Study Title: A Pilot Study to Evaluate Impact on Neurological Side Effects (Cognition, Memory, and Tremor) in Elderly (Age>65) Patients

NCT03461445

Date: November 21, 2018

1) Protocol Title

Title: Evaluating the difference in neurocognitive side effects between tacrolimus IR vs Envarsus XR ® in elderly renal transplant recipients.

Protocol Version Date: 11/21/18

2) Objectives

Primary objective: Change in neurocognitive side effects

Secondary Objectives: Change in self-reported side effects, Tacrolimus dose over concentration ratio, Graft survival, Patient survival

Null Hypothesis: Elderly patients will not experience a reduction in neurocognitive side effects when transitioned to Envarsus XR ® when compared to elderly patients maintained on tacrolimus IR therapy.

3) Background

Renal transplant is widely accepted as the superior treatment for end stage renal disease in terms of mortality, morbidity, healthcare cost and quality of life[1]. Elderly patients (>65 years) also benefit from transplantation. Studies have been conducted to evaluate the quality of life that elderly transplant recipient's experience. These studies have demonstrated that in appropriate recipients, quality of life is improved post-transplant[2]. However, the medications required to prevent graft rejection come with toxicities that elderly patients may be more uniquely sensitive to.

In particular, neurologic toxicities such as tremor, headaches, confusion and neuropathy are common side effects of Tacrolimus immediate release[3]. When used in combination with mycophenolate mofetil, a common immunosuppressant regimen, the incidences of these adverse effects are significant[4]. Per Prograf ® package insert, about one-third of patients experience tremors and one-fourth of patients experience headaches[4]. These neurologic side effects may impose profound limitations on patients' daily activities and quality of life. These studies were conducted in the general population with an average age of 48 years (range 17-77 years). Elderly patients tend to be more sensitive to medications, both the intended effects and the toxicities. The elderly patient experiences changes in organ function and body composition, leading to effects on drug metabolism and disposition[5]. Studies have demonstrated that elderly patients achieve higher trough drug levels even when normalizing for patient weight and dosage[6]. In addition, elderly patients tend to have more co-morbidities and are more vulnerable to polypharmacy, leading to more potential drug interactions. All of these factors combined may increase the likelihood and severity of toxicities experienced by the elderly patient.

University of California, Davis Health, is the leading renal transplant center in the nation. In 2016 alone, over 400 renal transplants were performed. Of those, 72 transplants were in patients age 65 years or greater. With about one-fourth of our transplants performed in the elderly patient population there is great opportunity to improve outcomes in this patient population. The UC Davis Health renal transplant patient population is very diverse, with no one ethnicity claiming majority. Between May 2016 and July 2017, 30% of transplant recipients self-identified as white, 11% as black, 29% as Hispanic, 26% as Asian and 4% as other. As a large academic institution, UC Davis Health is well equipped to successfully manage research projects and see them to completion. With a dedicated office for research within our campus, research coordinators, biostatisticians and other research services available ensures research that is conducted at UC Davis Health is robust and valuable to our patients as well as to the broader health care audience.

Our research aims to focus on the neurocognitive effects of Envarsus ® versus tacrolimus immediate release. There is a correlation between peak levels of tacrolimus and CNS toxicities such as tremor[7]. As previous studies have shown that elderly patients experience higher trough levels of tacrolimus and are more sensitive to the effects of medications, they experience higher occurrence and severity of such medication related toxicities[5,6]. Therefore, it is our hypothesis that by transitioning patients from tacrolimus immediate release to Envarsus ® we will eliminate the peak-dose effect and see a significant decrease in toxicities in the older patient population.

References

1. Kostro, J,Hellmann, A et al. “Quality of life after kidney transplantation: a prospective study”. Transplant Proc. 48.1 (2016): 50-54.
2. Weber, M, Faravardeh, A et al. “Quality of Life in Elderly Kidney Transplant Recipients.” *The American Geriatrics Society*. 62 (2014):1877-1882.
3. Tacrolimus. Lxi-Drugs. Lexicomp. Wolter Kluwer Health, Inc. Riverwoods, IL. Accessed July 19,2017.
4. Prograf® [package insert]. Northbrook,IL: Atellas Pharmaceuticals 2005.
5. Klotz, U. “Pharmacokinetics and drug metabolism in the elderly”41.2(2009):67-76.
6. Jacobson, P and Schaldt, D et al. “Lower Calcineurin Inhibitor Doses in Older Compared to Younger Kidney Transplant Recipients Yield Similar Troughs.” *American Journal of Transplantation* 12 *(2012):*3326–3336
7. Langone A, Steinberg SM, Gedaly R, et al. Switching Study of Kidney TRansplant pAtients with Tremor to LCP-TacrO (STRATO): an open-label, multicenter, prospective phase 3b study. *Clinical Transplantation.* 2015;29(9):796-805

4) Inclusion and Exclusion Criteria

Inclusion Criteria:

1. Recipient of a kidney transplant
2. Age 65 or greater at the time of transplant
3. Kidney graft is functional (not dialysis dependent) by 4 weeks post-transplant
4. Have IR tacrolimus as maintenance therapy
5. Have BMI < 35 at time of transplant
6. Achieve therapeutic tacrolimus level within 4 weeks post-transplant

Exclusion Criteria:

1. Recipient of a simultaneous non-kidney transplant (pancreas)
2. Had an episode of rejection before study enrollment
3. Had a TIA/CVA after transplantation and before study enrollment
4. Had a neurologic injury after transplantation and before study enrollment
5. Blindness
6. Have an mTOR inhibitor as maintenance therapy
7. Nonadherence, as determined by a trough level less than 7 ng/mL after achieving therapeutic level with no other rationale for sub-therapeutic levels.
8. Adults unable to consent
9. Pregnant women
10. Prisoners

5) Study Timelines

Expected date of data collection and analysis completion by July 2019.

The duration of an individual subject's participation in the study is 6-8 weeks from initial study enrollment.

The enrollment period is expected to occur from IRB approval through December 2018, or until 60 subjects have been enrolled into to the study.

6) Study Endpoints

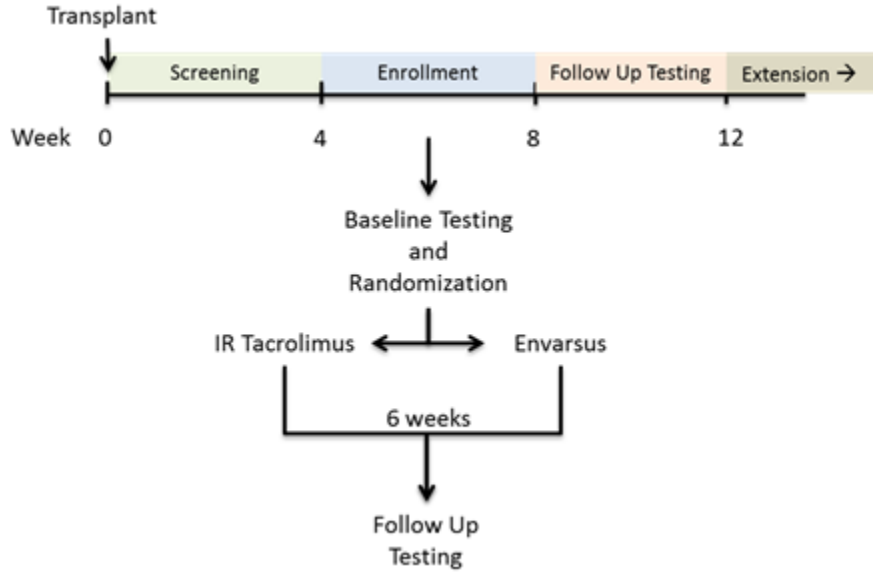
Primary Endpoints: Change in neurocognitive side effects assessed by MOCA scale, Digit symbol substitution test and tremor assessment scale.

Secondary Endpoints: Change in self-reported side effects, tacrolimus dose over concentration ratio, graft survival and patient survival.

7) Procedures Involved

Single-center, prospective, open-label, randomized study to evaluate the difference in neurocognitive side effects of Envarsus versus immediate release tacrolimus.

Figure 1. Flow diagram of study design



Enrollment:

1. Rolling enrollment of patients 65 years or older that fit the inclusion criteria outlined above
2. Plan to enroll 30 patients to each arm
3. Anticipated enrollment rate:
    a. 6-8 patients in first month
    b. 10 patients per month thereafter
    c. Until total of 60 patients have enrolled
    d. If any patients were to withdraw or be dropped from the study prior to completion of follow up testing, we will try to enroll more patients to replace them

Protocol:

1. Potential study participants will be screened within 4 weeks after transplantation.
    - Patients who meet study criteria will be consented and enrolled by 8 weeks post-transplantation
2. Patients who consent to the study will be administered a baseline panel of neurocognitive tests. (Of note, these tests are not regularly administered to our post-transplant patients and are not part of the standard of care.)

- Tests include: the MOCA, digit symbol substitution test, tremor assessment.
- They will also answer a side effects questionnaire.
- These tests will be performed in the mornings, between 1-4 hours after patients' morning tacrolimus dose administration.

3. Subjects who enroll will then be randomized to either remain on IR tacrolimus (current standard of care) or be converted to Envarsus.
    - Those randomized to Envarsus will begin conversion immediately based on a dosing ratio of 0.8 x the total 24-hour IR tacrolimus dose that will lead to therapeutic tacrolimus trough levels.
    - Therapeutic drug level monitoring and will occur as per usual standard of care for all patients.
    - Blood draws for all subjects will occur as per usual standard of care and will be managed as per usual by the patients' post-transplant team.
    - Envarsus to be supplied by the pharmaceutical company.
    - IR tacrolimus to be supplied by patient's insurance
    - Any applicable vital signs or labs if collected as patient's standard of care may be used during the study period for study purposes.
4. Subjects' tacrolimus levels will be monitored and titrated as per usual practice at our center.
    - The target tacrolimus trough is 8-14ng/mL for patients within the first 3 months of transplantation.
    - They will obtain labs per standard of care (weekly) or at provider discretion.
    - Tacrolimus dose adjustment will be made per clinical judgement and expected to reach target goal range within 2 blood draws one week apart. (Total of two weeks).
5. 6 weeks after study enrollment (+/- 5 days), subjects will be administered the same panel of neurocognitive testing and self-reported questionnaires as at baseline.
    - The tests will be performed in the mornings, between 1-4 hours after patients' morning tacrolimus dose administration.
    - At this appointment the patients will receive a $20 check to help with travel expenses for additional appointments.
6. After this study period, subjects who were randomized into the Envarsus arm will be given the option to remain on Envarsus or return to IR tacrolimus. Those who remain on Envarsus will be part of the extension phase of this study. The funding for the patients' Envarsus at this phase would revert back to their insurance coverage, with potential for coverage by Veloxis if further study will be completed (see below).
7. The extension phase of this study will create a cohort for the assessment of long term graft and patient outcomes.
    - We anticipate that if sufficient numbers plan to remain on Envarsus, we can apply for further funding for this phase. If further funding is approved, we will seek another IRB approval for continuation of this study.

- We do not anticipate long-term data to be collected about subjects beyond their period of participation in this study.

Note: Envarsus is approved by the FDA for use in kidney transplant patients for prevention of rejection.

Below are the neurocognitive tests that we will perform on each patient. These tests will be administered by clinical research coordinators, who will be trained on how to complete each test in order to achieve standardized testing practice.

1. Montreal Cognitive Assessment (MOCA) Test
    a. Available as a paper test or an app (See attachment)
    b. Well researched and accepted in the literature as a measure of mild to moderate cognitive impairment[8,9]
    c. MOCA test version 7.1 will be administered at Day 0, MOCA test version 7.2 will be administered at final 6-week visit.
2. Digit Symbol Substitution (DSS) Test
    a. Available as a paper test or an app (See attachment)
    b. Instrument to measure memory and processing speed[10]
3. Tremor Assessment:
    a. Patient Global Impression of Change Scale (PGI)
    b. Clinicial Global Impression of Improvement (CGI)
    c. Both are 7-point scales assessing tremor change. Both were used in STRATO.[7]

Below is the self-reported assessment we will use on each patient:

1. **The Organ Transplant Symptom and Wellbeing Instrument (OTSWI)**.
2. **Quality of Life in Essential Tremor Questionnaire (QUEST).**

References

7. Langone A, Steinberg SM, Gedaly R, et al. Switching Study of Kidney TRansplant pAtients with Tremor to LCP-TacrO (STRATO): an open-label, multicenter, prospective phase 3b study. *Clinical Transplantation.* 2015;29(9):796-805

8. Vichitvejpaisal, P., Preechakoon, B., Supaprom, W., Sriputtaruk, S., Rodpaewpaln, S., Saen-Ubol, R., & Vessuwan, K. (2015). The Montreal Cognitive Assessment as a Screening Tool for Preoperative Cognitive Impairment in Geriatric Patients. JOURNAL OF THE MEDICAL ASSOCIATION OF THAILAND, 98(8), 782.

9. Tiffin-Richards, Frances E., et al. "The Montreal Cognitive Assessment (MoCA)-A Sensitive Screening Instrument for Detecting Cognitive Impairment in Chronic Hemodialysis Patients." PloS one 9.10 (2014): e106700.

10. Hoyer, W. J., Stawski, R. S., Wasylyshyn, C., & Verhaeghen, P. (2004). Adult age and digit symbol substitution performance: a meta-analysis. Psychology and aging, 19(1), 211.

8) Data and/or Specimen Management and Confidentiality

All individuals with access to participant information will be HIPAA trained and data will be stored using password protected computers and accounts. Data will be stored via a secured,

encrypted online data management system (REDCap) using password protected computers. Due to the nature of the study, we will need to include patient identifiers in the database in order to assess adverse events for the duration of the study. The data will be stored until 1 year after publication of the study.

Data analysis plan: We will compare the neurocognitive scores between the Envarsus and IR Tacrolimus arms of the study. Sample size calcuation was done to determine sample size needed to detect a 1 point difference for each neurocognitive test we plan to use. The two groups will be compared using two-sample mean comparison via t test.

We will not be collecting or banking any patient specimens for this study.

9) Data and/or Specimen Banking

Participant data will be stored for potential future use by the PI and co-PIs pending further IRB approval. Data will only be released upon approval of PI with IRB approval. Data will be stored on encrypted devices requiring password protection. Passwords will not be shared by any users. Paper records of patient testing will be stored in locked cabinets with access only by research staff.

10) Provisions to Monitor the Data to Ensure the Safety of Subjects

Data will be extracted from the EMR and stored in a password protected folder on a secure, encrypted network. This network is only accessible by staff at UC Davis Health. This password protected folder will only be authorized to be accessed by study personnel. When this data is removed from this folder such as for the purposes of data analysis, each patient's data will be coded with a de-identified number. The identified patient information stored in the protected file will be destroyed at the end of this study.

For the duration of a subject's participation in the study, their clinical events and laboratory values will be monitored for any adverse events, including acute rejection, surgical complication, infections, cardiovascular events, neurologic events, and other events or side effects that may potentially be related to IR tacrolimus or Envarsus therapy. These data will be reviewed by the PI and co-PIs to determine if they are the direct result of use of the investigational drug.

Once 50% of total enrollment is reached, the proportion of each arm with either acute rejection or sub-therapeutic tacrolimus trough levels will be compared. If there is a significant difference ($p < 0.05$) between the two arms in terms of rejection or sub-therapeutic tacrolimus trough (level < 8), the PI and co-PI may choose to terminate the study early.

11) Withdrawal of Subjects

Discontinuation criteria from study for individual subjects:

- Subject develops allograft loss (as defined by subject death, re-transplantation, transplant nephrectomy, or return to dialysis) within the period of their study participation
- Subject develops unacceptable toxicity or is withdrawn at the discretion of the patient's supervising physician
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject
- Subject withdraws consent for further treatment or expires during the course of the study
- Subject begins taking any prohibited medications
- Subject develops a severe neurologic condition (ie – stroke, neurologic injury, blindness, or other incapacitating event) that prevents further neurocognitive testing during the period of their enrollment in the study.
- Conversion to a non-tacrolimus-based maintenance regimen in either study arm if required to
- manage toxicities
- With regard to patients receiving Envarsus, an inability to maintain a tacrolimus trough concentration >8 ng/mL for > 2 consecutive weeks during the course of the study, or conversion to twice-daily, immediate-release Tacrolimus
- With regard to patients receiving immediate-release tacrolimus, an inability to maintain a tacrolimus trough concentration >8 ng/mL for > 2 consecutive weeks during the course of the study, or conversion to Astagraf XL or Envarsus.
- Patients meeting inclusion criteria at time of randomization and not initiated on Envarsus or immediate-release tacrolimus within 7 days of study enrollment will be classified as a recruitment failure and not included in the full analysis set (FAS) or per protocol set (PPS) analysis.

Individuals who were enrolled in the study and completed their initial neurocognitive assessment but were not able to complete their follow up assessment due to any of the above will still be included in the baseline testing results. These individuals' further clinical data will not be collected upon their termination from the study.

Individuals who were initially randomized to the Envarsus study arm whose participation is terminated at any point after their study enrollment will be converted back to IR tacrolimus as per usual conversion dosing.

12) Risks to Subjects

This study poses minimal risk to subjects. Envarsus has equivalent rates of rejection compared with IR tacrolimus in large controlled trials so we do not anticipate subjects to be at any increased risk as a result of taking Envarsus. Subjects will, however, need to spend more time in transplant clinic undergoing the testing needed for the study. This may mean more visits to the transplant center for the duration of their participation in the study.

This study also poses an unlikely and minimal risk of breach of confidentiality. The risk of loss of confidentiality will be minimized by assigning a unique study ID number to the patient at the time of study entry. Study information stored by the research personnel at UCDMC, which may include name

and medical record number, will be kept strictly confidential and only available to the principal investigator and trained staff assigned to this study. All information will be kept secure in locked file cabinets accessible only by research personnel.

13) Potential Benefits to Subjects

The study will provide each enrolled patient $20 at the beginning and $20 at the end to compensate them for the time and effort they spend participating in this study. There is a potential benefit for those patients randomized to the Envarsus if there are any improved neurocognitive side effects lessened by Envarsus as opposed to IR tacrolimus.

14) Multi-Site Research

N/A

15) Community-Based Participatory Research

N/A

16) Sharing of Results with Subjects

Results will not be shared with the subjects. The testing that is part of the study do not impact clinical care.

17) Prior Approvals

Funding from Veloxis will be obtained prior to conducting this study.

18) Provisions to Protect the Privacy Interests of Subjects

Only research personnel who are HIPAA trained will interact with patients or have access to their records. All patient interactions will occur in the privacy of dedicated exam and interview rooms that provide confidentiality. All subjects will be informed in advance (at the time of consent) of the types of questions we will be asking for the study and the information that we will be obtaining upon study follow up.

19) Compensation for Research-Related Injury

N/A

20) Economic Burden to Subjects

Participating in this study may involve additional clinic appts which may pose a financial burden to the patient in terms of time away from home/work. To minimize the financial burden to the patient, the study will provide transportation stipends to the patients participating in this study.

21) Drugs or Devices

■ I confirm that all investigational drugs will be received by the Investigational Drug Service (IDS). The IDS will store, handle, and administer those drugs so that they will be used only on subjects and be used only by authorized investigators.

☐ I confirm that all investigational devices will be labelled in accordance with FDA regulations and stored and dispensed in such a manner that they will be used only on subjects and be used only by authorized investigators.

22) ClinicalTrials.gov Registration

Section 1: NIH Funded Studies

If yes to BOTH, the study must be registered on Clinicaltrials.gov.

NO	This study is funded by the NIH. (If this study is not funded by NIH, go to Section 2.)
YES	One or more human subjects will be prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

Section 2: Studies subject to FDA jurisdiction

If yes to ANY the study must be registered on Clinicaltrials.gov.

no	This is a prospective clinical study of health outcomes in human subjects that compares an intervention with an FDA-regulated device against a control. This is not a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes.

no	This is a pediatric postmarket surveillance of a device as required under section 522 of the Federal Food, Drug, and Cosmetic Act.
no	This is a controlled clinical investigation, other than a phase I clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of the Public Health Service Act.

To view a flowchart describing applicable clinical trials subject to FDA jurisdiction click here.

Section 3: Publishing the results

If yes to BOTH the study must be registered on Clinicaltrials.gov.

YES	This study prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the cause-and-effect relationship between a health-related intervention *and* a health outcome.
YES	The PI has access to and control over all the data from the clinical trial and has the right to publish the results of the trial and plans to publish the results in a journal that follows the ICMJE recommendations.

This requirement includes studies of behavioral interventions.

Section 4: Registration on Clinicaltrials.gov is not required

NO	I have read sections 1-3 above and registration on clinicaltrials.gov is not required for this research.

23) Criteria for 10 Year Approval

If yes to all items below this research may qualify for a 10-year approval period.

Yes	
No	This research involves no more than minimal risk.

yes	This research does not receive any federal or state government funding or funding from a private funder who requires annual review per contract.
No	This research is not subject to FDA jurisdiction.
yes	This research does not include prisoners as participants.
yes	This research is not subject to SCRO oversight.
yes	This research is not subject to oversight by the Research Advisory Panel of California (RAP of C).
yes	This research does not involve identifiable information held by the State of California Department or Agency
yes	No personnel involved in the design, conduct, or reporting of this research have a new unreported related financial interest (RFI) in this study.