Project Title: A pilot study of stable kidney transplant recipients taking tacrolimus with CNS symptoms switched to Envarsus

Principal Investigator: Laurence Chan, MD

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Hypotheses and Specific Aims:

The use of once-daily Envarsus XR® (tacrolimus extended-release tablets) will have significant improvement in the patients reported CNS symptoms.

Background and Significance:
Graft survival in renal transplant patients has improved steadily over the last decades as a result of improved immunosuppressive therapies. Immunosuppressive regimens continue to have side effects which patients find burdensome and which may lead to sub-therapeutic dosing and non-compliance by the patient.

Patients on different immunosuppressant regimens may be bothered by Central Nervous System (CNS) side effects or report better health-related quality of life (HRQL). We will evaluate the reliability and validity CNS-specific outcome instruments (CNS Symptom Rating Scale; higher scores = increased severity) and Quality of Life Index (higher scores = better CNS-specific HRQL) in renal transplant patients.

Neurotoxicity in transplant patients occurs in >40-50% of the patients treated with tacrolimus (1). Tacrolimus was approved by the US Food and Drug Administration (FDA) in April of 1994 for the prophylaxis of organ rejection in patients receiving allogeneic liver transplants under the **brand name Prograf®** (tacrolimus capsules, Astellas Pharma US, Inc.).

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. (2) 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. (3, 4) In more severe cases, immunosuppressant regimens may be changed from tacrolimus to cyclosporine, an agent which also is associated with similar neurotoxicity and a reduced clinical effectiveness. Literature documents that the neurotoxicity is associated with peak tacrolimus concentrations in transplant as well as autoimmune diseases and shows that the neurotoxicity essentially abates when tacrolimus treatment is discontinued, providing proof that tacrolimus is a reversible neurotoxic agent. (5)

Envarsus XR (Veloxis Pharmaceuticals) is an extended-release formulation of tacrolimus designed for once-daily administration that has been developed utilizing Veloxis Pharma's proprietary MeltDose® drug-delivery technology (Veloxis Pharmaceuticals A/S, Hørsholm, DK). Envarsus XR is designed and has been approved by FDA to deliver equivalent whole blood concentrations to the immediate-release formulation of tacrolimus over the 24-hour dosing interval. As previously reported, The ASERTAA trial demonstrated that patients on Envarsus achieved therapeutic drug levels with a 30% lower peak concentration and 20% lower average dose compared to tacrolimus immediate-release regardless of genotype status. Importantly, patients expressing the CYP3A5*1 genotype on tacrolimus immediate-release reached a peak concentration as high as 26 ng/mL.

This high peak levels might related to the high incidence of CNS related side effects. The PK data collected for Envarsus XR® demonstrated similar exposure, lower Cmax, prolonged Tmax, and increased bioavailability when compared to tacrolimus immediate-release.

The study is designed in such a way that patient will report objectively their experience related to CNS symptoms using a standard questionnaire before staring on Envarsus XR. The OPTN/SRTR 2011 Annual Data Report shows that approximately 90% of Recipients transplanted in 2010 were initiated on tacrolimus as part of their immunosuppression regimen and were continuing to take tacrolimus at one-year post-transplant.

Envarsus XR is designed to deliver equivalent whole blood concentrations to the immediate-release formulation of tacrolimus over the 24-hour dosing interval. This formulation works better with the enzyme systems in the lower gastrointestinal (GI) tract, facilitating a constant stable absorption of tacrolimus through the GI tract leading to improved bioavailability and constant plasma levels over the full day.

In a prior study in stable renal transplant recipients converted from Prograf to Envarsus XR (LCP-Tacro), showed 30% greater bioavailability compared to Prograf, as well as a steadier and more consistent concentration time profile over 24 hours, and reduced peak-to-trough fluctuations and swing compared to Prograf, with good tolerability and a robust AUC/Cmin correlation (correlation coefficients from 0.86 to 0.91).

A Phase III study in stable renal transplant recipients converted from Prograf to Envarsus XR demonstrated non-inferior efficacy and similar safety for Envarsus XR compared to Prograf. Total daily Envarsus XR dose was about 20% lower than preconversion Prograf twice-daily dose.

The Expanded access Study Envarsus 3007 conducted to provide patients the opportunity for an alternative tacrolimus treatment and/or continuation of therapy for patients previously on Envarsus clinical studies.

Envarsus XR tablets are an extended-release formulation of tacrolimus, intended for once-daily administration, the anticipated risks of Envarsus XR are expected to be the same as for Prograf though the severity and frequency may be less due to reduced maximal blood

concentrations. Based on the Prograf package, insert and the overall experience with Prograf in solid organ transplantation the anticipated risks from Envarsus XR include: nephrotoxicity, new onset diabetes mellitus, hypertension, neurotoxicity, hyperkalemia, and latent viral infections. Given the low peak tacrolimus levels when taking Envarsus, we might expect less CNS side effects. (6.7).

Overall, the study would provide renal transplant patients the opportunity to an alternative tacrolimus treatment with possible less CNS side effects.

CNS side effects are one of the main reasons that patients complain after having a kidney transplant while on tacrolimus (Prograf). The side effects can be debilitating and can affect patients overall well-being. In severe cases may lead to non-compliance. So the advantage of the study of using Envarsus XR for the patients is the ability to avoid those debilitating CNS side effects, like tremor, headache, and difficulty in concentrating and sleep disturbances. Envarsus XR has been approved and has similar efficacy as tacrolimus (Prograf, so there is no disadvantages or risk to the patients.

III. Preliminary Studies/Progress Report:

This is the first study on Envarsus XR using Patients reported questionnaire methodology to examine the CNS side-effects of Tacrolimus (Prograf). There is no need for a cross over study and each patient will serve as its own control. The design and methodology will be similar to the PROGIS study that was published by Chan et al (8).

Prior studies including the Phase III study in stable renal transplant recipients converted from Prograf to Envarsus XR demonstrated non-inferior efficacy and similar safety for Envarsus XR compared to Prograf. Total daily Envarsus XR dose was about 20% lower than preconversion Prograf twice-daily dose. Additional Expanded access Study Envarsus 3007 conducted to provide patients the opportunity for an alternative tacrolimus treatment and/or continuation of therapy for patients previously on Envarsus clinical studies. In addition to comparable efficacy and non-inferiority of Envarsus XR, there was better pharcokinetics and possible less CNS side effects. However, the studies were not specifically designed to test this hypothesis.

IV. Research Methods

Outcome Measure(s):

This is a population-based, longitudinal, prospective, minimal risk interventional study of renal transplant patients in routine practice. This approach is designed to generate hypotheses (rather than test hypotheses) concerning the impact of current and newly emerging immunosuppressive regimens and decision-making on regimen tolerability, safety, patient co-morbidities, and graft and patient outcomes in the real world. We expect patients will have improvement in quality of life

related to sleep disturbance and upper extremity fine motor skills/ADL. Tacrolimus drug levels, serum creatinine and other parameters related to graft function, graft function, and other adverse events will be documented during the study period. Standard of care immunosuppression for kidney transplant recipients at UC Health is either Prograf twice a day or Envarsus XR once a day, Myfortic and steroids**.** Serum creatinine and tacrolimus levels (drug level monitoring) is required for both Prograf and Envarsus XR and is standard of care for this population.

Description of Population to be enrolled:

Inclusion

- Kidney transplant recipients with stable graft function will be switched from Prograf twice/day to Envarsus XR once a day per standard of care
- More than 1 months post-transplant
- 18+ years of age with some CNS problems secondary to Prograf (tacrolimus)

Exclusion

- Multi-organ patients (kidney/pancreas, kidney/liver)
- Evidence of graft rejection or treatment of acute rejection within 14 days prior to baseline visit
- Inability to self-administer the QOL questionnaires

Study Design and Research Method

Pilot study documenting the neurotoxic side effects including tremors in patients with stable graft who are receiving Tacrolimus following kidney transplantation. Standardized questionnaire will be used to document these symptoms. Envarsus XR® will be provided to the subjects by Veloxis Pharmaceuticals (manufacture of the drug) for the duration of the study (6 months). After a subject completes the study, they will continue taking Envarsus XR® through their insurance/self-pay.

Description, Risks and Justification of Procedures and Data Collection Tools:

After informed consent, the subject will complete the PROMIS questionnaire before switching to Envarsus XR. Subjects will repeat questionnaires at 1 month and 6 months focusing on quality of life (QOL) questionnaire related to sleep disturbance and upper extremity fine motor skill/activities of daily living (ADL)

Questionnaires

- Sleep Disturbance-Short Form 8a
- Upper Extremity Function (Fine Motor, ADL)-Short Form
- Upper Extremity-Short Form 7a
- Global Health Scale v1.2

Review medical record for demographics, medical history (including kidney transplant) and other basic information:

- vital signs,

- minimal lab collected as standard of care (serum creatinine, tacrolimus level)

Adverse events
Graft function

Potential Scientific Problems:

Each patient will serve as its own control. No scientific problem will be expected. Although the study is an open-label and no placebo group; but the patient reported outcomes will serve as its own control and any improvement in symptoms may not be placebo related as reported in previous studies using the same methodology.

Data Analysis Plan:

Research is conducted according to the ICH Harmonized Tripartite Guidelines for Good Clinical Practice and in compliance with the ethical principles of the Helsinki Declaration. Appropriate Institutional Review Board/Ethics Committee approval will be obtained prior to study initiation. Patients are eligible for participation if they are at least 18 years of age; willing to provide informed consent and adhere to study requirements; have received a renal transplant at least 1 month prior to the study enrollment; and have been on an immunosuppressive regimen including Tacrolimus (Prograf) for at least four weeks prior to enrollment.

All analyses will be performed with SAS version 8.02 (SAS Institute, Cary NC). Demographic variables and clinical conditions will be evaluated by descriptive analyses. For the descriptive analyses, chi-square tests will be used to evaluate categorical data; t-tests and analyses of variance (ANOVA) will be used to evaluate continuous data. Scoring – including imputations for missing data if necessary – will be performed according to each questionnaire's guidelines.

Reliability refers to the consistency of items within an instrument, either over time or internally within the instrument. Internal consistency reliability is the extent to which all items measure the same construct; values are presented descriptively, on an internal level scale from 0 to 1.0, with higher scores indicating a more reliable (precise) instrument

Summarize Knowledge to be Gained:

Immunosuppressive therapies have burdensome side effects which may lead to sub-therapeutic dosing and non-compliance.

The study will provide renal transplant patients the opportunity to an alternative tacrolimus treatment with possible less CNS side effects. CNS side effects are one of the main reasons that patients complain after having a kidney transplant while on tacrolimus (Prograf). The side effects can be debilitating and can affect patients overall well-being. In severe cases may lead to non-compliance. So the advantage of the study of using Envarsus for the patients is

the ability to avoid those debilitating CNS side effects and afford better compliance with the patients taking the medicine.

Study Calendar

Procedure	Baseline	M1	M6/EOS
Consent	X		
VS (BP, P, weight)	X	X	X
Serum creatinine	X	X	X
Tacrolimus level	X	X	X
Pregnancy test (as needed)	X		
Global health questionnaire	X	X	X
Sleep Disturbance-Short Form 8a	X	X	X
Upper Extremity Function (Fine Motor, ADL)-Short Form	X	X	X
Upper Extremity-Short Form 7a	X	X	X
Switch to Envarsus	X		
Adverse events		X	X

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