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PILOT STUDY COMPARING EARLY CONVERSION TO EXTENDED-RELEASE TACROLIMUS (ENVARSUS XR) TO IMMEDIATE-RELEASE TACROLIMUS IN LUNG TRANSPLANT RECIPIENTS

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8th Addendum: December 10, 2021

Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

Table of Contents

List of Abbreviations

ACR	Acute Cellular Rejection
AE	Adverse Event/Adverse Experience
AMR	Antibody-mediated Rejection
CFR	Code of Federal Regulations
CKD	Chronic Kidney Disease
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSA	Donor-Specific Antibody
DSMB	Data and Safety Monitoring Board
FFR	Federal Financial Report
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IR	Immediate Release
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
US	United States

Protocol Summary

Title	Pilot Study Comparing early conversion to Extended-release Tacrolimus (ENVARSUS XR) to immediate-release Tacrolimus in lung transplant recipients
Short Title	Envarsus XR in Lung Transplant
Brief Summary	Patients undergoing a lung transplant will be enrolled. All patients will undergo lung transplantation with standard post-operative management, including triple immunosuppression. As soon as the patient is deemed appropriate to take medications via the oral route, they will be converted from IR tacrolimus to Envarsus XR. Patients will be followed per site's standard of care.
Phase	Pilot study
Objectives	To determine the feasibility of early conversion to Envarsus XR in patients who receive a lung transplant. To compare the impact of tacrolimus formulation on CKD, ACR, AMR, and de novo DSA within the first year post-lung transplant.
Methodology	Single-center, open-label study
Endpoint	Incidence of CKD, ACR, AMR, and de novo DSA in the first year post-lung transplant
Study Duration	Two years
Participant Duration	One year
Duration of IP administration	One year
Population	Adult patients undergoing lung transplantation
Study Sites	NYU Langone Hospital
Number of participants	Sixty patients (20 patients who received IR tacrolimus and 40 patients who will receive Envarsus XR)
Description of Study Agent/Procedure	Lung transplantation will be performed per standard-of-care techniques. All post-transplant management, including initial triple immunosuppression, will be carried out per standard of care. Once the patient is able to take medications via the oral route, they will be converted to Envarsus XR, which will be maintained for the first year post-lung transplant.
Reference Therapy	IR tacrolimus
Key Procedures	Patients in the Prospective Cohort will receive lung transplantation and post-operative management per standard protocol, including frequency of laboratory assays, surveillance bronchoscopy, and DSA assessment by single-antigen bead assay.
Statistical Analysis	Categorical variables will be compared using chi-square test or Fisher's exact test, as appropriate. Continuous variables will be compared using the Mann-Whitney U test for nonparametric data.

Schematic of Study Design

Envarsus XR	ARM 1	n=40	Envarsus XR to be initiated once patient is tolerating oral medications
IR tacrolimus (historical control)	ARM 2	n=20	Historical cohort of patients maintained on IR tacrolimus following transplant

1 Key Roles

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2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

Lung transplantation remains the definitive cure for many end-stage lung diseases. Despite advances in surgical technique and medical therapy, morbidity and mortality remain unacceptably high.[1] Chronic lung allograft dysfunction (CLAD) is the major barrier to long-term survival in lung transplant recipients.[2] The risk for CLAD is heterogenous, yet acute cellular rejection (ACR) has consistently been identified as a risk factor for the development of CLAD, with just one episode of A1 ACR portending a higher likelihood of CLAD.[3-5] Minimizing ACR in the first year post-lung transplant may therefore reduce the incidence of CLAD.

Tacrolimus is the backbone of rejection prevention following lung transplantation. Interpatient variability in tacrolimus pharmacokinetics make achieving consistent systemic exposure challenging and necessitate the use of therapeutic drug monitoring (TDM).[6] Even with TDM, tacrolimus trough levels will vary over time potentially leaving patients at increased risk for ACR.

Tacrolimus trough level variability was first described as a risk for ACR in lung transplant recipients by Chiang and colleagues.[7] They measured trough level variability utilizing the standard deviation (SD). In their cohort, the risk of ACR was increased by 23% for every 1 unit increase in SD within the first 3 months post-transplant. Counterintuitively, the mean tacrolimus trough level was higher in patients who had rejection, and the mean tacrolimus trough level pre-rejection was not predictive of rejection.[7] A similar study retrospectively reviewed 110 lung transplant recipients to evaluate the effect of tacrolimus SD on CLAD.[8] Tacrolimus SD was greatest in the first 6 months post-transplant, but was similar between months 6-12 and 12-24. Again it was observed that for each 1 unit increase in tacrolimus SD the risk of CLAD and death was significantly increased.[8] Recent data in lung transplant recipients found that increasing the time-in-therapeutic range for tacrolimus by 10% within the first year post-transplant reduced the burden of ACR by 54%.[9] Similar data was recently published in heart transplant recipients where patients with high tacrolimus variability had an increased rate of chronic rejection despite similar mean C0 levels.[10] Taken

together, this data suggests that the tacrolimus trough level in and of itself is not sufficient monitoring to protect against rejection and that trends in trough levels should be monitored as well.

Envarsus XR is a once-daily, extended-release formulation of tacrolimus that utilizes MeltDose technology optimize the pharmacokinetics of tacrolimus.[11,12] Pharmacokinetic studies in kidney transplant recipients demonstrated more consistent peak and peak-to-trough levels, decreased Cmax and increased Tmax for Envarsus XR as compared to IR tacrolimus. Additionally, bioavailability was improved with a stronger correlation between trough concentration (C_0) and AUC.[13-15] The randomized, phase III MELT trial was the first to compare the efficacy and safety of IR tacrolimus with conversion to Envarsus XR in kidney transplant recipients. The primary efficacy endpoint was a composite of death, graft failure, biopsy-proven acute rejection (BPAR), or loss to follow-up over a 12 month period. Tacrolimus TDD was decreased by 30% in patients converted to Envarsus XR. There was a significant decrease in TDD with conversion to Envarsus XR despite similar trough levels. The efficacy endpoint was similar between groups (2.5 vs. 2.5%, p>0.999). Additionally, there were no differences between individual components of the composite endpoint. A subsequent prospective, double-blind, double-dummy, multicenter, phase III comparison of IR tacolimus and de novo Envarsus XR was conducted to demonstrate non-inferiority at 24-months follow-up. Treatment failure defined as death, transplant failure, BPAR, or loss to follow-up was similar between the two drugs (Envarsus XR 23.1%, IR tacrolimus 27.3%) and well below the 10% non-inferiority margin. There was no significant difference in safety outcomes, including changes in estimated glomerular filtration rate (eGFR) and serum creatinine (Scr) was similar between groups. Certain subgroup populations (African-American race, age > 65, female gender) demonstrated trends towards significant efficacy benefit with Envarsus XR, however these groups were too small reach statistical significance.[16]

A phase II study comparing the pharmacokinetics of Envarsus XR to another unique prolonged-release tacrolimus formulation (Advagraf) is the only published experience to date in lung transplant recipients. This open-label, single-arm, prospective evaluated 20 lung transplant recipients stable on Advagraf who were then converted to Envarsus XR at a conversion dose of 1:0.7. Mean AUC was similar despite significantly lower dosing requirements in the Envarsus XR arm (5.05 vs. 3.36 mg, p=0.00002). Time to peak concentration was prolonged with Envarsus XR compared to Advagraf (325 vs. 125 minutes, p<0.001). Adverse events did not differ between the two formulations over the 6 month follow-up, and no major adverse events were considered related to the tacrolimus formulation or required withdrawal of therapy.[17] It is unknown if Envarsus XR would improve immunologic outcomes in lung transplant recipients by providing a stable pharmacokinetic profile and minimizing variability.

Currently at NYU Langone Health (NYULH), our practice has been to convert lung transplant recipients from IR tacrolimus to Envarsus XR following discharge from the hospital because of our observations of improved adherence and reduced side effects in this population. The only deterrent to inpatient use is the lack of availability on NYULH formulary. We have however experienced subtherapeutic tacrolimus C_0 during the outpatient conversion due to the inability to measure frequent C_0 concentrations. Early conversion to Envarsus XR in the hospital would allow for daily monitoring of C_0 levels and appropriate dose adjustments to be made leading to stable Envarsus XR dosing and potentially minimizing the risk of rejection during the early post-transplant period.

2.2 Name and Description of the Investigational Agent

Envarsus XR (tacrolimus extended-release tablets)
Manufactured by Rottendorf Pharma GmbH, North Rhine-Westphalia, Germany
Manufactured for Veloxis Pharmaceuticals, Cary, NC

Envarsus XR is an FDA-approved drug for the prophylaxis of organ rejection in de novo kidney transplant patients or in kidney transplant patients converted from IR tacrolimus when used with other immunosuppressants.

Envarsus XR is a novel extended-release formulation of tacrolimus created using MeltDose technology.

2.2.1 Preclinical Data

Compared to IR tacrolimus, Envarsus XR has improved bioavailability, a lower peak concentration (C_{max}), similar area-under-the-concentration-time curve (AUC) despite lower total daily dosing (TDD).[18]

2.2.2 Clinical Data to Date

A phase II study comparing the pharmacokinetics of Envarsus XR to another unique prolonged-release tacrolimus formulation (Advagraf) is the only experience to date in lung transplant recipients. This open-label, single-arm, prospective evaluated 20 lung transplant recipients stable on Advagraf who were then converted to Envarsus XR at a conversion dose of 1:0.7. Mean AUC was similar despite significantly lower dosing requirements in the Envarsus XR arm (5.05 vs. 3.36 mg, p=0.00002). Time to peak concentration was prolonged with Envarsus XR compared to Advagraf (325 vs. 125 minutes, p<0.001).[17]

The randomized, phase III MELT trial was the first to compare the efficacy and safety of IR tacrolimus with conversion to Envarsus XR in kidney transplant recipients. The primary efficacy endpoint was a composite of death, graft failure, biopsy-proven acute rejection (BPAR), or loss to follow-up over a 12 month period. Tacrolimus TDD was decreased by 30% in patients converted to Envarsus XR. There was a significant decrease in TDD with conversion to Envarsus XR despite similar trough levels. The efficacy endpoint was similar between groups (2.5 vs. 2.5%, p>0.999). Additionally, there were no differences between individual components of the composite endpoint. A subsequent prospective, double-blind, double-dummy, multicenter, phase III comparison of IR tacolimus and *de novo* Envarsus XR was conducted to demonstrate non-inferiority at 24-months follow-up. Treatment failure defined as death, transplant failure, BPAR, or loss to follow-up was similar between the two drugs (Envarsus XR 23.1%, IR tacrolimus 27.3%) and well below the 10% non-inferiority margin. There was no significant difference in safety outcomes, including changes in estimated glomerular filtration rate (eGFR) and serum creatinine (Scr) was similar between groups. Certain subgroup populations (African-American race, age > 65, female gender) demonstrated trends towards significant efficacy benefit with Envarsus XR, however these groups were too small reach statistical significance.[16]

A phase IIIb prospective study compared continuation of IR tacrolimus to Envarsus XR conversion in patients on IR tacrolimus with significant tremor. Improvement in tremor with conversion to Envarsus XR was documented by two separate clinical scoring systems and by patient-reported quality-of-life (78.9% reported improvement with conversion).[19]

2.2.3 Dose Rationale (if applicable)

Dosing will be converted on an individual basis. Because all patients will be initiated on IR tacrolimus via the sublingual or enteral route, conversion will be dependent on several factors: tacrolimus TDD, tacrolimus trough level, and patient clinical status (i.e. infection, rejection, acute kidney injury, etc.). Envarsus XR conversion dose will be decided upon by the attending pulmonologist and the clinical pharmacotherapy specialist caring for the patient, who are also members of the study team.

2.3 Rationale

Tacrolimus is the primary immunosuppressant medication administered following lung transplant. Despite its widespread use, tacrolimus is limited by inconsistent pharmacokinetics (PK), variability in systemic exposure, difficulties with therapeutic drug monitoring, concentration-related neurologic side effects, and poor patient adherence. Envarsus XR is a once-daily, extended-release formulation of tacrolimus that utilizes MeltDose technology to optimize the pharmacokinetics of tacrolimus. Phase II studies in kidney transplant recipients demonstrated more consistent peak and peak-to-trough levels for Envarsus XR as compared to IR tacrolimus. Additionally, bioavailability was improved to 30% from 17% with a stronger correlation between trough concentration (C_0) and AUC.

Recent data in lung transplant recipients found that increasing the time-in-therapeutic range for tacrolimus by 10% within the first year post-transplant reduced the burden of ACR by 54%.[9] Similar data was recently published in heart transplant recipients where patients with high tacrolimus variability had an increased rate of chronic rejection despite similar mean C_0 levels.[10] Taken together, these data highlight the clinical

consequences of inconsistency in systemic exposure to tacrolimus. Envarsus XR may improve immunologic outcomes in lung transplant recipients by providing a stable pharmacokinetic profile and minimizing variability.

2.4 Potential Risks & Benefits

2.4.1 Known Potential Risks

There is likely to be no potential risk to the patient as Envarsus XR has been shown to produce equivalent outcomes to IR tacrolimus in stable kidney transplant recipients. Adverse effects have similarly been equivocal or typically improved compared to IR tacrolimus.[19] This study involves minimal to no risk to individual patients as it is a retrospective review of medical records and will involve collection and storage of de-identified patient data only.

2.4.2 Known Potential Benefits

The potential benefits of this study include improved adherence and convenience of maintenance immunosuppressive therapy, reduction in neurologic adverse effects (e.g. tremor) as demonstrated in the STRATO trial,[19] and a decrease in the burden of ACR within the first-year post-transplant. There is no direct benefit to the historical control cohort.

3 Objectives and Purpose

3.1 Primary Objective

The primary objective will be to assess the feasibility of early conversion to Envarsus XR at 1-year follow-up.

3.2 Secondary Objectives (if applicable)

Secondary objectives will be to assess immunologic outcomes that may be impacted by conversion to Envarsus XR and potential mitigation of concentration-related side effects.

4 Study Design and Endpoints

4.1 Description of Study Design

This study will be a prospective, open-label, non-randomized, parallel arm, single-center trial comparing new lung transplant recipients converted to Envarsus XR to a historical cohort of patients who received IR tacrolimus.

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

The primary endpoint will be percentage of patients remaining on Envarsus XR at 1-year follow-up.

4.2.2 Secondary Study Endpoints

Secondary endpoints will include freedom from ACR at 1-year follow-up, ACR burden at 1-year follow-up as assessed by the composite rejection standardized score (CRSS),[20] treated episodes of rejection, the incidence of chronic lung allograft dysfunction (CLAD) at 1-year, incidence of de novo DSA in the first postoperative year, change in estimated glomerular filtration rate (eGFR) over the first post-operative year, and 1-year survival.

5 Study Enrollment and Withdrawal

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

Prospective arm:

1. Age ≥ 18 years
2. Received a lung or heart-lung transplant at NYU Langone Health
3. Be able to convert to Envarsus XR within the first month post-transplant
4. Able and willing to provide informed consent

Historical control:

1. Age ≥ 18 years
2. Received a lung or heart-lung transplant at NYU Langone Health
3. Completed one year from transplant on IR tacrolimus

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

Prospective arm:

1. Contraindication to tacrolimus due to allergic or adverse reactions
2. Pregnant or nursing women

Historical control:

1. Contraindication to tacrolimus due to allergic or adverse reactions (not including chronic kidney disease)

5.3 Vulnerable Subjects

Vulnerable subjects will not be eligible for enrollment.

5.4 Strategies for Recruitment and Retention

Recruitment of patients in the Prospective Cohort will occur during routine evaluation visits to determine candidacy for a lung transplant at NYU Langone Health by a member of the study team. Patients will be informed of the option to enroll in this study, and if interested, detailed information pertaining to the risks and benefits of the trial will be provided. Historical control patients will be reviewed retrospectively because they have already completed the study period and thus will not require recruitment into the study.

No additional information about potential candidates will be collected to determine interest or candidacy for this trial than would otherwise be normally collected as per standard of care for evaluation for a lung transplant.

Written informed consent for enrollment in the study will occur once the patient has been listed for lung transplantation in a private patient clinic room. Timing of consent for enrollment in relation to transplant date will vary between patients as acuity of disease is variable and waiting time to transplant is unpredictable.

The target sample size for the Prospective Cohort is 40 patients with early conversion to Envarsus XR.

5.4.1 Use of DataCore/Epic Information for Recruitment Purposes

This study will utilize EPIC to identify subjects.

Any recruitment information sent by email will utilize Send Safe email.

Potential subjects will already be known to the study team, as they will be under their care as candidates and/or waitlist registrants for lung transplant. The study team will conduct an in person consultation with the patients to explain the study as well as discuss the risks, benefits, and alternatives

Approved recruitment language will be used to communicate the reason they are being contacted and subjects will be asked if they are interested in participating in this specific study. Should the potential subjects agree, the study team will provide the subjects with information regarding the next steps for participation.

If a subject requests information regarding opting out of further recruitment for all research, subjects will be directed to contact research-contact-optout@nyumc.org or 1-855-777-7858.

5.5 Duration of Study Participation

Duration of study participation is expected to be 12 months minimum.

5.6 Total Number of Participants and Sites

Forty patients are expected to be enrolled and switched to Envarsus XR post-transplant. No sites outside of NYU Langone Health will enroll patients.

5.7 Participant Withdrawal or Termination

5.7.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

5.7.2 Handling of Participant Withdrawals or Termination

In the event a patient requests to withdrawal or is terminated from the study, the patient will either be continued on Envarsus XR or converted back to IR tacrolimus at the discretion of the transplant pulmonologist. If a patient withdrawals from the trial due to a hypersensitivity or severe adverse reaction to tacrolimus, future anti-rejection regimen will be determined by the transplant pulmonologist.

5.8 Premature Termination or Suspension 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, and 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 FDA.

6 Study Agent (Study drug, device, biologic, vaccine etc.) and/or Procedural Intervention

6.1 Study Agent(s) and Control Description

Envarsus XR is available in tablet form. It is available in 0.75, 1, and 4 mg tablets.

In accordance with 21 CFR 312.2(b)(1):

(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) 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

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

6.1.1 Acquisition

The study agent will be shipped to the Investigational Pharmacy from the manufacturer and stored according to standard protocols.

6.1.2 Formulation, Appearance, Packaging, and Labeling

This is an open label study and the drug will appear as it provided directly from the manufacturer, Veloxis Pharmaceuticals, Inc. The tablets are oval, white to off-white uncoated extended-release tablets, debossed with “TCS” on one side and “0.75”, “1”, or “4” on the other side depending on the strength of the tablet. The drug will be packed in the standard manufacturer’s packing and all standard package inserts will be retained. This product is commercially available and is FDA-approved for use in kidney transplant recipients in the proposed dosage form.

6.1.3 Product Storage and Stability

Store at 25 °C (77 °F); excursions permitted to 15 °C to 30 °C (59 °F to 86 °F).

6.1.4 Preparation

The drug is a tablet for oral ingestion, which requires no preparation.

6.1.5 Dosing and Administration

The dose of Envarsus XR is administered once daily, most commonly prior to the morning meal. The precise dose will be determined by TDM of tacrolimus C_0 levels with dose adjustments to achieve the goal prescribed by the transplant pulmonologist. The dose can include any combination of the 0.75, 1 and 4 mg tablets. The tablet should be swallowed whole, and should not be split, chewed or crushed.

6.1.6 Route of Administration

Tablets are administered orally.

6.1.7 Starting Dose and Dose Escalation Schedule

The initial dose of Envarsus XR will be determined by the transplant pulmonologist and the clinical pharmacotherapy specialist based on the patients current dose of sublingual or enteral IR tacrolimus and the corresponding C_0 level.

6.1.8 Dose Adjustments/Modifications/Delays

Dose adjustments will be made based on corresponding C_0 tacrolimus levels to achieve the goal prescribed by the transplant pulmonologist.

6.1.9 Duration of Therapy

Duration of therapy will be a minimum of 12 months.

6.1.10 Tracking of Dose

While in the hospital, nursing staff will give any doses and accountability will be maintained in the electronic medical record. Once outpatient, patients will attend regularly scheduled clinic appointments for routine care following a lung transplant and medication review will occur on each of these visits to ensure that the medication is being taken properly. Tacrolimus C_0 levels will be followed per routine post-operative care to ensure therapeutic levels are maintained.

6.2 Study Agent Accountability Procedures

The Investigational Pharmacist must complete the study drug accountability record. Any deviations or discrepancies must be reported to the PI immediately. The PI or co-investigator will review drug accountability during routine monitoring visits.

The accountability records will contain complete records of receipt, storage, dispensation and return for all used and unused tablets of Envarsus XR. Documentation will include batch numbers, expiry dates, and quantities received/dispensed/returned/destroyed. The accountability records and the study drug must be reconciled and discrepancies between the amount received, dispensed and returned/destroyed drug must be accounted for. This is applicable for unused, used and partially used and deliberately or accidentally damaged tablets of study drug.

Unused or damaged study drug must be kept at the Investigational Pharmacy until study closure and then returned to Veloxis Pharmaceuticals unless otherwise agreed upon with Veloxis Pharmaceuticals. Used study drug will be destroyed by the Investigational Pharmacist according to local guidelines after reviewed by the PI and confirmed by Veloxis Pharmaceuticals.

6.2.1 Assessment of Subject Compliance with Study Intervention

Assessment of compliance to study intervention will be performed during routine clinic follow-up post-lung transplantation. Tacrolimus C_0 levels will be followed per routine post-operative care to ensure therapeutic levels are maintained.

7 Study Procedures and Schedule

7.1 Study Procedures/Evaluations

7.1.1 Study Specific Procedures

Note that the medical history and medication history that pertains to candidacy for lung transplantation, physicals, height, weight, and vital signs are considered standard-of-care procedures and evaluations

for lung transplantation, and are not considered here as study specific procedures. Patients are not considered candidates for this trial if there is any contraindication to their standard candidacy for a lung transplant. As such, there are no procedures and evaluations specific to participation in this study that are outside of routine post-lung transplant management

7.1.2 Standard of Care Study Procedures

Lung transplantation and all associated procedures will be considered standard-of-care including: the transplant procedure itself and requisite intra-operative procedures and hemodynamic monitoring, post-operative ICU-level care, inpatient hospital unit care, outpatient post-operative care including, standard induction and maintenance immunosuppression, and standard post-transplant anti-infectious prophylaxis (anti-fungal, anti-pneumocystis, and anti-CMV prophylaxis). In accordance, clinical data resulting from these procedures will be collected at the following timepoints:

- Pathological rejection grading from transbronchial biopsies performed at 1, 3, 6, and 12 months post-transplant
- Any requirement for augmented immunosuppression for treatment of documented or presumed rejection
- Forced expiratory volume in 1 second (FEV_1) measurements monthly
- De novo DSA as assessed by single antigen bead assay measured at 1, 3, 6, 9, and 12 months post-transplant

7.2 Laboratory Procedures/Evaluations

7.2.1 Clinical Laboratory Evaluations

The following tests will be reviewed for patients who are included in the study but will be performed as standard of care for lung transplant recipients:

- **Hematology:** white blood cells (WBC) collected weekly for the first 3 months and monthly for months 4-12
- **Biochemistry:** potassium and creatinine collected weekly for the first 3 months and monthly for months 4-12
- **Tacrolimus:** C_0 levels will be obtained at all routine post-transplant follow-up visits and more frequently as needed for sub- or supra-therapeutic levels collected weekly for the first 3 months and monthly for months 4-12

7.2.2 Retrospective data to be collected in the Historical Control Cohort

Specific data pertaining to primary and secondary outcomes to be collected in the Historical Control Cohort is the same as listed above in the Prospective Cohort and at the same time points.

7.3 Concomitant Medications, Treatments, and Procedures

The subjects will receive concomitant medications, which would otherwise be given as standard of care for patients undergoing a lung transplant.

7.3.1 Precautionary Medications, Treatments, and Procedures

Treatment with potent CYP3A4 inducers (e.g. rifampin, St. John's Wort, efavirenz, carbamazepine, phenytoin, phenobarbital, etc.) or inhibitors (ritonavir, cobicistat, darunavir, lopinavir, atazanavir, etc.) requires special dosing considerations and potentially more frequent monitoring of tacrolimus C_0 levels.

Management of these significant drug interactions will be discussed by the study team and any dose adjustment plan documented.

7.4 Prohibited Medications, Treatments, and Procedures

As frequent tacrolimus C_0 level monitoring is available, no medications will be explicitly prohibited from the study.

7.5 Participant Access to Study Agent at Study Closure

Patients will be eligible to continue Envarsus XR through standard prescription coverage at completion of the study. The study team will assist with ensuring continuance of therapy is secured. Based on our current experience, Envarsus XR is readily obtainable for lung transplant recipients with the assistance of pharmacy liaisons who provide prior authorization support. The cost of any copayment for Envarsus XR past the one year study window would be the responsibility of the patient. If insurance coverage of Envarsus XR is not able to be obtained, the patient would then be converted back to IR tacrolimus at the discretion of the treating transplant pulmonologist, who would also be a study team member.

8 Assessment of Safety

8.1 Specification of Safety Parameters

8.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

8.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. 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)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

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.

8.2.2 Relationship to Study Agent

The clinician's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- **Related** – The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

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 (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge 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 (dechallenge). Rechallenge 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.

8.2.3 Expectedness

The Principal Investigator 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.

8.3 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 RF. 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 informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. 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 or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

8.4 Reporting Procedures – Notifying the IRB

8.4.1 Adverse Event Reporting

All AEs will be recorded in AE CRFs by a member of the study team only if they are related to the study drug. AEs will be recorded within 3 business days of the study team being made aware of the AE. The relationship of the AE to the study drug will be noted by the PI. AEs that are deemed definitely related or probably related to the study drug will be reported to the IRB. within 3 days of their designation as such. AEs that are deemed unrelated or not likely related to the study drug will be recorded on CRFs as described above and will be reviewed at quarterly safety review meetings with the Safety Monitor, and at annual review by the IRB.

8.4.2 Serious Adverse Event Reporting

All SAEs will be recorded in SAE CRFs by a member of the study team. SAEs will be recorded within 3 business days of the study team being made aware of the SAE. The relationship of the SAE to the study drug will be noted by the PI. SAEs that are both unexpected and deemed related to the study drug will be reported to the IRB and the Safety Monitor within 24 hours of the PI designation as such. The Safety Monitor will determine the need for an emergency meeting between the Safety Monitor and the study team (see safety oversight below) or whether these can be reviewed at quarterly meetings. SAEs that are deemed unrelated or not likely related to the study drug will be recorded on CRFs, will be reported to IRB and Safety Monitor within 3 days of their designation as such and will be reviewed at quarterly safety meetings.

8.4.3 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the PI's responsibility to report UPs to their IRB and notify the Safety Monitor. 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.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB within 3 days the investigator becoming aware of the event.
- Any other UP will be reported to the IRB within 3 days of the investigator becoming aware of the problem.

8.4.4 Reporting of Pregnancy

If any pregnancy occurs in a study subject, the PI will be notified immediately and the IRB will be notified within 3 days of discovery of the pregnancy. Data regarding safety of tacrolimus in pregnant women suggests an increased risk of premature delivery and potential for fetal harm. Standard of care medications utilized for lung transplant recipients have known contraindications in pregnancies therefore any pregnancies will need to be managed as per standard of care with the lung transplant team. Counseling of pregnant subjects with regard to the risks of continuing versus discontinuing Envarsus XR will occur with patients once counseling with regard to the contraindications of the standard of care transplant medications has occurred.

8.5 Reporting Procedures – Notifying the Study Sponsor

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 study sponsor within 24 hours of site awareness. See Section 1, Key Roles for contact information.
- Other SAEs regardless of relationship will be submitted to the study sponsor within 72 hours of site awareness.

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 the study sponsor and should be provided as soon as possible.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

8.6 Safety Oversight

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

The study will not have a formal DSMB as there are no anticipated SAE from routine testing and monitoring post-lung transplant, along with the off-label use of an approved FDA medication (Envarsus XR) for prevention of acute rejection following lung transplant and with the recommended dosing. Additionally, this trial will not be looking for a new indication or use of Envarsus XR.

Safety oversight will be under the direction of the PI and a Safety Monitor with expertise in transplantation (Claudia Gidea, MD – Transplant Cardiology). This individual will be involved as a consultant but not as an investigator of the trial and will provide an independent evaluation of each one of the SAE related to the treatment with Envarsus XR. Furthermore, the PI and the Safety Monitor will meet at least quarterly to discuss patient progress and any relevant study related events that meet criteria for routine review. The Safety Monitor will review de-identified data only.

9 Clinical Monitoring

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).

10 Statistical Considerations

10.1 Statistical and Analytical Plans (SAP)

No formal SAP is required as the study will employ only a single prospective arm with comparison to a historical control.

10.2 Statistical Hypotheses

We hypothesize that freedom from ACR within the first year post-lung transplant will be reduced by early and continued prescription of Envarsus XR as compared to IR tacrolimus. Additionally, we hypothesize that key related immunologic outcomes, de novo DSA and CLAD, may be reduced due to less frequent rejection.

10.3 Analysis Datasets

All subjects will be entered into a database containing de-identified information. All patients who take one dose of the study drug will be included in the safety analyses (intention-to-treat). However, only patients completing the full first year post-lung transplant will be included in the efficacy analysis (per-protocol analysis).

10.4 Description of Statistical Methods

10.4.1 General Approach

The study is a two-arm, non-randomized study comparing a prospective arm of patients receiving Envarsus XR to a historical control who received IR tacrolimus. Descriptive statistics will be used for baseline characteristics and to compare nominal outcomes such as de novo DSA and the incidence of CLAD at 1 year post-transplant. These data will be presented as frequencies and will be compared using Chi-square tests or Fishers exact test, as appropriate. The primary outcome freedom from ACR will be compared using Kaplan-Meier survival analysis and analyzed with the log-rank test. Continuous data will be presented as median (interquartile range) and compared using Mann-Whitney U test. A two-tailed P value of < 0.05 will be considered as significant for inferential tests.

10.4.2 Analysis of the Primary Efficacy Endpoint(s)

The primary endpoint, percentage of patients remaining on Envarsus XR at 1-year, will be measured as a single endpoint on a nominal scale. It will be analyzed using descriptive statistics.

10.4.3 Analysis of the Secondary Endpoint(s)

1. Freedom from ACR will be compared using Kaplan-Meier survival analysis and the log-rank test.
2. Composite rejection standardized score at 1 year follow-up will be presented as median (IQR) and will be compared using the Mann-Whitney U test
3. Treated episodes of rejection will be presented as frequencies and compared using chi-square test
4. Incidence of CLAD at 1 year will be presented as odds ratio with 95% confidence intervals and compared between groups using logistic regression.
5. Incidence of *de novo* DSA at 1 year will be presented as odds ratio with 95% confidence intervals and compared using between groups using logistic regression.
6. Mortality a 1 year post-transplant will be compared using Kaplan-Meier survival curves and log-rank analysis.

10.4.4 Safety Analyses

Safety endpoints include worsening chronic kidney disease and discontinuation of therapy will be analyzed as changes from baselines and summary data during the course of treatment, respectively. These will be compared as linear regression and frequencies using the chi-square test, respectively. All AEs will be ascertained and reported by the PI.

10.4.5 Adherence and Retention Analyses

Adherence to the protocol will be assessed by the study team in direct conversation with subjects during routine visits, and will be assessed clinically by evaluation tacrolimus C_0 levels. Failure to maintain significant tacrolimus C_0 levels will prompt more detailed direct patient inquiries regarding medication adherence.

10.4.6 Baseline Descriptive Statistics

Baseline statistics including but not limited to age, gender, etiology of lung disease, type of lung transplant, lung allocation score, details of the requirement for mechanical ventilation or extracorporeal membrane oxygenation, and ischemic time of the organ will be collected for each group. These data will be compared using chi-square tests to assess for baseline imbalances.

10.4.7 Planned Interim Analysis

No interim analysis is planned.

10.4.7.1 Safety Review

Any patient death will result in halting of any further enrollment in the study and an assessment of whether the death was related to Envarsus XR exposure or complications thereof. Even in the event of a patient death, currently enrolled patients who are actively being treated with Envarsus XR and tolerating therapy will continue to receive therapy so as not to put them at risk for rejection as a consequence of converting therapy. If the patient death is deemed related to Envarsus XR, enrolled patients receiving Envarsus XR will be switched to an alternative therapy including, but not limited to: IR tacrolimus, cyclosporine, sirolimus, everolimus, mycophenolate, belatacept, or some combination thereof.

10.4.7.2 Efficacy Review

There will be no interim analyses performed due to the small sample size and anticipated short duration of enrollment for the study.

10.5 Sample Size

We plan to prospectively enroll 40 patients into the Envarsus XR arm to provide a 2:1 sample size with a historical control of patients who received IR tacrolimus. The sample size of 40 patients for the Prospective Cohort was chosen based on the expected number of lung transplants performed in one year at NYULH. The Historical Control Cohort sample size includes all patients who were transplanted at NYULH and completed one year of follow-up post lung transplant while maintained on IR tacrolimus. The 2:1 sample size was chosen as the purpose of the study is to gain experience with Envarsus XR in lung transplant recipients and IR tacrolimus has many years of clinical use. As this is a pilot study, there will be no power calculations.

11 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and 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, copies or transcriptions certified after verification as being accurate and complete, 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. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries will be stored in REDCap.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups 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.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13 Ethics/Protection of Human Subjects

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

13.3.1 Consent/Assent and Other Informational Documents Provided to Participants (Envarsus XR Prospective Cohort)

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. The informed consent document to be used is submitted with this protocol.

13.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have

the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

13.4 Participant and Data Confidentiality

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). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

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.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the site and by NYU Langone Medical Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Data will be directly entered from the electronic medical record into electronic CRFs in the Institution-approved HIPAA Compliant and Encrypted version of REDCap. The original CRFs will be provided for use as source documents and maintained for recording if and when study visits occurred for each participant enrolled in the study.

Once all subjects have completed the study visits, Laboratory Evaluation windows will open up to +/-14 days of the target date to allow for the retrospective collection of data that accurately reflects the status of these subjects month-to-month as there is variability in the scheduling of labs due to many clinical factors. This will also more closely align with the window, +/- 28 days, for the bronchoscopies and DSAs that happen at these monthly visits as well.

The window for the Year 1 visits (Study Visit Week 52) will also open to +/- 30 days once all patients have completed the study for retrospective data collection. This enables Year 1 visits to properly capture data 1 year post-transplant and balances out the enrollment window given that the enrollment window for the trial is within 30 days post-transplant.

De-identified clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be assimilated in the study subject binders. Clinical data will be entered directly to electronic CRFs in REDCap.

14.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the investigation is discontinued. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (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.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 3 working days of the scheduled protocol-required activity.

All protocol deviations must be addressed in study source documents, reported to the PI and Safety Monitor. During the course of routine follow-up, certain adjustments from routine clinical, laboratory, and bronchoscopy schedules are deemed necessary per the clinical judgement of the treating transplant

pulmonologist. If study procedures or assessments are not performed based on clinical judgement, these routine adjustments shall not be deemed as protocol deviations or result in a report to the IRB.

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

14.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

15 Study Finances

15.1 Funding Source

This study will be financed by an investigator-initiated study grant from the manufacturer of Envarus XR, Veloxis Pharmaceuticals, Inc.

15.2 Costs to the Participant

Participants will not incur any costs associated with participating in this trial.

16 Study Administration

16.1 Study Leadership

The Principal Investigator will govern the conduct of the study. The PI, together with at least one coinvestigator will meet in person or by teleconference with the Safety Monitor at least quarterly

and documentation of the meeting will be maintained.

17 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the <specify NIH IC> has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities 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 the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

18 References

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19 Attachments

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

20 Schedule of Events

Activity	Screening Visit (POD 0 to30)	SVD0*	SVW1 (+/- 5 days)	SVW2 (+/- 5 days)	SVW3 (+/- 5 days)	SVW4 (+/- 5 days)	SVW5 (+/- 5 days)
Study team procedures							
Consent	X						
Medical History	X						
Physical Exam	X						
Height	X						
Weight	X						
Vitals signs	X						
Review all recipient inclusion/exclusion criteria	X						
Study drug dispensation		X					
Participant study drug compliance check and accountability						X	
Bronchoscopy with biopsy						X	
Spirometry (FEV1)						X	
Donor-specific antibody						X	
Laboratory Evaluations							
Biochemistry			X	X	X	X	X
Hematology			X	X	X	X	X
Tacrolimus C_0			X	X	X	X	X

SVD=study visit day; SVW=study visit week
**Study visit day 0 = day of first drug dispensation and may occur on the same day as screening visit.*
**For SVW4 and SVW12: Bronchoscopies and DSAs will be done per SOC and as close to the specified study visit week as possible with a window of +/- 14 days.*

Activity	SVW6 (+/- 5 days)	SVW7 (+/- 5 days)	SVW8 (+/- 5 days)	SVW9 (+/- 5 days)	SVW10 (+/- 5 days)	SVW11 (+/- 5 days)	SVW12 (+/- 5 days)
Study team procedures							
Participant study drug compliance check and accountability			X				X
Bronchoscopy with biopsy							X
Spirometry (FEV1)			X				X
Donor-specific antibody							X
Laboratory Evaluations							
Biochemistry	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X
Tacrolimus C_0	X	X	X	X	X	X	X

Activity	SVW16 (+/- 5 days)	SVW20 (+/- 5 days)	SVW24 (+/- 5 days)	SVW28 (+/- 5 days)	SVW32 (+/- 5 days)	SVW36 (+/- 5 days)	SVW40 (+/- 5 days)
Study team procedures							
Participant study drug compliance check and accountability	X	X	X	X	X	X	X
Bronchoscopy with biopsy			X				
Spirometry (FEV1)	X	X	X	X	X	X	X
Donor-specific antibody			X			X	
Laboratory Evaluations							
Biochemistry	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X
Tacrolimus C_0	X	X	X	X	X	X	X

Activity	SVW44 (+/- 5 days)	SVW48 (+/- 5 days)	SVW52 (+/- 5 days)
Study team procedures			
Participant study drug compliance check and accountability	X	X	X

Medical History			X
Physical Exam			X
Height			X
Weight			X
Vitals signs			X
Bronchoscopy with biopsy			X
Spirometry (FEV1)	X	X	X
Donor-specific antibody			X
Laboratory Evaluations			
Biochemistry	X	X	X
Hematology	X	X	X
Tacrolimus C_0	X	X	X

**For SVW24, SVW36, and SVW52: Bronchoscopies and DSAs will be done per SOC and as close to the specified study visit week as possible with a window of +/- 28 days.*