Envarsus XR in Delayed Graft Function (E-DGF)

A phase IV, randomized, single center study among kidney transplant recipients with delayed graft function (DGF) to study the effect of Envarsus XR in the DGF recovery

NCT03864926

Principal Investigator: Sandesh Parajuli, MD, MBBS

PROTOCOL VERSION and AMENDMENTS

Protocol Version	Date	Change Initiated (Initials)	Brief description of protocol modification/actions requested, if any
Template V6	9/6/16	TNK	Input from IRB, OCT, MARCH, IND/IDE services, PIs
Version 1	9/28/17	TLO	Draft reviewed by ICTR Data Monitoring Committee (DMC) and ICTR Study Monitoring Service (SMS)
Version 2	10-23-17	SAJ	Susan Johnston (PRC) edits
Version 3	09/24/18	CLL	Cassandra Leopard, OCT Edits
Version 4	04/24/19	CLL	Cassandra Leopard, OCT Edits
Version 5	06/17/22	CLL	Cassandra Leopard, Add Transplant Database as data source

Contents

STATEMENT OF COMPLIANCE

The signature below constitutes confirmation that the research will be conducted in accordance with the approved protocol, applicable regulations, laws and institutional policies.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator: _____
Print/Type Name

Signed: _____

LIST OF TABLES and FIGURES

List of Abbreviations

AE	Adverse event
ANOVA	Analysis of covariance
BPAR	Biopsy proven acute rejection
CFR	Code of Federal regulations
CLIA	Clinical Laboratory Improvement Amendments
CNI	Calcineurin Inhibitors
CRF	Case Report Form
CRO	Contract Research Organization
DBD	Donation after brain death
DCD	Donation after cardiac death
DGF	Delayed Graft Function
DHHS	Department of Health and Human Services
DMC	Data Monitoring Committee
DSMP	Data and Safety Monitoring Plan
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH E6	International Conference on Harmonisation Guidance for Industry, Good Clinical Practice: Consolidated Guidance
ICMJE	International Committee of Medical Journal Editors
ICTR	Institute for Clinical and Translational Research
IF/TA	Tubulo-interstitial fibrosis/tubular atrophy
IND	Investigational New Drug Application
IRB	Investigational Review Board
KDPI	Kidney donor profile index
MOP	Manual of Procedures
NIH	National Institutes of Health
NODAT	New onset diabetes after transplant
OHRP	Office for Human Research Protections
OnCore	Online Collaborative Research Environment, clinical trial management software
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SMS	Study Monitoring Service

1. Study Summary

Title	**Envarsus XR in Delayed Graft Function (E-DGF)**
Short Title and Precis	Envarsus in DGF (E-DGF)
Protocol Number	*2018-0530*
ClinicalTrials.gov number	NCT03864926
Phase	Phase IV
Methodology	Single center, open randomized trial
Study Duration	2.5 years
Study Center(s)	Single Center
Objectives	Envarsus XR is an extended release tacrolimus designed to deliver tacrolimus more consistently, thus avoiding large fluctuations of tacrolimus trough levels with Envarsus XR compared to immediate release tacrolimus. It is expected that patients with DGF on Envarsus XR will have more stable tacrolimus levels and facilitate early recover from DGF compared to immediate release tacrolimus.
Number of Subjects	Total of 100, 50 in each arm
Diagnosis	Kidney transplant recipients with the diagnosis of DGF
Main Inclusion Criteria	New kidney transplant recipients with DGF transplanted at UW hospital
Main Exclusion Criteria	Multi-organs transplant recipients Patients not on or not planned to be on tacrolimus based regimen after transplant Complications requiring allograft nephrectomy
Study Product, Dose, Route, Regimen	Per UW Abdominal Transplant Immunosuppression Management Adult-Inpatient/Ambulatory Clinical Practice Guideline: immediate release tacrolimus (generic) 0.05 to 0.1 mg/kg/day in two-divided dose by mouth will be used in all patients after kidney transplant as the standard of care (SOC). All subject will receive at least one dose of SOC tacrolimus. Extended release Envarsus XR (study drug) 80% of the total daily dose of SOC tacrolimus or close to the available strength of 0.75 mg, 1 mg and 4 mg tablet as a single tablet or combination of two or more tablets of Envarsus XR once a day by mouth will be used in the study arm and SOC immediate release tacrolimus will be continued in the SOC arm.
FDA status of product	IND Exempt Determination
Duration of administration	Until recovery of DGF to a maximum of 3 months
Reference therapy	Immediate release tacrolimus
Statistical Methodology	Data Analysis: Descriptive statistics for the data will be compiled. Any trends for differences between two groups for the composite endpoints will be assessed.

Figure 1: Schematic of Study Design

Flow diagram:

Prior to enrollment

Total 100 patients: Obtain informed consent. Screen potential subjects by inclusion and exclusion criteria, review labs and documentation. All patients will have received or will be receiving immediate release tacrolimus as standard of care (SOC)

Randomize

Arm 1
N=50: Tacrolimus
(SOC)

Arm 2
N=50: Envarsus XR
(Study)

Visit 1 (Diagnosis of DGF)

Perform baseline assessments.
Medical records and the Transplant Database will be reviewed for the following: Routine blood test, urine test and other radiological investigation based on the clinical judgment. Commonly used test include: CBC, Lytes, BUN, Creatinine, glucose, urinalysis, urine protein/creatinine, immunosuppressive level

Visit 2 (Diagnosis of DGF)

Randomize into Tacrolimus (SOC) or Envarsus XR (study) group

Visit 3 (Daily while inpatient Or in clinic visit)

Medical records and the Transplant Database will be reviewed for the following:
Follow up assessments of study endpoints and safety.
Evaluate for need of dialysis or not. Review routine blood test performed in the morning along with urine output in last 24 hours and examinations to assess the

Visit 4 (recovery from DGF)

Medical records and the Transplant Database will be reviewed for study endpoints and safety, Routine blood test performed, H&P documenting discharged from the DGF clinic

Visit X (Time Point)

Medical records and the Transplant Database will be reviewed for the following;
Interval between transplants to the recovery of DGF
Interval between first and last dialysis
Total number of dialysis
Total number of tacrolimus or Envarsus XR dose adjustment required

2. Key Roles

2.1. Investigator and Study Center:

Principal Investigator:	Sandesh Parajuli, MD, MBBS Assistant Professor (CHS) Department of Medicine-Nephrology UW Medical Foundation Centennial Building 4175 MFCB 1685 Highland Avenue Madison, WI 53705 Phone Number: (608) 265-0152 Email: sparajuli@medicine.wisc.edu
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ICTR Study Monitoring Service Contact:	2112C Health Sciences Learning Center School of Medicine and Public Health Madison, WI 53706 Ph: 608-262-4910
Funding Sponsor:	Veloxis Pharmaceuticals, Inc 1001 Winstead Drive, Suite 310, Cary, North Carolina 27513, USA Phone: (919) 591-3090 Fax: (919) 678-8026 www.veloxis.com

3. Background and Introduction

This document is a clinical research protocol for a human subjects study. This study is to be conducted according to the US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

3.1. Background and Rationale

There are multiple definitions of delayed graft function (DGF), but the most common definition is the need for dialysis within the first seven days of kidney transplantation (1). The incidence of DGF ranges from 20% to 40% and is increasing as more donation after cardiac death (DCD) and higher kidney donor profile index (KDPI) kidneys are utilized. DGF is associated with significant adverse outcomes including increased risk of readmission, rejection, graft loss and even death (2-6). Addressing maintenance immunosuppression at time of DGF is challenging. Calcineurin inhibitors (CNIs) are the main maintenance immunosuppressive medication in the current era of transplant. But CNIs have recognized vasoconstrictive properties and their discontinuation in presence of DGF appears intuitive but may be non-beneficial or even harmful (6). There is diminishing evidence to support delayed introduction or avoidance or withdrawal of CNI in DGF. Supratherapeutic levels can increase the risk of infections, such as BK. Decreased levels of CNI, tacrolimus is recommended to achieve acceptably low rates of rejection in these patients. Unfortunately, tacrolimus has a narrow therapeutic window. It can lead to acute as well as chronic nephrotoxicity if levels are supratherapeutic or rejection if levels are sub-therapeutic. Acute tacrolimus nephrotoxicity due to high tacrolimus levels typically presents early after kidney transplant with impaired renal function clinically and as isometric vacuolizations of tubular cells on the allograft biopsy. In fact, even as early as one month after kidney transplant, glomerulosclerosis in renal allografts can be associated with CNI nephrotoxicity. Typical chronic CNI-related allograft changes include tubule-interstitial fibrosis/tubular atrophy (IF/TA), tubular microcalcifications, glomerulosclerosis and arteriolar hyalinosis (7-10). Given all these adverse outcomes of DGF and deleterious effects of subtherapeutic or supratherapeutic tacrolimus levels, it is essential to achieve steady therapeutic levels of tacrolimus especially during the early phase of kidney transplant recipients with DGF.

3.2. Hypothesis

With extended release Envarsus XR, designed to deliver tacrolimus more consistently, it is hypothesized that there will be less fluctuation of tacrolimus levels requiring less dose adjustment and ultimately early recovery of the DGF.

3.3. Study Agent

Tacrolimus is a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*. Chemically, tacrolimus is designated as [3*S*-[3*R**[*E*(1*S**,3*S**,4*S**)], 4*S**,5*R**,8*S**,9*E*,12*R**,14*R**,15*S**,16*R**,18*S**,19*S**,26a*R**]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclo-hexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1- *c*] [1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate. Tacrolimus has an empirical formula of C44H69NO12•H2O and a formula weight of 822.03. Tacrolimus appears as white crystals or crystalline powder. It is practically insoluble in water, freely soluble in ethanol, and very soluble in methanol and chloroform.

Tacrolimus (generic; immediate release) is FDA approved for the prophylaxis of organ rejection in heart, kidney and liver transplant recipients.

Envarsus XR is FDA approved for the prophylaxis of organ rejection in kidney transplant recipients converted from tacrolimus immediate-release formulations, in combination with other immunosuppressants. Envarsus XR, is designed to deliver tacrolimus more smoothly over the whole day.

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

Note: extended release products (Envarsus XR) are not interchangeable or substitutable with immediate release tacrolimus.

3.4. Summary of Relevant Preclinical Data

The FDA approval of Envarsus XR was based on a conversion study (11). The conversion study was a randomized, open-label, multinational study evaluating once daily Envarsus XR when used to replace immediate-release tacrolimus administered twice daily for maintenance immunosuppression to prevent acute allograft rejection in stable adult kidney transplant patients. Patients who received a kidney transplant 3 months to 5 years before study entry and on a stable dose of tacrolimus immediate-release of at least 2 mg per day and tacrolimus whole blood trough concentrations between 4 and 15 ng/mL were randomized to 1) switch from twice daily tacrolimus immediate-release to once daily Envarsus XR (N=163) or 2) continue tacrolimus immediate-release twice daily (N=163). Mycophenolate mofetil (MMF) or mycophenolate sodium (MPS), or azathioprine (AZA) and/or corticosteroids were allowed as concomitant immunosuppressants during the study period according to the standard of care at the participating site. In the conversion study, stable kidney transplant patients converted to Envarsus XR at an average daily dose that was 80% of their tacrolimus immediate-release daily dose prior to conversion. Mean tacrolimus whole blood trough concentrations were maintained within a relatively narrow range throughout the duration of the study for both the Envarsus XR conversion group and the tacrolimus immediate-release continuation group. At week 1 (after 7 days of stable dosing), the mean ± SD tacrolimus trough concentrations were 7.2 ± 3.1 ng/mL for the Envarsus XR conversion group and 7.7 ± 2.5 for the tacrolimus immediate-release continuation group; the baseline values were 7.8 ± 2.3, and 8.0 ± 2.3, respectively. The average daily mycophenolate equivalent doses in the conversion study were comparable between the Envarsus XR and tacrolimus immediate-release treatment groups. The efficacy failure rates including patients who developed biopsy proven acute rejection (BPAR), graft failure, death, and/or lost to follow-up at 12 months, as well as the rates of the individual events were essentially the same between the tacrolimus immediate-release and tacrolimus extended-release groups (Envarsus XR).

In another large randomized control trial (12), once a day Envarsus XR in new kidney transplant recipients had a comparable efficacy and safety profile compared to that of immediate release twice a day tacrolimus even at 24% lower total dose suggesting Envarsus XR to have better absorption and bioavailability. In another, Phase III randomized trial, Envarsus XR achieved target tacrolimus trough levels more rapidly compared to twice daily tacrolimus group (13).

Envarsus XR is a calcineurin-inhibitor immunosuppressant indicated for the prophylaxis of organ rejection in kidney transplant patients converted from tacrolimus immediate-release formulations in combination with other immunosuppressants. It is administered 80% of the pre-conversion daily dose of tacrolimus immediate-release by mouth once a day. Its side effects and drug interactions are similar to the immediate-release tacrolimus.

3.5. Potential Risk and Benefits to Subjects

3.5.1. Known Potential Risks

Immunosuppressants, including extended release Envarsus XR, increase the risk of developing lymphomas and other malignancies, particularly of the skin. Other risks include, an increased risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections. Medication errors, including substitution and dispensing errors, between tacrolimus immediate-release products and tacrolimus extended-release products were reported outside the U.S. This led to serious adverse reactions, including graft rejection, or other adverse reactions due to under- or over-exposure to tacrolimus. Envarsus XR caused new onset diabetes after transplant (NODAT) in kidney transplant patients, which may be reversible in some patients. African-American and Hispanic kidney transplant patients are at an increased risk of NODAT. Envarsus XR, like other CNIs, can cause acute or chronic nephrotoxicity, may cause a spectrum of neurotoxicities. Other risks includes, hyperkalemia, rise in creatinine, electrolytes disturbance, hypertension, QT prolongation, drug interaction with CYP3A inducers and inhibitors. Live attenuated vaccines during treatment with Envarsus XR is contraindicated. Other post marketing experience includes- blood and lymphatic system disorders, ear disorders, eye disorders, gastrointestinal

disorders, hepatobiliary disorders, hypersensitivity reactions, immune system disorders, metabolic and nutrition disorders, musculoskeletal and connective tissue disorders, neoplasm, nervous system disorders, renal and urinary disorders, respiratory, thoracic and mediastinal disorders and skin and subcutaneous disorders. When comparing Envarsus XR with immediate release tacrolimus, potential risks were almost similar between the two groups.

Refer to the FDA approved package insert for Envarsus XR in Appendix 1.

3.5.2. Protection Against Risks

Together with the UW ICTR Data Monitoring Committee (DMC) we will develop a detailed data and safety monitoring plan (DSMP) which will ensure ongoing safety of participating patients commensurate with the level of risk and complexity of the protocol treatment to minimize risks, integrity of trial data and scientific validity of the trial. The development of the DSMP will be guided by the NIH Policy for Data and Safety Monitoring and by the FDA Guidance on the Establishment and Operation of Clinical Trial Data Monitoring Committees. The plan will make certain that review of the conduct of research is rigorous, independent and objective, interim safety and efficacy data is collected and presented and progress towards achieving study goals is made. It will cover policies and procedures for reporting adverse events to the DMC, IRB, and the FDA. Refer to Appendix 2: Data Monitoring Committee Charter and Appendix 3: Data and Safety Monitoring Plan (DSMP)

3.5.3. Potential Benefits to the Subjects

It is anticipated that the subject will benefit through early recovery of DGF, with shorter duration of dialysis treatment after transplant. This ultimately will lead to the prolonged graft survival.

3.5.4. Risk Minimization

Serious Adverse Events (SAEs) will be reviewed to determine if additional risk could be posed to the subject in question or others participating in the study. If it is determined that a serious adverse event, new information, or an unanticipated event could pose a potential risk to subjects, the DMC and/or the investigator may decide to stop the study.

4. Study Objectives and Purpose

- Primary Objective: Early recovery from DGF
- Secondary Objective: To assess the efficacy of Envarsus XR in kidney transplant recipients with DGF in achieving steady state tacrolimus levels compared to immediate release tacrolimus administration (SOC).

5. Study Design and Endpoints

5.1. General Design

This is a single center randomized phase IV trial of comparing extended release Envarsus XR once a day vs immediate release tacrolimus twice a day in a new kidney transplant recipients with DGF. The duration of study is expected to be around 2 to 2.5 years.

5.1.1. Primary Study Endpoints

The primary endpoint of the study will be the interval between first dialysis and last dialysis after kidney transplant (duration of DGF).

5.1.2. Secondary Study Endpoints

The secondary endpoint will be number of tacrolimus or Envarsus XR dose adjustments required during the period of DGF.

5.1.3. Primary Safety Endpoints

Primary safety endpoints include: infections, malignancies, hematological complications including leukopenia, anemia, and thrombocytopenia, cardiovascular complications and events, neuropathy, tremors, gastrointestinal symptoms, uncontrolled hypertension, serious electrolytes abnormalities and immunosuppression-related adverse effects.

6. Study Subjects – Enrollment and Withdrawal

- A total of 100 subjects (50 subjects in each arm) with the diagnosis of DGF will be enrolled over a period of 2 years.
- DGF is defined as the need for a dialysis within the first week of transplant. Once potential DGF patients are identified, the transplant nephrology team will be consulted and the transplant nephrology provider will perform initial evaluation of a patient, discussion with the patient about his/her interest in participating in the research study and inform the research coordinator.
- Subjects will participate in the study until the recovery of DGF as documented by the provider as “discharged from the DGF clinic” or no need for dialysis for more than one week (7 days).
- Subject would be followed for maximum of 3 months. If they still need dialysis beyond 3 months, will be declared as primary dysfunction and will disqualify from the study.

6.1. Subject Population

All adult kidney only transplant recipients age 18 years or older at time of the transplant with the diagnosis of DGF will be determined if they are eligible for this study using the criteria described below. This study is not restricted based upon the race or ethnic origin.

6.2. Inclusion Criteria

Inclusion Criteria	
1	Willing and able to provide written informed consent
2	Willing to comply with all study procedures and be available for the duration of the study
3	Male or female, at least 18 years of age
4	Documented diagnosis of DGF or need for dialysis or had dialysis within the first week of kidney transplant
5	Current treatment with tacrolimus based regimen or planned to start tacrolimus based immunosuppressive regimen
6	Females of childbearing potential must have a negative urine or serum pregnancy test prior to randomization and agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to randomization, for the duration of study participation, and for 7 days following completion of therapy. • A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria: o Has not undergone a hysterectomy or bilateral oophorectomy; or o Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

6.3. Exclusion Criteria

Exclusion Criteria
1. History of hypersensitivity or allergy to any of the study drugs or drugs of similar chemical classes
2. Current use of non-tacrolimus based immunosuppressive regimen or no plan to start tacrolimus based regimen
3. Women who are or plan to become pregnant or breast-feeding during the study period
4. Not suitable for study participation due to other reasons at the discretion of the investigator
5. Major post-surgical complications requiring allograft nephrectomy
6. Multi-organ transplant recipients
7. Non kidney transplant recipients

6.4. Subject Screening for Recruitment

6.4.1. Subject Identification

The screening visit will occur within the first week of transplant when transplant nephrology service is consulted for the potential need of dialysis. Basic information about the study will be provided to the patients to assess their interest to participate in the study. All of the recruitment will be performed while patient is still in the hospital after kidney transplant. The following procedures will occur as part of clinical care and will be collected from the subject's medical record:

- Physical exam
- Vital Signs (Temperature, pulse, respirations, and blood pressure)
- Medication History
- Routine labs (CBC, serum pregnancy test for females of child-bearing potential, BMP, or any imaging performed recently)
- Dialysis indicated or not

6.4.2. Recruitment and Retention Strategies

A total of 100 patients will be recruited from and enrolled at a single center, the University of Wisconsin Hospital and Clinics. Patients will be recruited and enrolled through the UW hospital inpatient transplant service and will be followed until the recovery of DGF. Based on the demographics of the state of Wisconsin and previous transplant history, more than 80% are expected to be Caucasian, approximately 40% are expected to be female.

6.5. Subject Capacity

Patient's capacity to consent will be assessed by the nephrology provider. If patient is unable to consent for the study, consent to enroll will be obtained only when they are capable of giving informed consent.

6.6. Informed Consent

The PI will be responsible for ensuring that valid consent is obtained and documented for all subjects. Consent will be obtained and documented during an in-person visit.

6.6.1. Informed Consent Document

The Informed Consent Document will include the required elements per 45 CFR 46, as well as Good Clinical Practice (GCP) Guidelines.

6.6.2. Process of Consent

Written informed consent will be obtained by the research coordinator or the treatment team member after the potential subject has been presented the information necessary to make a voluntary decision and all questions have been addressed.

6.6.3. HIPAA

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). The elements of the HIPAA Authorization Form will be included in the Informed Consent Document, allowing the use of one document to fulfill both requirements.

6.6.4. Revoking HIPAA Authorization

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

6.6.5. Costs to the Subject

There is no extra cost to the patients to be enrolled in the study. Extended release Envarsus XR will be provided through the Veloxis pharmacy for the entire period of the study. Immediate release tacrolimus will fall under the SOC and will be provided through the standard medication distribution system.

6.6.6. Payment for Participation

There are no reimbursements or payments such as cash payments, coupons and gift certificates that the subjects will receive for participation.

6.7. Early Withdrawal of Subjects

6.7.1. Premature termination of study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator, funding agency, or regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or regulatory authorities. Subject's data will be stored in the secure place during this period.

6.7.2. When and How to Withdraw Subjects

If patient is unable to tolerate the study drug Envarsus XR or SOC drug tacrolimus, the subject will be withdrawn from the study, and likely be switched to other immunosuppressive medications for example cyclosporine, or belatacept or any other immunosuppressive medications based on the clinical discretion. Subjects that are withdrawn will be asked to return for one last study visit to conduct the procedures described in the last visit in the protocol.

6.7.3. Data Collection and Follow-up for Withdrawn Subjects

Data for the study purpose will not be collected from subjects who have withdrawn from the study but have active treatment either with SOC tacrolimus or with study drug, Envarsus-XR.

7. Study Agent

Subjects will be randomized to receive (in a 1:1 manner) to either the standard of care arm or the experimental arm:

- Standard of Care: Immediate release tacrolimus
- Experimental: Envarsus XR

This study is exempt from the requirements of an IND based on meeting the criteria defined in the FDA information sheet "Off-Label and Investigational Use Of Marketed Drugs, Biologics, and Medical Devices".

21 CFR 312.2(b) Exemptions. (1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:

(i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;

(ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;

(iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and

(v) The investigation is conducted in compliance with the requirements of 312.7.

7.1. Starting Dose and Dose Escalation Schedule

Tacrolimus Immediate Release:

Dosing will be per institutional standards at a range from 0.05mg/kg/day to 0.1mg/kg/day in two divided doses by mouth.

Dosage will be adjusted based upon trough levels per the UW Abdominal Transplant Immunosuppression Management Adult-Inpatient/Ambulatory Clinical Practice Guideline. Dosage adjustments will occur after a patient has received 4 doses of the current regimen. Tacrolimus levels will be ordered daily while inpatient and patient has received daily tacrolimus doses (either post-operatively or during readmission)

Once discharged, tacrolimus levels will be monitored as follows:

- Day 0-90: not less than once weekly
- Day 91-180_ not less than twice monthly
- Day 181-240: not less than once monthly

Additional monitoring of tacrolimus trough level is warranted if there is a change in medication formulation or patient status that may affect levels or if the creatinine has increased 0.3mgdL above baseline. Levels must be checked within 3-7 days of each dose adjustment and potassium and creatinine levels will be monitored with each tacrolimus level. Additional monitoring is per the UW Abdominal Transplant Immunosuppression Management Adult-Inpatient/Ambulatory Clinical Practice Guideline.

The study team will make all modifications in dosage.

Envarsus XR:

To convert from a tacrolimus immediate-release product to Envarsus XR, administer a once daily dose that is 80% of the total daily dose of the tacrolimus immediate-release product. Tablets should be taken once

daily, preferably in the morning at the same time each day. Tablets must be swallowed whole; subjects must be instructed not to chew, crush or split Envarsus XR tablets. Envarsus XR will be used in the patient population, dose and route of administration that it is FDA approved for, however it will be used in this study as a first line of treatment, rather than a second line of treatment (FDA approved).

Monitor tacrolimus whole blood trough concentrations and titrate Envarsus XR dosage to achieve target whole blood trough concentration ranges of 4 to 11 ng/mL. Measure tacrolimus whole blood trough concentrations at least two times on separate days during the first week after initiation of dosing and after any change in dosage, after a change in co-administration of CYP3A inducers and/or inhibitors, or after a change in renal or hepatic function. When interpreting measured concentrations, consider that the time to achieve tacrolimus steady state is approximately 7 days after initiating or changing the Envarsus XR dose. The study team will make all modifications in dosage.

7.2. Description/Formulation/Packaging and Storage:

Tacrolimus (immediate release) will be sourced locally by the institution and handled per standard of care. Immediate release tacrolimus is available in 0.5mg, 1mg and 5mg capsules; bottles all contain 30 capsules. Tacrolimus Immediate release is stored accordingly to the product label.

Envarsus XR will be provided by Veloxis Pharmaceuticals in 0.75 mg, 1 mg and 4 mg tablets; bottles of 30 tablets. Envarsus XR must be stored at controlled room temperature ([15 *C to 30*C] or [59*F to 86*F]).

7.3. Prior and Concomitant Therapy/ Standard of Care

The following medications and procedures are permitted during the study:

- Antiemetics, including 5-HT3 serotonin receptor antagonists, may be used at the discretion of the primary provider
- Loperamide or other antidiarrheal should be used for symptomatic diarrhea at discretion of the primary provider.
- Growth factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], recombinant erythropoietin) are permitted. Their use should follow published guidelines and/or institutional practice.
- Subjects should be transfused with red cells and platelets as clinically indicated and according to institutional guidelines.
- Antiviral therapy, antifungal and antibacterial therapy may be administered if medically appropriate.
- Concomitant treatment with multivitamins, calcium, phosphorus, magnesium supplement will be permitted, as appropriate.
- Hypertensive medications, medication to control blood sugar or pain will be permitted, as appropriate
- Concomitant use of other immunosuppressive medications for induction (example, basiliximab, alemtuzumab or anti-thymocyte globulin) or maintenance (example: mycophenolic acid, steroids) will be acceptable
- Dialysis as indicated
- Kidney allograft biopsy as indicated
- Supportive measures consistent with optimal patient care may be given throughout the study.
- Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy Concomitant use with strong CYP3A for inducers and/or inhibitors may alter tacrolimus whole blood concentrations, potential leading to rejection and/or increased toxicity respectively. Tacrolimus whole blood trough concentrations will be monitored closely.
- Grapefruit juice, a CYP3A4 inhibitor may increase serum level and/or toxicity of tacrolimus, subjects must be instructed to avoid.

7.4. Randomization and Blinding of Study Drug

This study will be a randomized, unblinded study involving extended release tacrolimus called Envarsus XR once a day and immediate acting tacrolimus twice a day.

8. Study Procedures

8.1. Laboratory Tests

Patients will have similar labs in both groups and will be drawn as part of the standard of care. Labs will be obtained on a daily basis while they are inpatient and on the day of clinic visit or before dialysis when they are outpatient. Commonly obtained labs include, CBC, BMP, magnesium, phosphorus level, tacrolimus level, serum calcium, urinalysis and protein/creatinine ratio. Imaging including chest x-ray, ultrasound of the transplanted kidney, CT abdomen and pelvis, CT chest, head may be obtained based on the clinical judgement. All labs and imaging will be obtained at UW Hospital and Clinics, including the use of a CAP and CLIA-certified laboratory. Labs and imaging reports will be communicated to patients by the clinical care team.

Table 1. ***Schedule of Study Procedures***

Process	**Screening**	**Baseline *(Day 1)***	**Follow-up (every other day or 3 times a week till recovery from DGF) *)***	**Monthly Follow-up Visits until 3 months after transplant**	**Final Clinic Visit**
Informed Consent	X				
Eligibility Determination	X				
Obtain demographics	X				
Study Drug Administration		X	X	X	X
Dose adjustment of Envarsus XR or tacrolimus			X	X	X

Table 2. ***Typical Schedule of Standard of Care Procedures***

Process	**Screening**	**Baseline *(Day 1)***	**Follow-up (every other day or 3 times a week till recovery from DGF) *)***	**Monthly Follow-up Visits until 3 months after transplant**	**Final Clinic Visit**
Results of Clinical Laboratory Tests	X	X	X	X	X
Medical History	X	X	X	X	X
Physical examination		X	X	X	X
Vital Sign Measurement (Temperature, Pulse, Respirations, Blood Pressure)		X	X	X	X
IR Tacrolimus Administration		X	X	X	X
Dose adjustment of IR tacrolimus			X	X	X
Decision for dialysis		X	X	X	X

8.2. Study Visits

8.2.1. Screening/Baseline

At screening/baseline visit transplant nephrology provider will decide about the need of dialysis or not and based on that information will document patient to have DGF or not. In that visit, we will review the patient's medical records. Patient will also be informed about the study and their interest will be gauged. If they are interested, then research coordinator will be informed about the potential subject.

Table 2. Medical chart review of standard of care visits

Visit*	**Window**	**Data collection from medical record and Transplant Database**
Day 1 contact	+/- 1 days	H&P, brief updates about research project
Day 3	+/- 0 days	H&P, decision for dialysis, decision to adjust study or SOC dose
Day 5	+/- 0 days	H&P, decision for dialysis, decision to adjust study or SOC dose
Day 7	+/- 0 days	H&P, decision for dialysis, decision to adjust study or SOC dose
Additional visits every 2-3 days until DGF recovery	+/- 0 days	H&P, decision for dialysis, decision to adjust study or SOC dose
Monthly up through Month 3 post diagnosis of DGF	+/- 30 days	H&P, decision for dialysis, decision to adjust study or SOC dose

*visits could be more or less depending upon the timing of DGF recovery for maximum of 3 months post-transplant.

8.2.2. Unscheduled

Subjects may have unscheduled standard of care visits due to lab results, an acute illness of undetermined cause, for other reasons, or at the discretion of the Investigator. Data will be collected from unscheduled visits and may include any of the following information;

- Adverse Event Assessment
- Medication History
- Drug Accountability
- Physical Exam
- Vital Signs (Temperature, Pulse, Respirations, Blood Pressure)
- Lab work (CBC, LFTs, DSA , imaging, biopsy)

8.2.3. Final Standard of Care Visit

Patients will be off study once they recover from DGF as documented by the provider as discharged from the DGF clinic or no need for dialysis for more than 7 days. Patients will be given the opportunity to either continue on the study medication or switch to SOC after termination from the study. Envarsus XR will not be covered by the industry, but is covered by most of the health insurance coverage. If interested, Veloxis will provide discount coupons. The final standard of care visit will also include primary evaluation, need for dose adjustment of medication and decision for dialysis. Each subject will be asked to participate in the study for up to 3 months after transplant.

9. Study Analysis

9.1. Sample Size Determination

Goal is to analyze 100 subjects total (50 in each group), with a goal to decrease DGF duration to less than 10 days in Envarsus XR group from current mean of 13.9 +/- 7 days with tacrolimus based on the power calculation.

9.2. Statistical Methods

Continuous data will be compared using Student's t-test or the Wilcoxon Rank Sum test, as appropriate, while categorical data will be analyzed using Fisher's exact test or chi-square test. P values < 0.05 will be considered statistically significant. Kaplan-Meier analyses will be performed to study graft survival if appropriate.

9.3. Subject Population(s) for Analysis

All randomized and completed study patient data will be used for primary and secondary analysis. Primary analysis include needs for dose adjustment of the Envarsus XR or tacrolimus and secondary analysis include duration of recovery from the DGF.

9.4. Planned Interim Analysis

We will utilize the UW ICTR Data Monitoring Committee (DMC) to oversee the study and is described further in section 11.6. *S*ource documents may be reviewed to allow the DMC to independently judge whether the overall integrity and conduct of the protocol remain acceptable based on data provided and reported by the Principal Investigator. The DMC will make recommendations to the Principal investigator that could include actions of continuation, modification, suspension or termination.

10. Data Collection, Handling and Record Keeping

10.1. Data Confidentiality

Only PI and study team members will have access to the subject research records and the data entered in both the OnCore and REDCap systems. Data will not be shared with any other researchers outside of the study team. No personal identifiable information will be released to the third parties. Only summary of the data generated will be provided to the industry.

10.1.1. Confidentiality of Subject Records

By signing the protocol, the Investigator agrees that the, IRB, or Regulatory Agency representative may consult and/or copy study documents to verify case report form (CRF) data. By signing the consent form, the subject agrees to this process. If study documents will be photocopied during the process of verifying CRF information, the subject will be identified by unique code only and full names and similar identifying information (such as medical record number or social security number) will be masked.

The Clinical Site Investigators will ensure that the identity of subjects will be protected. All study records will be maintained in a secure fashion with access limited to essential study personnel only. The Clinical Site Investigators will maintain an enrollment log that includes subject identifying information and links subjects to their study-specific identification number. This information will also be available in the ICTR OnCore and REDCap systems.

10.2. Data Capture

10.2.1. Source Documents

A majority of the study data will be captured through the electronic medical record (EMR) and Transplant Database. The data source for the Transplant Database are Transplant Data Mart and Organ and Tissue Donation Database. Data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, transcriptions,

microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

10.2.2. Case Report Forms

The study CRF is a data-reporting instrument for the study. All data requested on the CRF will be recorded. All missing data will be explained. All entries will be printed legibly in black ink. If any entry error has been made, to correct such an error, a single straight line will be drawn through the incorrect entry and the correct data will be entered above it. All such changes will be initialed and dated.

10.2.3. Electronic Case Report Forms (eCRFs)

Some of the data that will be exported for analysis will not be captured on paper CRFs, rather directly entered into the ICTR OnCore or ICTR REDCap Data Management System, including but not limited to results of laboratory tests, physical examinations, imaging, etc.

10.2.4. Missing Data

Every attempt will be made to capture all data. If data is missing, additional review of available data from the electronic medical record and/or Transplant Database will be conducted.

10.2.5. Data Collection Tools

Online Collaborative Research Environment (OnCore) will serve as the Clinical Trial Management System for this study. ICTR OnCore is supported by the UW School of Medicine and Public Health Information Technology (SMPH-IT) staff and managed by UW ICTR.

OnCore is a sophisticated, web-based data management system that: a) ensures secure, easy data entry at multiple sites; b) integrates multiple data sources; c) provides controlled, secure access to sensitive data using role-based access control; d) provides workflow automation; and e) allows export and reporting of data for Data and Safety Monitoring Boards and biostatisticians. This software provides protocol management functions (e.g. subject scheduling; screening, data organization), maintains updated forms, addresses budget development, billing, and fiscal management, generates summary reports, and provides essential links with other research administration and electronic medical records systems. ICTR OnCore eases the burden of the individual researcher and unifies protocol management within research programs and across research sites, enhancing protocol integrity and regulatory compliance efforts.

Data extracted from the EMR will be entered into the REDCap system managed by ICTR. This data will be combined with the data exported from the OnCore system and imported in to the same project, allowing REDCap to serve as the final data repository for this study.

10.3. Data Management

The PI is responsible for implementing and maintaining quality control and quality assurance procedures to ensure that trial is conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice (International Conference on Harmonization E6), and all applicable federal, state, provincial, and local laws, rules, and regulations relating to the conduct of the clinical trial in an ongoing and auditable manner.

10.4. Records Retention

Study records will be retained for a minimum of 7 years after study completion per the UW Madison policy and IRB guidance: https://kb.wisc.edu/sbsedirbs/page.php?id=42378. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

11. Assessment of Safety

The investigator is responsible for monitoring the safety of subjects who have enrolled in the study. For this study, adverse events will be solicited from subjects to identify an occurrence or worsening of an unintended sign or symptom,

related to the ingestion of the study drug as per standard of care. The clinical team will ask subjects in each visit if they experienced any new medical related signs or symptoms since taking the study drug. Subjects will be asked about any adverse events they may have experienced. Only the adverse events considered related (possibly, probably or definitely) to the ingestion of the study drug will be entered into and managed in the data management system.

11.1. Specifications of Safety Parameters

The risks to subjects in this trial will be minimized by compliance with eligibility criteria, clinical monitoring, adherence to protocol contraception requirements and investigator guidance regarding specific safety areas. The specific safety areas that will be closely monitored in this subject population are; thrombocytopenia, diarrhea, fatigue, nausea, vomiting, rash, risk of reactivation of viral infection, neutropenia, fluid deficit, uncontrolled hypertension, posterior reversible encephalopathy syndrome (PRES).

11.1.1. Definition of Adverse Events (AE)

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug. AEs will be assessed at study visits and during the final follow-up study visit. Only the adverse events considered related (possibly, probably or definitely) to the ingestion of the study drug will be entered into and managed in the data management system

For the purposes of this study, baseline symptoms will be collected prior to the administration of study intervention. Only those symptoms identified as new or worsened compared to the baseline assessment will be recorded as an AE. In addition, only those abnormal laboratory values or physical examination assessments that are considered clinically significant will be recorded in the study documents. Pain and hematoma at transplant incision site will not be considered an AE.

11.1.2. Definition of Serious Adverse Events (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event*
- Inpatient hospitalization or prolongation of existing hospitalization
    - Subjects must be admitted to an inpatient unit to be eligible for the study, thus the initial hospitalization will not be considered an SAE in and of itself, rather it will only be considered an SAE if the subject is discharged and then re-admitted.
- A congenital anomaly/birth defect
- Persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life function
- Important medical events that, may not result in death, be life-threatening, or require hospitalization may be considered when, based upon appropriate medical judgement, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

*Life-threatening adverse event: An adverse event is considered “life-threatening” if, in the view of the investigator, its occurrence places the subject at immediate risk of death. It does not include an adverse event which, had it occurred in a more severe form, might have caused death.

11.1.3. Definition of Unanticipated Problems (UP)

OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

The following changes or actions will be considered in response to an UP:

- Modification of inclusion or exclusion criteria to mitigate the newly identified risks
- Implementation of additional safety monitoring procedures
- Suspension of enrollment of new participants or halting of study procedures for enrolled participants
- Modification of informed consent documents to include a description of newly recognized risks
- Provision of additional information about newly recognized risks to previously enrolled participants.

11.2. Classification of an Adverse Event

11.2.1. Severity of Event

All AEs will be assessed by the clinician using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4, each event searchable using the Safety Profiler website (https://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx). For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

11.2.2. Relationship to Study Agent

In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory re-challenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and

follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.

- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

11.2.3. Expectedness

PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent in the clinical protocol, the package insert(s), the IRB application or the informed consent document.

11.3. Time period and frequency for event assessment and follow-up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.
Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after the administration of the study drug and for up to 30 days after the date of the last dose of study drug. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution, stabilization, or completion of study participation.

11.4. Reporting procedures

Together with the UW ICTR Data Monitoring Committee (DMC) we will develop a detailed a data and safety monitoring plan (DSMP) which will ensure ongoing safety of participating patients commensurate with the level of risk and complexity of the protocol treatment to minimize risks, integrity of trial data and scientific validity of the trial. The development of the DSMP will be guided by the NIH Policy for Data and Safety Monitoring and by the FDA Guidance on the Establishment and Operation of Clinical Trial Data Monitoring Committees. The plan will make certain that review of the conduct of research is rigorous, independent and objective, interim safety and efficacy data is collected and presented, and progress towards achieving study goals is made. It will cover policies and procedures for reporting adverse events to the DMC, IRB, and the drug manufacturer(s).

11.4.1. Adverse Event Reporting

Only the adverse events considered related (possibly, probably or definitely) to the ingestion of the study drug will be entered into and managed in the data management system and be made available to the study team for cumulative review, as well as the DMC and SMS.

Based on the subject population, it is anticipated that the laboratory results that will be abstracted from the EMR for study purposes will be abnormal. The PI will not make clinically significant/non-clinically significant determinations of these results, as this subject population is expected to be abnormal and clinically significant hence their current clinical treatment. All reportable events related to the study protocol and its associated procedures will be reported to the IRB. It is the responsibility of the Investigator to promptly notify the Institutional Review Board of all unanticipated problems involving risk to human research subjects. Reportable events, such as protocol noncompliance, serious adverse events, new information, and unanticipated problems will be reported to the IRB and DMC in accordance with the UW IRB guidelines.

11.4.2. Serious adverse event reporting

The study clinician will complete a SAE Form within the following timelines:

All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the funding sponsor and drug manufacturer(s) within 24 hours of site awareness. See **Section 1, Key Roles** for contact information.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by those providing regulatory oversight and should be provided as soon as possible. The funding sponsor and drug manufacturer(s) will be responsible for notifying FDA of any events that meet the applicable reporting criteria.

The study investigator shall complete a Serious Adverse Event (SAE) Form and submit the information to the funding sponsor, drug manufacturer(s), DMC and to the reviewing IRB as soon as possible. Events that are considered Unexpected, Related and fatal, life threatening or severely debilitating must be immediately reported (within 24 hours) to the IRB and DMC. Events that are Unexpected, Related and Serious (not fatal, life threatening, or severely debilitating), must be reported to the IRB and DMC within fourteen (14) business days of learning of the event. The funding sponsor contact information is provided in **Section 1, Key Roles**.

11.4.3. Unanticipated Problem (UP) reporting

Incidents that meet the OHRP criteria for UPs will be reported according to the funding sponsor and IRB requirements. UPs that are SAEs will be reported to the IRB and DMC within the required reporting timelines described above)

The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

11.4.4. Events of special interest

The safety data that will be reviewed includes the number and seriousness of infections, malignancies, hematological complications including leucopenia, anemia, and thrombocytopenia, cardiovascular complications and events, neurological symptoms, gastrointestinal symptoms, and immunosuppression-related adverse effects

11.4.5. Reporting of pregnancy

It is unlikely that patient will be pregnant during that period as most of the child bearing age group females are required to be on the birth control measure and are recommended not to be pregnant. If patient get pregnant during the study period, subject will be monitored through child birth and report any birth defect.

11.5. Study Halting Rules

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. These subjects are at high risk for multiple complications and decision to halt the study based on SAEs will be on PI discretion. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator, funding agency and the regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and DMC and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

11.5.1. Subject Stopping Rules

Subjects will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study for any of the following reasons:

- If study drug is discontinued due to AE
- If a subject is withdrawn due to an adverse event, the dose adjustment, modification and withdrawal procedures related to adverse events will be followed and will be switched to other alternative medications..
- Protocol violation
- Lost to follow-up
- Study terminated
- Non-compliance

11.6. Safety Oversight

We will utilize the UW ICTR Data Monitoring Committee (DMC) to oversee the study. The UW ICTR DMC is comprised of experienced members with expertise required to oversee this study. In providing oversight for the conduct of this study, the ICTR DMC will meet annually in which subjects will have any study procedures. At these annual meetings, the DMC members will review protocol-specific reports created by statisticians using data pulled from both the ICTR OnCore and the ICTR REDCap systems. These standard reports will include an overview of study objectives, a review of actual and projected accrual rates, an evaluation of patient demographics, a summary of the number and seriousness of adverse events, and an analysis of the primary and secondary outcomes. An interim analysis of study results may be performed and source documents may be reviewed to allow the DMC to independently judge whether the overall integrity and conduct of the protocol remain acceptable based on data provided and reported by the Principal Investigator. The DMC will make recommendations to the Principal Investigator that could include actions of continuation, modification, suspension, or termination.

Serious adverse events will be reviewed by the DMC co-chairs once reported to the DMC. An ad hoc meeting of the DMC may be scheduled to discuss the SAE(s) and any potential action that is needed pertaining to study continuation.

12. Study Monitoring, Auditing, and Inspecting

12.1. Medical Monitoring

The investigator is responsible for monitoring the safety of subjects who have enrolled in the study. For this study, adverse events will be solicited from subjects to identify an occurrence or worsening of an unintended sign or symptom, related to the ingestion of the study drug. The study team will ask subjects on each evaluation if they experienced any new medication related signs or symptoms since taking the study drug. Subjects will be asked about any adverse events they may have experienced on each visit. Only the adverse events considered related (possible, probable or definite) to the ingestion of the study drug will be entered into and managed in the data management system.

12.1.1. Study Monitoring Plan

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).
Monitoring for this study will be performed by ICTR study monitoring service
While many institutions involved in clinical research conduct various types of quality assurance reviews and audits, University of Wisconsin Institute for Clinical and Translational Research (ICTR) is one of a few institutions to offer independent Study Monitoring Services, a robust academic equivalent to the industry Contract Research Organization (CRO) standards for ongoing study monitoring.

The sponsor-investigator has contracted with ICTR Study Monitoring Service (SMS) for the proposed study to provide ongoing monitoring services throughout the life cycle of the study. Refer to the Study Monitoring Plan in Appendix 4. .

For this study, UW ICTR SMS personnel will conduct a Site Initiation Visit (SIV) and ongoing Interim Monitoring Visits (IMVs), either on-site, remotely, centrally or a combination thereof, throughout the duration of the study. During IMVs, the monitors will review study materials, including but not limited to: regulatory files, consent forms, case report forms, and drug accountability logs. UW ICTR SMS personnel will conduct a Close-Out Visit (COV) upon completion of the study at the study site.

Monitoring will consist of all (100%) of the study-related records representing 10-20% of those enrolled at a minimum. SMS personnel could increase the percentage of study or subject records to be reviewed if warranted by the ongoing monitoring findings, resulting in a partial or full review of up to 100% of the study-related subject records. Based on the plan to review approximately 10-20% of the subject records, it is anticipated that the following monitoring visit schedule will implemented; 1 SIV, 1 IMV following the enrollment of the first subject(s), followed by approximately 12 IMVs through the end of the study, planned on an approximate quarterly basis. The frequency of the IMVs could increase based on subject enrollment and previous monitoring visit findings, but will not decrease.

The SMS will review the accuracy and completeness of completed consent and HIPAA documents for each enrolled subject. For approximately 10-20% of enrolled subjects, the SMS will evaluate the completeness and accuracy of the data collected and conduct a comparison with the electronic data captured, resulting in electronic queries with resolution or validation. In addition, the SMS staff will verify adherence to protocol eligibility criteria, verify documentation for the accountability and administration of the study product, verify documentation of study procedures, and verify that FDA required SAE reports were appropriately submitted.

The study monitor(s) will work closely with the ICTR DMC statistician and the study statistician to conduct periodic central data reviews, with follow-up conducted by the study monitors for any data discrepancies identified.

The PI will be provided copies of monitoring reports within 30 days of visit.

Details of clinical study monitoring are documented in a SMP (Study Monitoring Plan) that can be found in Appendix 4. The SMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

12.2. Protocol Deviations

A protocol deviation is any noncompliance with the applicable regulations, clinical trial protocol, GCP, or MOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.
These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

The site PI/staff will be responsible for continuous vigilance to identify and report deviations to the protocol. These will be reported within 5 working days of identification of the protocol deviation, or within 5 business days of the scheduled protocol-required activity. All deviations must be addressed in study source documents. Protocol deviations will be sent to the local IRB per their guidelines. The PI and study staff are responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

12.3. Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB (or their representatives), the sponsor, government regulatory bodies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

12.4. Subject Compliance Monitoring

UW ICTR SMS will review to ensure compliance with applicable regulations, guidelines, and institutional policies. UW ICTR SMS personnel will conduct a Close-Out Visit (COV) upon completion of the study at the study site.

13. Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations, applicable local and state laws, and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the funding sponsor before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. . The consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject, and the investigator-designated research professional obtaining the consent.

14. Study Finances

14.1. Funding Source

This study is financed through a grant from the Veloxis pharmaceuticals as an investigator initiative study.

14.2. Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved

by the study sponsor prior to participation in this study. All UW investigators will follow the UW conflict of interest policy.

14.3. Subject Stipends or Payments

None

15. Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

16. References

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17. Appendices

Appendix 1	Envarsus XR Package Insert
Appendix 2	Data Monitoring Committee Charter
Appendix 3	Data and Safety Monitoring Plan (DSMP)
Appendix 4	Study Monitoring Plan

17.1. Appendix 1: Envarsus XR Package Insert

http://www.envarsusxr.com/