Official Title: To Understand the Impact of Immunosuppression Using Once-per-day Envarsus XR on the Effect of Total Tacrolimus Dose/Trough Level Ratio on Renal Function (eGFR) in Kidney Transplantation

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Primary Objective: To compare the relationship of once daily tacrolimus extended release (Envarsus) versus twice daily tacrolimus immediate release (Prograf) doses to achieve target trough concentrations (C) relative to the total daily dose (D) given and the effect of C/D ratio on renal function at day 7 and months 1, 3, 6, and 12 months after transplantation utilizing concentration to dose ratio (C/D ratio).

Secondary Objective:

- Compare incidence of rejection between the groups at 90 and 365 days post-transplant (Banff grade I-III and antibody mediated rejection [AMR])
- Compare graft loss and death within 1 year post-transplant
- Death within 1 year post-transplant
- Compare and summarize serious adverse events (AEs) between study groups

Study Population: Living or deceased donor kidney transplant recipients 18 to 80 years of age.

Number of Subjects to be Enrolled / Randomized: 50 patients [25 patients in each arm]

Study Design Overview:
This is a one year, prospective, randomized, open-label trial examining once versus twice daily tacrolimus dosing regimen using two preparations, Envarsus vs Prograf. It will examine kidney function between the two groups using eGFR and also examine one year kidney outcomes, including graft loss and patient death. Biopsy will be performed on clinical indications only (not protocol) when rejection or other problem is suspected in face of deteriorating renal function in each study group utilizing Banff criteria. Patients will be screened prior to surgery and randomized 1:1 to receive, within 48 hours of transplantation, immediate release tacrolimus, administered twice daily, or Envarsus, administered once daily as a component of a standard immunosuppression maintenance regimen also consisting of mycophenolate sodium (MPA) (or mycophenolate mofetil equivalent). Induction therapy will be given and administered per center protocol (rabbit anti-thymocyte globulin 6mg/kg over 4 days except in HLA identical living donor/recipient pairs when basiliximab induction is used intraoperatively). Intravenous corticosteroids (methylprednisolone 500mg intraoperatively with a daily rapid taper to 250, 125, 80 mg) over 4 days will be administered prior to rabbit anti-thymocyte globulin and prior to revascularization as part of the initial induction regimen. Thereafter, patients will be followed for up to 1 year during the open label study period. After discharge from the hospital, the patients randomized to immediate-release tacrolimus will be permitted to receive any immediate release tacrolimus product available to them through normal dispensing mechanisms. Envarsus will be supplied by Veloxis and dispensed by the research pharmacy.

Inclusion Criteria:
Subject is eligible for the study if all of the following apply:

1. Kidney transplant patient ≥ 18 years and ≤ 80 years old

2. Institutional Review Board (IRB) approved written Informed Consent and privacy language must be obtained from the subject prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
3. Recipient of a *de novo* kidney from a living or deceased donor.
    a. If deceased donor, a Kidney Donor Profile Index (KDPI) ≤ 85% are eligible for enrollment.
4. Willingness to comply with study protocol.
5. Previous kidney transplants will be permitted. Patients who are receiving a secondary transplant and who previously received Envarsus or who are currently on Envarsus as a component of maintenance immunosuppression and re-listed for transplant will be eligible to enroll in this study and will be randomized at the time of transplant to either cohort.
6. Subject agrees not to participate in another study while on treatment.
7. Female subject must be either:
    a. Of non-child-bearing potential,
        i. Post-menopausal (defined as at least 1 year without any menses) prior to screening, or
        ii. Documented surgically sterile or status post-hysterectomy
    b. Or, if of childbearing potential,
        i. Agree not to try to become pregnant during the study and for 90 days after the final study drug administration
        ii. And have a negative serum or urine pregnancy test within 14 days prior to transplant procedure
        iii. And, if heterosexually active, agree to consistently use two forms of highly effective birth control (at least one of which must be a barrier method) which includes consistent and correct usage of established oral contraception, established intrauterine device or intrauterine system , or barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, starting at screening and throughout the study period and for 90 days after the final study drug administration.
8. Male subject and their female spouse/partners who are of childbearing potential must be using highly effective contraception consisting of two forms of birth control (one of which must be a barrier method) starting at screening and continuing throughout the study period and for 90 days after the final study drug administration).
9. Female subjects must agree to not breastfeed from screening through end of the study period.

Waivers to the inclusion criteria will NOT be allowed. Patients meeting inclusion criteria at the time of randomization and not initiated on Envarsus or immediate-release tacrolimus within 48 hours of transplant will be classified as a recruitment failure and not included in the analysis.

Exclusion Criteria:

Subject will be excluded from participation if any of the following apply:

1. Patient is known to have a positive test for latent tuberculosis (TB) and has not previously received adequate anti-microbial therapy or would require TB prophylaxis after transplant.
2. Uncontrolled concomitant infection or any unstable medical condition that could interfere with study objectives.

3. Significant liver disease, defined as having, during the past 28 days, consistently elevated AST (SGOT) and/or ALT (SPGT) levels greater than 3 times the upper value of the normal range of the investigational site.
4. Patient who will be maintained on a non-tacrolimus-based maintenance immunosuppressive regimen following his/her transplant procedure.
5. Patient currently taking, having taken within 30 days, or who will be maintained on an mTOR inhibitor following his/her transplant procedure.
6. Use of an investigational study drug in the 30 days prior to the transplant procedure.
7. Contraindication or hypersensitivity to drugs or any of their components that constitute the immunosuppression regimen.
8. Known infection or seropositivity for HIV (HBsAg and HCV positivity with negative viral load permitted).
9. Primaryfocal segmental glomerulosclerosis.
10. Subject has a current malignancy or history of malignancy (within the past 2 years), except non-metastatic basal or squamous cell carcinoma of the skin or carcinoma-in-situ of the cervix that has been successfully treated.
11. Recipient of multi-organ kidney transplants.
12. Recipient of an *en bloc*, adult or pediatric deceased donor kidney
13. Any condition which, in the investigator's opinion, makes the subject unsuitable for study participation.
14. Recipient has taken mTOR inhibitor within 30 days of transplant or with plans for mTOR inhibitor treatment post-transplant.
15. Recipient receiving en block kidney transplant.

Waivers to the exclusion criteria will NOT be allowed.

Treatments

Study participants will receive either Envarsus (single daily dose) or SOC, twice daily, immediate-release tacrolimus for 1 year following their transplant procedure. Because of its extended-release pharmacokinetics, it is critical that Envarsus be initiated at a dose of 0.12/mg/kg/day as a single daily dose. After the initial dose, Envarsus dosing will be titrated according to the clinical judgment of the attending physician and appropriate TDM of tacrolimus trough concentrations. This dosing should account for the fact that when identical trough levels are targeted, systemic exposure to tacrolimus is the same for both Prograf and Envarsus. Patients receiving immediate-release tacrolimus should be initiated on therapy per center protocol which is 0.1 mg/kg/day. After initial dosing, subsequent dosing in patients receiving either Envarsus or immediate-release tacrolimus should be predicated on clinical experience, patient tolerability, and monitoring of whole blood tacrolimus drug concentrations, the measurement of which, along with target tacrolimus levels, will be guided by the center protocol.

Study subjects will be counseled on the need to exhibit 100% compliance with their medication regimen in a manner that reflects a center's own standard of care.

Investigational Product and Dosing:

Tacrolimus, extended-release, oral (Envarsus); 0.75 mg, 1 mg, 4 mg tablets

Administered once daily at initial weight-based dose of 0.12 mg/kg. Dosing and monitoring thereafter predicated on clinical judgment to a minimum whole blood tacrolimus concentration of at least 8 ng/mL. When possible, patients will receive their daily dose of Envarsus using the fewest number of pills possible.

Comparative Drug and Dosing:
Tacrolimus immediate-release, oral; 0.5 mg, 1 mg, 5 mg capsules
Administered twice daily per clinical judgment of supervising physician (dosing and monitoring in accordance with center protocol) to a minimum whole blood tacrolimus concentration of at least 8 ng/mL.

Concomitant Medications:
All patients will receive induction immunotherapy (either T-cell depleting agent or IL-2 co-stimulation blocker). The dose and frequency of the chosen induction agent will be determined by the patient's treating physician and administered in conjunction with the participating transplant center's *de novo* kidney immunosuppression protocol. As a participant in this study, in addition to tacrolimus, study subjects will need to concomitantly receive mycophenolate sodium (or MMF equivalent). Anti-CMV, fungal, bacterial, and pneumocystis prophylaxis will follow standard of care. Non-tacrolimus based immunosuppressive regimens (i.e. cyclosporine, everolimus, sirolimus, belatacept), as well as all forms of extended-release tacrolimus other than Envarsus, are prohibited during the course of the study. *Measures to Treat Rejections:* The need for therapy to treat rejection will be determined by the supervising physician. Typical rescue drugs employed under these conditions include, but are not limited to rabbit anti-thymocyte globulin, intravenous immunoglobulin (IVIG), rituximab, and eculizumab.

Duration of Treatment:
Study enrollees will receive study medication (single daily dose of Envarsus or standard of care twice daily, immediate-release tacrolimus) for up to one year following their transplant procedure.

Formal Stopping Rules:
A decision to terminate the study early will be based on the event rate of rejections or AE's as determined by the Research Committee of the Renal Transplantation Service comprised of all nephrologists, surgeons, and transplant coordinators which meets monthly. The study duration will be such that patients will complete at least one year of study visits. Interim data analysis will be performed once all patients complete 6 months of study and final analysis will be performed when all patients complete 12 months of study.

Discontinuation Criteria from Treatment for Individual Subjects:
Subject develops allograft loss (as defined by subject death, re-transplantation, transplant nephrectomy, or return to dialysis of ≥ 6 consecutive weeks);
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;
Conversion to a non-tacrolimus-based maintenance regimen in either study arm if required to manage toxicities.

Endpoints for Evaluation:
***Primary*:** To compare the relationship of once daily tacrolimus extended release (Envarsus) versus twice daily tacrolimus immediate release (Prograf) doses to achieve target trough concentrations (C) relative to the total daily dose (D) given

and the effect of C/D ratio on renal function at day 7 and months 1, 3, 6, and 12 months after transplantation utilizing concentration to dose ratio (C/D ratio).

***Secondary*:** Comparison between treatment cohorts regarding incidence will rely upon assessments for each of the following results:

- Compare incidence of rejection between the groups at 90 and 365 days post-transplant (Banff grade I-III and antibody mediated rejection [AMR])
- Compare graft loss and death within 1 year post-transplant
- Compare and summarize serious adverse events (AEs) between study groups
- Death within 1 year post-transplant

Statistical Analysis:

Sample Size: The sample size for this pilot study is not sufficiently powered to document that the C/D ratio in each patient group will correlate directly with eGFR. We expect to see a trend suggestive that the Envarsus group by virtue of more stable Tacrolimus level and greater compliance over time will be less likely to develop calcineurin-induced nephrotoxicity and therefore result in a better e-GFR. This is not likely to be statistically significant in this inadequately powered study since the variability in donor organs themselves, as well as many other variables, will not permit a precise analysis in this small study sample. However, stratification for living donors and deceased donors may provide important trends in this pilot project which may then guide us to expand the study in more restricted categories of renal allograft recipients. The statistical summary and analysis of safety data, will consist of all subjects who enrolled into the study and took at least one dose of study medication. Demographics and other baseline characteristics will be summarized by treatment group. Descriptive statistics (e.g., n, mean, standard deviation, minimum, median, maximum) and inter-quartile range, coefficient of variation, and geometric mean will be provided for tacrolimus dose and whole blood concentrations of tacrolimus for both study cohorts. Tacrolimus concentrations will be summarized with descriptive statistics. The analysis of efficacy regarding C/D effectiveness in relation to number of rejection episodes and outcomes at various stated time points will be conducted using Student T test. The association between whole blood concentrations and the following endpoints will be assessed: rejection episode and eGFR, histopathology (Banff classification) and conventional measures of transplant outcomes.

H0: The probability of incidence for the primary endpoint is the same between patients receiving Envarsus and patients receiving immediate-release tacrolimus.

Safety: All adverse events (AE) will be listed. The number and percentage of AEs, significant AEs, AEs leading to discontinuation, and AEs related to study drug will be summarized by treatment group. The number and percentage of AEs by severity will also be summarized.

Randomization will be performed in excel prior to initiation: Allocation will consist of a 1:1 ratio for twice daily, immediate-release tacrolimus or Envarsus.

Institutional Review Board (IRB)

The clinical protocol, any protocol amendments, the informed consent, and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) will be reviewed by an IRB. The IRB will review the

ethical, scientific and medical appropriateness of the study before it is conducted. IRB approval of the study protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to drug shipment to our site. Any serious adverse events that meet reporting criteria, as dictated by local regulations, will be reported to Regulatory Agencies, as required. The investigator shall make an accurate and adequate final report to the IRB within 90 days after the close-out of the study - within one year after last subject out or termination of the study.

Subject Informed Consent

The investigator or his/her representative will explain the nature of the study to the subject or his guardian (if applicable), and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject or guardian and the person who administered the informed consent, and any other signatories according to local requirements. A copy of the signed informed consent form will be given to the subject and the original will be scanned into the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy. The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor, regulatory authorities and other applicable and permitted individuals upon request.

1. The investigator or his/her representative will immediately inform the subject whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue to participate in the study (e.g., report of serious drug adverse drug reaction). The communication must be documented in the subject's medical records and must document whether the subject is willing to remain in the study or not.
2. The investigator or his/her representative must obtain written informed consent from the subject throughout their participation in the study. The investigator or his/her designee must re-consent subjects with the updated files even if relevant information was provided orally. The investigator or his/her representative who obtained the written informed consent and the subject should sign and date the informed consent form. A copy of the signed informed consent form will be given to the subject and the original will be scanned into the subject's medical record. An entry must be made in the subject's records documenting the re-consent process.

Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential. Information may be given only after approval of the subject to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being. The investigators shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons. The investigator and collaborators affirm the subject's right to protection against invasion of privacy. Only a subject identification number and/or initials will identify subject data retrieved for analysis. However, Investigator will permit Veloxis, its representative(s), the IRB and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study. The use and disclosure of protected health information (PHI) obtained during this research study will comply with the federal and/or regional legislation related to the privacy and protection of personal information.

Patient Recruitment

Living Donor Recipients*:* Research subjects for a living donor kidney will be recruited from the clinical practice of the Principal Investigator and colleagues. All potential subjects are patients of members of the study team. The research coordinator will do a preparatory to research (allowed with HIPAA Form D) by reviewing the patient records to see if they meet criteria for the study. If they meet the eligibility criteria, the transplant physician, nephrologist or transplant coordinator will explain the basics of the study to the patient during the pre-transplant clinic visit, during the pre-operative visit, or over the phone. If the patient agrees to speak with the research team further about the study, the investigator or research coordinator will continue the informed consent process. Patients receiving living donor transplants will not be first approached for research the same day of transplant. All subjects will sign consent prior to any research activities take place.

Deceased Donor Recipients: This study calls for consenting deceased donor renal allograft recipients on the same day of surgery. Today, the waiting list for a deceased donor kidney transplant is up to 800 patients. Mailing out letters would be very expensive and may not reach the majority of the patients. On the day of surgery, the transplant coordinators will inform the research coordinators when they have called in a patient for transplant. The coordinator will come to the hospital and the study will be introduced to the subject by a clinician involved in the patient's care, most likely the transplant physician. If the subject is interested in learning more about the study, the research coordinator will explain the study in detail, and give the patient ample opportunity to ask questions about the study prior to surgery. The study will only be introduced while the patient is in the admitting area, in the outpatient clinic, or the outpatient counseling center. If the study has not been introduced by the time they are called to the holding area (the last step before they go to the operating room), the study will not be introduced. The study will be posted on the Department of Surgery website and on clinicaltrials.gov.

Background

Despite lower rates of acute rejection and short-term improvements in patient and graft survival, the rate of late allograft loss following kidney transplantation has remained unchanged [Lamb et al, 2011; Kaneku and Terasaki, 2006]. The link between chronic nephrotoxicity and the use of CNIs has proven somewhat elusive [Shihab et al, 2008; Ekberg, Grinyo, et al, 2007; Naesens et al, 2007; Nankivell et al, 2004; Seron et al, 2002]. Late allograft injury as evidenced by moderate-to-severe arteriolar hyalinosis (a hallmark of CNI nephrotoxicity) is found to a similar extent in patients never exposed to CNIs at 5 years [Stegall et al, 2011]. Achievement of therapeutic, minimally toxic, tacolimus concentrations early (within 30 days), after transplantation, is known to be important since achieving it has been associated with a lowered risk of acute rejection. We hypothesize that using extended release tacrolimus (Envarsus, Veloxis), will provide more stable, more effective, and less toxic levels of tacrolimus in renal allograft recipients. It is of high clinical importance to identify factors which can predict who is endangered to develop CNI toxicity. In a recent report Gerold Tholking *et al*, (Ann Transplant, 2016) hypothesized that the TAC metabolism rate expressed as the blood concentration normalized by the dose (C/D ratio) is a simple predictor. Therefore, we propose to analyze the impact of the C/D ratio on kidney function after renal transplantation in experimental group that will be treated with Envarsus and the SOC group treated with twice a day Prograf. Renal function will be analyzed 7 days and 1, 3, 6, and 12 months after transplantation. We propose to test this in a randomized comparison of renal allograft recipients treated either with Envarsus or with standard of care (SOC) treatment with immediate release TAC administered twice a day. Such randomized study in various well defined patient

populations (race, sex, age, and diabetes) should provide evidence for possible greater efficiency and lesser toxicity of extended release drug, Envarsus, as compared to SOC treatment with immediate release tacrolimus given twice per day. Envarsus is an oral, extended-release formulation of tacrolimus developed to enable a once daily dosing regimen. It decreases intra-patient variability and offers flatter kinetics which should ensure a more consistent immunosuppression exposure over the long-term without unpredictable high peaks which may be related to higher toxicity rate, including nephrotoxicity. There is little doubt that the once daily dosing has been described as improving medication adherence [Sabbatini et al, 2014; Doesch et al, 2013; Eberlin et al, 2013; Kuypers et al, 2013].

Since Tacrolimus, the mainstay of immunosuppression in renal transplant patients is known for drug induced nephrotoxicity, which may limit graft survival we propose a prospective randomized study to analyze the relationship of tacrolimus doses to achieve target trough levels (C/D) and renal function at different time-points after transplantation. In this analysis, all 1:1 randomized renal allograft recipients maintained with mycophenolate sodium will be treated either with tacrolimus (Prograf) in the SOC treated controls or with Envarsus in the experimental group. Renal function will be estimated by MDRD equation (eGFR MDRD). Such a prospective, randomized, controlled pilot trial to compare the use of once a day Tacrolimus (Envarsus) vs. twice a day Tacrolimus (Prograf) to test the hypothesis that the consistency of immunosuppression with Envarsus increases the C/D ratio, i.e. get effective stable trough levels with lower total Tacrolimus dose given as Envarsus, and lead to better eGFR, and reduce the likelihood of nephrotoxicity (lower total Tacrolimus exposure). In the course of this study, patients in the control arm will receive immediate-release formulations of tacrolimus in accordance with local SOC dispensing practices, thus preserving the real-world conditions in which the patient could receive any manufacturer's approved product. In this manner, it is hoped that this research will improve the understanding of chronic calcineurin inhibitor injury and provide greater insight into how tacrolimus exposure impacts long term, and even short term, renal function (eGFR).

Pharmacokinetics

Following oral administration, tacrolimus is generally rapidly absorbed (tmax) in approximately 1.5 hours. The mean oral bioavailability is low, approximately 20%, with a large amount of variation between individuals. In plasma, the drug is highly bound to plasma proteins (serum albumin and alpha-1-acid glycoprotein). Tacrolimus has a large volume of distribution and is cleared by hepatic metabolism- CYP3A system and p-glycoprotein, which decreases oral bioavailability of tacrolimus. Tacrolimus is primarily eliminated in the bile. Tacrolimus is an active substance with a narrow therapeutic index which requires regular monitoring to establish and maintain appropriate drug exposure. Immunosuppressive therapy with tacrolimus is usually initiated as a weight-based dose and adjusted on the basis of tacrolimus whole blood trough concentration monitoring. To ensure that appropriate systemic exposure is achieved, the prevailing practice is to conduct TDM based on the trough whole blood concentrations (Cmin). Although tacrolimus systemic exposure (AUC) is the critical parameter for both safety and efficacy in transplant recipients [Kuypers et al, 2004; Undre et al, 1999], AUC monitoring is not feasible in clinical practice. For this reason, Cmin (trough concentration) is used as a surrogate for overall exposure. For both Envarsus and Prograf formulations, the established trough concentration goals can be used to target the same systemic exposure level.

Clinical Studies of Efficacy and Safety

Tacrolimus as Prograf has been proven to be effective in liver, kidney, and heart transplant recipients. Several controlled clinical trials have confirmed that the efficacy of Prograf as therapeutically equivalent, in terms of preventing acute rejection, to a cyclosporine-based regimen. The efficacy of Envarsus in adult kidney transplant recipients indicate that Envarsus is non-inferior to Prograf.

Overall Safety Profile

The safety profile of Prograf has been established; clinically important events include impairment of renal function, abnormal glucose metabolism, and neurological disorders. Many of the adverse drug reactions are reversible and/or responded to dose reduction. Transplant patients on immunosuppressive therapy are also known to be at increased risk of developing post-transplant lymphoproliferative disorders and other malignancies. This risk is considered to be related to the overall immunosuppressive burden. The adverse events observed following administration of Envarsus in kidney transplant recipients were consistent with the established safety profile of Prograf. No new adverse events that would suggest a clinical concern were identified.

Study Design

This is an exploratory, pilot one year, prospective, randomized, open-label trial examining long-term kidney transplant outcomes. Specifically, it is designed to compare the effects of twice daily, immediate-release tacrolimus and once daily Envarsus on trough Tacrolimus concentrations (C) relative to the total daily dose (D) given and to determine the effect of C/D ratio on renal function at day 7 and months 1, 3, 6, and 12 months after transplantation utilizing concentration to dose ratio (C/D ratio). Patients will be screened prior to surgery and randomized 1:1 to receive, within 48 hours of transplantation, immediate-release tacrolimus, administered twice daily, or Envarsus once daily, as a component of a standard immunosuppression maintenance regimen also consisting of peri-transplant only corticosteroids and mycophenolate sodium (MPA), or equivalent. Induction therapy will be given and administered per center protocol. Intravenous corticosteroids will be administered prior to revascularization as part of the initial induction regimen, with dose and duration of therapy also determined by the standard protocol which tapers steroids off within 5 days of transplantation with few exceptions (patients who have been maintained on steroids prior to transplant and patients with IGA nephropathy). Thereafter, patients will be followed for up to 1 year during the open-label study period. Immediate-release tacrolimus will be obtained from pharmacies per the local standard of care. After discharge from the hospital, the patients randomized to immediate-release tacrolimus will be permitted to receive any immediate-release tacrolimus product available to them through normal dispensing mechanisms. Envarsus will be supplied by Veloxis and dispensed by the Research Pharmacy. Additionally, all local kidney biopsy results, local laboratory results, AEs, and concomitant medications pertaining to AEs will be recorded. At the terminal study visit at 12 months, the most recently obtained lab results as well as any episodes of rejection, graft loss, and deaths occurring beyond the first year will be detailed and reported to the IRB. Pathology results [hematoxylin and eosin (H&E), light microscopy, and immunofluorescence] will be recorded when local kidney biopsies are performed and interpreted during the course of clinical care. Substantiation by local biopsy will be required for cases of suspected rejection. A kidney biopsy will be graded by the most recent version of the 2007 Update to the Banff ’97 Classification by our renal pathologist blinded to clinical results.

Study Visits

Screening Period

The screening period can be any time from 21 days before your transplant until the day of transplant. At the screening visit, the following procedures and tests will be performed:

-A review of current health status, medical and surgical history, and list of medications

-Collection of blood samples for clinical purposes.

-A physical examination (including height and weight)

- Questions about any side effects that may occur from the medications taken.

-Female participants who are able to have children will also have a pregnancy test (either from a blood draw or a urine sample) within the 14 days before the kidney transplant as per standard-of-care.

For deceased donor, the screening and randomization procedures may take place on the day of transplant.

For living donors, randomization procedures may take place on the day of transplant.

Randomization

Subjects will be randomized to two open label treatment arms in a 1:1 ratio by a computer program. The two treatment arms are: Treatment Arm 1: Study medication is once daily Envarsus, or slow-release tacrolimus; Treatment Arm 2: Study medication is twice daily, Prograf, or immediate-release tacrolimus. Randomization will happen the day of transplant to ensure all questions have been answered prior to surgery and the subject wishes to remain in the study.

Subjects randomized to Envarsus will need to take the study medication once a day at the same time each day, by mouth. For both treatment arms, the medications that you take in preparation for your kidney transplant ("induction therapy") and the other medications that the study medication needs to be taken with (including steroids and mycophenolate mofetil [MMF]) will be given to you in the way your doctor normally gives them. These medicines will not be paid for or reimbursed by the study sponsor because they need to be taken whether or not you are in the study. ONLY the study medication Envarsus will be provided to you by the sponsor for no charge.

Follow Ups

Both Arms of the study will have the same 11 planned study visits to the research center, which will be done monthly post-transplant until the 1 year follow up is completed. When possible, all visits will be done in conjunction with standard-of-care-follow up visits with the nephrologist. If the subject is unable to return for an in-person appointment, a phone call visit will be used in its place with the research staff.

At these visits, the following study procedures and tests will occur:

• A review of any medications you take

• Adverse Events review

• Arm 1 (Envarsus) only: Return any used and unused bottles of study drug (week 52 only)

Study Drug Handling

Current ICH GCP Guidelines require the investigator to ensure that study drug deliveries from the Sponsor are received by the investigator/or designee and ● that such deliveries are recorded, ● that study drug is handled and stored

according to labeled storage conditions, ● that study drug with appropriate expiry is only dispensed to study subjects in accordance with the protocol. Drug inventory and accountability records for the study drugs will be kept by the investigator / research pharmacy.
Study drug accountability throughout the study must be documented and reconciled. The following guidelines are therefore pertinent: ● The investigator agrees not to supply study drugs to any persons except the eligible subjects in this study in accordance with the protocol. ● The investigator or designee will keep the study drugs in a pharmacy, accessible only to those authorized by the investigator to dispense these test drugs. ● A study drug inventory will be maintained by the investigator or designee. The inventory will include details of material received and a clear record of when they were dispensed and to which subject. Appropriate forms of deliveries and returns must be signed by the site staff delegated this responsibility. ● The site will return study drug to the Sponsor at the end of the study or upon expiration.
Medication will be dispensed by the research pharmacy. Tacrolimus, immediate-release will be obtained by the transplanting center during a participant's inpatient stay and by the patients, themselves, thereafter, at retail pharmacies.

Data collection

Demographics: Will be collected during screening: date of birth, sex, race, and ethnicity.
Medical History**:** Etiology of renal failure, viral serology (HBV, HCV, CMV, EBV), and diabetes history (as applicable).
Transplant Information**:** Day 0 visit: type of transplant (living related, living non-related, DD, and whether organ was obtained in the setting of DCD or CDC), number of prior transplants and reason for prior graft loss (if applicable), total cold and warm ischemia time in hours and minutes, KDPI, ABO blood typing, HLA typing of donor and recipient, degree of HLA mismatch between donor and recipient, and most recent panel reactive antibody testing. Donor viral serology information (HBV, HCV, CMV, EBV), if available, will be collected and recorded. Additional donor information includes age, sex, height, weight, donor cause of death, ethnicity, ABO typing, and results of any pre-implantation biopsies.
Height and Body Weight**:** Height and dry weight will be recorded at screening and pre-operatively on study day 0.

Efficacy Assessment

Estimated Glomerular Filtration Rate: Estimated glomerular filtration rate (eGFR) will be calculated at day 7 and months 1, 3, 6, and 12 using the Modification of Diet in Renal Disease (4 variable – MDRD) criteria.
Calculation of C/D Ratio**:** Calculation of the daily trough level over the average daily total tacrolimus dose delivered either by ENVARSUS or by SOC twice a day Tacrolimus will be performed monthly throughout the study.
Patient Survival**:** Patient survival is any subject that is known to be alive at the study conclusion.
Graft Survival**:** Graft survival is defined as any subject that does not fit the following definition of graft loss: subject death, re-transplantation, transplant nephrectomy, or return to dialysis for a period of ≥6 weeks by study end.
Acute Rejection**:** For study purposes, diagnoses of rejection require biopsy confirmation. Both acute cellular and antibody mediated rejection will be assessed and graded according to published criteria [Solez et al, 2008] by the NYPH Renal Pathology Division pathologist.

Adverse Events

Adverse event collection will begin once informed consent has been signed and continue throughout the subject's participation in the study. A subset of the routine laboratory assessments obtained per SOC, including creatinine, hemoglobin, hematocrit; platelet count; white blood cell count; serum sodium, potassium, blood urea nitrogen, glucose, urinalysis (including urinary protein), tacrolimus trough concentrations.

Physical Examination

A complete physical exam will be conducted at screening. Any abnormal findings must be assessed and documented as not clinically significant if a subject is to be enrolled in the study. The investigator or qualified designee will conduct the exam, determine findings, and assess any abnormalities as to clinical significance.

Causal relationship to the study drug may be:

1. Not Related in which case a clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and/or in which other drugs, chemicals, or underlying disease provide plausible explanations.

2. Possible in which case a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

3. Probable in which case a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on re-administration (rechallenge) or withdrawal.

Reporting of Serious Adverse Events (SAEs)

In the case of a serious adverse event (SAE), the investigator must contact the local IRB and the Sponsor by telephone or fax immediately (within 24 hours of awareness). Full details of the SAE should be recorded on the medical records, copies of which should be forwarded by fax to the local IRB and to the Sponsor (Veloxis).

The following minimum information is required: ● Internal Study number, ● Subject number, sex, and age, ● Date of report, ● Description of the SAE (event, seriousness of the event), and ● Causal relationship to the study drug.

All AEs occurring after informed consent is signed should be collected and recorded in the electronic chart. All new SAEs and Adverse Drug Reactions (non-serious and serious AEs related to systemic tacrolimus) will be captured and recorded in the medical record.

Follow-up of Adverse Events

All AEs occurring during the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized. If during AE follow-up, the adverse event progresses to an "SAE", or if a subject experiences a new SAE, the investigator must immediately report the information to the Sponsor. Local IRB will inform the investigator that some events reported as SAEs may not require expedited reporting to the IRB. The Sponsor will monitor these events throughout the course of the study.

Procedure in Case of Pregnancy

If a female subject or partner of a male subject becomes pregnant during the study dosing period or within 30 days from the discontinuation of dosing, the investigator should report the information as an SAE. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data etc., should be included in this information. The medical status of the mother, as well as the fetus, will be followed and outcome reported to the IRB.

DISCONTINUATION

Discontinuation is defined as a subject who enrolled in the study and for whom study treatment is permanently discontinued prematurely for any reason. The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants.

Discontinuation Criteria from Treatment for Individual Subjects:

● Subject develops allograft loss (death, re-transplantation, transplant nephrectomy, or return to dialysis ≥ 6 consecutive weeks);
● 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;
● Conversion to a non-tacrolimus-based maintenance regimen in either study arm if required to manage toxicities;

OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

Data Collection

The investigator or site designee will enter data collected using the local Electronic Medical Record (EMR) systems. In the interest of collecting data in the most efficient manner, the investigator or site designee should record data, including local laboratory values, in the hospital visit form during hospital admissions including the transplant admission (Eclipsys EMR) or office visit form (Crown) within 5days after the subject visit. The investigator or site designee is responsible to ensure that all data in the EMR are recorded within 5 days of the visit. Source data will be available at the site in the two EMR (inpatient- Eclipsys and outpatient- Crown in the Allscript System). Source data will include the medical treatment and history of the subject. The following information will be included: ● Demographic data (age, sex, race, ethnicity, height and body weight) ● Cross-match results ● Separate donor source data including donor demographics, KDPI of donor kidney and donor HLA typing ● Participation in study and original signed and dated informed consent ● Visit dates ● Medical history and physical examination details ● Adverse events(including causality) and concomitant medication ● Results of relevant examinations when appropriate ● Laboratory tests ● Reason for premature discontinuation (if applicable) ● Randomization number

Direct Access to Source Data/Documents

The investigator and the study site will provide assistance for any monitoring and auditing by Veloxis, as well as inspections from the IRB relevant regulatory authorities as requested. In these instances, the investigator or his designee will assist at the review of all study-related records, without allowing independent access to the records per the rules of

the hospital. The confidentiality of the subject's identities shall be well protected consistent with local and national regulations when the source documents are subject to inspection.

Protocol Deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and for protecting the rights, safety, and welfare of subjects. The investigator should not implement any deviation from, or changes to, the protocol, unless it is necessary to eliminate an immediate hazard to trial subjects. For the purposes of this protocol, deviations requiring notification to Sponsor and to the local IRB are defined as any subject who: ● Entered into the study even though they did not satisfy entry criteria. ● Received wrong treatment or incorrect dose. ● Received excluded concomitant treatment. When a deviation from the protocol is identified, the investigator or designee must ensure that local IRB is notified.

Documents and Records Related to the Clinical Study

The investigator will archive all study data in the patient's electronic data chart (e.g., Subject Identification Code List, source data, and eGFR,) and relevant correspondence. Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes.

Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments. Depending on the nature of the amendment, either IRB approval or notification may be required. The changes will become effective only after the approval of Veloxis, the investigator, and the IRB. Amendments to this protocol must be signed by Veloxis and the investigator. Written verification of IRB approval will be obtained before any amendment is implemented which affects subject safety or the evaluation of safety, and/or efficacy. Modifications to the protocol that are administrative in nature do not require IRB, but will be submitted to the IRB for their information. If there are changes to the Informed Consent, written verification of IRB approval must be forwarded to Veloxis. An approved copy of the new Informed Consent must also be forwarded to Veloxis.

Schedule of Events

	Screening (-21 to Day 0)	Randomization	Transplant (Day 0)	Month 1 - Month 12 (± 2 weeks)[3]
Consent	X			
Demographic	X			
Medical History	X			X
Height and weight[1]	X		X	X
Transplant information			X	
Randomization Assignment[2]		X		
IP Dispensation			X	X
Clinical Laboratory assessment	X			X
Pregnancy test (WOCBP only)	X			X
Concomitant Medications	X	X	X	X
Adverse Events	X	X	X	X
Study drug accountability			X	X

[1]Height and Body Weight: Height and dry weight will be recorded at screening and pre-operatively on study day 0.
[2]For living donors, the randomization will happen at the pre-operation check-up at the hospital, which happens about 7 days before transplant operation. For deceased donors, the randomization will happen at admission for the transplant operation.
[3]Month 1 to Month 12 Visits will be conducted in conjunction with SOC visits. Adverse events and drug accountability will be reviewed for research purposes.