**Title of Research Study: Once-Daily Extended-Release Tacrolimus Vs. Twice-Daily Tacrolimus: Impact On T-Cell Subpopulations And Markers Of Renal Tubule-Toxicity In Kidney Transplant Patients**

**Investigator: Lorenzo Gallon, MD**

**Supported By:** This research is supported by **Veloxis Pharmaceuticals Inc.**

**Financial Interest Disclosure:**
If your doctor is also the person responsible for this research study, please note that he is interested in both your clinical care and the conduct of this research study. You have the right to discuss this study with another person who is not part of the research team before deciding whether to take part in the research.

**Key Information:**
The first few pages of this document include a summary of this study to help you decide whether or not to participate. Detailed information is provided after the summary.

## Why am I being asked to take part in this research study?

We are asking you to take part in this research study to find out if the drug Envarsus® XR has beneficial effects in people, such as yourself, who are scheduled to receive a kidney transplant from from either a living or deceased donor.

## What should I know about a research study?

- Someone will explain this research study to you.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.
- You can ask all the questions you want before you decide.

## Why is this research being done?

This research study is sponsored by the pharmaceutical company Veloxis. You have been scheduled to have kidney transplant surgery. After receiving a kidney transplant, patients must take medications known as immunosuppressants that work to prevent rejection of the transplant. There are a number of such medicines available, e.g., cyclosporine (Neoral), tacrolimus (Prograf), everolimus (Certican, Zortress), MMF (Cellcept), EC-MPS (Myfortic), basiliximab (Simulect), steroids and others. These medications are typically taken in combinations to help reduce side effects and help prevent kidney rejection.

LCP-Tacro, also known as Envarsus® XR, is a new once-daily form of the drug tacrolimus, and was approved by the U.S. Food and Drug Administration (FDA) in 2015 to prevent rejection in kidney transplant recipients. It is a prolonged-release drug, which uses Veloxis MeltDose technology to deliver the dose of the tacrolimus over a longer period of time. It is taken once a day rather than twice a day.

The main purpose of this study is to compare the transplanted kidney function of recipients taking once-a-day or twice-a-day tacrolimus at 2 weeks, 3 months and 12 months post transplant.

## How long will the research last and what will I need to do?

We expect that you will be in this research study for 12 months.

At your pre-transplant visit, you will be assigned to one of two study medication (or "treatment") groups. The treatment you get will be chosen by chance, like flipping a coin. Neither you nor the study doctor will choose what treatment you get. You will have an equal chance of being give either treatment.

Depending on what treatment group you are assigned to, post-transplant you will receive either:

- Twice daily Tacrolimus given according to standard of care dosing
- Once daily extended release dose of tacrolimus (Envarsus® XR)

In either group you will receive MMF/myfortic according to standard of care dosing.

You will return to the clinic 3 times, at approximately 2 weeks, 3 months and 12 months post transplant. At each of these visits you will have blood and urine samples collected. In addition, tissue samples will be collected at your 3 and 12 month visits (from standard of care kidney biopsy scheduled at this visit).

In addition, blood, urine and tissue samples will be collected at the time of any for cause biopsy you might be required to have. No biopsies will be performed solely for this research protocol.

More detailed information about the study procedures can be found under the section **What happens if I say "Yes, I want to be in this research"?**

## Is there any way being in this study could be bad for me?

The most serious risks associated with either study group (either twice daily tacrolimus or Envarsus® XR) include high blood pressure, kidney damage, or diabetes.

The most serious risk in your standard of care kidney biopsies and the collection of additional tissue samples for research includes bleeding in or around your kidney which can lead to a fall in blood pressure and rise in heart rate.

More detailed information about the risks of this study can be found under **"Is there any way being in this study could be bad for me? (Detailed Risks)"**

## Will being in this study help me any way?

We cannot promise any benefits to you or others from your taking part in this research. However, you will receive close monitoring of your transplanted kidney and medical care during the study.

The benefits of LCP-Tacro/Envarsus XR are not known. Information from this study may help you and/or other people who receive a kidney transplant in the future.

## What happens if I do not want to be in this research?

Taking part in research is completely voluntary. You decide whether or not to participate. If you choose to not participate, there will be no penalty to you or loss of benefit to which you are entitled.

**Detailed Information:**
The rest of this document includes detailed information about this study (in addition to the information listed above).

## Who can I talk to?

For urgent clinical concerns, please call 312-695-8900.

If you have questions, concerns, or complaints, or think the research has hurt you, talk to Dr. Lorenzo Gallon at 312-695-4457. He is available Monday-Friday, 9am to 5pm.

You can also call this clinic after hours, on weekends, and holidays at 312-695-8900 and ask to speak with the kidney transplant research nurse on call.

This research has been reviewed and approved by an Institutional Review Board (IRB). You may talk to them at (312) 503-9338 or irb@northwestern.edu if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research participant.
- You want to get information or provide input about this research.

## How many people will be studied?

We expect about 50 people here will be in this research study.

## What happens if I say "*Yes, I want to be in this research*"?

As a subject in this study, you will be asked to come to Northwestern Medicine Kovler Organ Transplantation Center (676 North St. Clair Street, Suite 1900), Chicago, IL.

At your pre-transplant visit, you will be assigned to one of two study medication (or "treatment") groups. The treatment you get will be chosen by chance, like flipping a coin. Neither you nor the study doctor will choose what treatment you get. You will have an equal chance of being give either treatment. Both forms of tacrolimus (twice daily tacrolimus or once daily extended release dose of tacrolimus) are FDA approved.

The standard of care induction immunotherapy you receive at the time of your transplant will be the same whether you are assigned to treatment Group 1 or Group 2.

The post-transplant treatment groups (Group 1 and Group 2) are described below:

| Group | Medication | Tacrolimus | MMF/myfortic |
|---|---|---|---|

| | | | |
|---|---|---|---|
| **1** | Tacrolimus+MMF/myfortic | Twice daily Tacrolimus given according to standard of care dosing to achieve a 12 hour trough concentration of 8-12 ng/ml | Given according to standard of care dosing |
| **2** | LCP-Tacrolimus/ Envarsus® XR +MMF/myfortic | Once daily extended release dose of tacrolimus to achieve a 24-hour trough concentration of 8-12 ng/ml | Given according to standard of care dosing |

**Study Visit Schedule for All Subjects (Groups 1 and 2)**
Regardless of the group you are assigned to (Group 1 or Group 2), you will have blood, urine and tissue samples collected for research as outlined below:

| Time (all time points relative to transplant) | Blood Draw (50 ml or about 4 tablespoons) | Urine Samples (Up to 200 cc or 1 cup) | Kidney Biopsy |
|---|---|---|---|
| Pre-transplant | X | | |
| 2 weeks post (+/- 7 day) | | X | |
| 3 months post (+/- 10 Days) | X | X | X |
| 12 months post (+/- 10 Days) | X | X | X |
| Any For-Cause Biopsy | X | X | X |

**Blood Collection**
We will collect and store a sample of your blood at the following study visits: Pre-transplant, 3 month and 12 month post-transplant visits. In the case of any for-cause biopsy, we will also collect blood. At each of these visits we will collect 50 ml (about 4 Tablespoons) of blood.

## Urine Collection
We will collect and store samples of urine at the following study visits: 2 weeks, 3 months and 12 months post transplant. In the case of any for-cause biopsy, we will also collect urine samples. At each of these visits we will collect up to 200 cc (about 1 cup) of urine.

**Kidney Tissue Collection**
We will collect a piece of kidney tissue from you during standard of care biopsy procedures at the following time points: 3 months and 12 months post transplant. In the case of any for-cause biopsy, we will also collect tissue. No biopsies will be performed solely for this research protocol. The biopsy will be obtained if needed at time of standard of care visits.

Typically, only tissue viewed as excess for clinical purposes will be diverted for this study. If there is not enough tissue left from the biopsy for clinical purposes, study staff will ask your

permission for an additional pass to get biopsy tissue for the research study. A second biopsy pass can minimally increase the risk associated with the procedure. Samples will be obtained by trained practitioners fully informed of the needs for diagnosis and use of biopsies only in the situation where adequate biopsy samples are obtained.

From your blood, urine and tissue samples, we plan to examine the genes behind your body's immune response (how your body recognizes and protects itself from germs and other things that seem foreign and unsafe). The blood samples will also be used to examine your white blood cell function. Additionally, we will analyze the urine samples for kidney injury markers.

### What are my responsibilities if I take part in this research?

If you take part in this research, you will be responsible to take the study medication as directed. It is important that you tell the study site personnel about any other medication you are taking before and during the study including herbs and vitamins.

### What happens if I do not want to be in this research?

You may choose not to take part in this research study. Your decision whether to take part or not will not affect your relationship with your study doctor or with Northwestern. You will not lose benefits to which you would be otherwise entitled and your choice not to be in this study will not negatively affect your right to any present or future medical treatment.

### What happens if I say "Yes", but I change my mind later?

You can withdraw from this research study at any time and it will not be held against you. However, per standard of care treatment, you may not stop taking anti-rejection medication.

You will be asked to return to the clinic as soon as possible to check how you and your kidney is doing. For this visit, you should bring your study medications to the clinic. During this visit, you and the study doctor may choose to change your treatment. Please be aware though that you cannot stop immunosuppressive treatment as you will have an increased risk of rejection.

During this period data will be collected that will help the Sponsor understand the effect of study treatment on your health and the status of your transplanted kidney. This data would include vital signs, survival, graft loss/re-transplantation, any rejection of the kidney transplant or biopsies done, hospitalizations, laboratory assessments and certain side effects you may have during that time.

Because all of your visits are also regularly scheduled standard of care (SOC) visits, you will keep your clinic visits even if you leave the study.

If you stop being in the research study, already collected data may not be removed from the study database. You will be asked whether the study staff can collect data from your routine medical care. If you agree, this data will be handled the same as research data.

### Detailed Risks: Is there any way being in this study could be bad for me?

The risks of this study include any possible side effects of study medications and risks associated with the taking of your biological samples. Your doctor will discuss these risks with you before you begin taking the study medication.

You should report any side effects that you feel to your study staff as soon as possible. Every precaution will be taken to ensure that side effects will be acted upon immediately. As with all immunosuppressive medications, all patients are at an increased risk of infections and malignancies. In such situations, your doctor may have to treat you with other drugs and may have to stop or reduce your immunosuppressive drugs.

**Side effects of Tacrolimus (Prograf®, Envarsus® XR)**

- High blood pressure
- High blood sugar
- Diabetes
- Kidney damage
- Trembling
- Headaches
- Burning in the hands and/or feet,
- Itchy skin
- Increased levels of potassium in the blood (which can cause nausea and an irregular heartbeat)
- Increase in cholesterol and or fat levels in the blood
- Unsteady movements or clumsiness
- Thickening of the heart muscle
- Insomnia
- Abdominal pain
- Diarrhea
- Nausea
- Less common but more serious side effects include:
    - inflammation of the lung tissue
    - BK nephropathy (in subjects who receive a renal transplant), kidney damage caused by a BK virus infection
    - posterior reversible encephalopathy syndrome (PRES), a syndrome characterized by headache, seizures and vision changes
    - progressive multifocal leukoencephalopathy (PML), a serious infection that can lead to disability or death

**Side effects of Corticosteroids:**

- Fluid build-up
- Facial swelling
- Weight gain
- Increased appetite
- High blood pressure
- Muscle weakness
- Bone problems
- Fragile skin
- Wound healing problems
- Mental problem

**Side effects of MMF/Myfortic:**

- Diarrhea or constipation
- nausea/vomiting
- Leucopenia (fewer white cells in your blood)
- Pains in the abdomen, chest or back
- Headache
- Anemia (decrease in red blood cells)
- Tthrombocytopenia (fewer of the blood cells known as ‘platelets’)
- Hypertension (raised blood pressure)
- Edema (swelling).

**Blood Draws**

The risks of drawing blood include a bruise at the point where the blood is taken, redness and swelling of the vein and infection. There is a rare chance of getting dizzy or fainting. Care will be taken to avoid these complications.

**Urine Collections**

There are no anticipated risks with collecting urine.

**Biopsies and the Collection of Additional Tissue Samples for Research**

When patients have kidney tissue samples taken, 3 – 4 out of 100 people have bleeding in the kidney (3.5% chance) and 2 – 3 out of 100 people have bleeding around the kidney (2.5% chance). Bleeding in or around the kidney can lead to a fall in blood pressure and rise in heart rate. One out of 100 people who have a transplant kidney biopsy require a blood transfusion or placement of a urinary catheter (1% chance). In 1 out of 1,000 people, a kidney biopsy may lead

to a need for surgery or loss of the kidney (0.1% chance). Additional risks include pain and/or bleeding at the site of the biopsy, infection, discomfort, and blood-stained urine.

This study involves the use of your identifiable, personal information and there is a chance that a loss of confidentiality could occur. The researchers have procedures in place to lessen the possibility of this happening. See the section below titled: "What happens to the information collected for the research?".

### *What do I need to know about reproductive health and/or sexual activity if I am in this study?*

The research may hurt a pregnancy or fetus in ways that are unknown. These may be a minor inconvenience or may be so severe as to cause death.

You should not be or become pregnant, father a baby or breastfeed while on the study and for 3 months after the study is completed. If you are sexually active, both men and women should use a highly effective means of birth control while taking part in this research study and for 3 months after study participation is completed.

If you are sexually active, both men and women should use at least one effective means of birth control while participating in this research study. According to the World Health Organization and the United States Center for Disease Control and Prevention, the most effective forms of birth control include complete abstinence, surgical sterilization (both male and female), intrauterine devices (IUDs), and the contraceptive implant. The next most effective forms of birth control include injectables, oral contraceptive pills, the contraceptive ring, or the contraceptive patch. Acceptable but least effective methods of birth control include male condoms (with or without spermicide) and female condoms.

If you or your partner become pregnant while taking part in this research study or for 3 months after you complete the study, it is important that you tell the study doctor or other research team member immediately. You may be required to stop participation in this study; however, other treatment options will be discussed with you at that time if necessary.

If you or your partner are considered to be postmenopausal, you are not required to use contraception while participating in this research study. Postmenopausal women rarely become pregnant. If you or your partner become pregnant while taking part in this research study or for 3 months after you complete the study, it is important that you tell the study doctor or other research team member immediately. You may be required to stop participation in this study; however, other treatment options will be discussed with you at that time if necessary.

### Will it cost me anything to participate in this research study?

There will be no additional costs to you for taking part in this study. You will not be charged for any of the tests and procedures performed solely for research purposes.

You and your insurance company will be charged for the health care services that you would ordinarily be responsible to pay. This would include charges for all drugs given as standard of care, including tacrolimus and tacrolimus-LCP/Envarsus XR.

In some cases, insurance will not pay for services ordinarily covered because these services were performed in a research study. You should check with your insurance to see what services will be covered by your insurance and what you will be responsible to pay.

**Permission to Take Part in a Human Research Study**
***Do not sign this consent if today's date is later than the stated expiration date above.***

## Will being in this study help me in any way?

We cannot promise any benefits to you or others from your taking part in this research. However, you will receive close monitoring of your transplanted kidney and medical care during the study.

The benefits of LCP-Tacro/Envarsus XR are not known. Information from this study may help you and/or other people who receive a kidney transplant in the future.

## What happens to the information collected for the research?

Efforts will be made to limit the use and disclosure of your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete secrecy. Organizations that may inspect and copy your information include the IRB and other representatives of this institution, ethics committees, health authority inspectors, the FDA, Veloxis study monitors and auditors, and authorized clinical research organization representatives.

Your biological samples will be stored at the Immune Monitoring Core (IMC) under the leadership of Co-Investigator Dr. James Mathew of the Comprehensive Transplant Center (CTC) of Northwestern University.

After certain tests have been performed, de-identified samples will be sent to Adaptive Biotechnoligies, Seattle, for DNA purification and ImmunoSEQ analyses.

Leftover samples at the CTC may be stored for future research studies, if you give your consent to this option.

If the sponsor pays any of your medical expenses, we may be required to give the sponsor your name, date of birth, and Medicare ID or social security number.

The sponsor, monitors, auditors, the IRB, the Northwestern University Office for Research Integrity, the US Office of Research Integrity (ORI), the US Office for the Protection of Human Research Protections (OHRP), the US Food and Drug Administration (FDA) may be granted direct access to your medical records to conduct and oversee the research. By signing this document you are authorizing this access. We may publish the results of this research. However, we will keep your name and other identifying information confidential.

A description of this clinical trial will be available at http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

## Data Sharing

De-identified data from this study may be shared with the research community at large to advance science and health. We will remove or code any personal information that could identify you before files are shared with other researchers to ensure that, by current scientific standards and known methods, no one will be able to identify you from the information we share. Despite these measures, we cannot guarantee anonymity of your personal data.

## Can I be removed from the research without my OK?

The person in charge of the research study or the sponsor can remove you from the research study without your approval. Possible reasons for removal include:

1. Staying in the study would be harmful.
2. You need treatment not allowed in this study.
3. You fail to follow instructions.
4. You become pregnant.
5. The study is cancelled.
6. Your treatment arm is stopped.

We will tell you about any new information that may affect your health, welfare, or choice to stay in the research.

## What else do I need to know?

If you become ill or get injured as a result of this study (medications or procedures), you should seek medical treatment through your doctor or treatment center of choice. You should promptly tell the study doctor about any illness or injury.

The hospital [university, researchers] will not pay for medical care required because of a bad outcome resulting from your participation in this research study. This does not keep you from seeking to be paid back for care required because of a bad outcome.

**Travel Expenses:**
You will receive a coupon for free parking for your study visits. It is only valid if you park in the 222 E. Huron Street Garage which is connected to the Galter Pavilion (clinics) and the Feinberg Pavilion (hospital) by the street overpass on the second floor. The garage is also known as "University Parking Garage A." If you park in any other garage, this parking coupon will not be valid and you will need to pay for your own parking. If you do not drive in for your study visits, the study staff will discuss other options of equal value.

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

## HIPAA Authorization

We are committed to respect your privacy and to keep your personal information confidential. When choosing to take part in this study, you are giving us the permission to use your personal health information that includes health information in your medical records and information that can identify you. For example, personal health information may include your name, address, phone number or social security number. Your health information we may collect and use for this research includes:

- All information in a medical record
- Results of physical examinations
- Medical history

- Lab tests, or certain health information indicating or relating to a particular condition as well diaries and questionnaires
- Records about study medication or drugs
- Billing information
- HIV testing results
- Genetic health information: DNA Testing

During this study you may be coming to a Northwestern Memorial Healthcare Corporation entity (for example, Northwestern Memorial Hospital, Prentice Women's Hospital) for research appointments or to get clinical services, such as lab tests, needed for the study. When that happens, you will be scheduled for these services through the NMHC computer system. When a clinical exam or lab is done by NMHC or one of its employees for the purpose of this research study, that information will be kept in both NMHC's clinical records and in the study records.

The following clinical providers may give the researchers information about you: all current and previous health care providers, including but not limited to the Shirley Ryan AbilityLab (SRALAB), Northwestern Medical Group (NMG), Northwestern Memorial Hospital (NMH), Northwestern Lake Forest Hospital (NLFH).

Once we have the health information listed above, we may share some of this information with the following offices or entities outside of Northwestern University and its clinical partners (or affiliates): the Northwestern University Institutional Review Board Office and Office for Research Integrity; the US Office of Research Integrity; the US Office for Human Research Protections; the US Food and Drug Administration.

Any research information shared with outside entities will not contain your name, address, telephone or social security number or any other personal identifier unless disclosure of the identifier is necessary for review by such parties or is required by law or University policy [except that such information may be viewed by the Study sponsor and its partners or contractors at the Principal Investigator's office].

The following entities may receive your health information:

- Authorized members of the Northwestern University workforce, who may need to see your information, such as administrative staff members from the Office for Research, Office for Research Integrity and members of the Institutional Review Board.
- Clinical affiliates, including but not limited to the Shirley Ryan AbilityLab (SRALAB), Northwestern Medical Group (NMG), Northwestern Memorial Hospital (NMH), Northwestern Lake Forest Hospital (NLFH), and the Ann & Robert H. Lurie Children's Hospital of Chicago (Lurie Children's). Your participation in this clinical trial may be tracked in an electronic database and may be seen by investigators running other trials that you are enrolled in and by your healthcare providers.
- Clinical affiliates, including but not limited to Northwestern Medical Group (NMG), Northwestern Memorial Hospital (NMH), and Northwestern Lake Forest Hospital (NLFH), for purposes including, but not limited to, the affiliate's provision of care to you and/or the affiliate's scheduling of appointments and/or billing activities.
- Other University research centers and University contractors who are also working on the study,
- Study monitors and auditors who make sure that the study is being done properly,

- Veloxis Pharmaceuticals, who is sponsoring the study, and that company's contractors and partners.
- Government agencies and public health authorities, such as the Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS).
- The study doctor must report positive HIV tests to the Illinois Department of Public Health (IDPH)). The IDPH keeps track of all persons in the state with positive HIV tests. Information provided to IDPH include name, social security number, current address, telephone number, age, date of birth, age at diagnosis, race, ethnicity, sex, current gender, country of birth, residence at diagnosis and facility where diagnosis of HIV or AIDS was established.

Those persons who get your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it. Some of those persons may be able to share your information with others without your separate permission.

The results of this study may also be used for teaching, publications, or for presentation at scientific meetings.

Unless you revoke your consent, it will not expire.

Although you may revoke consent to take part in this research at any time and in any format, you must revoke authorization for use or disclosure of your health information in writing. To revoke your authorization, write to:

**Lorenzo Gallon, MD**
**Northwestern University Comprehensive Transplant Center**
**676 N. St. Clair St., Ste. 1900**
**Chicago, IL 60611**

You do not have to authorize the use or disclosure of your health information; however, you will not be allowed to take part in this research study. If you do not authorize the use or disclosure of your health information, it will not affect your treatment by health care providers, or the payment or enrollment in any health plans, or affect your eligibility for benefits.

A copy of this signed consent document, information about this study, and the results of any test or procedure done may be included in your medical records and may be seen by your insurance company.

## Optional Elements:

The following research activities are optional, meaning that you do not have to agree to them in order to take part in the research study. Please indicate your willingness to participate in these optional activities by placing your initials next to each activity.

| **I agree** | **I disagree** | |
|---|---|---|
| _____ | _____ | The researcher may contact me in the future to see whether I am interested in taking part in other research studies by the Principal Investigator of this study. |

## Permission to Take Part in a Human Research Study

***Do not sign this consent if today's date is later than the stated expiration date above.***

| **I agree** | **I disagree** | |
|---|---|---|
| _____ | _____ | The researcher may retain any leftover blood or tissue samples taken during the study. These samples may be used for other research not related to this study. These samples will be retained in non-identifiable form, meaning that there will be no information associated with the blood or samples that will allow anyone to know my identity. |
| _____ | _____ | If necessary, the researcher may take an additional tissue sample during a biopsy. |

Your signature documents your permission to take part in this research. You will be provided a copy of this signed document.

_____ _____
Signature of Participant Date

_____
Printed Name of Participant

_____ _____
Signature of Person Obtaining Consent Date

_____
Printed Name of Person Obtaining Consent