Study Title
Conversion from Immediate Release Tacrolimus to Envarsus XR® in Simultaneous Pancreas-Kidney Recipients: Assessment of functional, safety and quality of life outcomes (CIRGEN SPK)

Study sponsor: University of Wisconsin-Madison

Study funding provided by: Veloxis Pharmaceuticals

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<tr>
<th>Version</th>
<th>Version Date</th>
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<td>05/02/2018</td>
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<td>v.2</td>
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<td>v. 3</td>
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Background and Rationale

Envarsus XR® is a new approved once daily formulation of tacrolimus which uses a proprietary meltdose formulation to provide slow release of drug achieving equivalent immunosuppression in kidney transplant recipients with similar kidney rejection and graft survival outcomes compared to immediate release (IR) tacrolimus\(^1,2\). Studies have also shown effective trough levels are achieved with 20% less dosing\(^1-3\). A single study of Envarsus XR® in kidney transplant recipients has shown reduced tremors compared to TAC IR\(^4\). However, this has not been studied in pancreas transplant recipients, who have a high incidence of tremor with tacrolimus and whose tacrolimus levels often run higher on average than kidney transplant recipients. Other studies demonstrate that Envarsus XR® exhibits a similar PK profile and mean AUC in diabetic kidney transplant patients compared to non-diabetic kidney transplant patients\(^5\), which supports its use in diabetic patients receiving Simultaneous Pancreas Kidney (SPK) transplants. However, no data exist with respect to glycemia control.

Study aims:
- Determine if Envarsus XR® reduces tremor severity compared to IR tacrolimus
- Determine if Envarsus XR® improves renal function or glycemic control compared to IR tacrolimus
- Compare the efficacy of Envarsus XR® by comparing the outcomes (patient, pancreas graft and kidney graft survival) of patients treated with Envarsus XR to those of contemporary and historical controls at our center treated with IR tacrolimus, with the goal of showing non-inferiority.
- Compare insulin resistance and insulin sensitivity by defined measures post conversion between T1D and T2D recipients.

Study Population

This is a Phase II/III, Single-center, Prospective, Open-label, Single Arm Study of 30

Inclusion criteria:
- Adult, 18-70 years of age
- Subject must be able to understand and provide consent
- History of Diabetes Type 1 or Insulin-Dependent Diabetes Type 2 with Chronic Kidney Disease (CKD)
- Recipient of a Simultaneous Pancreas Kidney (SPK) transplant, 3-24 months prior to screening.
- Have a history of tremors following transplantation
- Stable pancreas allograft function as evidenced by no requirement of exogenous insulin or oral anti-diabetic agents and stable pancreatic enzymes
- Stable kidney allograft function
- Currently taking Immediate-Release (IR) tacrolimus
- Women of child-bearing potential (WOCPP) must have a negative pregnancy test at the time of study entry

Exclusion criteria:
- Currently maintained on an extended-release tacrolimus immunosuppressive regimen
- Previous history of tremors prior to transplantation
- Solitary pancreas transplant recipients
- History of solid organ transplant other than a kidney or pancreas
- Uncontrolled concomitant infection at the discretion of the investigator
- Presence of Donor Specific Antibodies

Study Design & Methods
This is a Phase II/III, Single-center, Prospective, Open-label, Single Arm Study of 30 Simultaneous Kidney Pancreas recipients who received a transplant at least 3 months, but no more than 2 years prior, with a history of tremors following transplantation.

Assessments before and after conversion:

1) Neurological Exam with Fahn-Tolosa-Marin Tremor Rating Scale before and at 1, 3, and 6 post-conversion.
2) Quality of Life in Essential Tremor Questionnaire (QUEST) before, and at 1, 3, and 6 months post-conversion.
3) BUN, Creat, eGFR, Fasting blood glucose, fasting C-peptide, HbA1c, tacrolimus and mycophenolate (MPA) levels per standard of care, before, and at 1, 3, and 6 months post-conversion.
4) Mixed Meal Glucose Tolerance Test (MMGTT) in transplant clinic: before and at 1, 3, and 6 months post-conversion.
   - Basal (fasting) and stimulated glucose and c-peptide levels will be determined using the MMTT. Subjects will be instructed not to eat after 8 PM the night before the test. Subjects will arrive fasting to the transplant or diabetes clinic where the capillary blood glucose (BG) will be checked. If the BG is ≤ 70 mg/dL (3.89 mmol/L) or ≥ 180 mg/dL (10 mmol/L), the test will be rescheduled for the next possible day. If the BG is 70 – 180 mg/dL, basal glucose and c-peptide levels will be drawn. Immediately after, the subject will receive 6 mL per kg BW (to a maximum of 360 mL) of Boost® High Protein Drink (or a nutritionally equivalent substitute) to consume in 5 minutes starting at time = 0. Then, at time = 60 and 120 minutes, stimulated glucose and c-peptide levels will again be drawn.
5) Modified Transplant Symptom Occurrence and Symptom Distress Scale (MTSOSD) Questionnaire Assessment of gastrointestinal (GI) side effects
## CIRTEN-SPK Trial

<table>
<thead>
<tr>
<th></th>
<th>Screen/Baseline</th>
<th>1 Month</th>
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<td>C-peptide(^2)</td>
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<td>Mixed Meal Tolerance Test(^3)</td>
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**Mixed Meal Tolerance Test\(^1,2,3\):** Fasting blood glucose (included in Basic Metabolic Panel) and fasting C-peptide drawn prior to oral glucose, and then stimulated blood glucose and C-peptide levels drawn at +60 and +120 minutes from the time of initiation of oral glucose.

**QUEST and MTSOSD Quality of Life Surveys\(^4,5\):** Quality of Life in Essential Tremor and Modified Transplant Symptom Occurrence and Symptom Distress Scale (MTSOSD) Questionnaires

**Adverse Events\(^6\):** Adverse Events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. Adverse Events ≥ CTCAE Grade 3 will be recorded. Serious Adverse Events will be reported to Veloxis Pharmaceuticals, Inc., within 24 hours of notification of the event. Non-serious events that meet the criteria for reporting to the Institutional Review Board will be reported to Veloxis Pharmaceuticals, Inc., on a quarterly basis.

**Laboratories responsible analyzing the samples:** The UW Madison Hospitals and Clinics will complete all sample analysis during the study life cycle.
Study Endpoints and Statistical Plan

Primary Endpoint:
1) Improvement in patient and physician-assessed degree of tremors based on FTM and QUEST scoring tools
2) Scores on Quality of Life in Essential Tremor and Modified Transplant Symptom Occurrence and Symptom Distress Scale (MTSOSD) Questionnaires

Secondary Endpoints:
1) Renal function – eGFR and serum creatinine
2) Glycemic control – AUC by MMTT, fasting BG, fasting C-peptide, calculated C-peptide/glucose ratio, calculated 20/(fasting Cpeptide x fasting BG) as a measure of insulin resistance, calculated HOMA-IR (fasting insulin x fasting BG)/22.5 as a measure of insulin sensitivity/resistance, calculated BETA-2 score to sensitive estimate beta cell function, and HbA1c.
3) Tacrolimus and Mycophenolate doses as well as TAC and MPA levels

Quantitative assessments will be performed on subjects repeatedly over time. We will compare average values of these quantitative assessments on the entire cohort performed pre-conversion to the average values obtained at 1, 3, and 6 months post-conversion. In addition, we will compare some endpoint values obtained on this group of EnvarsusXR® converted subjects to those obtained on a case-controlled group of 30 historical controls at similar times post-transplant. These endpoints would include generally standard of care clinical lab values (e.g. BUN, serum creatinine, eGFR, fasting C-peptide, fasting blood glucose, etc.). We will also report donor and recipient demographics of these converted patients and compare them to the historical case-control cohort.

We will evaluate historical and/or contemporaneous controls not treated with EnvarsusXR® from existing data in the Transplant Database, no prospective data will be collected from electronic medical records directly. The record review component will include already existing or contemporaneous data of patients, who received transplants within the same time frame, as those who were converted to EnvarsusXR®. The compared data will consist of patient, kidney graft and pancreas graft survival outcomes.

We also intend to compare Type 1 DM recipients to Type 2 DM recipients, which we expect to comprise approximately 10-15% of the study subjects. We will assess changes in insulin resistance and sensitivity post conversion by calculated values based on baseline glucose and insulin, according to published formulas in this reference.

Statistical Analysis - While there is limited published data for EnvarsusXR® use in the setting of pancreas transplantation, there is ample published efficacy and safety data in the setting of kidney transplantation. To this end, we here propose to study the safety and efficacy with several neurological, kidney and pancreas graft functional as well as QoL quantitative endpoints. Given the study design, all statistical analysis will be focused on differences in outcomes compared to baseline, for each endpoint in the entire cohort and for each subject. The donor and recipient demographics will be collected and reported. Graft and patient survival estimates will be calculated by Kaplan-Meier analysis and compared to contemporary and historical controls using a Wilcoxon Rank Sum and Log-Rank tests. Quantitative endpoints assessed over time will be analyzed by repeated measures ANOVA and ANCOVA. This single arm conversion trial involving a limited number of subjects achieves both adequate power and realistic enrollment. We perform 35-40
SPK transplants annually, of which it is estimated that 60-80% experience tremors post-transplant and would be eligible for the study. A power calculation was carried out based on the Langone et al. tremor study; results which show a 15% and 39% improvement in tremor based on the FTM and QUEST tremor scoring tools, respectively. We are proposing to use the same tools and have experience using them (LBD). Based on a desired power of 80% and allowing a false negative rate of 20% (Alpha, P<0.05) and using the mean change/effect observed for each of the tools in the Langone et al. publication, we have calculated that 17-18 subjects are needed in this single arm trial where subjects will be assessed before and after conversion. Enhanced power is derived from repeated measures in subjects serving as their own controls, which helps minimize the need for a large sample size. Alternatively it may be advantageous to consider higher stringency and greater power. To achieve 90% power with a p value of <0.02 (alpha =0.02) we would need approximately 26-28 subjects. Therefore, we would recommend plans to enroll 30 subjects to account for a possible 5-10% drop out rate. No adjustment for multiple testing will be made owing to the exploratory, pilot nature of the study. Given the prospective nature of the study, we expect to encounter little if any missing data. However in the event of missing data, no attempt to impute this missing data will be made in this pilot study; missing data will be treated as missing.

**Enrollment and Study Timeline**

The University of Wisconsin is among the largest pancreas transplant programs in the US, and consistently performs more SPK transplants than any other center in the US. On average we perform approximately 35-40 SPK transplant and 60 total pancreas transplants annually. We are currently actively following over 68 SPK transplants performed less than 2 years ago. These patients would be screened for subject enrollment.

We anticipate enrolling 2-3 subjects per month and all subjects within an 18 month period. With minimum of 1 year follow-up post-conversion, we anticipate the entire study would be completed within 2 ½ years.

**Conversion procedures**

To convert from a tacrolimus immediate-release product to ENVARSUS XR, the package insert recommends administering an Envarsus XR® once daily dose that is 80% of the total daily dose of the tacrolimus immediate-release product. The recommended reduction of 20%, along with the subject’s clinical status (current dose and trough level, degree of current side effects, risk factors for rejection, infections, etc.) are considered when determining the actual initial dose of Envarsus XR®. The tacrolimus whole blood trough concentrations will be monitored and titrate Envarsus XR® dosage to achieve target whole blood trough concentration.

The subjects will not be tapered off tacrolimus immediate-release products and there are no reported risks associated with the conversion process.

**Drug administration and dosing specifications**

The Envarsus XR® drug will be administered to study subjects once daily, orally. This is an open-label, single arm study. The conversion from a tacrolimus immediate-release product to Envarsus XR® will be administered by taking an Envarsus XR® once daily dose that is approximately 80% of the total daily dose.
of the tacrolimus immediate-release product. Dose adjustments are made by monitoring tacrolimus trough levels, similar to the twice-daily formulation.

Summary of Known and Potential Risks and Benefits to Human Subjects

1. Adverse reactions

1.1. Infections
The overall incidence of infections, serious infections, and infections with identified etiology reported in stable kidney transplant recipients treated with ENVARSUS XR or tacrolimus immediate-release product are shown in Table 1.

Table 1. Percentage of Stable Patients with Infections Through One Year Post-Treatment in the Conversion Study

<table>
<thead>
<tr>
<th></th>
<th>ENVARSUS XR ± Steroids, MMF/MPS or AZA N= 162</th>
<th>Tacrolimus immediate-release product ± steroids, MMF/MPS or AZA N=162</th>
</tr>
</thead>
<tbody>
<tr>
<td>All infections</td>
<td>46%</td>
<td>48%</td>
</tr>
<tr>
<td>Respiratory Infections</td>
<td>26%</td>
<td>28%</td>
</tr>
<tr>
<td>Urinary Tract Infections</td>
<td>10%</td>
<td>14%</td>
</tr>
<tr>
<td>Bacterial Infections</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>Fungal Infections</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Gastrointestinal infections</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>BY virus b</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Cytomegalovirus Infections</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Serious Infections</td>
<td>8%</td>
<td>9%</td>
</tr>
</tbody>
</table>

a The stable kidney transplant study was not designed to support comparative claims of ENVARSUS XR compared to tacrolimus immediate-release product for the adverse reactions reported in this table.

b BK virus associated nephropathy (BKVAN) occurred in 1.2% (2/162) and 0.6% (1/162) in the ENVARSUS XR and tacrolimus immediate-release treatment groups, respectively.

1.2. New Onset Diabetes After Transplantation (NODAT)
New onset diabetes after transplantation (NODAT) was defined by the composite occurrence of fasting plasma glucose values ≥126 mg/dL, 2-hour postprandial plasma glucose of at least 200 mg/dL (in oral glucose tolerance test) on 2 or more consecutive occasions post baseline, insulin requirement for ≥31 days, an oral hypoglycemic agent use ≥31 days, or HbA1c ≥6.5% (at least 3 months after randomization).
among kidney transplant patients with no medical history of diabetes. The incidence of NODAT for the stable kidney transplant study through one year post-transplant is summarized in Table 2 below.

**Table 2. Percentage of Stable Patients with NODAT Through 1 Year Post- Treatment in the Conversion Study**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ENVARSUS XR ± steroids, MMF/MPS or AZA (N=90)</th>
<th>Tacrolimus immediate-release product ± steroids, MMF/MPS or AZA (N=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite NODAT b</td>
<td>10%</td>
<td>11%</td>
</tr>
<tr>
<td>HbA1c ≥6.5%</td>
<td>3%</td>
<td>7%</td>
</tr>
<tr>
<td>Fasting Plasma Glucose Values ≥126 mg/dL on 2 consecutive occurrences</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>Oral hypoglycemic use</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Insulin Use ≥31 days</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

A The stable kidney transplant study was not designed to support comparative claims of ENVARSUS XR compared to tacrolimus immediate-release product for the adverse reactions reported in this table.

b Analyses restricted to patients at risk for NODAT

### 1.3. Common Adverse Reactions

The incidence of adverse reactions that occurred in ≥5% of ENVARSUS XR-treated patients compared to tacrolimus immediate-release product through one year of treatment in the conversion study is shown by treatment group in Table 3.

**Table 3. Adverse Reactions (≥ 5%) in Stable Kidney Transplant Patients Through 1 Year Post- Treatment in the Conversion Study**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ENVARSUS XR N=162</th>
<th>Tacrolimus immediate-release product N=162</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>14%</td>
<td>9%</td>
</tr>
<tr>
<td>Blood Creatinine Increased</td>
<td>12%</td>
<td>9%</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>9%</td>
<td>14%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>9%</td>
<td>11%</td>
</tr>
<tr>
<td>Headache</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>7%</td>
<td>9%</td>
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<td>----------------------------------</td>
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</tr>
<tr>
<td>Peripheral Edema</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4%</td>
<td>6%</td>
</tr>
</tbody>
</table>

aigned to support comparative claims of ENVARSUS XR compared to tacrolimus ase for the adverse reactions reported in this table.

2. Serious Adverse reactions

2.1. Lymphoma and Other Malignancies

Immunosuppressants, including ENVARSUS XR, increase the risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. Examine patients for skin changes and advise to avoid or limit exposure to sunlight and UV light.

Post-transplant lymphoproliferative disorder (PTLD), associated with Epstein-Barr Virus (EBV), has been reported in immunosuppressed organ transplant patients. The risk of PTLD appears greatest in those individuals who are EBV seronegative. Monitor EBV serology during treatment.

2.2. Serious Infections

Immunosuppressants, including ENVARSUS XR, increase the risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections. These infections may lead to serious, including fatal, outcomes. Serious viral infections reported include:

- Polyomavirus-associated nephropathy (especially due to BK virus infection),
- C virus-associated progressive multifocal leukoencephalopathy (PML), and
- Cytomegalovirus (CMV) infections: CMV seronegative transplant patients who receive an organ from a CMV seropositive donor are at highest risk of CMV viremia and CMV disease.

Monitor for the development of infection and adjust the immunosuppressive regimen to balance the risk of rejection with the risk of infection.

2.3. Graft Rejection and Other Serious Adverse Reactions due to Medication Errors

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 is not interchangeable or substitutable with tacrolimus immediate-release products or other tacrolimus extended-release products. Instruct patients and caregivers to recognize the appearance of ENVARSUS XR tablet.

2.4. New Onset Diabetes After Transplant
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. Monitor blood glucose concentrations and treat appropriately.

2.5. Nephrotoxicity due to ENVARSUS XR and Drug Interactions

ENVARSUS XR, like other calcineurin-inhibitors, can cause acute or chronic nephrotoxicity. Consider dosage reduction in patients with elevated serum creatinine and tacrolimus whole blood trough concentrations greater than the recommended range. The risk for nephrotoxicity may increase when ENVARSUS XR is concomitantly administered with CYP3A inhibitors (by increasing tacrolimus whole blood concentrations) or drugs associated with nephrotoxicity (e.g., aminoglycosides, ganciclovir, amphotericin B, cisplatin, nucleotide reverse transcriptase inhibitors, protease inhibitors).

2.6. ENVARSUS XR may cause a spectrum of neurotoxicities.

The most severe neurotoxicities include posterior reversible encephalopathy syndrome (PRES), delirium, seizure, and coma; others include tremors, paresthesias, headache, mental status changes, and changes in motor and sensory functions. As symptoms may be associated with tacrolimus whole blood trough concentrations at or above the recommended range, monitor for neurologic symptoms and consider dosage reduction or discontinuation of ENVARSUS XR if neurotoxicity occurs.

2.7. Mild to severe hyperkalemia, which may require treatment, has been reported with tacrolimus including ENVARSUS XR. Concomitant use of agents associated with hyperkalemia (e.g., potassium-sparing diuretics, ACE inhibitors, angiotensin receptor blockers) may increase the risk for hyperkalemia. Monitor serum potassium levels periodically during treatment.

2.8. Hypertension is a common adverse reaction of ENVARSUS XR therapy and may require antihypertensive therapy [see Adverse Reactions (6.1)]. Some antihypertensive drugs can increase the risk for hyperkalemia [see Warnings and Precautions (5.7)]. Calcium-channel blocking agents may increase tacrolimus blood concentrations and require dosage reduction of ENVARSUS XR.

2.9. Risk of Rejection with Strong CYP3A Inducers and Risk of Serious Adverse Reactions with Strong CYP3A Inhibitors

The concomitant use of strong CYP3A inducers may increase the metabolism of tacrolimus, leading to lower whole blood trough concentrations and greater risk of rejection. In contrast, the concomitant use of strong CYP3A inhibitors may decrease the metabolism of tacrolimus, leading to higher whole blood trough concentrations and greater risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) [see Warnings and Precautions (5.6 and 5.10)] Therefore, adjust ENVARSUS XR dose and monitor tacrolimus whole blood trough concentrations when coadministering ENVARSUS XR with strong CYP3A inhibitors (e.g., telaprevir, boceprevir, ritonavir, ketoconazole,itraconazole, voriconazole, clarithromycin) or strong CYP3A inducers (e.g., rifampin, rifabutin).

2.10. QT Prolongation
ENVARSUS XR may prolong the QT/QTc interval and cause Torsade de Pointes. Avoid ENVARSUS XR in patients with congenital long QT syndrome. Consider obtaining electrocardiograms and monitoring electrolytes (magnesium, potassium, calcium) periodically during treatment in patients with congestive heart failure, bradyarrhythmias, those taking certain antiarrhythmic medications or other products that lead to QT prolongation, and those with electrolyte disturbances (e.g., hypokalemia, hypocalcemia, or hypomagnesemia).

When coadministering ENVARSUS XR with other substrates and/or inhibitors of CYP3A, a reduction in ENVARSUS XR dosage, monitoring of tacrolimus whole blood concentrations, and monitoring for QT prolongation is recommended.

2.11. Immunizations
Whenever possible, administer the complete complement of vaccines before transplantation and treatment with ENVARSUS XR.
Avoid the use of live attenuated vaccines during treatment with ENVARSUS XR (e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines).
Inactivated vaccines noted to be safe for administration after transplantation may not be sufficiently immunogenic during treatment with ENVARSUS XR.

2.12. Pure Red Cell Aplasia
Cases of pure red cell aplasia (PRCA) have been reported in patients treated with tacrolimus. All of these patients reported risk factors for PRCA such as parvovirus B19 infection, underlying disease, or concomitant medications associated with PRCA. A mechanism for tacrolimus-induced PRCA has not been elucidated. If PRCA is diagnosed, consider discontinuation of ENVARSUS XR.

Data Safety and Monitoring Plan

1. The type of data or events to be captured under the monitoring plan

The University of Wisconsin-Madison study team will maintain a list of Adverse Events that meet the criteria set by the study agreement and the UW Health Sciences IRB. Adverse Events are monitored based on the methodology described in the protocol, specifically Adverse Events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. and Adverse Events ≥ CTCAE Grade 3 will be recorded. If any of the Adverse Events meet the Serious Adverse Event criteria listed below, it needs to be reported to the UBC on the SAE form provided upon study initiation.

The subset of SAEs to be reported are those that fit into either of the following categories and occur during the SAE reporting period in a Study subject assigned to receive the Veloxis Product.

(1) a death, regardless of whether it is considered related to treatment with the Veloxis Product,
(2) an SAE that is assessed by the Principal Investigator as both related to treatment with the Veloxis Product and unexpected for that Product.

An event should be considered "related" to the Veloxis Product if a relationship is at least a reasonable possibility, and "unexpectedness" should be based upon current Product labeling.

Reporting of Serious Adverse Events. Within 24 hours of first awareness of the event (immediately if the event is fatal or life-threatening), the Principal Investigator will report such SAEs using the UBC SAE Reporting Form v1.0 provided by Veloxis. SAEs should be reported as soon as they are determined to meet the definition, even if complete information is not yet available.

An SAE is any adverse event that is life-threatening or that results in any of the following outcomes:

- death;
- in-patient hospitalization or prolongation of existing hospitalization;
- persistent or significant disability or incapacity;
- or a congenital anomaly or birth defect.

Any other medical event that, in the medical judgment of the Principal Investigator, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above is also considered an SAE. A planned medical or surgical procedure is not, in itself, an SAE. Also specifically excluded from this definition of SAE is any event judged by the Principal Investigator to represent progression of the malignancy under study, unless it results in death within the SAE Reporting Period.

The SAEs that are subject to this reporting provision are those that occur from after the first dose of the Veloxis Product through 72 hours after discontinuation of the Veloxis Product. In addition, any and all related SAEs that occur after the reporting period of which the Principal Investigator becomes aware should also be reported.

Additionally, the study team will assist Veloxis in the investigation of any SAE and will provide any information requested by Veloxis.

2. The name(s) of the person(s) who will be responsible for monitoring the data collected (i.e. study accruals, protocol deviations, protocol violations, unanticipated problems, adverse events) and their respective roles (e.g. investigators, research sponsor)

The Principal Investigator:
Jon S. Odorico, M.D., F.A.C.S.
Professor of Surgery
Surgical Director of Pancreas Transplantation, Co-Director of Islet Transplantation
Department of Surgery, Division of Transplantation
University of Wisconsin School of Medicine and Public Health
600 Highland Avenue,
Madison, WI 53792-7375
3. The frequency of assessments/analysis of data or events captured by the monitoring plan.

Investigator will provide Veloxis with quarterly safety review report to include all serious adverse events regardless of relationship to test article, and to include start/stop date, relationship to test article, severity of event, and outcome until the study is concluded and the final study report/manuscript is completed.

4. The time frame for reporting unanticipated problems, adverse events, protocol deviations, and protocol violations

The timeframe to report unanticipated problems are required by the IRB as described in section 6.

Adverse Events are monitored based on the methodology described in the protocol: Adverse Events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. Adverse Events ≥ CTCAE Grade 3 will be recorded.

Protocol deviations and protocol violations will be monitored by the Principal Investigator and/or co-investigators.

5. Definition of specific events or stopping rules dictating when some action is required. Stopping rules are predetermined guidelines used to determine that the study should be altered or stopped based on review of study-related events occurring during the conduct of the study, specific study endpoints, and the decisions prompted.

The study team and/or Sponsor has the right to terminate this study at any time, if any of the following conditions are met:

- Death of the recipient probably related to the administration of the study drug, a life-threatening adverse drug experience, as determined by the Principal Investigator;
o Multiple Adverse Events, graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. Adverse Events ≥ CTCAE Grade 3.

6. Procedures and time frames for communicating outcomes of monitoring reviews to IRB

The Investigator will record, and report an AE/SAE to the IRB if it meets the definition of an unanticipated problem. An unanticipated problem is reportable if it is an AE/SAE that was unexpected, caused by or probably by the study drug and places subjects or others at a greater risk of harm than was previously known or recognized.

The reporting guidelines depend on how severe is the AE/SAE and whether the event occurred on a study under the purview of the UW-Madison site.

6.1. Immediate Report to the IRB

An AE/SAE meeting the above definition of an unanticipated problem must be reported to the IRB immediately if both of the following conditions are met:

A. The event occurred at a site under the purview of the UW Health Sciences (HS) IRB or Minimal Risk (MR) IRB  
B. The event is immediately life threatening or severely debilitating to other current subjects

SAEs that meet these conditions must be reported to the IRB Chair or IRB Director via telephone (preferred) or email as soon as possible, but no later than 1 business day after the local research team becomes aware of the event. The research team will then discuss with the IRB Chair or IRB Director what action needs to be taken related to the occurrence (e.g., suspension of study enrollment, change in treatment regimen) to prevent further harm from occurring. This initial report to the IRB Chair or IRB Director must be followed with the submission of a reportable event in ARROW within two business days after the local research team becomes aware of the event.

6.2. Report to the IRB within Fourteen (14) Business Days

Any other AE/SAEs that meet the definition of an unanticipated problem as described above must be reported to the HS or MR IRB within 14 business days.

Confidentiality protections
The study team is committed to respect the subject’s privacy and confidentiality. Each study participant will be assigned a study specific identification number and these numbers rather than names will be used to collect, store and report participant’s medical information.

All subjects assigned a study-specific ID number electronically on a password-protected UW SMPH Department of Surgery server and within the OnCore CTMS. The OnCore database will be used to maintain the electronic study data, which is secure, password-protected and is only accessible to study staff who are engaged in the research.

All data collected for this study from subjects will be done in a private patient exam room. Source documents for data, including signed Informed Consent and Research Authorization forms, will be maintained in subject study specific binders. These binders are stored in the locked office of the Office of Transplant Clinical Research, at 600 Highland Ave., F8/138 CSC, Madison WI 53792.

Study personnel will have access to a study enrollment log that links identifiable subject information to the assigned subject study code. This file will be stored on a password-protected computer that is part of the Department of Medicine secure network server. Only key personnel assigned to the study will have access to this file. Data including treatments, eGFR, AEs, may be included in OnCore for Data Safety Monitoring.

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**Data release plans**

Principal Investigator and the University of Wisconsin are free to publish the results of the study, subject to the provisions of the Study Agreement and to use the data generated from the Study for their own research and educational programs. The University of Wisconsin, however, will not use or permit others to use non-public or unpublished raw data from any study that involves the use of a Veloxis Product for the commercial benefit of any third party.

Within six months after completion or termination of the study, whichever occurs first, Principal Investigator will provide Veloxis with a written report of the study results. The written report should include, at minimum, the results of the acquired study data up until the date of termination.

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**Study Support Requested**

Please see attached documents.
References & Supporting Information


