0.6%)	0
Myocardial ischaemia	0	1 (0.6%)
Postural orthostatic tachycardia syndrome	0	1 (0.6%)
Sinus bradycardia	0	1 (0.6%)

Vascular Disorders

The overall incidence rates of TEAEs in the SOC of vascular disorders were 11.7% and 10.5% for the LCP-Tacro and Prograf groups, respectively. The most common TEAEs and respective incidence rates were: hypertension (4.3% and 6.2%) and hypotension (3.1% and 0.6%), for the LCP-Tacro and Prograf groups, respectively. Deep vein

thrombosis was reported in one patient (0.6%) in the LCP-Tacro group and in 2 patients (1.2%) in the Prograf group.

Clinical Reviewer's Comment
In the conversion Study 3001 which enrolled patients without stringent cardiac exclusion criteria unlike in the de novo Study 3002, a higher number of patients in the LCP-Tacro group are reported to have cardiac adverse events compared to the Prograf group. There is not a particular type of cardiac adverse event that seems to be driving the numerical imbalance but left ventricular hypertrophy (n=2) and cardiomegaly (n=1) which both may be representing the same condition are reported only in the LCP-Tacro group. Myocardial hypertrophy is among the adverse reactions included in the Prograf package insert. The exclusive appearance of these myocardial hypertrophy events in the LCP-Tacro group may be the consequence a possible overexposure or might have occurred due to reasons not related to the study treatments and the numbers are too small to draw any definitive conclusions.

Vascular disorders are balanced across the two groups similar to Study 3002.

7.3.4.5.3 Cardiac and Vascular Disorders in the Phase 2 Study 2017

Cardiac disorders were balanced across the study groups and were reported in 8 patients (25.0%) in the LCP-Tacro group and 9 patients (29.0%) in the Prograf group. Most frequent cardiac disorder was tachycardia reported in 4 patients (12.5%) in the LCP-Tacro group and 3 patients (9.7%) in the Prograf group. Left ventricular hypertrophy was reported in only one patient who was in the Prograf group.

Vascular disorders were reported in 10 patients (31.3%) in the LCP-Tacro group and in 13 (41.9%) patients in the Prograf group. No patients in the LCP-Tacro group and 3 patients (9.7%) were reported to have deep vein thrombosis.

Clinical Reviewer's Comment
Deep vein thrombosis events were exclusively reported in the Prograf group but it is not possible to make definitive assessments in this small Phase 2 study although a similar trend was observed in Study 3002.

7.3.4.6 New-Onset Diabetes Mellitus and Hemoglobin A1c

7.3.4.6.1 New-Onset Diabetes Mellitus and Hemoglobin A1c in Study 3002

The incidence of new-onset diabetes mellitus (NODM) was analyzed in patients at risk for NODM; patients were at risk for NODM if they met all of the following criteria to exclude patients who had diabetes at baseline:

- No medical history of diabetes
- Baseline FPG (fasting plasma glucose) <126 mg/dL
- No prior use of hypoglycemic agent for diabetes conditions
- No prior use of insulin for diabetes conditions
- Hemoglobin A1c <6.5% before transplant

New-onset diabetes mellitus was defined as a fasting plasma glucose (FPG) level of at least 126 mg/dL, or 2-hour postprandial plasma glucose of at least 200 mg/dL (in oral glucose tolerance test) on 2 or more consecutive occasions post baseline, or HbA1c at least 6.5% (at least 3 months after randomization), or new-onset hypoglycemic agent use, or new-onset insulin use greater than 30 days at any time during the study among those patients with baseline FPG and HbA1c levels not meeting the respective threshold values and with no prior medical history of diabetes as assessed during the screening period. The onset date for NODM was defined as the earliest date when one of the criteria is met. In the case of the FPG criterion, the date of the first of the 2 consecutive elevated values was considered to be the onset date. Only the events with an onset date before or on Study Day 404 were included in the 12-month analysis.

Within 12 months after randomization, 18 of 88 at-risk patients (20.5%) and 11 of 74 at-risk patients (14.9%) in the LCP-Tacro and Prograf treatment groups, respectively, had developed NODM (Table 48). This difference in favor of the Prograf group was not statistically significant (P = 0.414). The percentage of at-risk patients with an HbA1c of ≥6.5% at least 90 days after randomization was higher for the LCP-Tacro group compared with the Prograf group (12.5% vs 8.1%). The percentage of at-risk patients with new onset of insulin use at least 31 days after randomization was slightly lower and the percentage of at-risk patients with new onset of use of oral hypoglycemic agents was slightly higher for the LCP-Tacro group compared with the Prograf group.

Table 48. Incidence of New Onset Diabetes Mellitus (NODM) within 12 Months after Randomization in Patients At-Risk for Diabetes in Study 3002 (ITT)
(Source: Table 14.3.8, page 332 of CSR)

Parameter and Criterion	LCP-Tacro (N=268)	Prograf (N=275)	Difference Estimate (95% CI)
Patients at Risk for NODM	88	74	
Patients With NODM	18/88 (20.5%)	11/74 (14.9%)	5.59% (-6.5%, 17.1%)
FPG >= 126 mg/dL on Two Consecutive Occurrences	7/88 (8.0%)	8/74 (10.8%)	-2.86% (-12.81%, 6.34%)
HbA1c >= 6.5%	11/88 (12.5%)	6/74 (8.1%)	4.39% (-5.64%, 13.95%)
New Onset of Insulin Use >=31 Days	1/88 (1.1%)	3/74 (4.1%)	-2.92% (-10.18%, 2.77%)
New Onset of Use of Oral Hypoglycemic Agent	6/88 (6.8%)	4/74 (5.4%)	1.41% (-7.10%, 9.39%)

For patients with diabetes at the time of transplant, the proportion of patients with HbA1c ≥6.5% at Baseline was 54.0% and 61.1% for patients in the LCP-Tacro and Prograf groups, respectively. The proportion of patients with HbA1c ≥6.5% was similar between the 2 treatment groups at Month 3 but higher for the LCP-Tacro group compared with the Prograf group at Months 6 and 12.

7.3.4.6.2 New-Onset Diabetes Mellitus in Study 3001

Same criteria were applied in Study 3001 as in Study 3002 for the definition of patients at risk at baseline and for the definition of NODM.

At 12 months, 9 of 90 at-risk patients (10.0%) and 10 of 95 at-risk patients (10.5%) in the LCP-Tacro and Prograf treatment groups, respectively, had developed new-onset diabetes. These differences were not statistically significant. No table for NODM in Study 3001 is included in this review since the rates in the treatment groups are small and are not significantly different from each other.

Clinical Reviewer's Comment
In Study 3002, at the end of the 12 month study period more patients developed NODM in the LCP-Tacro group compared to the Prograf group (20.5% vs.14.9%) mainly driven by the higher number of patients with HbA1c >= 6.5% in the LCP-Tacro group but this difference did not reach statistical significance. This numerically higher incidence of NODM in the LCP-Tacro group of Study 3002 may be due to the initial high starting dose (0.17 mg/kg) and the consequent higher tacrolimus exposure during the early posttransplant period in the LCP-Tacrolimus group.

In the conversion study (3001) the NODM incidences are much lower and similar across the treatment groups (10.0% in the LCP-Tacro group and 10.5% in the Prograf group) compared to the de novo study (3002) as expected, parallel to the decrease in the intensity of immunosuppression over time.

7.3.4.6.3 New-Onset Diabetes Mellitus in the Phase 2 Study 2017

The definition of NODM in Study 2017 is different than in Study 3002 and Study 3002 since it is an older study and does not include the HbA1c and the postprandial glucose components. NODM was defined as a fasting plasma glucose ≥126 mg/dL, a requirement for insulin ≥30 days, or the need for an oral hypoglycemic agent in a patient with no prior medical history of diabetes. The cumulative incidence of NODM at Days 180 and 360 was estimated using the product-limit (Kaplan-Meier) method and compared between treatment groups using the z-statistic. Patients who were diabetic at the time of transplantation were excluded from the 'at-risk' group.

Twelve patients overall experienced diabetes adverse event during the study (preferred term: diabetes mellitus). Of these 12 patients, diabetes mellitus was reported either as a

pre-existing medical condition that worsened during the study (5 patients) or a newly-diagnosed condition during the study (7 patients). The 7 patients with NODM during the study included 2 (10.5%) patients (out of 19 at risk) in the LCP-Tacro group and 5 (20%) patients (out of 25 at risk) in the Prograf group.

Clinical Reviewer's Comment
Since the definition of NODM in the Phase 2 Study 2017 and the starting doses and target trough levels for tacrolimus in both arms are different than in the Phase 3 de novo Study 3002, cross study comparisons cannot be made. The number of patients is small so the NODM findings in the Phase 2 Study 2017 are limited to make a comparison between the two different treatment groups.

7.3.4.7 Proteinuria (Spot Urine Protein:Creatinine Ratio)

Clinical Reviewer's Background Information:

As stated in the NKF KDOQI Clinical Practice Guidelines for Chronic Kidney Disease[7] : Normal individuals usually excrete very small amounts of protein in the urine. Persistently increased protein excretion is usually a marker of kidney damage. Concentration of protein in a spot urine sample provides a rough index of the protein excretion rate, but is also affected by hydration. The concentration of protein in the urine is affected by urine volume as well as protein excretion rate. Urine volume is dependent primarily on the state of hydration. Urine protein-to-creatinine and albumin-to-creatinine ratios provide accurate estimates of the urinary protein and albumin excretion rate, and are not affected by hydration. A first morning urine specimen is preferred, but random urine specimens are acceptable if first morning urine specimens are not available.

In the general population a patient with a urine protein to creatinine ratio of 1 or more, the risk of progression of chronic kidney disease (CKD) is higher. In fact, any patient with an elevated ratio (≥1) should be evaluated for causes of glomerular disease, including diabetes, collagen vascular disease, malignancy and infections.[8]

The cause for post-transplant proteinuria is multifaceted, as it may originate from the allograft or from the native kidneys or may be associated with immunosuppressive medications. It is unclear whether proteinuria is due to focal glomerular disease or is an indication of progressive proximal tubular dysfunction. Studies show that 45% of renal transplant patients excrete protein even though it may not be in the nephrotic range. Measurement of protein excretion is a useful predictive marker after renal

7 https://www.kidney.org/professionals/kdoqi/guidelines_ckd/p5_lab_g5.htm
8 Paige NM1, Nagami GT. The top 10 things nephrologists wish every primary care physician knew. Mayo Clin Proc. 2009; 84(2):180-6

transplantation adding information in addition offered by other biochemical, or histologic variables.[9]

7.3.4.7.1 Spot Urine Protein:Creatinine Ratio in Study 3002

Samples for routine hematology, chemistry, and urinalysis tests and urinary spot protein:creatinine ratio were collected at all visits in the 12-month treatment period (beginning at Day 7), and at selected visits in the 12-month extension period.

Mean CFB in spot protein:creatinine values were similar in both treatment groups at Week 3 and Months 1, 1.5, and 4; slightly lower at Days 7 and 10 and Week 2; and slightly higher at Months 2, 3, 6, 9, and 12 for the LCP-Tacro group compared with the Prograf group (Table 49).

Table 49. Spot Protein:Creatinine Ratio and Change from Baseline in Study 3002
(Source: Table 14.3.1.2, page 25 of CSR)

Visit	LCP-Tacro (N=268)		Prograf (N=275)	
	Result	Change from Baseline	Result	Change from Baseline
Baseline	3.87		3.93	
Day 7	1.02	-2.79	1.11	-2.58
1 Month	0.34	-3.64	0.34	-3.62
6 Months	0.29	-4.24	0.26	-3.29
12 Months	0.38	-3.45	0.26	-4.11

7.3.4.7.2 Spot Urine Protein:Creatinine Ratio in Study 3001

The standard deviations for the mean change from baseline in spot urine protein:creatinine ratio at 3, 6 and 12 months were large, and no conclusions could be drawn from those results. The median change was small in both treatment groups at each time point.

Clinical Reviewer's Comment
Urinary protein excretion among other factors is also related to intraglomerular pressure. CNIs including tacrolimus generally decrease the intraglomerular pressure and decrease the proteinuria at the same time. In both Phase 3 studies since the active moiety is the same (tacrolimus) in both treatment groups any major differences between the treatment groups is not expected and this is what was observed.

7.3.4.7.3 Spot Urine Protein:Creatinine Ratio in the Phase 2 Study 2017
Not reported in this Phase 2 study.

9 Kesiraju S, Paritala P, Umamaheswara Rao Ch, Reddy VS, Soma Sekhar M, et al. (2014) Spot Urinary Protein to Creatinine Ratio as an Alternative Measurement for 24 Hour Urinary Proteins in Renal Transplant Recipients. J Immunol Clin Res 2(1): 1014.

7.3.4.8 Renal Function

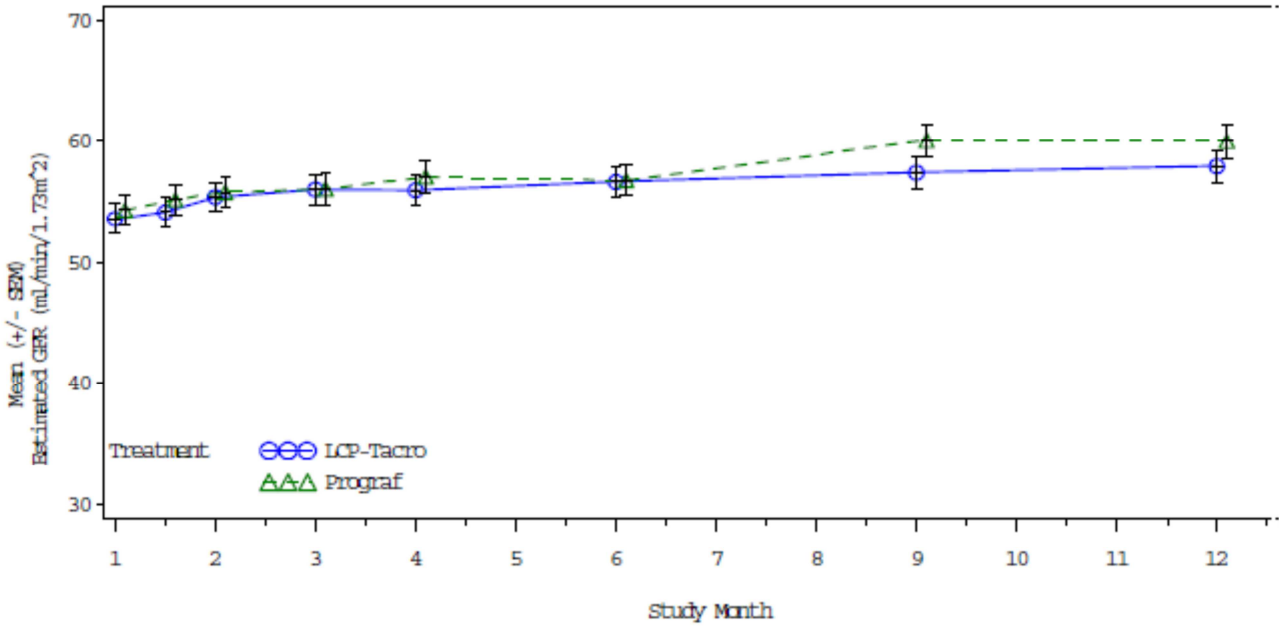
7.3.4.8.1 Renal Function in Study 3002

Beginning on Day 30, estimated glomerular filtration rate (eGFR) was measured using the Modification of Diet in Renal Disease 7 (MDRD7) formula. To allow the kidney graft to recover from perioperative ischemia-perfusion injury, baseline assessments for renal function (eGFR) began at Day 30. The value of eGFR, calculated on the basis of Day 30 measurements, was used as the baseline value for all eGFR data summaries and statistical analysis. Patients who experienced treatment failure or discontinued the study before Day 30 were excluded from the eGFR analysis.

Mean change from baseline in eGFR using observed values were similar in both treatment groups up through Month 6, and slightly greater in the Prograf group compared with the LCP-Tacro group at Months 9 and 12 (Figure 8). The difference in mean eGFR values between the two treatment groups was not statistically significant. No statistically significant difference occurred in mean eGFR between the treatment groups either when zero values were imputed for patients with graft failure.

Baseline eGFR values on Day 30 were 53.8 ml/min/1.73 m^2 in the LCP-Tacro group and 54.4 ml/min/1.73 m^2 in the Prograf group. At 12 months this small difference of 1ml/min between the groups was maintained and the values were 58.6 ml/min/1.73 m^2 in the LCP-Tacro group and 59.8 ml/min/1.73 m^2 in the Prograf group

Figure 8. Mean (±SEM) Observed Estimated Glomerular Filtration Rate (mL/min/1.73m2) (ITT Set) - Study 3002
(Source: Figure 12–3, page 180 of CSR)



7.3.4.8.2 Renal Function in Study 3001

Serum creatinine, BUN and serum albumin for calculating eGFR were measured at screening, day 0, week 4 and the end of months 3, 6 and 12. Since Study 3001 is a conversion study in stable kidney transplant patients the baseline eGFR was based on the day 0 measurement. The eGFR in Study 3001 was calculated using the MDRD7 equation as in Study 3002. At baseline mean eGFR values were similar and 61.5 ml/min/1.73 m^2 in the LCP-Tacro group and 60.0 ml/min/1.73 m^2 in the Prograf group. There was no clinically significant change in either group and the calculated eGFR values were 61.9 ml/min/1.73 m^2 and 62.0 ml/min/1.73 m^2 at six months and 62.0 ml/min/1.73 m^2 and 61.4 ml/min/1.73 m^2 at 12 months in the LCP-Tacro and Prograf groups respectively.

7.3.4.8.3 Renal Function in the Phase 2 Study 2017

Renal function evaluated on the basis of serum creatinine or estimated GFR (MDRD7 equation) progressively improved in both treatment groups from screening to day 360 and the magnitude of the change was similar in both groups. Baseline for these variables was defined as Day 42. At baseline the mean eGFR values were 48.5 ml/min in the LCP-Tacro group and 55.7 ml/min ml/min in the Prograf group. On day 360, eGFR was 57.0 ml/min in the LCP-Tacro group and 64.2 ml/min in the Prograf group.

Clinical Reviewer's Comment
Both in the de novo Study 3002 and the conversion Study 3001 the baseline and the follow up eGFR values throughout the 12 month study periods were similar across the two treatment groups with no clinically significant differences between them.

Tacrolimus, similar to the other CNIs decreases GFR due to its vasoconstrictive properties. Since the active moiety (tacrolimus) is the same in both the LCP-Tacro and the Prograf groups any differences in GFR if observed would be either the consequence of baseline differences or the differences in exposure to tacrolimus. Since the baseline measurements were similar and no significant differences were observed it may be concluded that the tacrolimus exposure were roughly similar in both groups in both Study 3002 and Study 3001 but it is important to note that the baseline values in the de novo Study 3002 are the values measured on Day 30 after transplantation. Therefore the eGFR values in Study 3002 do not reflect the tacrolimus exposure before Day 30.

In the Phase 2 Study 2017 there was approximately a difference of 7ml/min at baseline across the treatment groups which was maintained till the end of the study suggesting that the tacrolimus exposure in both treatment groups were similar as in the other two Phase 3 studies.

7.3.5 Submission Specific Primary Safety Concerns

Among the Cardiac Exclusion Criteria in the de novo Study 3002 were:

- Screening 12-lead electrocardiogram (ECG) demonstrating clinically relevant abnormalities (including QTc prolongation, reversible ischemia and clinically symptomatic congestive heart failure or documented ejection fraction of less than 45%)
- Patients with reversible cardiac ischemia (history of untreated reversible ischemia on stress test)
- Patients with clinically symptomatic congestive heart failure or documented ejection fraction of less than 45%

Similar cardiac exclusion criteria were not applied in the conversion Study 3001.

Clinical Reviewer's Comment
Chronic kidney disease is a major risk factor for the development of cardiovascular complications and cardiovascular disease is the leading cause of morbidity and mortality in chronic kidney disease (CKD) patients.[10,11] QTc prolongation on a 12-lead ECG is a common and independent predictor of mortality in ESRD patients being evaluated for renal transplantation.[5] In a study population from the University of Alabama consisting of 280 ESRD patients who were evaluated for possible renal transplantation the QTc was prolonged in 108 (39%) patients.[5] In the same study the mean LVEF (left ventricular ejection fraction) was found to be 47±12. According to the authors of the same study QTc prolongation is an independent predictor of mortality in ESRD patients being evaluated for renal transplantation and the prognostic information gained from the QTc is additive to that provided by the LVEF and the severity of coronary artery disease.

As stated in the Warnings and Precautions section (5.14) of the Prograf package insert tacrolimus may prolong the QT/QTc (corrected QT) interval and may cause Torsade de Pointes.

As specified in the exclusion criteria of Study 3002 patients with QTc prolongation and patients with ejection fraction of less than 45% were excluded. In Study 3002 the mean QT (uncorrected) values at baseline are 372 msec (milliseconds) in the LCP-Tacro group and 380 msec in the Prograf group. These values are lower than the mean QTc values observed in the published study from the University of Alabama which were 427 msec on average in the remaining 172 patients after excluding the 108 patients who had very prolonged QTc values. This substantial difference between the mean QT values in Study 3002 and the published Alabama University study raises the question of

10 Bellasi and Iorio. QT interval in CKD and haemodialysis patients. Clin Kidney J (2013) 0: 1–7
11 Iskandrian et al. QT Prolongation Is an Independent Predictor of Mortality in End-Stage Renal Disease. Clin. Cardiol. 33, 6, 361–366 (2010)

applicability of the Study 3002 safety findings to a general US kidney transplant patient population and needs to be considered in labeling. In addition to excluding patients with prolonged QT values patients with LVEFs less than 45% were also excluded. The mean LVEF in the published Alabama University study was 47%. Therefore it is likely that the selected population in Study 3002 is a lower cardiac risk population compared to the general transplant candidate population in US.

As explained in the Clinical Pharmacology Review by Gerlie Gieser and the relevant sections of this review the starting dose of 0.17 mg/kg/day in the LCP-Tacro group of Study 3002 did not result in unacceptable safety events despite the initial higher tacrolimus exposure and higher than protocol specified target trough levels during the early post-transplant period but this may not have been the case if highly selective cardiac exclusion criteria mentioned above were not utilized in the selection of the study population. Therefore in the decision to select the optimum starting dose of LCP-Tacrolimus the nature of the study population needs to be considered and the starting dose should be decided with consideration that kidney transplant patients with pre-existing cardiac disease including long QTc and low LVEF values may be prescribed LCP-Tacrolimus. Therefore I recommend that a more conservative initial starting dose for LCP-Tacrolimus be considered instead of the 0.17 mg/kg/day in Study 3002.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

7.4.1.1 Common Adverse Events in Study 3002

A summary of the TEAEs occurring in 5% or more of patients in any treatment group by SOC and preferred term for the ITT set is presented in Table 50. The incidence of TEAEs was similar between the 2 treatment groups; 260 (97.0%) patients in the LCP-Tacro group and 269 (97.8%) patients in the Prograf group.

The SOCs in which TEAEs were reported in more than half of all patients were: infections and infestations (67.4%), metabolism and nutrition disorders (68.4%), and GI disorders (62.4%). Preferred terms experienced by 20% or more of all patients were: diarrhea (32.0%), anemia (27.4%), urinary tract infection (24.5%), hypertension (22.8%), and constipation (21.4%). The only preferred term which occurred in a notably greater proportion of patients (ie, ≥5%) in the LCP-Tacro group compared with the Prograf group was headache (14.6% vs 9.5%).

Table 50. Treatment-Emergent Adverse Events Occurring in 5% or More of Patients in Any Treatment Group in Study 3002 (ITT Set)

(Source: Table 12-7, page 136 of the CSR)

Note: Cardiac disorders occurring in 4 or more patients in each group are included in the table by the Reviewer because of importance despite the incidence rates of each cardiac PT is below 5%

System Organ Class Preferred Term	LCP-Tacro (N=268)	Prograf (N=275)
Total number of TEAEs	3128	3214
Number of patients with ≥1 TEAE	260 (97.0)	269 (97.8)
Blood and lymphatic system disorders	117 (43.7)	132 (48.0)
Anaemia	70 (26.1)	79 (28.7)
Leukopenia	36 (13.4)	38 (13.8)
Polycythaemia	13 (4.9)	14 (5.1)
Cardiac Disorders	29 (10.8)	35 (12.7%)
Tachycardia	10 (3.7)	9 (3.3)
Atrial Fibrillation	4 (1.5)	6 (2.2)
Angina Pectoris	4 (1.5)	4 (1.5)
Gastrointestinal disorders	166 (61.9)	173 (62.9)
Diarrhoea	82 (30.6)	92 (33.5)
Constipation	49 (18.3)	67 (24.4)
Nausea	35 (13.1)	41 (14.9)
Abdominal pain	21 (7.8)	32 (11.6)
Vomiting	15 (5.6)	24 (8.7)
Dyspepsia	18 (6.7)	16 (5.8)
General disorders and administration site conditions	101 (37.7)	104 (37.8)
Oedema peripheral	42 (15.7)	57 (20.7)
Pyrexia	22 (8.2)	15 (5.5)
Immune system disorders	37 (13.8)	38 (13.8)
Kidney transplant rejection	25 (9.3)	30 (10.9)
Infections and infestations	188 (70.1)	178 (64.7)
Urinary tract infection	66 (24.6)	67 (24.4)
BK virus infection	16 (6.0)	25 (9.1)
Upper respiratory tract infection	23 (8.6)	14 (5.1)
Cytomegalovirus infection	19 (7.1)	16 (5.8)
Nasopharyngitis	16 (6.0)	11 (4.0)
Bronchitis	14 (5.2)	9 (3.3)
Injury, poisoning, and procedural complications	118 (44.0)	112 (40.7)
Complications of transplanted kidney	19 (7.1)	30 (10.9)
Wound complication	20 (7.5)	18 (6.5)
Procedural pain	13 (4.9)	18 (6.5)
Investigations	82 (30.6)	91 (33.1)
Blood creatinine increased	32 (11.9)	37 (13.5)
Weight increased	17 (6.3)	19 (6.9)
Metabolism and nutrition disorders	184 (68.7)	187 (68.0)

Diabetes mellitus	44 (16.4)	37 (13.5)
Hypophosphataemia	36 (13.4)	42 (15.3)
Hyperkalaemia	40 (14.9)	30 (10.9)
Hypokalaemia	32 (11.9)	33 (12.0)
Hypomagnesaemia	32 (11.9)	32 (11.6)
Hyperglycaemia	29 (10.8)	33 (12.0)
Hypocalcaemia	20 (7.5)	24 (8.7)
Vitamin D deficiency	21 (7.8)	20 (7.3)
Metabolic acidosis	22 (8.2)	14 (5.1)
Dyslipidaemia	17 (6.3)	15 (5.5)
Hypercholesterolaemia	13 (4.9)	15 (5.5)
Hyperuricaemia	10 (3.7)	16 (5.8)
Hypertriglyceridaemia	11 (4.1)	14 (5.1)
Musculoskeletal and connective tissue disorders	73 (27.2)	70 (25.5)
Back pain	19 (7.1)	18 (6.5)
Muscle spasms	12 (4.5)	15 (5.5)
Nervous system disorders	98 (36.6)	83 (30.2)
Tremor	51 (19.0)	46 (16.7)
Headache	39 (14.6)	26 (9.5)
Dizziness	14 (5.2)	14 (5.1)
Psychiatric disorders	72 (26.9)	59 (21.5)
Insomnia	35 (13.1)	29 (10.5)
Anxiety	20 (7.5)	22 (8.0)
Renal and urinary disorders	113 (42.2)	115 (41.8)
Renal impairment	20 (7.5)	25 (9.1)
Dysuria	19 (7.1)	14 (5.1)
Proteinuria	13 (4.9)	18 (6.5)
Haematuria	14 (5.2)	13 (4.7)
Respiratory, thoracic, and mediastinal disorders	55 (20.5)	64 (23.3)
Cough	20 (7.5)	26 (9.5)
Dyspnoea	7 (2.6)	20 (7.3)
Skin and subcutaneous tissue disorders	61 (22.8)	71 (25.8)
Acne	15 (5.6)	15 (5.5)
Alopecia	12 (4.5)	18 (6.5)
Vascular disorders	101 (37.7)	105 (38.2)
Hypertension	62 (23.1)	62 (22.5)
Hypotension	18 (6.7)	13 (4.7)
Lymphocele	6 (2.2)	15 (5.5)

7.4.1.2 Common Adverse Events in Study 3001

The incidence of TEAEs was similar between the two treatment groups. Overall, 268 (82.7%) patients experienced TEAEs, 135 (83.3%) patients in the LCP-Tacro group and 133 (82.1%) patients in the Prograf treatment group (Table 51). The most frequently reported TEAEs (reported in 5% or more of patients overall) included diarrhea (11.4%), urinary tract infection (UTI) (11.1%), increased blood creatinine (10.5%),

nasopharyngitis (10.2%), headache (8.0%), upper respiratory tract infection (8.0%), peripheral edema (6.5%) and hypertension (5.2%). The incidence of these individual AE preferred terms was similar in both treatment groups.

Table 51. Treatment-Emergent Adverse Events Occurring in 5% or More of Patients in Any Treatment Group in Study 3001 (ITT Set)
(Source: Table 11-3, page 99 of CSR)

Preferred Term	LCP-Tacro n=162	Prograf n=162	Total N=324
All TEAEs	135 (83.3%)	133 (82.1%)	268 (82.7%)
Diarrhoea	22 (13.6%)	15 (9.3%)	37 (11.4%)
Urinary tract infection	14 (8.6%)	22 (13.6%)	36 (11.1%)
Blood creatinine increased	20 (12.3%)	14 (8.6%)	34 (10.5%)
Nasopharyngitis	15 (9.3%)	18 (11.1%)	33 (10.2%)
Headache	15 (9.3%)	11 (6.8%)	26 (8.0%)
Upper respiratory tract infection	12 (7.4%)	14 (8.6%)	26 (8.0%)
Oedema peripheral	11 (6.8%)	10 (6.2%)	21 (6.5%)
Hypertension	7 (4.3%)	10 (6.2%)	17 (5.2%)

Clinical Reviewer's Comment
In both the Study 3002 and Study 3001 adverse events are balanced across the treatment groups in general. The types and rates of adverse events are as expected from the respective de novo and stable kidney transplant patient populations.

7.4.1.3 Common Adverse Events in the Phase 2 Study 2017

All 32 patients in the LCP-Tacro, group and 30 of the 31 patients in the Prograf group experienced an AE. AEs in different SOCs were balanced across the treatment groups (Table 52).

Table 52. Adverse Events by Preferred Term Occurring in ≥15% of Patients Overall - Study 2017
(Source: Table 20, page 59 of the CSR)

Preferred Term	LCP-Tacro (N=32)	Prograf (N=31)
All adverse events	32 (100.0%)	30 (96.8%)
Diarrhoea	16 (50.0%)	17 (54.8%)
Nausea	14 (43.8%)	17 (54.8%)
Constipation	15 (46.9%)	14 (45.2%)
Anaemia	13 (40.6%)	14 (45.2%)

Urinary tract infection	12 (37.5%)	12 (38.7%)
Hypomagnesaemia	11 (34.4%)	9 (29.0%)
Oedema peripheral	9 (28.1%)	10 (32.3%)
Hypertension	10 (31.3%)	8 (25.8%)
Insomnia	11 (34.4%)	6 (19.4%)
Hypophosphataemia	10 (31.3%)	7 (22.6%)
Vomiting	10 (31.3%)	7 (22.6%)
Leukopenia	9 (28.1%)	8 (25.8%)
Blood creatinine increased	8 (25.0%)	7 (22.6%)
Hyperkalaemia	5 (15.6%)	6 (19.4%)
Procedural pain	7 (21.9%)	6 (19.4%)
Diabetes mellitus	7 (21.9%)	5 (16.1%)
Pyrexia	5 (15.6%)	6 (19.4%)
Upper respiratory tract infection	5 (15.6%)	6 (19.4%)
Hyperglycaemia	5 (15.6%)	6 (19.4%)
Hyperlipidemia	6 (18.8%)	5 (16.1%)
Tremor	6 (18.8%)	5 (16.1%)
Haematuria	5 (15.6%)	5 (16.1%)
Hypokalaemia	4 (12.5%)	6 (19.4%)

7.4.2 Laboratory Findings

7.4.2.1 Hematology in Study 3002

Mean change from baseline in hematocrit (Hct) level was smaller for the LCP-Tacro group compared with the Prograf group throughout the treatment period, except at Week 3 when the levels were similar for the treatment groups and at Days 7 and 10, Week 2, and 1 month when the levels were higher for the LCP-Tacro group. Mean CFB in hemoglobin level was smaller for the LCP-Tacro group compared with the Prograf group throughout the treatment period, except at Days 7 and 10, Weeks 2 and 3, and 1 month when the levels were higher for the LCP-Tacro group. There were no notable trends in hematology laboratory results over time.

7.4.2.2 Hematology in Study 3001

There were no notable differences in hematology laboratory values between the treatment groups over time.

7.4.2.3 Hematology in the Phase 2 Study 2017

There were no notable differences in hematology laboratory values between the treatment groups over time.

7.4.2.3 Serum Chemistry in Study 3002

Mean change from baseline in bicarbonate level was greater at Day 7, Week 3, and Months 1, 3, 4, and 9 for the LCP-Tacro group compared with the Prograf group but otherwise similar. Mean change from baseline in BUN level was smaller for the LCP-Tacro group compared with the Prograf group throughout the treatment period, except at Month 3. Mean change from baseline in chloride level was smaller for the LCP-Tacro group compared with the Prograf group throughout the treatment period, except for Day 7 and Months 1.5 and 2 when the mean change from baseline was similar and at Day 10 when it was higher. Mean change from baseline in calcium level was similar for both treatment groups throughout the study period. Mean change from baseline in creatinine, FPG, and phosphorus levels were smaller for the LCP-Tacro group compared with the Prograf group throughout the treatment period. Mean change from baseline in HbA1c level was smaller at Months 3, 4, 9, and 12, similar at Week 3 and Month 1, and greater at Months 1.5, 2, and 6 for the LCP-Tacro group compared with the Prograf group throughout the treatment period. Mean change from baseline in potassium level was similar at most study visits but slightly lower at Days 7 and 10 and slightly greater at Weeks 2 and 3, and Months 1, 3, and 12 for the LCP-Tacro group compared with the Prograf group throughout treatment period. Mean change from baseline in sodium level was higher for the LCP-Tacro group compared with the Prograf group throughout treatment period, except at Months 6 and 9 when the levels where similar for both treatment groups. There were no notable trends in serum chemistry laboratory results over time.

7.4.2.4 Serum Chemistry in Study 3001

Mean changes from baseline in chemistry parameters were similar in both treatment groups. There were no notable trends in serum chemistry laboratory results over time.

7.4.2.5 Serum Chemistry in the Phase 2 Study 2017

Mean changes from baseline in chemistry parameters were similar in both treatment groups. There were no notable trends in serum chemistry laboratory results over time.

7.4.2.5 Hepatic Profile in Study 3002

Mean CFB in albumin levels were similar in both treatment groups. Mean CFB in alanine aminotransferase, aspartate aminotransferase, direct bilirubin, and gamma-glutamyltransferase levels were lowerat Months 1, 6, and 12 for the LCP-Tacro group compared with the Prograf group. Mean CFB in ALP levels were higher at Month 1 but lower at Months 6 and 12 for the LCP-Tacro group compared with the Prograf group. Mean CFB in indirect bilirubin levels were similar at Month 1, lower at Month 6, and higher at Month 12 for the LCP-Tacro group compared with the Prograf group. Mean CFB in total bilirubin levels were lower at Months 1 and 6 but higher at Month 12 for the

LCP-Tacro group compared with the Prograf group. There were no notable trends in hepatic profile laboratory results over time.

7.4.2.6 Hepatic Profile in Study 3001

Mean changes from baseline in hepatic profile laboratory parameters were similar in both treatment groups. There were no notable trends in hepatic profile laboratory results over time.

7.4.2.7 Hepatic Profile in Study 2017

Mean changes from baseline in hepatic profile laboratory parameters were similar in both treatment groups. There were no notable trends in hepatic profile laboratory results over time.

7.4.2.7 Fasting Lipid Profile in Study 3002

Mean CFB values in HDL, LDL, total cholesterol, and triglyceride levels were lower for the LCP-Tacro group compared with the Prograf group at Months 6 and 12. However, there were no notable changes in mean CFB in fasting lipid profile results over time for either treatment group. Fasting lipid profile categorical value results (low, normal, high) are summarized by visit in Table 14.3.13.2. Although the percentage of subjects with high HDL, LDL, total cholesterol, and triglyceride levels was higher at Months 6 and 12 compared with baseline, this difference was similar for both treatment groups.

7.4.2.8 Fasting Lipid Profile in Study 3001

Mean changes from baseline in fasting lipid profile laboratory parameters were similar in both treatment groups. There were no notable trends over time.

7.4.2.9 Fasting Lipid Profile in Study 2017

Mean changes from baseline in fasting lipid profile laboratory parameters were similar in both treatment groups. There were no notable trends over time.

7.4.2.9 Urinalysis in Study 3002

At baseline, mean urinalysis pH values were lower for the LCP-Tacro group compared with the Prograf group. Mean change from baseline in urinalysis pH values were lower for the LCP-Tacro group compared with the Prograf group throughout the treatment period, except at Day 7. However, there were no notable changes in mean urinalysis pH values or other urinalysis values over time for either treatment group.

7.4.2.10 Urinalysis in Study 3001

Urinalysis values were similar in both treatment groups and there were no notable trends over time.

7.4.2.11 Urinalysis in Study 2017

Urinalysis values were similar in both treatment groups and there were no notable trends over time.

7.4.3 Vital Signs

7.4.3.1 Vital Signs in Study 3002

Overall, mean changes from baseline in vital sign measurements were similar in both treatment groups with no notable trends over time.

7.4.3.2 Vital Signs in Study 3001

Mean changes from baseline in vital signs measurements were similar in both treatment groups with no notable trends over time.

7.4.3.3 Vital Signs in Study 2017

Mean changes from baseline in vital signs measurements were similar in both treatment groups with no notable trends over time.

7.4.4 Electrocardiograms

Reviewer's Note:
QT Prolongation[12]:
Despite long-standing recognition of the variability of the QTc (QT corrected for the heart rate) among healthy individuals, attempts have been made to define an upper limit of normal. The European regulatory body, the Committee for Proprietary Medicinal Products, has suggested upper limits of normal of 450 mille seconds (ms) for adult men and 470 ms for adult women. Although the precise relationship between the extent of QTc prolongation and the risk of sudden death is unknown, and it is recognized that an absolute threshold of risk for torsade de pointes (TdP) cannot be proved, it is evident that almost all reported cases of TdP have occurred in individuals with a measured uncorrected QT exceeding 500 ms. Consequently, values of QT greater than 500 ms should cause concern.

7.4.4.1 Electrocardiograms in Study 3002

There were no clinically relevant changes in any of the electrocardiogram (ECG) parameters. No patient had an absolute QT interval (uncorrected) of greater than 495

12 Peter R. Kowey and Marek Malik, The QT interval as it relates to the safety of non-cardiac drugs. European Heart Journal Supplements (2007) 9 (Supplement G), G3 – G8

msec post baseline (Table 53). There was no evidence of PR interval, QRS complex, or QT interval prolongation and no significant change from baseline for ECG parameters in either treatment group.

Table 53. QT Interval (uncorrected) and Change from Baseline - Study 3002
(Source: Table 14.3.17.1, page 880 of CSR)

		LCP-Tacro (N=268)		Prograf (N=275)	
Visit	**Statistics**	**Result at Visit**	**Change from Baseline**	**Result at Visit**	**Change from Baseline**
Baseline	N Mean (SE) SD Min, Max Median	245 372.2 (5.74) 89.80 0, 920 380.0		258 380.5 (4.23) 67.97 0, 540 388.0	
6 Months	N Mean (SE) SD Min, Max Median	182 371.1 (2.68) 36.10 280, 462 370.0	171 -12.2 (6.24) 81.59 -56-, 352 -12.0	192 371.3 (3.42) 47.38 170, 488 374.0	185 -12.8 (4.27) 58.14 -248, 320 -14.0
12 Months	N Mean (SE) SD Min, Max Median	194 368.3 (3.87) 53.93 37, 462 378.0	180 -7.6 (7.11) 95.45 -580, 362 -6.0	200 376.2 (3.41) 48.17 40, 495 381.0	194 -3.1 (4.36) 60.75 -160, 356 -4.0

Clinical Reviewer's Comment
Twelve-lead electrocardiogram (ECG) was performed at baseline and at Months 6, 12, 18, and 24. Therefore any transient ECG changes that might have occurred during the early posttransplant period due to high tacrolimus exposure in some patients are not captured in these ECGs.

7.4.4.2 Electrocardiograms in Study 3001

Similar to Study 3002, twelve-lead electrocardiograms (ECG) was performed at baseline and at Months 6, 12, 18, and 24. Mean changes from baseline in ECG results were similar in both treatment groups. There were no clinically relevant changes in any of the ECG parameters. No patient had an increase in QT interval (uncorrected) of >494 msec or an absolute QT interval (uncorrected) of >492 msec during the study.

7.4.4.3 Electrocardiograms in Study 2017

Twelve-lead electrocardiograms were performed at baseline, day 14 and at Months 6 and 12. Only one patient (LCP-Tacro group) had an absolute QT interval (uncorrected) of greater than 500 msec (504 msec) post baseline on day 360.

7.4.5 Special Safety Studies/Clinical Trials

The Applicant conducted one special safety study entitled LCP-Tacro 3003: Switching study of kidney transplant patients with tremor to LCP-Tacro (STRATO), to demonstrate that switching to the LCP-Tacro extended release formulation from the tacrolimus immediate release formulation is beneficial in reducing hand tremor in stable kidney transplant patients who had hand tremor at the time of the switch. The Applicant included the results of Study LCP-Tacro 3003 in the current NDA submission in support of their orphan exclusivity request as will be explained in this section of the review.

Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), orphan-drug designation was granted to the active moiety (tacrolimus) of LCP-Tacrolimus extended release tablets by the FDA for the prophylaxis of organ rejection in patients receiving allogeneic kidney transplant on December 20, 2013. Orphan designation was based on a plausible hypothesis that LCP-Tacrolimus extended release tablets may be clinically superior to the same drug that is already approved for the same orphan indication (Prograf and generics).

In order to obtain orphan-drug exclusivity upon approval, the Applicant needs to demonstrate that LCP-Tacrolimus extended release tablets are clinically superior to the already approved same drug (and any other versions of the same drug approved for the same orphan indication).

In the current NDA submission, in support of clinical superiority of the LCP-Tacrolimus extended release tablets over any other tacrolimus product approved for the same indication, the Applicant is claiming two different types of benefits:

1. An increase in oral absorption from LCP-Tacrolimus tablets resulting in a clinical necessity to administer lower doses to achieve the same target blood levels with other formulations.

2. As demonstrated in the controlled clinical trial LCP-Tacro Study 3003 a highly statistically significant reduction in tremors has been observed in kidney transplant patients who switched from traditional tacrolimus therapy to LCP-tacrolimus extended release tablets. These improvements in tremor were accompanied by a significant improvement in quality of life and positive scores in both patient and physician global assessments.

Study LCP-Tacro 3003 results are included in the current NDA submission to support the Applicant's clinical superiority claim for the LCP-tacrolimus extended release tablets. Regulatory history, study design and the results will be briefly reviewed with focus on the adequacy of study design to support the clinical superiority claim.

7.4.5.1 Rationale for the Study LCP-Tacro 3003: Switching study of kidney transplant patients with tremor to LCP-Tacro (STRATO)

Neurotoxicity in transplant patients occurs in >40-50% of the patients treated with tacrolimus.[13] The majority of the neurotoxicity events in tacrolimus treated transplant patients are headache and tremor, while less frequent and more severe neurotoxicity (encephalopathy, seizures) is also observed.[14] The current management of neurotoxicity varies by investigator and institution, but normally begins with a dose reduction of the tacrolimus, balancing increased risk of acute rejection and graft loss with the desire to improve the side effects observed for a given patient.[15,16] In more severe cases, immunosuppressant regimens may be changed from tacrolimus to cyclosporine, which also is associated with similar neurotoxicity. Information in the literature in transplant patients as well as those with autoimmune diseases suggests that neurotoxicity is reversible upon discontinuation of tacrolimus.[17]

Study 3003 was conducted in order to assess the potential benefit of LCP-Tacro over immediate-release tacrolimus on the neurological side effect of tremor. The Applicant's hypothesis was that there will be fewer tremors seen with LCP-Tacro than with immediate-release tacrolimus, presumably due to the lower anticipated Cmax with the extended-release formulation,

7.4.5.2 Regulatory History of Study LCP-Tacro 3003:

On September 16, 2011, the sponsor submitted the clinical protocol LCP Tacro 3003 under IND 75-250 in which they proposed to evaluate the incidence of tremor in patients (with baseline hand tremor at enrollment) who receive LCP-Tacro compared to immediate-release tacrolimus (Prograf or generics) in a cross-over study and they proposed to evaluate the outcome using a number of neurologic scales and measures.

Study 3003 was designed as a a two-sequence, open-label study. As proposed by the Applicant, from Days 1 through 7, patients would continue on their pre-study twice daily regimen of Prograf or generic tacrolimus. At Day 8, subjects would be switched to once-daily LCP-Tacro for a total of 7 days (Days 8 to 14). Patients would be followed for safety information until Day 30. Tacrolimus trough level on Days 7 and 14 would be within the target range of 3-12 ng/mL. Patients would be allowed to receive one LCP-Tacro dose adjustment on Day 11 to achieve trough concentrations in the target range

13 Prograf® (package insert). Astellas Phanna US, Inc. Deerfield (IL); July 2011
14 Wijdicks EFM, Weisner RH, Dahlke LJ, Krom RAF. FK5 06-induced neurotoxicity in liver transplantation. Ann Neurol 1994;35:498-501.
15 Appignani B, Bhadelia R, Blacklow S, Wang A, Roland S, Freeman R. Neuroimaging findings in patients on immunosuppressive therapy: experience with tacrolimus toxicity. Am J Roentgenol 1996; 166: 683-688.
16 Reinohs M, Straube T, Baum P, Berrouschot J, Wagner A. Recurrent reversible cerebral edema after long term immunosuppression with tacrolimus. J Neurol 2002;249:780-781.
17 Bechstein WO. Neurotoxicity of calcineurin inhibitors: impact and clinical management. Transpl Int 2000; 13:3:1-326.

of 3-12 ng/mL. Patients would continue use of all other immunosuppressant medications including mycophenolate mofetil (MMF), mycophenolate sodium (MPS), and/or prednisone or equivalent (<10 mg/day) that they have been using.

Approximately 70 adult kidney transplant recipients (who received their transplant between one month and 5 years ago) would be enrolled. Patients who are currently on stable doses of immediate-release tacrolimus (Prograf brand or generic) with baseline hand tremor would serve as their own controls by switching to LCP-Tacro for 7 days before being re-evaluated for tremor.

For those patients who qualify for extended use of LCP-Tacro, based on the discretion of the physician and the patient, they would be offered a supply of LCP-Tacro for an additional two years beginning on Day 15.

Proposed primary efficacy endpoint was the mean change from baseline (i.e. Day 7) in the Fahn-Tolosa-Marin (FTM) clinical rating scale for overall tremor score 7 days after LCP-Tacro conversion (i.e., Day 14).

FDA reviewed the protocol and sent comments to the Applicant in two separate letters dated October 18, 2011 and December 20, 2011. FDA October 18, 2011 letter contained specific comments on the design of LCP-Tacro 3003 and the changes to be made so that the study (b) (4) and the December 20, 2011 letter contained recommendations from the Division of Neurology Products (DNP) which was consulted for this protocol.

In this NDA review only the most important comments from these two FDA letters directly related to the study design are included (below) with original comment numbers as in the letters. For full set of comments see the original letters in DARRTS.

<u>FDA Comments Specific to Protocol LCP-Tacro 3003 design in the October 18, 2011 Letter:</u>

Currently, this clinical trial is not considered to be designed in such a way to support (b) (4) (b) (4) We are providing the following recommendations on how the trial can be redesigned to collect more usable information.

We have also consulted the Division of Neurology Products regarding your proposed study design, eligibility criteria, measures used to evaluate tremor, and the clinical relevance of a 6 point change in tremor using the Fahn-Tolosa-Marin (FTM) rating scale. We will provide additional comments to you once the consult review is complete.

4. This is an open-label, non-randomized trial. Such a study design is prone to biases and will not lead to any reliable results that could potentially be used for any labeling claim. Therefore, we recommend changing the trial design to include a control group and use a double-blind, double-dummy approach. Two alternative potential trial designs include:

• a parallel design where patients would be randomized to continue Prograf/generic tacrolimus or to switch to LCP-Tacro.

• a two-sequence, two-period crossover study where patients would be randomized to one of two sequences, to either continue Prograf/generic tacrolimus or to switch to LCP-Tacro in the first period and then switch to the other treatment during the second period.

The primary efficacy endpoint is the mean change from baseline (i.e. Day 7) in the Fahn-Tolosa-Marin (FTM) clinical rating scale for overall tremor score 7 days after LCP-Tacro conversion (i.e., Day 14). We consider the timing of this assessment to be too early. The half-life of LCP-Tacro is 30 hours so the time to reach steady state is about 7 days, assuming no dosage adjustments are needed following conversion from Prograf on Day 7. We also note that according to the protocol patients are allowed to receive one LCP-Tacro dose adjustment on Day 11 to achieve trough concentrations in the therapeutic range (i.e., 3-12 ng/mL for this study).

We recommend you extend the duration of study treatment and follow-up to 6 months and include repeat assessments of tremor and monitor for episodes of acute rejection following conversion.

8. In the Prograf US Package Insert, the observed tacrolimus whole blood trough concentration range was 4-11 ng/mL for the first 12 months of receiving Prograf orally with MMF and an IL-2 receptor antagonist in a large trial of adult kidney transplant patients. In the study protocol, please provide the justification or rationale for your proposal to maintain Prograf and LCP-Tacro patients in this study at target tacrolimus trough concentrations of 3-12 ng/mL. Additionally, please clarify in the study protocol what you mean by allowing a one-time dose adjustment of LCP-Tacro at the latest on Day 11 should it be "found incidentally" that the subject has an out-of-range trough level.

11. You indicated that the peak whole blood concentrations of tacrolimus influence the neurotoxicity potential of tacrolimus. We agree with your proposal to perform tremor assessments at 2 hours ± 15 minutes after the dose of Prograf and generic tacrolimus tablets, given that the Tmax of Prograf immediate-release tablets is approximately 2 hours. However, in consideration of the Tmax (approximately 6 hours) of LCP-Tacro extended release tablets, we recommend that the tremor assessments on protocol specified visits be done at 6 hours ± 15 minutes instead of at 2 hours ± 15 minutes after the dose of LCP-Tacro.

12. In your sample size calculation, the sample size is increased with the assumption that 15% of subjects will have a trough tacrolimus concentration that falls outside of therapeutic range of 3 to 12 ng/mL (either Day 7 or Day 14) and that another 10% dropout due to reasons unrelated to trough concentration. Please note that we have concerns about excluding subjects based on post-randomization information as it might bias the overall results of the study. Sensitivity analyses could take into account whether or not subjects reached trough levels. Note that interpretation of even a controlled trial might be difficult if there is an imbalance in the percent of subjects within target trough levels. Please make sure that your protocol is clear as to who will be included or excluded in all analysis populations.

Comments Regarding Final Study Report for LCP-Tacro 3003

14. In the final study report, we recommend that you include a comparison of the descriptive statistics of the observed tacrolimus trough concentrations, by tacrolimus formulation (immediate-release versus extended release LCP-Tacro), and explore the relationship between tacrolimus trough concentrations and tremor scores.

FDA December 20, 2011 Letter containing DNP Comments on Protocol LCP-Tacro 3003:

We have the following comments/requests based on our consultation with DNP:

1. The inclusion criteria allow men and women between 18 and 65 years of age who are recipients of a kidney transplant between 1 month and 5 years prior to the screening date to be enrolled. The inclusion criteria should be modified to only allow patients who are at least 6 months post-transplant into the study. Before this time point their medications and dosage regimens are changing and they are not considered to be "stable" patients eligible for conversion.

2. The inclusion criteria specify "Subjects with at least one complaint of tremor and existence of postural tremor or action tremor on finger to nose as demonstrated by a score of at least 2 on any of the 4 upper extremity postural or action and intention assessments on the FTM [Fahn-Tolosa-Marin] clinical rating scale." We recommend the inclusion criteria be changed to only allow inclusion of patients with a tremor severity considered to be disabling to the subject, as measured by a FTM score of >2 (moderate to severe) in dominant hand (Part A). This will ensure that patients have clinically meaningful tremor severity. In addition, Part B of the FTM Scale is weighted towards evaluation of tremor affecting upper limb function (writing).

3. Since tremor can be caused by a variety of factors, the inclusion/exclusion criteria should limit inclusion to patients with tremor due to tacrolimus and exclude those with other neurologic co-morbidities (e.g., Essential Tremor, Parkinson's disease, uremia).

4. We recommend the following assessments during the study:

- Clinical and accelerometry measurements (using the Tremorometer) should be repeated periodically once steady state with tacrolimus is achieved.

- Clinical rating scales and accelerometry measurements (using the Tremorometer) should be obtained before blood samples are drawn at pre-dose and at Tmax. Given the different times to tacrolimus Cmax of LCP-Tacro and immediate release tacrolimus, we recommend that you perform these clinical measurements at both 2 hours and 6 hours post-dose in all patients in both treatment arms of the study, in addition to pre-dose. Several baseline and on treatment measurements of tremor should be taken within the same day and on different days using the Tremorometer; and the average of these measurements should be used for the analysis in order to minimize the effects of within subject variability and also avoid regression to the mean.

5. In your IND submission you note it is assumed that tremors associated with tacrolimus are most pronounced at Tmax and that increases in tremor are reported in patients with "toxic levels" of tacrolimus. However, the PK/PD relationship between tacrolimus and tremor has not been well

established. We recommend you collect data in the study to demonstrate that tremor severity is associated with the Cmax of tacrolimus within the therapeutic range of plasma concentrations. A PK/PD analysis of tremor severity (amplitude and disability) related to plasma concentration (i.e., Cmax, Cmin) should be incorporated into the protocol. In the final study report, you should submit an analysis of individual plots of tremor severity versus tacrolimus plasma concentrations, in addition to plots of the mean and median plasma concentrations and tremor severity.

6. The primary efficacy endpoint in the study is the mean change from baseline in the FTM clinical rating scale for overall tremor and your proposed responder criterion is a reduction in the FTM of greater than 5 points (i.e., representing a clinically meaningful change). We recommend you change the primary endpoint to a co-primary endpoint based upon a clinically meaningful change in scores in the FTM and the Patient Global Impression Evaluation (PGI-I). In order to consider the trial successful, a two-sided alpha level of 0.05 on both the FTM and PGI-I scores for the difference between the treatment groups would have to be met. We do not agree with your responder criterion (reduction in FTM > 5 points) as the data used to support that threshold is considered to be of poor quality. The concept of the minimally important difference on any clinical rating scale, such as the FTM, is typically anchored by a certain level of improvement on a global measure. Therefore, the threshold for considering the observed change on the FTM as meeting the criteria for being clinically meaningful should be at least slightly improved and perhaps even moderately improved on the PGI-I. Finally, we would also expect that the accelerometry data would go in the same direction as the FTM scale.

7. Quality of life assessed by the Quality of Life in Essential Tremor (QUEST) score is a secondary endpoint in the study. We would like to comment that the QUEST is designed to evaluate patients with essential tremor (ET) and many of the items in the QUEST may not be relevant to kidney transplant patients receiving tacrolimus. ET patients are generally > 65 years of age and may have fewer co-morbid illnesses than transplant patients. In addition, several of the QUEST items relate to disability caused by vocal or head/neck tremor, which is not reported to be associated with tacrolimus-induced tremor.

8. Measurements using the tremorometer will also be used as a secondary efficacy endpoint. We agree that the parameters measured by the device are acceptable, but you should also conduct a power analysis. Power calculations in tremor measurement are a standard analysis measuring the tremor amplitude within a designated frequency band, typically the peak frequency band. There are publications of accelerometry protocols in tremor that describe how to perform power calculations.

9. We previously mentioned that you should consider alternative trial designs and suggested either:

- a parallel design where patients would be randomized to continue Prograf/generic tacrolimus or to switch to LCP-Tacro.

- a two-sequence, two-period crossover study where patients would be randomized to one of two sequences, to either continue Prograf/generic tacrolimus or to switch to LCP-Tacro in the first period and then switch to the other treatment during the second period. Of the two designs we believe that a parallel design may be more appropriate. Patients who experience disabling tremor (as described above) on tacrolimus would be randomized to continue their tacrolimus or to switch to LCP-Tacro and assessed for a

clinically meaningful improvement in tremor using the PGI-I and FTM (as discussed above).

10. We previously commented to you that the current study duration is too short and patients should be assessed for clinical outcome, including acute rejection, in addition to tremor. Demonstration of less tremor cannot be considered a positive outcome if it is associated with an increased risk for acute rejection. Therefore, we continue to recommend a 6-month treatment duration with assessments for acute rejection, in addition to tremor.

10. A claim that LCP-Tacro is associated with reduced tremor compared to immediate-release tacrolimus is a comparative (i.e., superiority) claim. To support (b) (4)

7.4.5.3 Synopsis of the Study LCP-Tacro 3003 Design and Results:

The Applicant did not respond to the comments in the FDA letters dated October 18, 2011 and December 20, 2011 but conducted the Study LCP-Tacro 3003 as proposed in their original protocol submitted on September 16, 2011 without any modifications as recommended by the FDA. The design and the results of the study will be briefly reviewed here with emphasis on the sections of the Protocol that FDA commented on. Clinical Reviewer's comments are included at the end.

This was a two-sequence, open-label, multi-center study conducted on 38 stable kidney transplant patients with tremor at 12 study sites in the USA.

Main Criteria for Inclusion:
Adult male and female stable kidney transplant recipients who had their renal transplant at least 1 month, but no more than 5 years, prior to screening, were between the ages of 18 and 65 years of age, and who had tremor were eligible for enrollment.

Other Important Inclusion Criteria:

- Men and women between 18 and 65 years of age who were recipients of a kidney transplant between 1 month and 5 years prior to the screening date;
- Patients with at least one complaint of tremor and existence of postural tremor or action tremor on finger to nose as demonstrated by a score of at least 2 on any of the 4 upper extremity (UE) postural or action and intention assessments on the FTM clinical rating scale;
- Patients experiencing symptomatic drug-induced hand tremor associated with use of Prograf or generic tacrolimus as demonstrated by responding 'no' to each of the following questions:

  'Did you have a tremor that you noticed prior to starting Prograf or generic tacrolimus for your kidney transplant?' and 'Are you aware of a tremor that runs in your family?'

- Patients taking a stable dose of oral Prograf capsules or generic tacrolimus for at least 7 days with trough levels of tacrolimus between 3 to 12 ng/mL.

Important Exclusion Criteria:

- Patients who have essential tremor (ET), Parkinsonism, or tremor from any cause other than tacrolimus-induced tremor;
- Patients currently taking or had taken within the past 30 days drugs known to promote tremors, or taking within the past 6 months the dopamine blocking agents, or had taken other medications considered as reason for exclusion by investigator and Sponsor;
- Patients who were taking drugs that reduce tremor, and are not on stable doses of the treatment;
- Patients on concurrent immunosuppression with MMF (CellCept) or MPS delayed release tablets (Myfortic), or generic versions of these medications, who had not been on stable doses for at least 7 days prior to Screening;
- Taking prednisone or equivalent at a dose >10 mg per day;
- Patients who had an episode of acute rejection requiring treatment or patients who had an episode of biopsy-proven or suspected acute rejection that required treatment within 3 months of Screening;

Study Design:

This was a 2-sequence, open-label, multicenter, prospective Phase 3b clinical study to assess drug-induced hand tremors in stable kidney transplant patients on a stable dose of immediate release tacrolimus formulation (Prograf or generic) twice daily converted to LCP-Tacro extended release tablets once daily.

The trial was designed to determine if the test drug, LCP-Tacro, is associated with fewer and/or less severe drug-induced hand tremor than observed with Prograf or generic immediate release tacrolimus treatment; each therapy was concomitantly administered with mycophenolate mofetil (MMF), mycophenolate sodium (MPS), including generic versions of each, and/or prednisone or equivalent as long as doses remained stable during the study.

All prophylaxis and other medication were allowed per standard of care (SOC) in each of the participating sites. No medications that interact with the pharmacokinetics of tacrolimus were allowed unless dosing remained unchanged during the 2-week treatment phase of the study.

Following screening, the 2-week treatment period consisted of 1 week of Prograf or generic tacrolimus (Days 1 through 7), and 1 week of LCP-Tacro (Days 8 through 14). Patients who completed the 2-week treatment period (hereafter often referred to as “the study period”) had a choice to participate in an extended-use LCP-Tacro period and continue LCP-Tacro treatment for an additional 2 years. Patients who early terminated

during the study period or chose not to enter the extended-use period resumed their previous treatment. A follow-up safety assessment was conducted by telephone interview 30 days after the patient's last LCP-Tacro dose.

The study design is depicted below in Figure 9. Following the Screening/Enrollment visit on Day 0/1, scheduled study visits were to be conducted on Day 7 and Day 14. From Days 1 through 7, patients continued on their pre-study regimen of Prograf or generic tacrolimus. On Day 8, patients switched to LCP-Tacro for a total of 7 days.

Seventy adult male and female patients were planned; 44 patients were analyzed for safety; 38 patients were analyzed for efficacy. Forty patients entered the extension phase of the study which is currently ongoing.

The primary efficacy endpoint:

Mean change from baseline in the FTM (Fahn-Tolosa-Marin) Clinical Rating Scale for overall tremor score 7 days after LCP-Tacro conversion.

Secondary efficacy endpoints:

- Percent change in FTM overall tremor score from baseline to 7 days after LCP-Tacro conversion;
- FTM subscales scores;
- Tremorometer measurements;
- Patient Global Impression of Improvement (PGI-I) scores;
- Quality of Life in Essential Tremor (QUEST); and
- Clinical Global Impression of Improvement (CGI-I) scores.

Figure 9. Design of Study 3003
(Source: Figure 1, CSR, page 26)

Two-week Treatment Period (Days 1-14) with Optional Extended Use-Period				
Day -7 to Day 0	Day 1 to Day 7	Day 8 to Day 14	Additional (optional) 2-year Extended use	30-Day Follow-up
⇦Screening⇨	⇦Prograf or ⇨ Generic Tacrolimus	⇦LCP-Tacro Treatment⇨	⇦Extended Use⇨	⇦Follow-up⇨
Kidney Transplant / Prograf or Generic Tacrolimus Treatment	*Prograf Capsules or Generic Tacrolimus Twice Daily*	*LCP-Tacro Tablets Once Daily*	*LCP-Tacro Tablets Once-Daily Extended use*	*30-Day Follow-up*

Study Treatments:

Test Product:
LCP-Tacro orally qd (morning) based on a conversion factor from Prograf or generic tacrolimus to LCP-Tacro of 0.7 for non-African Americans and 0.85 for African Americans to maintain target trough level of 3 to 12 ng/mL (measured 30 minutes before morning dose on Days 1, 7, and 14) with dose adjustment permitted as needed.

Reference Therapy:
Prograf or generic tacrolimus orally in 2 divided daily doses to maintain target trough level of 3 to 12 ng/mL (measured 30 minutes before morning dose on Days 1, 7, and 14) with no dose adjustment permitted.

Procedures and Assessments (Table 54)

Screening/Enrollment (Visit 1)
Screening procedures and assessments were conducted on Day 0/1. Thirty minutes prior to the morning dose of Prograf or generic tacrolimus, whole blood was drawn to measure tacrolimus trough level and other tests.

Table 54. Schedule of Study Activities - Study 3003
(Source: Table 3-1, CSR, page 21)

	Screening Phase		Prograf or generic tacrolimus SOC	LCP-Tacro treatment	Early withdrawal	End-of-study follow up phone call[a]	Extended-Use Period	
	Days -7 to -1	Day 0/1	Day 7	Day 14	As soon as possible after last dose	30 days after last dose of LCP-Tacro	Day 15/16	Every 3 months/ early withdrawal[b]
Study Activity								
Informed consent	X							
Inclusion/exclusion criteria	X	X						
Demographics		X						
Medical history		X						
Physical examination		X	X	X	X			
Vital signs		X	X	X	X			X
Pregnancy test (serum)	X[c]	X[c]						
Concomitant drugs		X[d]	X[d,e]	X[e]	X	X		X
Safety Labs (Metabolic profile and CBC)	X[c]	X[c]						X
Tacrolimus trough samples[f]		X	X	X				X
Efficacy Assessments								
PGI-I				X[g]				
QUEST			X[g]	X[g]				
Tremorometer measure			X[g]	X[g]				
FTM measure		X[h]	X[g]	X[g]				
CGI-I				X[g]				
Dispense LCP-Tacro			X				X	X[j]
Adverse event assessment		X[i]	X	X	X	X		X

Efficacy assessments are to be performed in the following sequence on Day 7: QUEST, tremorometer, and FTM, and in the following sequence on Day 14: PGI-I, QUEST, tremorometer, FTM and CGI-I. The PGI-I

and QUEST are to be completed only by the subject themselves without input from clinical staff or family or friends.

Day 7 (Visit 2)
On Day 7 (+3 days), 30 minutes prior to the morning dose of Prograf (or generic) blood was drawn for the assessment of tacrolimus trough level and other assessments performed. Post dose administration, the QUEST (Quality of Life in Essential Tremor) questionnaire was administered. Two hours (± 15 minutes) after the time of dosing, the tremorometer and FTM clinical rating assessments were conducted. Patients whose Day 7 trough levels were outside the range of 3-12 ng/mL were discontinued from the study. Patients remaining in the study were given their supply of LCP-Tacro tablets with instructions for the next 6 days.

Day 14 (Visit 3)
On Day 14 (+3 days, a minimum of 7 days post Visit 2) and at 30 minutes prior to the morning dose of LCP-Tacro, whole blood sample was taken for tacrolimus trough measurement and the safety assessments were performed. Post dose administration, the PGI-I (Patient Global Impression of Improvement) and QUEST evaluations were administered and 2 hours (± 15 minutes) after the time of dosing tremorometer and FTM measurements were conducted.

Assessment of the Primary Efficacy Endpoint

The FTM clinical rating scale contained 21 elements. FTM assessment was conducted after 2 hours (± 15 minutes) of the morning dose on the visit day. Site coordinator assessed FTM scale on Day 0/1 for eligibility evaluation. On Day 7 and Day 14 the full FTM scale was conducted. A video recording was made for each patient when performing FTM assessment and was sent to independent neurologists to be reviewed in a blinded fashion (i.e., neurologists were not able to differentiate whether the FTM test was taken on Day 7 or Day 14).

Tremorometer Measurements

Tremorometer measurements were recorded after 2 hours (± 15 minutes) of the morning dose on the visit day, prior to administration of FTM scale. Measurements were taken from both left and right hands.

Study Results

Demographics:

Forty-four patients were included in the ITT/Safety Population and 40 (90.9%) completed the study period. Four (9.1%) patients withdrew prematurely from the treatment period. No patients withdrew from study due to an AE. Of the 40 patients who

completed the study period, 38 (86.4%) patients were evaluable for efficacy and were included in the mITT population.

Applicant's Efficacy Results:

Of 44 patients enrolled in the 2-week treatment phase of the study, 38 (86.4%) took at least one dose of LCP-Tacro and had evaluable pre- and post-conversion FTM scores, and included in the mITT population.

Primary efficacy endpoint:

After the switch from Prograf/generic tacrolimus and completion of treatment with LCP-Tacro for one week, the mean (SD) absolute change in FTM total tremor score (TTS) from baseline (Day 7) was -5.35 ([7.50]; P<0.0001) on Day 14.

Secondary efficacy endpoints:

- FTM TTS mean absolute change from baseline showed an improvement of -5.35 (P<0.0001) and a -16.0% change in the TTS (P<0.005).

- The FTM scale indicated that in 38 patients both specific motor tasks and functional disabilities resulting from tremor showed statistically significant improvements (*P*<0.05 and *P*<0.0001, respectively).
- The tremorometer indicated that 36 patients had a mean improvement in measured amplitude for posture position of the dominant hand that was statistically significant (*P*<0.05). Tremorometer results demonstrate that amplitude indicators are reduced across all three positions, most notable in posture and load-bearing positions.

- The PGI-I indicated that 78.9% of patients reported an improvement of "much better" (23.7%) or "a little better" (55.3%) after switching to LCP-Tacro (*P*<0.0005). Similarly, 86.8% of physicians on the CGI-I reported an improvement of "very much improved" (2.6%), "much improved" (28.9%), or minimally improved" (55.3%) (*P*<0.0005).

- The Quest evaluation indicated that for 38 patients there was a statistically significant (*P*<0.001) improvement in QUEST QOL SI score at Day 14. The mean (SD) absolute change from baseline was -7.04 (9.41) and the mean percent change from baseline was -39.08% (39.43).

The Applicant's Efficacy Conclusions:

- Results of this 2-week treatment phase of the study showed renal transplant patients that experience tacrolimus-induced neurotoxic hand tremors demonstrate significant improvement after conversion to LCP-Tacro while maintaining comparable trough levels/exposure.

- Clinical global impression of tremor results, rated by both patient and physician, supported the clinical FTM-TTS measures, confirming the clinical relevance of the improvement.

- Results suggest a significant improvement of QOL can be experienced by kidney transplant recipients experiencing tremors who switch from Prograf or generic tacrolimus to LCP-Tacro especially in physical and psychosocial domains, and is consistent with improvement of tremor assessed by the tremor rating scale.

- It was demonstrated that LCP-Tacro can reduce a troubling side effect and improve QOL in kidney transplant recipients.

Clinical Reviewer's Comments for the Tremor Study 3003

As previously stated, the Applicant did not respond to the comments in the FDA letters dated October 18, 2011 and December 20, 2011 and conducted the Study LCP-Tacro 3003 as proposed in their original protocol submitted on September 16, 2011 without implementing any of the important modifications recommended by the FDA. Therefore all the FDA recommendations in the October 18, 2011 and December 20, 2011 letters remain unaddressed. The main purpose of the FDA recommendations was to have the Applicant change the study design so that the study results would be able to support a safety claim (b) (4).

FDA also stated in the December 20, 2011 letter that to (b) (4) the Applicant would need to demonstrate replication of results, in a second clinical trial.

Some of the important outstanding deficiencies which were recommended but not addressed by the Applicant hence preclude the study results from supporting a safety (clinical superiority) claim:

1. Study LCP-Tacro 3003 is an open-label, non-randomized trial which is prone to biases. FDA had recommended a parallel design where patients would be randomized to continue Prograf/generic tacrolimus or to switch to LCP-Tacro as an option to be considered by the Applicant.

2. FDA recommended adding the Patient Global Impression Evaluation (PGI-I) score to the current primary endpoint of the mean change from baseline in the FTM clinical rating scale as a co-primary endpoint which was not implemented.

3. The timing of the assessment of the primary efficacy endpoint (change in the FTM clinical rating scale for tremor) which is only seven days after the conversion is too early.

4. Patients as early as one month after transplantation were enrolled into the Study LCP-Tacro 3003. Patients who are at least 6 months post-transplant should have been allowed into the study since before this time point patients are not considered to be "stable" patients eligible for conversion.

5. The Applicant did not provide a justification for the protocol specified tacrolimus target trough levels of 3-12 ng/mL which is different than the label recommended 4-11 ng/mL for this patient population.

6. In Study LCP-Tacro 3003, FTM tremor assessments were performed at 2 hours ± 15 minutes after the tacrolimus dose in all patients. This is acceptable for patients on Prograf or generics since the Tmax of Prograf immediate-release tablets is approximately 2 hours. However, the Tmax of LCP-Tacro extended release tablets, is approximately 6 hours and the tremor assessments in patients receiving LCP-Tacro should have been be done at 6 hours ± 15 minutes instead of at 2 hours ± 15 minutes as recommended by the FDA.

7. In the study clinical and accelerometry measurements (using the Tremorometer) were performed only at one time point (Day 14 of the study) after the conversion. These assessments should have been repeated periodically once steady state with tacrolimus is achieved as recommended by the FDA.

Because of the main reasons summarized above and other reasons explained in the FDA letters Study LCP-Tacro 3003 is not designed to support a clinical superiority claim. Additionally the Applicant needs (b) (4)

The Applicant's claim of clinical superiority based on decreased tremor rates with LCP-Tacro extended release formulation is also not supported by the tremor rates observed in the two Phase 3 studies LCP-Tacro 3002 and LCP-Tacro 3001. In the Applicant's analysis, the tremor rates (reported as an adverse event) in Study LCP-Tacro 3002 were 19.0% in the LCP-Tacro group vs. 16.7% in the Prograf group and in Study LCP-Tacro 3001, 2.5% in the LCP-Tacro group vs. 1.2% in the Prograf group.

Another important observation made from the tremor rates reported in the de novo Study 3002 and the conversion Study 3001 is the dramatic decrease in the tremor rates in stable transplant patients (Study 3001) compared to the de novo transplant patients (Study 3002) regardless of the treatment as expected. Interestingly only 1.2% (n=2) of

stable Prograf patients in Study 3001 experienced tremor and none of them were classified as severe by the investigator.

7.4.6 Immunogenicity

Not applicable for the currently reviewed orally administered tacrolimus extended release formulation.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Please see the Clinical Pharmacology NDA Review in DARRTS for detailed information.

7.5.2 Time Dependency for Adverse Events

Not applicable due to various reasons including the fact that immunosuppression is a lifelong treatment and some of the adverse events are related to the extent of immunosuppression hence to the level of drug exposure rather than the duration of treatment. In transplant patients some adverse events like CMV infections show a time dependency but this may be more related to the general course of the transplant patients rather than the type of immunosuppression. Multitude and etiological diversity of adverse events may not always permit a time dependency analysis or yield meaningful results.

No specific analyses of time to onset of adverse events, duration of event and the extent to which the adverse event resolves are included in this submission.

7.5.3 Drug-Demographic Interactions

Please refer to the Clinical Pharmacology NDA Review.

7.5.4 Drug-Disease Interactions

Please refer to the Clinical Pharmacology NDA Review.

7.5.5 Drug-Drug Interactions

Prograf® package insert includes a section on drug-drug interactions which is also applicable to the current tacrolimus extended release formulation. These are included in the Applicant's proposed package insert for the current product. Please also refer to the Clinical Pharmacology NDA Review for more information.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Carcinogenicity is the same as in the approved immediate release formulation of the same product, Prograf®.

7.6.2 Human Reproduction and Pregnancy Data

Current NDA submission does not contain any new human reproduction and pregnancy data. The information included in the approved Prograf package insert should also apply to the current tacrolimus extended release formulation.

7.6.3 Pediatrics and Assessment of Effects on Growth

Only adult patients were enrolled into the completed trials, hence no assessment of effect on growth was conducted. Pediatric transplant patients often receive other Immunosuppressants in combination with tacrolimus that may affect growth which makes it difficult to assess the isolated effect of tacrolimus on growth.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

PREA requirements do not apply to the current NDA submission since it has been granted orphan designation by the FDA. (b) (4) The Applicant will also be notified that the PREA requirements do not apply to the current NDA because of the granted orphan designation.

(b) (4)

(b) (4)

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The overdose experience would be similar to that observed with Prograf®. Please refer to the Overdose section in the Prograf® package insert.

Tacrolimus is not a drug with abuse potential. Tacrolimus is intended for life-long use as long as the transplanted organ is viable. If tacrolimus is discontinued because of transitioning to another immunosuppressant, withdrawal symptoms or rebound in the form of severe rejection episodes are not generally expected.

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

Not applicable

9 Appendices

9.1 Literature Review/References

Relevant references are given in the text.

9.2 Labeling Recommendations

The Applicant submitted their proposed label as part of the NDA submission. At the time of writing of this review a final label has not been agreed to. A draft label including the Division's questions and comments was sent to the Applicant on August 14, 2014. An addendum review for labeling recommendations will be checked in DARRTS when the label is finalized.

9.3 Advisory Committee Meeting

The Division decided that an Advisory Committee Meeting is not required for this NDA submission.

9.4 Clinical Investigator Financial Disclosure Forms

Below are the Clinical Investigator Financial Disclosure forms for the three main studies reviewed in support of efficacy and safety of the Envarsus XR tablets.

Clinical Investigator Financial Disclosure
Review of the Phase 3 Study LCP-Tacro (b) (6)

Application Number: 206-406

Submission Date(s): December 30, 2013

Applicant: Veloxis

Product: Envarsus XR (Tacrolimus extended-release tablets)

Reviewer: Ergun Velidedeoglu

Date of Review: September 17, 2014

Covered Clinical Study (Name and/or Number): LCP-Tacro (b) (6)

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from applicant)
Total number of investigators identified: (b) (6)		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

Clinical Reviewer's Assessment of the Applicant's Financial Disclosure for Study LCP-Tacro [redacted]

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.

There are no investigators who are sponsor employees and no lack of disclosure despite due diligence is reported by the Applicant.

Interests/arrangements:

[redacted] from the [redacted] worked as an advisor to LCP-Tacro for Phase [redacted] with summary of payments below:

2007: €5,200
2008: €9,112
2009: €8,744
2010: €8,559
2011: €2,800
2012: €2,800
2013: €8,000
Total: €45,216

The disclosed financial interests/arrangements, do not affect the approvability of the application for the following reasons:

- [redacted] Phase [redacted] studies were multicenter studies and [redacted] was only one of the investigators.
- Study [redacted] is a double-blind study. Therefore none of the investigators knew the treatment arm assignment of the randomized patients.
- As stated by the Applicant, [redacted] like all the other investigators was not aware of the study results other than periodic safety updates from the DSMB. These updates did not include any safety or efficacy data during the conduct of the study.
- The primary and secondary endpoints of the study were objective leaving no room for investigator bias on the determination of reaching a particular endpoint for each study patient.

Clinical Investigator Financial Disclosure
Review of the Phase 3 Study LCP-Tacro (b) (6)

Application Number: 206-406

Submission Date(s): December 30, 2013

Applicant: Veloxis

Product: Envarsus XR (Tacrolimus extended-release tablets)

Reviewer: Ergun Velidedeoglu

Date of Review: September 17, 2014

Covered Clinical Study (Name and/or Number): LCP-Tacro (b) (6)

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from applicant)
Total number of investigators identified: (b) (6)		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

Clinical Reviewer's Assessment of the Applicant's Financial Disclosure for Study LCP-Tacro (b) (6)

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators.*

There are no investigators who are sponsor employees and no lack of disclosure despite due diligence is reported by the Applicant.

Interests/arrangements:

1. (b) (6) from the (b) (6) worked as an advisor to LCP-Tacro in (b) (6) Phase (b) (6) clinical studies (b) (6) (b) (6) with summary of payments below:

   2007: €5,200
   2008: €9,112
   2009: €8,744
   2010: €8,559
   2011: €2,800
   2012: €2,800
   2013: €8,000
   Total: €45,216

2. (b) (6) from the (b) (6) worked as an advisor to LCP-Tacro in (b) (6) clinical studies including Study (b) (6) with summary of payments below:

   2007: $2,717
   2008: $11,830
   2009: $7,688
   2010: $18,250
   Total: $40,486

The disclosed financial interests/arrangements, do not affect the approvability of the application for the following reasons:

- Study (b) (6) is a multicenter study. (b) (6) were only two investigators among the (b) (6) investigators in this study.
- As stated by the Applicant, (b) (6) like all the other investigators were not aware of the study results other than periodic safety updates from the DSMB. These updates did not include any safety or efficacy data during the conduct of the study.
- The primary and secondary endpoints of the study were objective leaving no room for investigator bias on the determination of reaching a particular endpoint for each study patient.

Clinical Investigator Financial Disclosure
Review of the Phase2 Study LCP-Tacro (b) (6)

Application Number: 206-406

Submission Date(s): December 30, 2013

Applicant: Veloxis

Product: Envarsus XR (Tacrolimus extended-release tablets)

Reviewer: Ergun Velidedeoglu

Date of Review: September 17, 2014

Covered Clinical Study (Name and/or Number): LCP-Tacro (b) (6)

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from applicant)
Total number of investigators identified: (b) (6)		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

Clinical Reviewer's Assessment of the Applicant's Financial Disclosure for Study LCP-Tacro (b) (6)

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators.*

There are no investigators who are sponsor employees and no lack of disclosure despite due diligence is reported by the Applicant.

Interests/arrangements:

3. (b) (6) from the (b) (6) worked as an advisor to LCP-Tacro in (b) (6) clinical studies including Study (b) (6) with summary of payments below:

2007: $2,717
2008: $11,830
2009: $7,688
2010: $18,250
Total: $40,486

The disclosed financial interests/arrangements, do not affect the approvability of the application for the following reasons:

- Study (b) (6) is a multicenter study. (b) (6) is one of the (b) (6) investigators in this Phase (b) (6) tudy.
- As stated by the Applicant, (b) (6) like all the other investigators was not aware of the study results other than periodic safety updates from the DSMB. These updates did not include any safety or efficacy data during the conduct of the study.
- The primary and secondary endpoints of the study were objective leaving no room for investigator bias on the determination of reaching a particular endpoint for each study patient.

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

/s/

HUSEYIN E VELIDEDEOGLU
09/25/2014
Clinical Review of NDA 206-406 (Envarsus XR)

OZLEM A BELEN
09/25/2014

RENATA ALBRECHT
09/25/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 206-406 **Applicant: Veloxis Pharmaceuticals** **Stamp Date: December 30, 2013**

Drug Name: LCP-Tacro **NDA/BLA Type: 505(b)(2)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			2.5 Clinical Overview page 72
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(2)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?				Prograf® (tacrolimus)
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	X			
15.	Describe the scientific bridge (e.g., BA/BE studies)				BA studies and the applicant also conducted their own efficacy and safety trials.
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms:	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Location in submission:				
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 **LCP-Tacro 3002:**A Phase 3, Double-Blind, Double-Dummy, Multi-Center, Prospective, Randomized Study of the Efficacy and Safety of LCP-Tacro™ Tablets, Once Daily, Compared to Prograf® Capsules, Twice Daily, in Combination With Mycophenolate Mofetil for the Prevention of Acute Allograft Rejection in De Novo Adult Kidney Transplant Recipients Indication: prophylaxis of organ rejection in kidney transplant patients Pivotal Study #2 **LCP-Tacro 3001:**A Phase 3, Open-label, Multicenter, Prospective, Randomized Study of the Efficacy and Safety of Conversion From Prograf® Capsules Twice Daily to LCP-Tacro™ Tablets Once Daily for the Prevention of Acute Allograft Rejection in Stable Kidney Transplant Patients Indication: prophylaxis of organ rejection in kidney transplant patients	X			
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	505(b)(2) Applicant relies on Prograf® label for QT risk information (Warnings and Precautions 5.14)
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			2.7.4 Summary of Clinical Safety, page 81

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?		X		The Applicant will be requested to submit the coding dictionary used for mapping investigator verbatim terms to preferred terms.
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?		X		For Study LCP-Tacro 3001, the applicant will be requested to submit the missing narratives for discontinuations due to reasons other than AEs
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Orphan designation granted by the Office of Orphan Products Development which releases the applicant from conducting any pediatric studies (b) (4) [redacted]

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					(b) (4) [redacted]
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			Subgroup analyses for US vs. non-US patients submitted
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _(X)_Fileable (See comments below)_____

The Applicant will be requested to submit:

- The coding dictionary used for mapping investigator verbatim terms to preferred terms
- missing narratives for discontinuations due to reasons other than AEs for Study LCP-Tacro 3001

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Ergun Velidedeoglu	February 11, 2014
Reviewing Medical Officer	Date
Joette Meyer	February 11, 2014
Clinical Team Leader	Date

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

/s/

HUSEYIN E VELIDEDEOGLU
02/11/2014
Clinical Filing Checklist - NDA 206406.doc

JOETTE M MEYER
02/11/2014