Cognitive Outcomes and Quality of Life in Stable Renal Transplant Patients Switched from Twice-Daily Tacrolimus to Envarsus XR™ (OPERATOR)

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Original protocol: May 15, 2020

Amendment 1: March 24, 2021

Amendment 2: December 21, 2021

PI: Anthony Langone, MD

Co-I: James Jackson, PhD

Project Manager: Mohammed Sika, PhD

Summary of changes, Amendment 2: Administrative changes, clarifications, and corrections are highlighted in the "track-changes" version of the protocol

Protocol section	Original text	Updated text	Reason for change
Throughout	Window of 4 to 7 days between Visit 1 and Visit 2	Window of 1 to 30 days	To allow flexibility on when participants start Envarsus XR
Throughout	Month 4 ± 2 weeks	Month 4 ± 30 days	To allow flexibility for follow up visits and align with standard of care
Throughout	Month 8 ± 2 weeks	Month 8 ± 30 days	To allow flexibility for follow up visits and align with standard of care
Throughout	Conversion factor from Tacrolimus IR to ENVARSUS XR of 1:0.8 (see **Appendix 2**)	Conversion factor from Tacrolimus IR to ENVARSUS XR of 1:0.8 (see **Appendix 2 or https://www.envarsusxr.com/hcp/professional-resources/envarsus-xr-dose-converter/ and PI discretion**)	To allow for PI discretion based on participant medical status
Throughout	renal transplant recipients between the ages of 18-70 years	renal transplant recipients between the ages of 18-80 years	To capture the targeted population
Throughout	N/A	Envarsus XR will be started as soon as possible but no later than the next 30 days after Visit1/Visit2 or Visit 2	To ensure access to Envarsus XR
Throughout	MoCA Test Blind	TICS	Affordability
Throughout	complete the cognitive testing within 2-4 hrs. of TAC-IR or Envarsus XR dose	complete the cognitive testing after the TAC-IR or Envarsus XR dose	Convenience

Summary of changes, Amendment 1: Administrative changes, clarifications, and corrections are highlighted in the "track-changes" version of the protocol

Protocol section	Original text	Updated text	Reason for change
Throughout	Day 15 (Visit 3)	Month 4 (Visit 3)	To align with standard of care visits
Throughout	Month 3 (Visit 4)	Month 8 (Visit 4)	To align with standard of care visits
Throughout	Short form Health Survey (SF 36)_	World Health Organization Disability Assessment Schedule 2.0	Availability and cost
Throughout	Recipients of a renal transplant 4 weeks to 24 months prior to screening	Recipients of a renal transplant 4 weeks to 10 years prior to screening	To evaluate the long-term effect
Throughout	Patients with eGFR ≤ 50 mL/min at screening	Patients with eGFR < 25 mL/min at screening	To evaluate the effects at low and stable eGFR for at least 6 months
Throughout	N/A	Assessment of neurocognitive function via a phone battery, if needed	Safety precautions for COVID-19 and using tests that have been widely used and validated in the context of telephone administration

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1. LIST OF ABBREVIATIONS

AE	adverse event
AUC	area under the concentration-time curve
BDI	Beck Depression Inventory
b.i.d.	twice daily
BUN	blood urea nitrogen
CBC	complete blood count
CFR	US Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CI	confidence interval
CO_2	carbon dioxide (bicarbonate)
CRF	case report form
CRO	contract research organization
CsA	cyclosporine A
CYP	cytochrome P450
DR	delayed recall
DUN	Dispensing Unit Number
eCRF	electronic case report form
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EDC	electronic data capture
ELiTE	Efficacy Limiting Toxicity Elimination Symphony Study
EMA	European Medicines Agency
FDA	US Food and Drug Administration
GAMP®	Good Automated Manufacturing Practice (trademark of ISPE)
GCP	Good Clinical Practice
GI	gastrointestinal
HDPE	high density polyethylene
HEENT	head, ears, eyes, nose, throat
HIV	human immunodeficiency virus
HRT	hit reaction time
ICF	informed consent form

ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IETF	International Essential Tremor Foundation
IRB	Institutional Review Board
ITT	intent-to-treat
ISPE	International Society of Pharmaceutical Engineers
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCS	Mental Component Summary
MCV	mean corpuscular volume
MDRD	Modified Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
MMF	mycophenolate mofetil
MPA	mycophenolic acid
MPV	mean platelet volume
MPS	mycophenolate sodium
ng	nanogram
PCS	Physical Component Summary
PGI-I	Patient's Global Impression of Improvement
PID	patient identification
PIRS	Pittsburgh Insomnia Rating Scale
PRO	patient reported outcomes
q.d.	once daily
QoL	quality of life
QT	time from the start of the Q wave to the end of the T wave (ECG)
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RBC	red blood cell
RDW	red cell distribution width
SAE	serious adverse event
SD	standard deviation

SOC	standard of care
SOP	standard operating procedure
SRL	sirolimus
Tac	tacrolimus
TAC-IR	tacrolimus immediate release
TMT-A	Trail Making Test A
TMT-B	Trail Making Test B
US	United States of America
Veloxis	Veloxis Pharmaceuticals, Inc.
WBC	white blood cell
WOCBP	women of childbearing potential
XR	extended release

2 SYNOPSIS

Title of Study: Cognitive Outcomes and Quality of Life in Stable Renal Transplant Patients Switched from Twice-Daily Tacrolimus to Envarsus XR™	
Investigator(s): Anthony Langone, MD; James Jackson, PhD	
Study Center(s): Single center study	
Study Period: 8-month study treatment phase	**Phase of Development:** 4

Study Objectives:

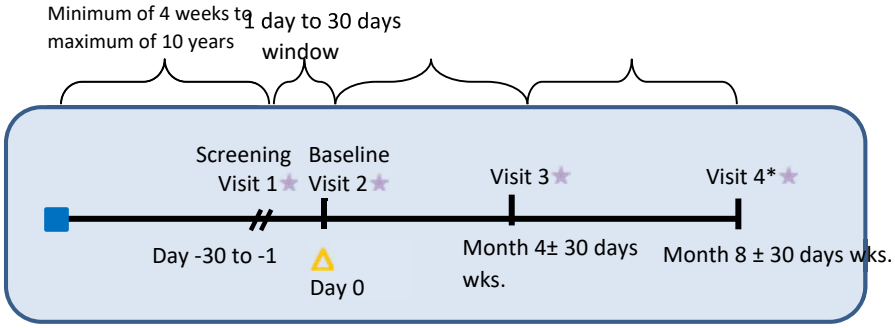
This is an exploratory study to:

- assess cognitive outcomes in stable renal transplant patients treated with twice-daily oral tacrolimus at baseline and following conversion to ENVARSUS XR and
- assess the quality of life (QoL) in patients after renal transplantation treated with twice daily oral tacrolimus at baseline and following conversion to ENVARSUS XR.

Methodology:

An open-label, single center, prospective Phase 4 clinical study to assess tacrolimus-induced cognitive outcomes in stable kidney transplant patients converted from oral tacrolimus twice daily immediate-release (TAC-IR) to ENVARSUS XR (tacrolimus extended-release tablets; Veloxis Pharmaceuticals, Inc.) once daily (q.d.). The study is designed to determine if the test drug, ENVARSUS XR, is associated with improved cognitive function relative to that observed with tacrolimus treatment. Each therapy may be concomitantly administered with mycophenolate mofetil (MMF) and/or mycophenolate sodium (MPS), including generic versions of each, as long as doses remain stable during the screening period through Visit 3 of the study. All prophylaxis and other medication will be allowed per standard of care (SOC). Medications that inhibit or induce cytochrome P450 3A (CYP3A) are allowed only if medically necessary, but when using such agents, increased monitoring of tacrolimus drug concentrations is recommended. Stable renal transplant patients are defined as patients who are recipients of a renal transplant 4 weeks to 10 years prior to screening and have received a stable dose (i.e., no dose adjustments) of TAC-IR for a minimum of 4-7 days at the time of screening. Following baseline, study visits will be conducted over a 8-month treatment period with ENVARSUS XR.

Study Design Diagram:



Renal transplantation at least 4 weeks but no more than 10 years prior to date of screening

Study assessments, per schedule of assessments

Switch all subjects to ENVARSUS XR: Envarsus should be started as soon as possible but no later than 30 days after Visit 2 o combined Visit 1/Visit 2

* Subjects who discontinue ENVARSUS XR prior to Visit 4 will complete an early withdrawal visit

Drugs Used in Study:
Each patient will receive the following:
 Investigational product: ENVARSUS XR (tacrolimus extended-release tablets)

ENVARSUS XR tablets will be administered orally q.d. in the morning based on a conversion factor from tacrolimus to ENVARSUS XR of 1:0.8 (see **Appendix 2 or https://www.envarsusxr.com/hcp/professional-resources/envarsus-xr-dose-converter/ and PI discretion**) to maintain target trough level of 3-12 ng/mL. Dose adjustments are not permitted between Visits 2 and 3 unless it is deemed medically necessary at the discretion of the Investigator. If a dose adjustment is required the patient will be required to be on a stable dose of ENVARSUS XR (no dose adjustment) for a minimum of 4 days before Visit 3 assessments are performed (i.e., if a dose adjustment is medically necessary and occurs anytime between Visits 2 and 3 there should be a minimum of 4 days on a stable ENVARSUS XR dose before the Visit 3 assessments take place).

Tacrolimus Trough Level Monitoring:

Tacrolimus whole blood trough levels will be measured prior to the morning dose on Visits 2, 3, and 4. Tacrolimus whole blood trough levels obtained from local laboratories will be used to ensure patient's treatment exposure is maintained in the therapeutic range.

Concomitant Therapy:

Immunosuppressants:

Only CellCept® (MMF, Roche Laboratories, Nutley, NJ), Myfortic® (MPS, Novartis Pharmaceuticals, East Hanover, NJ), including generic versions of each, or prednisone (or equivalent <10 mg/day) with choice and doses per SOC at the participating site are allowed (but not required). Patients receiving immunosuppressants should be on a stable dose throughout the treatment period from Visit 2 to Visit 3 of the study.

CYP3A inhibitors or inducers:

Whenever feasible, CYP3A inhibitors or inducers should be avoided; however clinical circumstances may necessitate using such agents. When this is the case, increased monitoring of tacrolimus concentrations is recommended.

Other:

All prophylaxis and other medications, including herbal products, will be allowed per SOC as long as ENVARSUS XR dosing remains stable throughout the treatment period from Visit 2 to Visit 3 of the study

Study Population:

Inclusion Criteria

1. Patients must be able to understand English and provide written informed consent;
2. Males and females between 18 and 80 years of age;
3. Recipients of a primary or secondary kidney transplant 4 weeks to 10 years prior to screening;
4. Patients receiving a stable dose (i.e., no dose adjustments) of TAC-IR for a minimum of 4-7 days at screening;
5. Patients with a screening tacrolimus trough level of 3-9 ng/mL, measured between Day -7 to 0;
6. Women of childbearing potential must have a negative urine pregnancy test at screening;
7. Patients must be willing to commit to and comply with the schedule of study visits.
8. The patient is not scheduled to begin any new medication that could interfere with tacrolimus blood levels, including prescription and over-the-counter medications, herbal, or food supplements (including grapefruit and pomegranate products), or medications listed in **Appendix 1**.

Exclusion Criteria

1. Recipients of any transplanted organ other than kidney;
2. Patients with an estimated glomerular filtration rate (eGFR) (modified diet in renal analysis 4 [MDRD4]) <25 mL/min at screening;
3. Patients with significant visual impairments affecting their ability to complete the study requirements and assessments: patient's vision is 20/200 or worse;[1]
4. Patients with significant hearing impairments affecting their ability to complete the study requirements and assessments, based on Investigator discretion;[1]

[1] Patients with visual aids (glasses or contact lenses) should be considered, provided their vision is adequately improved with the use of the aid.

5. Patients with any severe medical condition (including infection) requiring acute or chronic treatment that in the Investigator's opinion would interfere with study participation;
6. Patients who have a history of any of the following, based on documentation of clinical conditions and concomitant medications in the medical records:
    - Cognitive decline associated with stroke, per Investigator discretion
    - Dementia
    - Resected or existing brain tumor
    - Acute or chronic bipolar psychosis or schizophrenia per Investigator discretion
    - Mental retardation
    - Moderate or severe traumatic brain injury
    - Failure of any major organ other than the kidneys (e.g., end-stage liver disease)
    - Known non-adherence (defined as documentation in the patient chart of multiple missed visits and/or medication doses) which in the investigator's opinion would interfere with the objectives of the study
7. Patients with medical history of hypertension or diabetes which is unmanageable by medically approved intervention (e.g., medication/diet) as assessed by the Investigator;
8. Patients with acute or chronic depression, corresponding to a score of ≥20 (corresponding to moderate depression) on the Beck Depression Inventory (BDI-II) at screening;
9. Patients who are taking any acute or chronic medications that may impact reaction time, memory, or sleep habits, based on Investigator discretion;
10. Patients on concurrent immunosuppression with MMF (CellCept) or MPS delayed release tablets (Myfortic), or generic versions of these medications, as per SOC, who have not been on stable doses (i.e., no dose adjustments or formulation change) for at least 4-7 days prior to screening;
11. Patients receiving prednisone or equivalent >10 mg/day;
12. Patients with an episode of biopsy-proven or suspected acute rejection that requires treatment within 3 months of screening;

[1] Patients with hearing aids should be considered, provided their hearing is adequately improved with the use of the aid.

13. Patients who are being actively treated for cancer (with the exception of non-invasive basal cell or cutaneous squamous cell carcinoma);
14. Patients known to be human immunodeficiency virus (HIV) positive;
15. Patients with any form of current drug or alcohol abuse as assessed by the Investigator;
16. Patients who were treated with any other investigational agent within 1 month prior to screening;
17. Pregnant or nursing women or women planning to become pregnant, where pregnancy is defined as a state of the female patient after conception and until the termination of gestation, confirmed by a positive urine pregnancy laboratory test; women of childbearing potential, defined as all women physiologically capable of becoming pregnant who are unwilling to use a defined SOC birth control method; UNLESS they are:
    - Women whose career, lifestyle, or sexual orientation preclude intercourse with a partner
    - Women whose partners have been sterilized by medically approved means

Criteria for Withdrawal:

Patients have the right to withdraw from the study at any time for any reason without penalty or prejudice. The Investigator also has the right to withdraw patients from the study if he/she feels it is in the best interest of the patient (see **Section 8.3.1**). For early withdrawal patients, an early withdrawal visit will be scheduled.

A patient may be withdrawn from the study treatment by the Investigator if: (1) the Investigator feels it is not in the patient's best interest to continue in the study, (2) the patient fails to follow the Investigator's instructions, (3) the patient experiences an adverse reaction that requires other medical treatment, or (4) the patient becomes pregnant.

Evaluation Criteria:

The primary endpoint is:

- Change in cognitive function from Visit 2 to Visit 3, as measured by the Global Composite Score on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) , or the global composite score of the Covid-19 Telephone Battery, should that be the primary outcome battery that we employ.The secondary endpoints are as follows:

- Change in cognitive function from Visit 2 to Visit 3, as measured by the following:
- Trail Making Test A & B ([TMT-A, TMT-B] visual attention/executive functioning)
- Change in QoL from Visit 2 to Visit 3 and from Visit 2 to Visit 4, as measured by WHODAS.
- Assessment of Patient Global Impression of Improvement and Clinical Global Impression of Improvement (PGI-I and CGI-I, respectively) at Visit 3.
- Change in quality of sleep from Visit 2 to Visit 3, as measured by the Pittsburgh Insomnia Rating Scale-20 Item Version (PIRS-20)
- Safety evaluation will include adverse events (AEs), serious AEs (SAEs), vital sign measurements, and physical examinations.

Should safety precautions for COVID-19 preclude us from seeing patients in person, neurocognitive function will be assessed via a phone battery derived from standard cognitive tests and proven feasible and valid to assess memory, attention, reasoning, and executive function. These will include the TICS (Telephone interview for Cognitive Testing), WAIS-IV (Digit Span and Similarities), WMS-IV (Logical Memory I & II), Controlled Oral Word Association (COWA), and Hayling Sentence Completion. Psychological status will be assessed using the Beck Depression Inventory II (BDI-II) and the Posttraumatic Stress Disorder-8 (PTSD-8). Quality of life will be assessed using the WHODAS. Age, race, sex, and level of education will also be collected.

Study Visits:

The study includes 4 scheduled visits (unless Visits 1 and 2 are combined). Visits should be scheduled to coincide with SOC visits, where possible. Withdrawal visits will be scheduled for all enrolled patients who terminate early prior to Visit 4. Visit times as well as follow up testing windows are "approximate."

Visit 1 – Screening (Days -30 to -1): Patients will be confirmed to have had a minimum of 4 to 7 days on a stable dose of TAC-IR. Screening activities will include informed consent and eligibility review, including the Beck Depression Inventory (BDI-II).

Visit 2 – Enrollment/Baseline (Day 0): Patients will be confirmed to have had a stable dose of

TAC-IR (pre-conversion). This visit will include baseline cognitive assessments, a demographics survey, the WHODAS and PIRS-20. Patients will take their morning dose of TAC-IR and complete all of the baseline assessments; once completed, ENVARSUS XR will be prescribed and the first dose of ENVARSUS XR will be taken as soon as possible but no later than the next 30 days. (Patients who are unable to start ENVARSUS XR the next morning are to have the Visit 3 date adjusted accordingly).

Visit 1 and Visit 2 may be combined if no dose adjustments were performed and the patient has been maintained on a stable dose of tacrolimus with trough level between 3-9 ng/mL and the physician does not deem any dose adjustment required and Envarsus XR will be started as soon as possible but no later than the next 30 days

Note that the designation of Visit 2 as occurring on 'Day 0' is meant to reflect that ENVARSUS XR dosing is to start as soon as possible but no later than the next 30 days (Envarsus start day is the anchor point for subsequent visits).

Visit 3 (Month 4± 30 days): Patients will be confirmed to have been on a stable dose of once-daily ENVARSUS XR before Visit 3 assessments are performed. Patients will take their morning dose of ENVARSUS XR and complete the following activities: PGI-I, WHODAS, PIRS-20, and cognitive outcomes assessments (listed above under primary and secondary endpoints). The physician will perform CGI-I and prescribe a 4-month supply with refills of ENVARSUS XR.

Visit 4 (Month 8± 30 days): Patients will be confirmed to have been on a stable dose of once-daily ENVARSUS XR before Visit 4 assessments are performed. Patients will take their morning dose of ENVARSUS XR and complete the following activities: PGI-I, WHODAS, PIRS-20, and cognitive outcomes assessments (listed above under primary and secondary endpoints). The physician will perform CGI-I. The continuation of ENVARSUS XR will be at the discretion of the patient's treating nephrologist.

Early Withdrawal Visit: This visit should be scheduled as soon as possible for patients who withdraw from the study. Assessments of concomitant medication use, and AEs will be performed at this visit as well as all visit 3 assessments.

Sample Size Considerations:

The study aims to enroll approximately 60 patients. With an expected drop-out rate of 10% to 15%, a maximum of fifty-two (52) evaluable patients are expected to reach the end of study.

In order to detect an effect size of 0.5 with 80% power and a one-sided type I error rate of 0.025, a sample size of 34 evaluable patients is needed. (NOTE: We simply need at least 34 patients to have adequate power, but we anticipate approximately having 52, meaning that this study will almost certainly NOT be underpowered). An interim analysis will be conducted when data are available for 17 (half of 34) evaluable patients, to better estimate the variation and effect of the treatment.

The rule for sample size adjustment is as follows:

Denote the planned sample size (n) = $n_1 + n_2$, where $n_1 = 17$; and n = 34 (i.e., $n_2 = 17$)

Let r=1.5 be the rate of adjustment (which leads to the maximum sample size of 52). Define

N_{new} (final sample size) as

$$N_{new} = \begin{cases} n_1 + K, & n \le N \le rn \\ n, & N < n \\ rn, & N > rn \end{cases}$$

where K is the calculated additional required sample size (beyond first 17 evaluable patients) and N is the calculated total required sample size based on the observed change and variation from the interim analysis.

The range of possible total sample sizes based on the interim analysis is from 34 and 52, i.e., the sample size remains at 34 if the adjusted estimate is below 34 and increases to a maximum of 52 if the adjusted estimate is beyond 52.

Analysis Sets:

Intent-to-Treat (ITT) Dataset: Includes all patients who are enrolled. The efficacy analyses will be performed using this dataset.

Evaluable Dataset: Includes all patients who are enrolled and received at least one dose of ENVARSUS XR and within targeted trough level of 3-9 ng/mL. In addition, the patients must have baseline and post-conversion evaluation for at least one of the cognitive tests (RBANS, TMT-A/TMT-B) without major protocol violation/deviation that would affect the cognitive measurement. The efficacy analyses will also be performed using this dataset.

Safety Dataset: Includes all patients who are enrolled and received at least one dose of ENVARSUS XR. The safety analyses will be performed using this dataset.

Patients whose tacrolimus trough level at Visit 3 (or as measured at other SOC visits between Visit 2 and Visit 3) is outside the tacrolimus suggested target trough level of 3-9 ng/mL will still remain in the study. If a dose adjustment is required, the patient will be required to be on a stable dose of ENVARSUS XR (no dose adjustment) for a minimum of 4 days before Visit 3 assessments are performed (i.e., if a dose adjustment is medically necessary and occurs anytime between Visits 2 and 3 there should be a minimum of 4 days on a stable ENVARSUS XR dose before the Visit 3 assessments can take place). However, they will not be evaluable and will be included in the ITT population.

Analysis Methods:

In general, continuous variables will be summarized with number of non-missing observations, mean, standard deviation (SD), median, minimum, and maximum displayed. Categorical variables will be summarized as counts and percentages.

The primary efficacy endpoint is the Global Composite Score on the RBANS. Raw scores on the RBANS will be age adjusted and converted into a series of Index Scores (reflecting domains such as immediate memory, delayed memory, attention, etc.) which will in turn be combined to generate the aforementioned Global Composite Score, a summary score reflective of overall neuropsychological status (scores have a mean of 100, SD of 15, impairment is typically defined as a score of <78 (1.5 SD below the mean). Descriptive summaries of patients 'scores and percentiles at baseline (i.e., Visit 2) and post-baseline (i.e., Visit 3) will be provided. The mean change (absolute change) in -score the RBANS composite score from baseline to post-baseline will be evaluated using paired t-test at 0.05 significance level. A 95% confidence interval (CI) will be constructed for the mean change. Same methods will be used to analyze other cognitive test scores.

CGI-I and PGI-I will be summarized by number and percentages of patients in each category as well as combined categories of improvement (e.g., "Minimum improved", "Much improved", "Very much improved [CGI-I]/Very much better [PGI-I]").

Safety analyses (i.e., ENVARSUS XR exposure, adverse events, and trough level of ENVARSUS XR), as well as vital signs will be summarized descriptively.

Interim Analysis:

An interim analysis will be conducted when cognitive data are available for 17 evaluable patients who have completed Visit 3. An estimate of the variation and effect of ENVARSUS XR for CPT-III omission measures will be calculated. A sample size adjustment may be made according to the algorithm described above (Sample Size Considerations).

3 Schedule of Study Activities

Study Activity	Screening Visit	Enrollment Visit	Visit 3	Visit 4	SOC Visits for ENVARSUS XR Dose Adjustments	Early Withdrawal
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**N/A**	**N/A**
Day Number	**Day -30 to -1**	**Day 0[a]**	**Month 4 ± 30 days.**	**Month 8 ± 30 days.**	**As needed[b]**	**When withdrawn[c]**
Informed consent	X					
Eligibility review (inclusion/exclusion criteria)	X	X				
Demographics/Demographics Survey		X				
Medical history	X					
eGFR level[i]	X					
Safety laboratory results (metabolic profile and CBC)[i]		X	X	X		X
Physical examination		X	X	X		X
Vital signs		X	X	X		X
Concomitant drugs	X	X	X	X		X
Tacrolimus trough samples[i]	X[d]	X[d]	X	X	X	X
BDI-II	X					
PGI-I			X	X		X
WHODAS		X	X	X		X
PIRS-20		X	X	X		X

Study Activity	Screening Visit	Enrollment Visit	Visit 3	Visit 4	SOC Visits for ENVARSUS XR Dose Adjustments	Early Withdrawal
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**N/A**	**N/A**
Day Number	**Day -30 to -1**	**Day 0[a]**	**Month 4 ± 30 days.**	**Month 8 ± 30 days**	**As needed[b]**	**When withdrawn[c]**
TMT-A, TMT-B (visual scanning speed/visual attention)		X	X	X		X
RBANS		X	X	X		X

Telephonic/Virtual Covid-19 battery (to be employed if in-person testing is deemed unsafe).		X	x	X		X
CGI-I			X	X		X
Safety monitoring		X[f]	X	X	X	X
Prescribe ENVARSUS XR[g]		X[h]	X	X	X	
Dose administration record		X	X	X	X	X
Study drug/reconciliation			X	X		X

Abbreviations: N/A = not applicable; eGFR = estimated glomerular filtration rate; CBC = Complete blood count; SOC = standard of care; BDI-II = Beck Depression Inventory; PGI-I = Patient's Global Impression of Improvement; WHODAS = World Health Organization Disability Assessment Schedule 2.0; PIRS-20 = Pittsburgh Insomnia Rating Scale; TMT-A/TMT-B = Trail Making Test A & B; CGI-I = Clinical Global Impression of Improvement;

[a] If both Visits 1 and 2 are combined, all items denoted by an 'X' in the table for both Visits 1 and 2 must be completed at this combined screening and enrollment visit. Only need to capture start date of ENVARSUS XR.

[b] Anytime between Visit 3 and last dose of ENVARSUS XR

[c] As soon as possible following last dose of ENVARSUS XR

[d] Whole blood for tacrolimus trough level (prior to the morning dose of tacrolimus) can be drawn on Day -1 such that the results are available for the determination of patient eligibility at Visit 2, in which case the draw does not need to be repeated at Visit 2.

[e] Pregnancy test must be completed for women of childbearing potential prior to enrollment.

[f] AE/SAE collection begins after the first dose of ENVARSUS XR.

[g] At enrollment patients should be prescribed a minimum of 4 months' supply; patients should be prescribed ENVARSUS XR at the end of Visit 3 (4-month supply), and/or SOC visit for ENVARSUS XR dose adjustment as needed.

[h] Patients will begin taking ENVARSUS XR as soon as possible but no later than the next 30 days.

[i] Labs should be charged to study if the visits don't coincide with standard of care of visits

4 INTRODUCTION

4.1 Background on Tacrolimus and Envarsus® XR

Tacrolimus is a calcineurin inhibitor approved in the United States (US) for the prophylaxis of organ rejection in patients receiving allogeneic liver, kidney, or heart transplants.[1] Tacrolimus has been approved since the mid 1990's in the US, Japan, Canada, Switzerland, and the European Union, as well as other countries worldwide. Tacrolimus is currently marketed in the US under the brand name Prograf (tacrolimus) and Astagraf® (tacrolimus extended-release capsules) by Astellas Pharma (Tokyo, Japan) and in Canada and Europe under brand names Prograf, Advagraf (tacrolimus extended-release capsules, Astellas Pharma, Tokyo, Japan) and Modigraf® (tacrolimus, granules for oral suspension, Astellas Pharma, Tokyo, Japan).

Tacrolimus twice daily (b.i.d) represents a cornerstone of immunosuppression therapy in kidney transplant with more than 90% of all kidney transplant recipients in the US being treated with tacrolimus at the time of discharge from the hospital.[2] Tacrolimus, given as capsules (Prograf®), exhibits significant inter- and intra-individual variability in absorption and metabolism.[1,3] The low bioavailability is thought to be a result of the combination of poor water-solubility, presystemic metabolism of tacrolimus in the gastrointestinal (GI) tract, and activity of the P-glycoprotein efflux pump found in the enterocytes of the GI tract.[1,4] Therefore, in clinical practice, the dose of tacrolimus is adjusted based on monitoring of tacrolimus whole blood trough concentrations, which correlate well with the area under the concentration-time curve (AUC) and provide an acceptable measure of exposure.[5]

ENVARSUS XR Tablets are an extended-release formulation of tacrolimus designed for q.d. administration. The XR formulation has been developed utilizing Veloxis's proprietary MeltDose® drug-delivery technology. ENVARSUS XR is designed to deliver a constant stable absorption of tacrolimus leading to improved bioavailability, consistent concentration levels over the full day, reductions in peak, peak-to-trough fluctuations and once a day administration.[6,7]

4.2 Tacrolimus-associated Neurotoxicity

Neurotoxicity associated with the introduction of immunosuppressive agents has remained a significant postoperative complication. Neurotoxicity is particularly prevalent in agents active through the mechanism of calcineurin inhibition.[8,9] The spectrum of neurotoxicity has changed over the years, and differences in severity of manifestation are apparent.[10] Neurological side effects observed with tacrolimus in transplant patients include headache, tremor, neuralgia, encephalopathy, peripheral neuropathy, or severe symptoms such as psychoses, hallucinations, blindness, seizures, cerebellar ataxia, motoric weakness, or seizures.[8,11] Moreover, a well-recognized phenomenon is the poor correlation with tacrolimus and cyclosporine trough levels. Peak levels have not been studied systematically but may prove more useful. Thus, the most severe reversible manifestations may appear in patients with sub therapeutic trough levels. It is important first to consider discontinuation of cyclosporine or tacrolimus therapy.[10] In addition, peak levels

may correlate more closely with neurotoxicity.[12] Low dose and increasing frequency of administration of tacrolimus strategies has been studied. The Efficacy Limiting Toxicity Elimination (ELiTE)-Symphony study allowed for low doses of cyclosporine A (CsA), tacrolimus (Tac), or sirolimus (SRL) to be used directly after transplantation, with benefits in terms of efficacy and safety. The relationship between drug levels and selected AEs was assessed. The major finding of the analysis was that, despite low doses, CsA, Tac and SRL retained distinct toxicity profile components.[13] In two studies, three-times-daily doses of tacrolimus were administered to a few patients to significantly lower peak concentration levels (C_{max}) while maintaining targeted trough levels and reducing adverse effects.[14,15]

4.3 Nonclinical Studies

4.3.1 Carcinogenesis

Carcinogenicity studies were conducted in male and female rats and mice. In the 80-week mouse oral study and in the 104-week rat oral study, no relationship of tumor incidence to tacrolimus dosage was found. The highest dose used in the mouse was 3.0 mg/kg/day (0.84 times the area under the concentration-time curve [AUC] at the maximum clinical dose of 0.14 mg/kg/day) and in the rat was 5.0 mg/kg/day (0.24 times the AUC at the maximum clinical dose of 0.14 mg/kg/day). [16]

A 104-week dermal carcinogenicity study was performed in mice with tacrolimus ointment (0.03%-3%), equivalent to tacrolimus doses of 1.1-118 mg/kg/day or 3.3-354 mg/m^2/day. In the study, the incidence of skin tumors was minimal, and the topical application of tacrolimus was not associated with skin tumor formation under ambient room lighting. However, a statistically significant elevation in the incidence of pleomorphic lymphoma in high-dose male (25/50) and female animals (27/50) and in the incidence of undifferentiated lymphoma in high-dose female animals (13/50) was noted in the mouse dermal carcinogenicity study. Lymphomas were noted in the mouse dermal carcinogenicity study at a daily dose of 3.5 mg/kg (0.1% tacrolimus ointment; 2.5-fold the human exposure in stable adult renal transplant patients converted from tacrolimus immediate-release product to ENVARSUS XR). No drug-related tumors were noted in the mouse dermal carcinogenicity study at a daily dose of 1.1 mg/kg (0.03% tacrolimus ointment). The relevance of topical administration of tacrolimus in the setting of systemic tacrolimus use is unknown. [16]

The implications of these carcinogenicity studies are limited; doses of tacrolimus were administered that likely induced immunosuppression in these animals, impairing their immune system's ability to inhibit unrelated carcinogenesis. [16]

4.3.2 Mutagenesis

No evidence of genotoxicity was seen in bacterial (*Salmonella* and *E coli*) or mammalian (Chinese hamster lung-derived cells) in vitro assays of mutagenicity, the *in vitro* CHO/HGPRT assay of mutagenicity, or *in vivo* clastogenicity assays performed in mice; tacrolimus did not cause unscheduled DNA synthesis in rodent hepatocytes. [16]

4.3.3 Impairment of Fertility

Tacrolimus given orally at 1.0 mg/kg (1.2 times the maximum clinical dose based on body surface area) to male and female rats, prior to and during mating, as well as to dams during gestation and lactation, was associated with embryolethality and adverse effects on female reproduction. Effects on female reproductive function (parturition) and embryolethal effects were indicated by a higher rate of pre-implantation loss and increased numbers of undelivered and nonviable pups. When given at 3.2 mg/kg (3.7 times the maximum clinical dose based on body surface area), tacrolimus was associated with maternal and paternal toxicity as well as reproductive toxicity including marked adverse effects on estrus cycles, parturition, pup viability, and pup malformations.[16]

4.4 Safety in Clinical Studies of ENVARSUS XR

Safety findings for all ENVARSUS XR clinical studies conducted and analyzed to date are summarized in Section 6 of the ENVARSUS XR Full Prescribing Information.[16]

4.5 Anticipated Risks from ENVARSUS XR

As ENVARSUS XR tablets are an extended-release formulation of tacrolimus, intended for once-daily administration, the anticipated risks of ENVARSUS XR include nephrotoxicity, new onset diabetes mellitus, hypertension, neurotoxicity, hyperkalemia, and latent viral infections. Refer to the ENVARSUS XR Full Prescribing Information[16] for a more detailed description of each of these anticipated risks.

4.6 Rationale for Study

This is an open-label, prospective Phase 4 clinical study to assess tacrolimus-induced cognitive impairment in stable kidney transplant patients converted from oral tacrolimus twice-daily immediate-release (TAC-IR) to ENVARSUS XR once daily. The study is designed to evaluate whether switching patients from TAC-IR to ENVARSUS XR treatment improves cognitive function. Given the reduction in the peak-to-trough ratio of ENVARSUS XR vs. TAC-IR, ENVARSUS XR is expected to offer kidney transplant patients experiencing potential tacrolimus-induced cognitive impairment a better alternative to TAC-IR as part of their immunosuppressive regimen.

- ENVARSUS XR is a new FDA-approved formulation of tacrolimus. A hallmark difference between ENVARSUS XR and other forms of once- and twice-daily tacrolimus products is the unique, proprietary MeltDose® drug delivery technology (Veloxis Pharmaceuticals, Hørsholm, Denmark) which reduces tacrolimus' particle size to a molecular level. The decreased surface area of the drug particles results in complete absorption and increased bioavailability in a once-daily dosing formulation. In stable kidney transplant patients, ENVARSUS XR pharmacokinetics are characterized by a steadier and more consistent concentration time profile over 24 hours, reduced peak and peak-to-trough fluctuations and similar exposure while benefiting from ~ 20% less total daily dose than twice daily tacrolimus.[7,17]

- In a previous study (STRATO) conducted, it was hypothesized that the lower peak concentration and flatter profile experienced with ENVARSUS XR may result in a reduction of tremor severity in kidney transplant recipients previously prescribed twice daily tacrolimus. The results showed that the majority of kidney transplant patients in the study experiencing tacrolimus-induced hand tremors also experienced significant improvement in severity and QoL after conversion to ENVARSUS XR while maintaining comparable tacrolimus exposure.[18,19]

- It is possible that the benefit shown in the STRATO study may extend to other widely reported, troubling side effects as well, including cognitive dysfunction. Further clinical study is worth undertaking to explore these additional potential benefits and improvement in cognitive function and QoL post-conversion to ENVARSUS XR.

Patients with chronic kidney disease most commonly show cognitive impairments involving attention, memory, executive functions, and mental processing speed.[20,21] Although data have demonstrated improvements in cognition following kidney transplant and the reversibility of the memory problems evidenced in dialysis,[22] neurotoxicity in transplant patients occurs in >40-50% of the patients treated with tacrolimus.[1] Attention and working memory impairment have been observed in patients treated with sirolimus or tacrolimus, while cyclosporine-treated patients demonstrated performance similar to that of healthy volunteer controls, which may indicate that the cognitive deficit found was partly related to treatment.[28]

Tacrolimus-induced neurotoxicity can occur despite low trough levels; maximum concentration level and fluctuations in serum levels seem more relevant indicators of potential manifested side effects of neurotoxicity.[23] Insomnia[24,25,26,27] and cognitive dysfunction including memory impairment,[25,28] visual and attention disturbances[11,29,30] are two most frequently documented tacrolimus-induced neurotoxic side effects, which may in turn impact patient quality of life and/or work-related productivity.

Neurotoxicity is associated with peak tacrolimus concentrations in transplant as well as autoimmune diseases and shows that the neurotoxicity essentially abates when tacrolimus treatment is discontinued, providing proof that tacrolimus is a reversible neurotoxic agent.[8] The current management of neurotoxicity varies by Investigator and institution, but typically begins with a dose reduction of the tacrolimus, balancing increased risk of acute rejection and graft loss with the desire to improve the side effects observed for a given patient.[31,32] The results demonstrated in STRATO that showed lower peak concentration and a flatter profile of ENVARSUS XR may result in a reduction of neurotoxicity in kidney transplant patients;[18,19] therefore, further study of ENVARSUS XR on potential cognitive impact is warranted.

5 STUDY OBJECTIVES

This is an exploratory study to:

- assess cognitive outcomes in stable renal transplant patients treated with twice-daily oral tacrolimus at baseline and following conversion to ENVARSUS XR, and

- assess quality of life in patients after renal transplantation treated with twice-daily oral tacrolimus at baseline and following conversion to ENVARSUS XR.

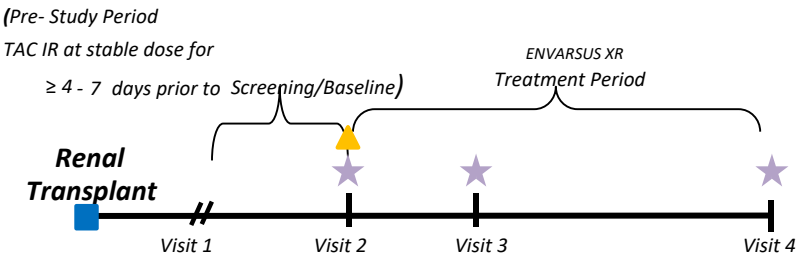
6 STUDY DESIGN

6.1 Overall Study Design

This is an open-label, single site, prospective Phase 4 clinical study to assess tacrolimus-induced cognitive impairment in stable kidney transplant patients converted from oral twice-daily TAC-IR to ENVARSUS XR once daily. Approximately 60 adult male or female patients who received a primary or secondary kidney transplant 4 weeks to 10 years prior to study start will be enrolled.

The study design is depicted in **Figure 6-1**. Patients will be required to have been receiving a stable regimen of TAC-IR (i.e., no dose adjustments) for a minimum of 4-7 days prior to Baseline. At Baseline, patients will be switched to ENVARSUS XR for a total of 3 months.

Figure 6-1 Study Design Diagram



Renal transplantation at least 4 weeks but no more than 10 years prior to date of screening

Study assessments, per schedule of assessments

Switch all subjects to ENVARSUS XR: as soon as possible but no later than the next 30 days

* Subjects who discontinue ENVARSUS XR prior to Visit 4 will complete an early withdrawal visit

At screening visit (Visit 1), a minimum of 4-7 days on stable dose of TAC-IR formulation will be confirmed, informed consent will be documented, and eligibility review, including the Beck Depression Inventory (BDI-II), will be performed.

On Visit 2,, a sequence of cognitive tests will be administered after the morning dose of TAC-IR in the following order: Repeatable Battery for the Assessment of Neuropsychological Status Update (RBANS Update); Trail Making Test A & B (TMT-A, TMT-B); and in addition, a Demographics Survey, the WHODAS, a quality of life measure, and the Pittsburgh Insomnia Rating Scale (PIRS-20) will also be completed by patients prior to the cognitive tests. Patients will take their last dose of TAC-IR in the evening of Visit 2 or combined Visit 1/Visit 2, and ENVARSUS XR will be prescribed and started as soon as possible but no later than the next 30 days

On Visit 3 , after their morning dose of ENVARSUS XR, the same sequence of cognitive tests will be administered in the order noted above, PGI-I will be assessed prior to the administration

of WHODAS and PIRS-20. Additionally, the CGI-I will be completed by the Investigator after all the assessments are completed for the visit.

At Visit 4 after their morning dose of ENVARSUS XR, same activities as Visit 3 are repeated.

Please refer to **Section 10** for additional information on study visits and activities.

6.2 Study Endpoints

6.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change in cognitive function from Visit 2 to 3 as measured by the Global Cognition Score on the RBANS, a composite score reflecting performance in areas of immediate and delayed memory, visuospatial construction, language, and attention.

6.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include the following:

- Change in cognitive function from Visit 2 to 3 as measured by the following:
- TMT-A and TMT-B (visual scanning speed/visual attention)
- Change in QoL from Visit 2 to 3 and from Visit 2 to 4 as measured by the WHODAS
- PGI-I and CGI-I at Visit 3
- Change in quality of sleep from Visit 2 to 3 as measured by the PIRS-20

6.2.3 Safety Endpoints

The safety endpoints in this study are the incidence of AEs, SAEs, and discontinuations due to AEs.

7 RATIONALE FOR STUDY DESIGN

The open-label switch study design provides the benefit of having patients serve as their own control, thus minimizing other confounding factors that may impact cognitive function and/or other measurements.

8 STUDY POPULATION

The study population will consist of adult male and female renal transplant recipients between the ages of 18-80 years who had received their transplant at least 4 weeks, but not more than 10 years, prior to the screening date. Recipients of any other organ transplant or bone marrow transplant are not eligible. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient.

8.1 Enrollment

Approximately 60 adult male or female kidney transplant recipients will be enrolled at Vanderbilt University Medical center.

Patients who are willing to participate in the study and who have given written informed consent may be screened up to 7 days prior to enrollment. Screening procedures are detailed in **Section 10.1.1**.

8.2 Eligibility Criteria

8.2.1 Inclusion Criteria

1. Patients must be able to understand English and provide written informed consent;
2. Males and females between 18 and 80 years of age;
3. Recipients of a primary or secondary kidney transplant 4 weeks to 10 years prior to screening;
4. Patients receiving a stable dose (i.e., no dose adjustments) of TAC-IR for a minimum of 4-7 days at screening;
5. Patients with a screening TAC-IR trough level of 3-9 ng/mL, measured between Day -7 to 0;
6. Women of childbearing potential must have a negative urine pregnancy test at screening;
7. Patients must be willing to commit to and comply with the schedule of study visits.
8. The patient is not scheduled to begin any new medication that could interfere with tacrolimus blood levels, including prescription and over-the-counter medications, herbal, or food supplements (including grapefruit and pomegranate products), or medications listed in **Appendix 1**.

8.2.2 Exclusion Criteria

1. Recipients of any transplanted organ other than kidney;

2. Patients with an estimated glomerular filtration rate (eGFR) (MDRD4) <25 mL/min at screening;
3. Patients with significant visual impairments affecting their ability to complete the study requirements and assessments: patient's vision is 20/200 or worse;[1]
4. Patients with significant hearing impairments affecting their ability to complete the study requirements and assessments, based on Investigator discretion;[2]
5. Patients with any severe medical condition (including infection) requiring acute or chronic treatment that in the Investigator's opinion would interfere with study participation;
6. Patients who have a history of any of the following, based on documentation of clinical conditions and concomitant medications in the medical records:
    - Cognitive decline secondary to stroke
    - Dementia
    - Resected or existing brain tumor
    - Acute or chronic bipolar psychosis or schizophrenia per Investigator discretion
    - Mental retardation
    - Moderate or severe traumatic brain injury
    - Failure of any major organ other than the kidneys (e.g., end-stage liver disease)
    - Known non-adherence (defined as documentation in the patient chart of multiple missed visits and/or medication doses) which in the Investigator's opinion would interfere with the objectives of the study
7. Patients with medical history of hypertension or diabetes which is unmanageable by medically approved intervention (e.g., medication/diet) as assessed by the Investigator;
8. Patients with acute or chronic depression, corresponding to a score of ≥20 (corresponding to moderate depression) on the BDI-II at screening;
9. Patients who are taking any acute or chronic medications that may impact reaction time, memory, or sleep habits, based on Investigator discretion;
10. Patients on concurrent immunosuppression with MMF (CellCept) or MPS delayed release tablets (Myfortic), or generic versions of these medications, as per SOC, who have not been on stable doses (i.e., no dose adjustments or formulation change) for at least 4-7 days prior to screening;
11. Patients receiving prednisone or equivalent >10 mg/day;
12. Patients with an episode of biopsy-proven or suspected acute rejection that requires treatment within 3 months of screening;

[1] Patients with visual aids (glasses or contact lenses) should be considered, provided their vision is adequately improved with the use of the aid.
[2] Patients with hearing aids should be considered, provided their hearing is adequately improved with the use of the aid.

13. Patients who are being actively treated for cancer (with the exception of non-invasive basal cell or cutaneous squamous cell carcinoma);
14. Patients known to be human immunodeficiency virus (HIV) positive;
15. Patients with any form of current drug or alcohol abuse as assessed by the Investigator;
16. Patients who were treated with any other investigational agent within 1 month prior to screening;
17. Pregnant or nursing women or women planning to become pregnant, where pregnancy is defined as a state of the female patient after conception and until the termination of gestation, confirmed by a positive urine laboratory test; women of child-bearing potential, defined as all women physiologically capable of becoming pregnant who are unwilling to use a defined SOC birth control method, UNLESS they are:
    - Women whose career, lifestyle, or sexual orientation preclude intercourse with a partner
    - Women whose partners have been sterilized by medically approved means

8.2.3 Contraception Guidelines

ENVARSUS XR has a pregnancy category C rating. Per the Full Prescribing Information, there are no adequate and well-controlled studies in pregnant women. Tacrolimus is transferred across the placenta. The use of tacrolimus during pregnancy in humans has been associated with neonatal hyperkalemia and renal dysfunction. Tacrolimus given orally to pregnant rabbits at 0.6 times the maximum clinical dose and pregnant rats at 0.9 times the maximum clinical dose was associated with an increased incidence of fetal death *in utero*, fetal malformations (cardiovascular, skeletal, omphalocele, and gallbladder agenesis) and maternal toxicity. ENVARSUS XR should be used during pregnancy only if the potential benefit to the mother justifies potential risk to the fetus. [16]

As stated in the exclusion criteria, patients of childbearing potential who are unwilling to use a defined SOC birth control unless they are women whose career, lifestyle, or sexual orientation preclude intercourse with a partner and/or whose partners have been sterilized by medically approved means are not eligible to enter the study.

8.3 Interruption or Discontinuation of Treatment

8.3.1 Withdrawal from Study

1. Patients have the right to discontinue study treatment at any time for any reason without penalty or prejudice.

2. The Investigator also has the right to discontinue patients from study treatment if he/she feels it is in the best interest of the patient.

3. A patient may be withdrawn from the study treatment by the Investigator if: (1) the Investigator feels it is not in the patient's best interest to continue in the study, (2) the

patient fails to follow the Investigator's instructions, (3) the patient experiences an adverse reaction that requires other medical treatment, or (4) the patient becomes pregnant.

In the absence of a medical contraindication or significant protocol violation, every effort should be made by the Investigator to keep the patient in the study. Should a patient not complete the study, the patient should complete all the procedures outlined under early withdrawal in the Study Schedule (refer to **Table 3-1**). Reasons for discontinuation will be documented on the case report forms (CRFs).

If, in the opinion of the Investigator, the clinical observations in the study suggest that it may be unwise to continue, the Investigator may suspend or terminate the study.

A written statement will be provided to the Institutional Review Board (IRB) and regulatory authorities, if required.

All patients whose Visit 1 TAC-IR trough level is outside the 3-9 ng/mL range can be rescreened up to 2 times after at least 4-7 additional days on stable dose of TAC-IR.

Procedures for discontinuation

If a patient withdraws from the study for any reason all early termination procedures should be completed. Reason for withdrawal, date of discontinuation, and date of the last dose of study medication ENVARSUS XR should be recorded in the study termination section of the CRF. The Investigator is to complete, sign and date the study termination page on the CRF upon completion of the termination visit.

At the time of discontinuation, every effort should be made to ensure that all procedures and evaluations scheduled for the early withdrawal visit are performed. Except in the case of a medical emergency, the following will be performed upon the discontinuation of the study:

- AE assessment
- Review of concomitant medications and ENVARSUS XR

8.3.2 Interruption of Therapy with a Study Drug (ENVARSUS XR)

Patients who require interruption of immunosuppressive therapy for clinical cause anytime between Visit 2 and 3 will be required to be on a stable dose of ENVARSUS XR for a minimum of 4 days before Visit 3 assessments are performed.

9 TREATMENTS

9.1 Investigational Therapy and Reference Therapy (Current Standard of Care)

The investigational therapy ENVARSUS XR and TAC-IR will be provided by the patient's individual supply. The formulation for the investigational therapy is listed below.

Study Drug: ENVARSUS XR (tacrolimus extended-release tablets), once daily, for oral use; provided in 0.75 mg, 1.0 mg, and 4.0 mg dosage strengths.

9.2 Study Drug Dosing and Administration

ENVARSUS XR tablets will be administered orally q.d. in the morning based on a conversion factor from tacrolimus to ENVARSUS XR of 1:0.8 (see **Appendix 2 or https://www.envarsusxr.com/hcp/professional-resources/envarsus-xr-dose-converter/ and PI discretion**) to maintain target trough level of 3-9 ng/mL. The following dosing instructions should be observed:

- Patients should take ENVARSUS XR on an empty stomach at the same time of the day, preferably in the morning (to ensure consistent and maximum possible drug exposure).
- Patients should swallow ENVARSUS XR whole with fluid (preferably water) and should not chew, divide, or crush the tablets.
- If a dose is missed, the patient should take it as soon as possible within 14 hours after the scheduled time and inform the study investigator; beyond the 14-hour time frame, the patient should wait until the usual scheduled time to take the next regular daily dose.
- Patients should avoid eating grapefruit or drinking grapefruit juice or alcoholic beverages while taking ENVARSUS XR.

Patients should be encouraged to take their study treatment on a consistent schedule with regard to time of day and relation to meals except on their study visit days. Patients will be instructed not to take their morning dose of TAC-IR prior to their clinic visit (Visit 2) but to take their morning concomitant medications as they normally would. Once at the clinic at Visit 2, after the TAC-IR trough level blood sample has been drawn, the patient will take the morning dose of TAC-IR. ENVARSUS XR will be prescribed, and patients will be instructed to begin taking ENVARSUS XR the following morning.

Likewise, for Visit 3, patients will be instructed not to take their morning dose of ENVARSUS XR prior to their clinic visit (Visit 3), after the ENVARSUS XR trough level blood sample has been drawn, the patient will take the morning dose of ENVARSUS XR.

For Visit 4, patients will be instructed not to take ENVARSUS XR before coming to the clinic; after their ENVARSUS XR trough blood draw and other procedures for the visit, they will take their last single daily dose of ENVARSUS XR.

9.3 Dose Adjustments

Patients who require a TAC-IR dose adjustment as a result of screening assessments are not to be considered stable and cannot enter the study, but may be re-screened up to 2 times after at least 4-7 additional days on stable dose of TAC-IR.

Dose adjustments of ENVARSUS XR are not permitted between Visits 2 and 3 unless it is deemed medically necessary at the discretion of the Investigator. If a dose adjustment is required the patient is required to be on a stable dose of ENVARSUS XR (no dose adjustment) for a minimum of 4 days before Visit 3 assessments are performed (i.e., if a dose adjustment is

medically necessary and occurs anytime between Visits 2 and 3 there should be a minimum of 4 days on a stable ENVARSUS XR dose before the Visit 3 assessments can take place). If multiple dose adjustments are required, the Investigator must first obtain Sponsor approval.

ENVARSUS XR dose adjustments to meet therapeutic range in ENVARSUS XR trough levels are permitted after Visit 3 per SOC. In these cases, ENVARSUS XR trough level should be measured, a safety assessment should be completed, and ENVARSUS XR should be dispensed (if applicable).

9.4 Concomitant Therapy

9.4.1 Immunosuppressants

Only CellCept® (MMF, Roche Laboratories, Nutley, NJ), Myfortic® (MPS, Novartis Pharmaceuticals, East Hanover, NJ), including generic versions of each, or prednisone (or equivalent <10 mg/day), with choice and doses per SOC at the participating site, are allowed (but not required). Patients receiving immunosuppressants should be on a stable dose throughout the treatment period from Visit 2 to Visit 3 of the study.

9.4.2 Drug Interactions

Tacrolimus is metabolized by the CYP3A oxidase system. Substances which inhibit this enzyme can decrease metabolism and increase concentrations of tacrolimus, including study drug, and substances which induce CYP3A oxidase may increase metabolism and decrease blood concentrations (see **Appendix 1** for a partial listing of these medications). Whenever feasible, CYP3A inhibitors or inducers should be avoided, but clinical circumstances may necessitate using such agents. When this is the case, increased monitoring of tacrolimus concentrations is recommended.

Please consult the current prescribing information of MMF for drug interactions associated with MMF.

9.4.3 Other Medications

All prophylaxis and other medications will be allowed per SOC at each of the participating sites as long as dosing remains stable throughout the treatment period Visits 1 – Visit3of the study.

9.5 Treatment Compliance

Participants will be encouraged to bring their study medications to each study visit and reviewed by the research nurse with the participants.

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10 STUDY VISITS AND ACTIVITIES

10.1 Study Activities by Visit

The specific study procedures to be performed at each visit are provided in the Schedule of Study Activities (**Table 3-1**). Permissible visit schedule changes are provided in **Section 10.1.7**. Visits should be scheduled to coincide with SOC visits, where possible.

10.1.1 Screening (Visit 1)

Prior to screening activities, each patient must be given an opportunity to ask questions and to understand the details of study participation. This consent process must be documented in the patient's source documents and evidenced by the patient signing the informed consent form (ICF). After signing the ICF, each patient will be assigned a patient identifier (PID) number that will be used on all patient documentation. PID numbers will be assigned in ascending sequential order.

Only patients who satisfy all of the inclusion and exclusion criteria specified in **Sections 8.2.1 and 8.2.2** will be eligible for entry into the study. If a patient's trough level is outside the 3-9 ng/mL range, the patient is not qualified for the study. All patients whose Visit 1 TAC-IR trough level is outside the 3-9 ng/mL range can be dose adjusted and re-screened up to 2 times (after at least 4-7 additional days on stable dose of TAC-IR).

Screening procedures and assessments will be conducted on Day -7 to -1. The Screening evaluations include the following:

- Assessment of entry criteria (including BDI-II).
- Recording of the patient's medical history.
- Urine pregnancy test (for female patients of child-bearing potential).
- Assessment of eGFR by MDRD4.
- Prior to the morning dose of TAC-IR, whole blood will be drawn to measure TAC-IR trough level (approximately 5 mL).
- Concomitant medication use (including an assessment of drug supply for each medication, including herbal products, to ensure adequate supply for the duration of the treatment phase) will be evaluated and recorded.
- .

Note that, in the event that screening laboratory results cannot be obtained on the same day as the visit to determine patient's eligibility for the study, the pregnancy and safety laboratory tests can be evaluated during the Day -7 to Day -1 time frame and the TAC-IR trough evaluation can be performed on Day -1. These evaluations do not need to be repeated at Visit 2 in these cases.

10.1.2 Enrollment (Visit 2)

Note that the designation of Visit 2 as occurring on 'Day 0' is meant to reflect that ENVARSUS XR dosing is to start as soon as possible but no later than the next 30 days . Visit 1 and Visit 2 may be combined if no dose adjustments were performed and the patient has been maintained on a

stable dose of TACIR with trough level between 3-9 ng/mL, and the physician does not deem any dose adjustment required.

Upon arrival at the clinic at Visit 2 the following assessments will be performed:

- Prior to the morning dose of TAC-IR, the patient will have approximately 5 mL of whole blood drawn for the assessment of TAC-IR trough.
- After confirmation of patient eligibility, a blood drawn for safety laboratory parameters (approximately 15 mL, for complete blood count [CBC] and a metabolic profile [blood glucose, calcium, sodium, potassium, CO_2 (carbon dioxide, bicarbonate), chloride, blood urea nitrogen (BUN) and creatinine]).
- Physical examination and vital signs measurements.
- Patients will then be instructed to take their morning dose of TAC-IR.
- QoL and cognitive tests will then be performed after the morning TAC-IR dose in the following order:

  o WHODAS; o PIRS-20; o RBANS, o TMT-A and TMT-B;

  o After cognitive tests, ENVARSUS XR will be prescribed and patients will be instructed to take the first dose of ENVARSUS XR as soon as possible but no later than the next 30 days . Patients must be instructed to take their evening dose of TAC-IR.
- Concomitant medication use (including compliance to immunosuppressive therapy and adequate drug supply) and the safety monitoring processes will be initiated.
- Prior to leaving the clinic, the patient will be prescribed ENVARSUS XR with instructions to take the medication as soon as possible but no later than the next 30 days prior to noon each day for the remainder of the study. Patients will be reminded not to take their daily dose of ENVARSUS XR prior to their clinic at Visit 3 and to bring all remaining ENVARSUS XR medications to that visit.

10.1.3 Month 4 (Visit 3)

Upon arrival at the clinic on Visit 3 (month 4 ±30 days) the following assessments will be performed:

- Prior to the morning dose of ENVARSUS XR, patients will have approximately a 5 mL whole blood sample taken for tacrolimus trough measurement.
- Vital signs measurements.
- Patients will then be instructed to take their morning dose of ENVARSUS XR.
- QoL and cognitive tests will then be performed after the morning ENVARSUS XR dose including PGI-I, WHODAS, PIRS-20, and cognitive tests (in the same order as described above for Visit 2).

- CGI-I will be used to evaluate global change by the Investigator or designated back-up physician.
- Concomitant medication use (including evaluating compliance to immunosuppressive therapy) and AEs will be evaluated and recorded.
- Prior to leaving the clinic, all patients will be prescribed ENVARSUS XR for 4-month with refills with instructions to take the medication prior to noon each day for the remainder of the study. Patients will be reminded not to take their daily dose of ENVARSUS XR prior to their clinic at Visit 4 and to bring all remaining ENVARSUS XR medications to that visit.
-

10.1.4 Month 8 (Visit 4)

Upon arrival at the clinic on Visit 4 (Month 8 ± 30 days) same assessments as Visit3 will be performed:

- Prior to the morning dose of ENVARSUS XR, patients will have approximately a 5 mL whole blood sample taken for tacrolimus trough measurement.
- Vital signs measurements.
- Patients will then be instructed to take their morning dose of ENVARSUS XR.
- QoL and cognitive tests will then be performed after the morning ENVARSUS XR dose including PGI-I, WHODAS, PIRS-20, and cognitive tests (in the same order as described above for Visit 3).
- CGI-I will be used to evaluate global change by the Investigator or designated back-up physician.
- Concomitant medication use (including evaluating compliance to immunosuppressive therapy) and AEs will be evaluated and recorded.
- .
- All patients will be asked to bring ENVARSUS XR with them to be reviewed by the study nurse. The continuation of ENVARSUS XR will be at the discretion of the patient's treating nephrologist.

10.1.5 Standard of Care (SOC) Study Visits

At any time during the treatment period, an SOC study visit may be necessary for clinical cause, such as a sign or symptom of drug toxicity/intolerance, an AE, or a suspected acute rejection episode. A whole blood tacrolimus trough level should be recorded, if applicable, for patients for whom dose-adjustment of ENVARSUS XR is indicated.

10.1.6 Early Withdrawal Study Visits

An early-withdrawal visit should be scheduled as soon as possible for patients who withdraw from the study. Assessments of concomitant medication use, and AEs will be performed at this visit. .

Patients who withdraw from the study will not be replaced. Follow-up will occur for any ongoing AEs at the time of withdrawal. The Investigator will be responsible for informing IRBs of the early termination of the study.

10.1.7 Permissible Visit Schedule Changes

Visit variations are allowed for logistic considerations and to accommodate scheduling conflicts. A +7-day window is permitted for scheduling visits.

Table 10-1 Permissible Visit Schedule Changes

Screening: Day -30 to Day -1 (Visit 1)	Target date is 4 weeks to 10 years post-transplant, **1 to 30 days prior to enrollment date.**
Enrollment: Day 0 (Visit 2)	**Enrollment date**
Visit 3 (Month 4): Month 4 ± 30 days Window (Visit 3)	Target date ± 30 days Target date is **Enrollment (Visit 2) date + 4 months**.
Visit 4 (Month 8): Month 8 ± 30 days Window (Visit 4)	Target date ± 30 days Target date is **Enrollment (Visit 2) + 8 months.**

10.2 Study Assessments

This section provides the assessments to be performed in the study. The case report forms will be developed in REDCap.

10.2.1 Screening Assessment: Beck Depression Inventory (BDI-II)

The BDI-II is a widely used 21-item, self-report instrument that measures severity of depression in adults and adolescents in clinical and nonclinical settings.[33] Each item is a list of four statements arranged in increasing severity about a particular symptom of depression. Scores for each item range from 0 to 3. The total BDI-II score is the sum of all responses, ranging from 0 to 63. Cut score guidelines for patients diagnosed with major depression are as follows: minimal (013), mild (14-19), moderate (20-28), and severe (29-63).[33] The recall period of the BDI-II is the past two weeks, including today.

The BDI-II will be administered at the Screening Visit. Patients with a score of ≥20 (corresponding to moderate depression) will be excluded from the study. Administration time: approximately 5-10 minutes.

10.2.2 Baseline and Post-Baseline Assessments

The clinician should begin each study visit with the clinical assessments as specified in **Table 3**, with the exception of Visit 3, where the clinical assessments are preceded by administration of the PGI-I. Following the clinical assessments, the corresponding assessments will be administered in the order specified in the following subsections, as per the schedule of assessments in **Table 3**. Each visit will conclude with an assessment of adverse events for safety reporting and, if

applicable, dispensing of study drug, completion of the dose administration record, and study drug reconciliation (in that order).

10.2.2.1 Demographics Survey

The Demographics Survey provides overall demographic background on the patient population; survey is completed at Visit 2 at the same time when collecting demographics.

10.2.2.2 Patient Global Impression of Improvement (PGI-I)

The PGI-I measures change since initiating a medication and is assessed on a 7-point Likert-type scale ranging from very much better (1) to very much worse (7). The PGI-I will be administered at Visit 3 prior to other patient-reported outcomes (PRO) measures and clinical assessments. The PGI-I should be completed by the patient without input from clinical staff or friends or family members. Administration time: approximately 1 minute.

10.2.2.3 World Health Organization Disability Assessment Schedule 2.0 (WHODAS)[34]

The 12-item WHODAS 2.0 includes 12 items assessing 6 disability domains in 2 components. The component "activities" includes cognition (learning and concentration), mobility (standing and walking) and self-care (washing and dressing oneself), and the component "participation" includes getting along (dealing with strangers and maintaining friendships), life activities (doing housework and working ability), and social participation (emotional functions and engaging in community). Each of the 12 items is rated according to a 5-point Likert-type scale, which grades the difficulty experienced by the participant in performing a given activity. The scoring is from 0 to 4, where 0 means no (0–4%), 1 means mild (5–24%), 2 means moderate (25–49%), 3 means severe (50–95%), and 4 means extreme or complete (96–100%) difficulty in this specific activity. The total score of WHODAS is the sum of all these 12 sub-scores and ranges from 0 to 48, with lower scores indicating better functioning. Total scores of 1–4 belong to mild disability, 5–9 to moderate disability, and 10–48 to severe disability (http//www.who.int/classifications/ICF/who/whodasii/en/).

The WHODAS will be administered at Visit 2, Visit 3, and Visit 4 in this study

10.2.2.4 Pittsburgh Insomnia Rating Scale (PIRS-20)

The PIRS-20 is the short version of the original PIRS, both copyrighted by the University of Pittsburgh.[38] The original PIRS is a 65-scale item, widely used instrument in clinical and research practice. It was designed to rate the severity of insomnia in clinical trials and clinical practice. Domains of the PIRS-20 include subjective distress (12 items), subjective sleep parameters (4 items) and quality-of-life (4 items). The recall period of the PIRS-20 is the past 7 days.[38] The PIRS-20 total score is the sum of all items and ranges from 0 (good sleep) to 60 (bad sleep).[38] The PIRS-20 should be administered following the WHODAS at Visit 2 and Visit 3. Administration time: approximately 5-10 minutes.

10.2.2.5 Repeatable Battery for the Assessment of Neuropsychological Status Update (RBANS Update)

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was developed for the dual purposes of identifying and characterizing abnormal cognitive decline in the older adult and as a neuropsychological screening battery for younger patients. It is widely used in both clinical contexts and clinical trials. While easily tolerated by patients and easily administered, it is also psychometrically robust and sensitive in the detection of even mild expressions of cognitive impairment. The entire battery takes less than 30 minutes to administer, and yields scaled scores for five cognitive domains, known as Index Scores). These domains include Immediate Memory (List Learning and Story Memory), Visuospatial/Constructional (Figure Copy and Line Orientation), Language (Picture Naming and Semantic Fluency), Attention (Digit Span and Coding), and Delayed Memory (List Recall, List Recognition, Story Memory, and Figure Recall). The RBANS utilizes parallel forms, ideal for measuring change over time, and takes approximately 30 minutes to administer.

10.2.2.6 Trail Making Tests A & B ([TMT-A & TMT-B] visual scanning speed/visual attention)

Trail Making Tests (TMT) has been extensively used in neuro-psychological assessment. The Trail Making Test A (TMT-A) involves visual, conceptual, and visio-motor tracking. TMT-A requires primarily perceptual-motor speed, visual scanning, attention, and numeric sequencing.[42] The Trail Making Test B (TMT-B) is a task of visual, conceptual, and visio-motor tracking which requires primarily perceptual-motor speed, visual scanning, attention, working memory and secondarily the ability to shift conceptually between numerical and alphabetical order.[42] TMT-B is administered according to standard procedures.[54] Both parts of the Trail Making Test consist of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1 – 25, and the patient should draw lines to connect the numbers in ascending order. In Part B, the circles include both numbers (1 – 13) and letters (A – L); as in Part A, the patient draws lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The patient should be instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper. The patient is timed as he or she connects the "trail." If the patient makes an error, it should be pointed out immediately and patient is allowed to correct it. Errors affect the patient's score only in that the correction of errors is included in the completion time for the task. Maximum time given for TMT A is 150 seconds and for TMT B is 300 seconds. Results for both TMT A and TMT B are reported as the number of seconds required to complete the task; therefore, higher scores reveal greater impairment. Although trail making tests are very simple, they have been hypothesized to reflect a wide variety of cognitive processes including attention, visual search, and scanning, sequencing, and shifting, psychomotor speed, abstraction, flexibility, ability to execute and modify a plan of action, and ability to maintain two trains of thought simultaneously.

Administration time: approximately 5-10 minutes. Normative data information are available.[55]

10.2.2.7 Clinician Global Impression of Improvement (CGI-I)

The CGI-I measures change since initiating a medication and is assessed on a 7-point Likert-type scale ranging from very much improved (1) to very much worse (7). The CGI-I will be

administered at Visits 3 and 4 after the administration of the PIRS-20. Administration time: approximately 1 minute.

10.2.3 Adverse Events

An AE is any untoward sign, symptom or medical condition occurring at any time after the patient receives his/her first dose of study drug (ENVARSUS XR), even if the event is not considered to be related to the study drug. Information about all Aes, whether volunteered by the patient, discovered by Investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded on the AE CRF and followed as appropriate.

Abnormal laboratory values or test results constitute Aes only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy. They will be recorded on the AE CRF under the signs, symptoms, or diagnosis associated with them.

As far as possible, each AE will also be described by:

- its duration (start and end dates)
- the severity grade (mild, moderate, severe)
- its relationship to the study drug (suspected / not suspected)
- the action(s) taken and, as relevant, the outcome

Criteria for determining the severity of an AE and its relationship to study drug are shown below in **Table 10-2**. These criteria are guidelines. It is the responsibility of the Investigator to make a determination of severity and whether or not a relationship to study drug is suspected.

Table 10-2 AE Severity and Relationship to Study Drug

AE Severity	
Mild	Awareness of sign or symptom but easily tolerated.
Moderate	Discomfort sufficient to cause interference with normal activities.
Severe	Incapacitating, with inability to perform normal activities.
AE Relationship	
Suspected	A clinical event, including laboratory test abnormality, with a reasonable time sequence to drug administration, which might or might not be also explained by concurrent disease or other drugs or chemicals.
Not suspected	A clinical event, including laboratory test abnormality judged to be clearly and incontrovertibly due to extraneous causes (diseases, environment, etc.), or with a temporal relationship to drug administration which makes a causal relationship improbable, and/or for which other drugs, chemicals or underlying disease provide a much more plausible explanation.

Adverse event monitoring and reporting will be followed for the 3-month duration of the study until the AE becomes chronic, or until the patient is deemed "lost to follow-up" by the Investigator or designee.

10.2.4 Serious Adverse Events

An SAE is an undesirable sign, symptom, or medical condition which:

- is fatal
- is life threatening
- requires or prolongs hospitalization
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly or a birth defect
- is medically significant, in that it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above

Serious adverse events must be reported to IQVIA, the pharmacovigilance provider for intake of SAE forms contracted by Veloxis, the developer of Envarsus XR. within 24 hours of the occurrence of the event or at least within 24 hours of awareness of an event occurring at any time after the patient receives his/her first dose of study drug (ENVARSUS XR). The Investigator must complete the SAE form with as much information available at the time of completion and transmit a facsimile notification form to IQVIA.

Events not considered to be SAEs are hospitalizations for:

- treatment which was elective or preplanned for a preexisting condition that is unrelated to the indication under study and did not worsen
- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission

10.2.5 Laboratory Test Abnormalities

Laboratory test results will be maintained at the site and must be reviewed and signed by the Investigator or Sub-Investigator. Laboratory test value abnormalities should not be reported on the AE page of the CRF as Aes unless they indicate a clinically relevant condition.

10.2.6 Physical Examination

A complete physical examination will include body weight and the examination of the following body systems: general appearance, skin, HEENT (head, ears, eyes, nose, throat), cardiovascular, pulmonary, abdomen, neurological, lymph nodes, spine, and extremities (skeletal). Height will be measured at screening only.

Any abnormalities will be recorded on the CRF. Information about the physical examination must be present in the source documentation at the study site. Significant findings that are present before the start of the study must be included in the Relevant Medical History/Current Medical Conditions

CRF. Significant findings made after the start of study drug that meet the definition of an AE must be recorded on the AE CRF.

10.2.7 Vital Signs

Vital signs, including blood pressure, heart rate and body temperature, will be measured using clinically acceptable methods and devices at each clinic visit. Blood pressure should be recorded with the patient seated (all visits) **or** supine (all visits).

Any patient with vital signs outside of the acceptable range (blood pressure between 100 and 140 mmHg systolic and 60 and 90 mmHg diastolic; heart rate between 60 and 99 beats/minute) will have his/her vital signs repeated within 15 minutes. If the repeat measurement remains outside of the acceptable range, the Principal Investigator or Sub-Investigator will determine the course of action. An AE will be reported for the out-of-range measurements if deemed clinically significant.

10.2.8 Biochemistry / Hematology

Blood samples will be collected for the purposes of determining a patient's eligibility as indicated in the Schedule of Study Activities (**Table 3-1**). The Screening laboratory tests include a basic metabolic profile and CBC. Samples will be analyzed at local laboratories using the laboratory's normal ranges. The local laboratory procedures and normal ranges will be collected from the site prior to beginning enrollment. Each patient sample will be analyzed to provide the result for each parameter.

Laboratory tests included are listed below.

> **CBC:** Hemoglobin, hematocrit, white blood cell (WBC) count, red blood cell (RBC) count, platelet count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), and mean platelet volume (MPV).
>
> **Basic Metabolic Profile:** Glucose, calcium, sodium, potassium, CO_2, chloride, blood urea nitrogen (BUN), creatinine, and calculated eGFR.

If any laboratory result is in question, it will be repeated. It is the Investigator's responsibility to review the results of all lab tests once available. For each lab value outside the normal range, the Investigator is to determine if this in a clinically significant change from baseline for that patient. An AE will be reported for the out-of-range measurements if deemed clinically significant or requires therapy. Repeat lab tests of additional tests to verify original lab results may be needed.

10.2.9 Study Drug Dose and Monitoring of Whole Blood Trough Level for Tacrolimus

The dose of TAC-IR or ENVARSUS XR being administered to the patient will be recorded on the appropriate CRF.

Whole blood, for the purpose of tacrolimus trough level measurement, will be drawn at the designated time points listed in the Study Schedule and analyzed at the local laboratory. The local laboratory procedure for tacrolimus trough level measurement will be collected from each site prior to enrollment.

10.2.10 Concomitant Medications

All current concomitant medication will be recorded and documented for dose, brand name and/or generic name. The reason for any change in the dose or choice of concomitant immunosuppressant medication will also be recorded on the appropriate CRF.

11 SAFETY MONITORING

Routine safety assessments will consist of monitoring and recording all Aes, including SAEs, the regular monitoring of vital signs and physical condition as described in **Section 10**.

11.1 Warnings and Precautions

ENVARSUS XR tablets are an extended-release formulation of tacrolimus, intended for once daily oral administration. Refer to the ENVARSUS XR Full Prescribing Information[16] for detailed description of the warnings and precautions associated with this formulation of tacrolimus.

11.2 Pregnancies

Any pregnancy that occurs during study participation should be reported using a Pregnancy Form. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and newborn complications. For additional instructions for rapid notification of pregnancies please see **Section 16.1.2**.

12 PROTOCOL AMENDMENTS, OTHER CHANGES IN STUDY CONDUCT

12.1 Protocol Amendments

Any substantial changes will be made as formal amendments to the protocol and will be submitted to the local IRB for appropriate review and approval, and to regulatory authorities.

12.2 Other Changes in Study Conduct

Material changes in study conduct as defined in this protocol are not permitted.

Any unforeseen changes in study conduct will be recorded in the case report forms.

13 DATA MANAGEMENT

13.1 Data Recording and Documentation

Data collection will involve the use of source documents and REDCap , to which only authorized personnel will have access.

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidance for electronic records. All electronic record systems will be fully qualified and validated for the intended use per the International Society of Pharmaceutical Engineers (ISPE) Good Automated Manufacturing Practice (GAMP®) guidelines, 21 Code of Federal Regulations (CFR) Part 11 (FDA regulation for Electronic Records and Electronic Signatures) and the International Conference on Harmonization (ICH) Guidance on Good Clinical Practice (ICH E6).

Also, data will be stored and evaluated in such a way as to guarantee patient confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (e.g., copies of CRFs, regulatory documents) will be retained at the study center, along with adequate source documentation, according to FDA and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use requirements. All study records must be available for inspection by Sponsor, its authorized representatives, the FDA, and other regulatory authorities.

13.2 Database Management and Quality Control

Data items from the source documents will be entered into the REDCap.

14 STATISTICAL METHODS

All analyses will be performed using SAS® for Windows statistical software (SAS Institute, Cary, NC) using validated implementations of each application or SAS custom programming. Programs, logs, and output will be reviewed for accuracy according to relevant Standard Operating Procedures (SOPs). A full Statistical Analysis Plan will be developed and finalized prior to data base lock. The plan will include a thorough description of the statistical methods to be used to address study objectives.

In general, continuous variables will be summarized with number of non-missing observations, mean, standard deviation (SD), median, minimum, and maximum displayed. Categorical variables will be summarized as counts and percentages.

14.1 Sample Size

The study aims to enroll approximately 60 patients. With an expected drop-out rate of 10% to 15%, a maximum of fifty-two (52) evaluable patients are expected to reach the end of study.

In order to detect an effect size of 0.5 with 80% power and a one-sided type I error rate of 0.025, a sample size of 34 evaluable patients is needed. (NOTE: We simply need at least 34 patients to have adequate power, but we anticipate approximately having 52, meaning that this study will almost certainly NOT be underpowered). An interim analysis will be conducted when data are available for 17 (half of 34) evaluable patients, to better estimate the variation and effect of the treatment.

The rule for sample size adjustment is as follows:

Denote the planned sample size (n) = $n_1 + n_2$, where $n_1 = 17$; and n = 34 (i.e., n_2 = 17) Let

r=1.5 be the rate of adjustment (which leads to the maximum sample size of 52). Define

N_{new} (final sample size) as

$$N_{new} = \begin{cases} n_1 + K, & n \le N \le rn \\ n, & N < n \\ rn, & N > rn \end{cases}$$

where K is the calculated additional required sample size (beyond first 17 evaluable patients) and N is the calculated total required sample size based on the observed change and variation from the interim analysis.

The range of possible total sample sizes based on the interim analysis is from 34 and 52, i.e., the sample size remains at 34 if the adjusted estimate is below 34, and increases to a maximum of 52 if the adjusted estimate is beyond 52.

14.2 Analysis Sets

Intent-to-Treat (ITT) Dataset: Includes all patients who are enrolled. The efficacy analyses will be performed using this dataset.

Evaluable Dataset: Includes all patients who are enrolled and received at least one dose of ENVARSUS XR and within targeted trough level of 3-9 ng/mL. In addition, the patients must have baseline and post-baseline conversion for at least one of the cognitive tests (without major protocol violation/deviation that would affect the cognitive measurement. The efficacy analyses will also be performed using this dataset.

Safety Dataset: Includes all patients who are enrolled and received at least one dose of ENVARSUS XR. The safety analyses will be performed using this dataset.

14.3 General Considerations

14.3.1 Definition of Study Days

For the purpose of listing and summarizing data, time-in-study for each patient observation will be defined using study days. Study day is defined as the difference between the date of interest and the date of first dose of ENVARSUS XR. One day will be added if this difference is 0. The day prior to the first dose date is considered as "Study Day -1". There is no "Study Day 0" for analysis purposes. In general, it is expected that enrollment date is the same date of the first dose date of ENVARSUS XR.

14.3.2 Analysis Time Point

Nominal visits will be used for analysis unless otherwise specified. No specific analysis visit window will be utilized for analysis purposes.

14.3.3 Baseline Evaluation

Patient demographics (including patient demographic survey) and baseline assessments will be summarized. Baseline evaluation is defined as the last non-missing evaluation prior to the first dose of ENVARSUS XR.

14.3.4 Missing Data Handling

Unless clearly specified, missing data will not be imputed for analysis; hence, in the summaries of continuous variables the sample size will be the number of patients with non-missing data; in the summary of categorical variables, patients with missing data will be excluded from the percentage calculation in general (with exception of demographic and baseline information).

14.4 Patient Population Summary

Summary tables will provide frequency counts for patient disposition, including enrolled patients, treated patients, patients who completed Visit 4, and patients who discontinued early with reasons for discontinuation.

14.5 Efficacy Analysis

14.5.1 Primary Efficacy Analysis

The primary efficacy endpoint is the Global Composite Score on the RBANS. Raw scores on the RBANS will be age adjusted and converted into a series of Index Scores (reflecting domains such as immediate memory, delayed memory, attention, etc.) which will in turn be combined to generate the aforementioned Global Composite Score, a summary score reflective of overall neuropsychological status (scores have a mean of 100, SD of 15, impairment is typically defined as a score of <78. Descriptive summaries of patients 'scores and percentiles at baseline (i.e., Visit 2) and post-baseline (i.e., Visit 3) will be provided. The mean change (absolute change) in -score

the RBANS composite score from baseline to post-baseline will be evaluated at 0.05 significance level and analyses will be conducted based on both ITT and Evaluable analysis datasets.

14.5.2 Secondary Efficacy Analysis

Same methods as described above will be used to analyze other cognitive test scores or the global composite score of the Covid-19 Telephone Battery, should that be the primary outcome battery that we employ. In addition, the correlation among tests will be explored at each time point as well as the changes from baseline at Visit 3. Correlation coefficients and corresponding p-values will be displayed.

CGI-I and PGI-I will be summarized by number and percentages of patients in each category as well as combined categories of improvement (e.g., "Minimum improved", "Much improved", "Very much improved [CGI-I]/ Very much better [PGI-I]").

PIRS-20 total score (sum of all 20 item scores with one missing item allowed) will be summarized at baseline and post-baseline visit. Absolute values at each time point as well as changes from baseline to post-baseline visit (i.e., Visit 3) will be analyzed.

All analyses will be based on ITT and Evaluable analysis datasets.

14.6 Safety Analysis

14.6.1 Extent of Exposure

All patients who qualify for the study are expected to receive ENVARSUS XR for 3 months. Duration and total doses of ENVARSUS XR will be summarized for period up to Visit 3 and Visit 4. Reasons for dose change will be listed.

All analyses will be based on Safety analysis dataset.

14.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to classify all Aes with respect to system organ class and preferred term. Adverse events will be summarized by presenting the number and percentage of patients having any AE, having an AE in each body system, and having each individual AE preferred term. Any other information collected (e.g., severity or relatedness to study drug) will be listed as appropriate. Incidence of Aes/SAEs will be summarized up to Visit 4. All analyses will be based on Safety analysis dataset.

14.6.3 Other Analysis

Trough level of ENVARSUS XR at individual scheduled visits will be summarized. Changes from baseline value will be described as well. Vital signs will be summarized similarly. The analyses will be based on Safety analysis dataset.

14.7 Interim Analysis

An interim analysis will be conducted when cognitive data are available for 17 evaluable patients who have completed Visit 3. An estimate of the variation and effect of ENVARSUS XR for CPT-III omission measures will be calculated. A sample size adjustment may be made according to the algorithm described in **Section 14.1**. Given the exploratory nature of the study, the final analyses described above will not be adjusted for this additional look. The inflation of type I error is minimum (~0.005).[64]

15. LABORATORY VALUE CRITERIA

Investigator will treat patients based on the local standards.

16 PROCEDURES AND INSTRUCTIONS

16.1 Special Safety-Related Procedures

16.1.1 Instructions for Rapid Notification of Serious Adverse Events

16.1.1.1 Reporting Responsibility

Each SAE must be reported by the Investigator to the IRB for this study according to the guidelines of the IRB of record within 24 hours of learning of its occurrence and IQVIA, the pharmacovigilance provider for intake of SAE forms contracted by Veloxis, the developer of Envarsus XR.

If the SAE is considered to be related to study drug and confirmed to be unexpected for the investigational product, IQVIA may urgently require further information from the Investigator for health authority reporting.

16.1.1.2 Reporting Procedures

Serious adverse events must be reported within 24 hours of the occurrence of the event whenever possible, but at least within 24 hours of awareness of the event. The Investigator must complete the AE/SAE CRF with as much information available at the time of completion and transmit an SAE Fax Notification Form to IQIVIA (refer to **Section 16.1.1.3** for contact numbers).

As follow-up information is received, the Investigator must update the AE/SAE CRF and/or email or fax any written/supporting documentation within 24 hours of receipt of the new information. Investigators should be ready to provide copies of any relevant data from the hospital notes (e.g., electrocardiograms [ECGs], laboratory tests, discharge summary, postmortem results, etc.), if requested. An SAE Notification Form must be completed and faxed to IQVIA when any new information is obtained, or information has been changed in the system on the AE/SAE CRF.

All SAEs should be followed up until resolution or permanent outcome of the event. Refer to the Study-specific Expedited SAE Recording and Reporting Plan for further reporting information.

16.1.1.3 Instructions for Rapid Notification of SAEs and Pregnancies

Any SAE must be reported on the AE/SAE CRF (refer to **Section 16.1.1.2**) IQVIA, the pharmacovigilance provider for intake of SAE forms contracted by Veloxis, the developer of Envarsus XR. Pregnancies and pregnancy follow up should be reported on the Pregnancy Form within the CRF. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, the presence or absence of any congenital abnormalities, birth defects, maternal or newborn complications and their relation to this study. Refer to the Pregnancy Completion Guidelines as needed for instructions for completing the Pregnancy Form.

SAE and pregnancy reporting contact numbers (telephone/facsimile) will be generated upon contract execution and including on the reporting form.

16.2 Administrative Procedures

16.2.1 Changes to the Protocol

Any change or addition to this protocol affecting the safety of patients, the scope of the investigation, or the scientific quality of the study requires approval by the IRB, If an immediate change to the protocol is felt to be necessary by the Investigator and is implemented by him for safety reasons, IRB should be notified within 10 working days.

Protocol changes affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval, but the IRB must be kept informed of such administrative changes.

16.2.2 Recording of Data and Retention of Documents

All data will be transcribed into REDCap.

Data on patients collected on CRFs during the study will be documented in an anonymous fashion and the patient will only be identified by the Patient Identification (PID) number and by initials if also required. If, as an exception, it is necessary for safety or regulatory reasons to identify the patient, the Investigator is bound to keep this information confidential.

The Investigator must maintain source documents for each patient in the study, consisting of all demographic and medical information, and must keep a copy of the signed ICF. Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the CRFs) would include patient hospital/clinic records, physicians' and nurses' notes, appointment book, original laboratory reports, and signed ICFs. All information on CRFs must be traceable to these source documents in the patient's file. Data without a written or electronic record will be defined before study start and will be recorded directly on the CRFs, which will be documented as being the source data.

Essential documents, as listed below, must be retained by the Investigator for as long as needed to comply with national and international regulations. The Investigator agrees to adhere to the document retention procedures by signing the protocol.

Essential documents include:

1. IRB approvals for the study protocol and all amendments;
2. All source documents and laboratory records;
3. CRF copies;
4. Patients' ICFs (with study number and title of study);
5. Form FDA 1572;

.

16.2.3 Auditing Procedures

The Investigator must understand that source documents for this study must be made available to the IRB and/or to health authority inspectors after appropriate notification. The verification of the CRF data must be by direct inspection of source documents. A regulatory authority may also wish to conduct an inspection (during the study or even after its completion).

16.2.4 Publication of Results

An integrated clinical and statistical report will be generated at the completion of the study. However, it is intended that the results of the study will be included on http://clinicaltrials.gov and published and/or presented at scientific meetings.

16.2.5 Disclosure and Confidentiality

By signing this protocol, the Investigator agrees to keep all information provided in strict confidence and to request similar confidentiality from his/her staff and the IRB. Study documents (protocols, CRFs, and other material) will be stored appropriately to ensure their confidentiality.

The Investigator must assure that patients' anonymity will be maintained and that their identities are protected. The Investigator will keep a patient enrollment log relating codes to the names of patients. The Investigator will maintain documents e.g., patients' signed consent forms, in strict confidence.

16.3 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and:

- ICH Guidance on Good Clinical Practice (ICH E6)
- Title 21 of the US FDA Code of Federal Regulations Parts 50 and 56
- World Medical Association. Declaration of Helsinki: Ethical principles for medical research involving human subjects, current version

16.3.1 Institutional Review Board

Before implementing this study, the protocol, the proposed ICF and other information to patients, must be reviewed by a properly constituted IRB. A signed and dated statement that the protocol and ICF have been approved by the IRB must be given to Sponsor before study initiation. The name and occupation of the chairperson and the members of the IRB must be supplied to Sponsor. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

16.3.2 Informed Consent

The Investigator or designee must explain to each patient (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each patient must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time

and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The patient should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the patient cannot read or sign the documents, oral presentation may be made or signature given by the patient's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

The ICF must be submitted by the Investigator for IRB approval. Sponsor will supply a proposed ICF which complies with regulatory requirements and is considered appropriate for the study. Any changes to the proposed ICF suggested by the Investigator must be agreed to by Sponsor before submission to the IRB and a copy of the approved version must be provided to the site monitor after IRB approval.

16.3.3 Declaration of Helsinki

The Investigator must conduct the study in accordance with the principles of the current version of the Declaration of Helsinki. Copies of the Declaration of Helsinki and amendments will be provided upon request or can be accessed via the website of the World Medical Association at http://www.wma.net/en/30publications/10policies/b3/index.html.

17 INVESTIGATOR SIGNATURE

I confirm that I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol, in accordance with ICH Guidance on Good Clinical Practice (ICH E6) and applicable local requirements.

Investigator

Signature:_____

Date:_____

Name (block letters):_____

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Appendix 1: Drugs That May Affect Tacrolimus Levels

Effects of Other Drugs/Substances on ENVARSUS XR[a]

Drug/Substance Class or Name	Drug Interaction Effect	Recommendations
Grapefruit or grapefruit juice[b]	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation)	Avoid grapefruit or grapefruit juice
Alcohol	May modify the rate of tacrolimus release	Avoid alcoholic beverages
Strong CYP3A Inducers[c] such as: Antimycobacterials (e.g., rifampin, rifabutin), anticonvulsants (e.g., phenytoin, carbamazepine, and phenobarbital), St John's Wort	May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection	Increase ENVARSUS XR dose and monitor tacrolimus whole blood trough concentrations
Strong CYP3A Inhibitors[c], such as: Protease inhibitors (e.g., nelfinavir, telaprevir, boceprevir, ritonavir), azole antifungals (e.g., voriconazole, 60osaconazole, itraconazole, ketoconazole), antibiotics (e.g., clarithromycin, troleandomycin, chloramphenicol), nefazodone	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation)	Reduce ENVARSUS XR dose (for voriconazole and 60osaconazole, give one-third of the original dose) and adjust dose based on tacrolimus whole blood trough concentrations
Mild or Moderate CYP3A Inhibitors, such as: antibiotics (e.g., erythromycin), calcium channel blockers (e.g., verapamil, diltiazem, nifedipine, nicardipine), amiodarone, danazol, ethinyl estradiol, cimetidine, lansoprazole and omeprazole, azole antifungals (e.g., clotrimazole, fluconazole)	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation)	Monitor tacrolimus whole blood trough concentrations and reduce ENVARSUS XR dose if needed
Other drugs, such as: Magnesium and aluminum hydroxide antacids Metoclopramide	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation)	Monitor tacrolimus whole blood trough concentrations and reduce ENVARSUS XR dose if needed

Mild or Moderate CYP3A Inducers, such as: Methylprednisolone, prednisone	May decrease tacrolimus concentrations	Monitor tacrolimus whole blood trough concentrations and adjust ENVARSUS XR dose if needed

[a] ENVARSUS XR dosage adjustment recommendation based on observed effect of coadministered drug on tacrolimus exposures, literature reports of altered tacrolimus exposures, or the other drug's known CYP3A inhibitor/inducer status [b] High dose or double strength grapefruit juice is a *strong* CYP3A inhibitor; low dose or single strength grapefruit juice is a *moderate* CYP3A inhibitor [c] Strong CYP3A inhibitor/inducer, based on reported effect on exposures to tacrolimus along with supporting *in vitro* CYP3A inhibitor/inducer data, or based on drug-drug interaction studies with midazolam (sensitive CYP3A probe substrate)

Appendix 2: Converting from Tacrolimus-Immediate-Release to Envarsus XR™

A reduction of 20% and/or **PI discretion** should be used when converting from TAC-IR to ENVARSUS XR. Please use the below table which rounds to the nearest 20% reduction in total daily dose (TDD).

TAC-IR TDD (mg)	ENVARSUS XR			
	TDD (mg)	Tablets Used		
		0.75 mg	1 mg	4 mg
1	0.75	1	0	0
2	1.5	2	0	0
3	2.5	2	1	0
4	3.25	3	1	0
5	4	0	0	1
6	4.75	1	0	1
7	5.5	2	0	1
8	6.25	3	0	1
9	7.25	3	1	1
10	8	0	0	2
11	8.75	1	0	2
12	9.5	2	0	2
13	10.25	3	0	2
14	11.25	3	1	2
15	12	0	0	3
16	12.75	1	0	3
17	13.5	2	0	3
18	14.5	2	1	3
19	15.25	3	1	3
20	16	0	0	4

Appendix 3: ENVARSUS XR drug insert

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ENVARSUS XR® safely and effectively. See full prescribing information for ENVARSUS XR.

ENVARSUS XR® (tacrolimus extended-release tablets), for oral use
Initial U.S. Approval: 1994

WARNING: MALIGNANCIES AND SERIOUS INFECTIONS
See full prescribing information for complete boxed warning.

Increased risk for developing serious infections and malignancies with ENVARSUS XR or other immunosuppressants that may lead to hospitalization or death. (5.1, 5.2)

----------RECENT MAJOR CHANGES----------

Indications and Usage, Prophylaxis of Organ Rejection in De Novo Kidney Transplant Patients (1.1)	12/2018
Dosage and Administration, Dosing in De Novo Kidney Transplant Patients (2.2)	12/2018

----------INDICATIONS AND USAGE---------- ENVARSUS XR is a calcineurin-inhibitor immunosuppressant indicated for:

- The prophylaxis of organ rejection in de novo kidney transplant patients in combination with other immunosuppressants (1.1)
- The prophylaxis of organ rejection in kidney transplant patients converted from tacrolimus immediate-release formulations in combination with other immunosuppressants (1.2)

----------DOSAGE AND ADMINISTRATION---------- • Take once daily on empty stomach at the same time of the day, preferably in the morning. (2.1)

- Avoid eating grapefruit or drinking grapefruit juice or alcohol. (2.1)
- African-American patients may need to be titrated to higher dosages to achieve the target tacrolimus concentrations. (2.4) • Patients with severe hepatic impairment may require a lower starting dose. (2.4)
- Frequent monitoring of trough concentrations is recommended. (2.5)

Recommended ENVARSUS XR Initial Dosage		
	Initial Oral Dosage	Whole Blood Trough Concentration Range
De novo kidney transplantation with antibody induction	0.14 mg/kg/day	Month 1: 6-11 ng/mL >Month 1: 4-11 ng/mL
Conversion from tacrolimus immediaterelease formulations	80% of the preconversion dose of tacrolimus immediaterelease	Titrate to 4-11 ng/mL

----------DOSAGE FORMS AND STRENGTHS----------
Extended-release tablets: 0.75 mg, 1 mg, 4 mg (3)

----------CONTRAINDICATIONS----------

Known hypersensitivity to tacrolimus (4)

----------WARNINGS AND PRECAUTIONS----------

- Not Interchangeable with Other Tacrolimus Products: Instruct patients or caregivers to recognize appearance of ENVARSUS XR tablets. (5.3)
- New Onset Diabetes after Transplant: Monitor blood glucose. (5.4)
- Nephrotoxicity (acute and/or chronic): May occur due to ENVARSUS XR, drug interactions or concomitant nephrotoxic drugs. Monitor renal function; consider dosage reduction. (5.5)
- Neurotoxicity: Including risk of posterior reversible encephalopathy syndrome (PRES); monitor for neurologic abnormalities; reduce dosage or discontinue ENVARSUS XR. (5.6)
- Hyperkalemia: Risk may be increased with other agents associated with hyperkalemia; monitor serum potassium levels. (5.7)
- Hypertension: May require antihypertensive therapy; monitor relevant drug interactions. (5.8)
- QT Prolongation: Consider obtaining electrocardiograms and monitoring electrolytes in patients at high risk. (5.10)
- Immunizations: Avoid live vaccines. (5.11)
- Pure Red Cell Aplasia: Consider discontinuation. (5.12)

----------ADVERSE REACTIONS----------

- De novo kidney transplant patients: Most common adverse reactions (incidence ≥15%) include diarrhea, anemia, urinary tract infection, hypertension, tremor, constipation, diabetes mellitus, peripheral edema, hyperkalemia, and headache. (6.1)
- Conversion of kidney transplant patients from immediate-release to extended-release tacrolimus: Most common adverse reactions (incidence ≥10%) include: diarrhea and blood creatinine increased. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Veloxis Pharmaceuticals, Inc. at 1-844-VELOXIS (1-844-835-6947) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- Risk of rejection with strong CYP3A inducers and risk of serious adverse reactions with strong CYP3A inhibitors: Adjust dose and monitor tacrolimus concentrations. (2.4, 5.9, 7.2)
- See Full Prescribing Information for clinically significant drug interactions. (7.1, 7.2)

----------USE IN SPECIFIC POPULATIONS---------- Pregnancy: Can cause fetal harm. Advise pregnant women of the potential risk to the fetus. (8.1, 8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: MALIGNANCIES AND SERIOUS INFECTIONS

Increased risk for developing serious infections and malignancies with ENVARSUS XR or other immunosuppressants that may lead to hospitalization or death ***[****see Warnings and Precautions (5.1, 5.2)]*.

1 INDICATIONS AND USAGE

1.1 Prophylaxis of Organ Rejection in De Novo Kidney Transplant Patients

ENVARSUS XR is indicated for the prophylaxis of organ rejection in kidney transplant patients in combination with other immunosuppressants *[see Clinical Studies (14.1)]*.

1.2 Prophylaxis of Organ Rejection in Stable Kidney Transplant Patients Converting from Immediate-Release Formulations

ENVARSUS XR is indicated for the prophylaxis of organ rejection in kidney transplant patients converted from tacrolimus immediate-release formulations, in combination with other immunosuppressants *[see Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- ENVARSUS XR (tacrolimus extended-release tablets) is not interchangeable or substitutable with tacrolimus extended-release capsules, tacrolimus capsules, and tacrolimus for oral suspension. Under or overexposure to tacrolimus may result in graft rejection or other serious adverse reactions *[see Warnings and Precautions (5.3)]*. ENVARSUS XR should not be used without the supervision of a physician with experience in immunosuppresive therapy.
- ENVARSUS XR should be taken on an empty stomach consistently at the same time of the day, preferably in the morning to ensure consistent and maximum possible drug exposure, at least 1 hour before a meal or at least 2 hours after a meal *[see Clinical Pharmacology (12.3)]*.
- Advise patients to swallow ENVARSUS XR capsules whole with fluid (preferably water); patients must not chew, divide, or crush the tablets.
- If a dose is missed, instruct the patient to take it as soon as possible within 15 hours after missing the dose. Beyond the 15-hour time frame, instruct the patient to wait until the usual scheduled time to take the next regular daily dose. Instruct the patient not to double the next dose.
- Patients should avoid eating grapefruit or drinking grapefruit juice or alcoholic beverage while taking ENVARSUS XR *[see Drug Interactions (7.2)]*.

2.2 Dosing in De Novo Kidney Transplant Patients

The recommended starting dose of ENVARSUS XR in de novo kidney transplant patients is 0.14 mg/kg/day. Titrate ENVARSUS XR dosage based on clinical assessments of rejection and tolerability and to achieve whole blood trough concentration ranges (see **Table 1**).

Table 1. Recommended Tacrolimus Whole Blood Trough Concentration Ranges in Kidney Transplant Patients with Antibody Induction

Time Period Post Transplant	Target Tacrolimus Whole Blood Trough Concentration Ranges

During Month 1	6 to 11 ng/mL
> Month 1	4 to 11 ng/mL

2.3 Dosing for Conversion from Tacrolimus Immediate-Release Formulations

To convert from a tacrolimus immediate-release product to ENVARSUS XR, administer ENVARSUS XR once daily at a dose that is 80% of the total daily dose of the tacrolimus immediate-release product. Monitor tacrolimus whole blood trough concentrations and titrate ENVARSUS XR dosage to achieve whole blood trough concentration ranges of 4 to 11 ng/mL.

2.4 Dosing Adjustments in African-American Patients, Patients with Hepatic Impairment, Drug Interactions African-American patients, compared to Caucasian patients, may need to be titrated to higher ENVARSUS XR dosages to attain comparable trough concentrations *[see Use in Specific Populations (8.8), Clinical Pharmacology (12.3)].*

Due to reduced clearance and prolonged half-life seen in patients with severe hepatic impairment (Child-Pugh ≥10) these patients may require a lower starting dosage of ENVARSUS XR *[see Clinical Pharmacology (12.3)].*

Dose adjustments of ENVARSUS XR may be necessary when administered concomitantly with CYP3A inducers or CYP3A inhibitors *[see Warnings and Precautions (5.9), Drug Interactions (7.2)].*

2.5 Therapeutic Drug Monitoring

Measure tacrolimus whole blood trough concentrations at least two times on separate days during the first week after initiation of dosing and after any change in dosage, after a change in co-administration of CYP3A inducers and/or inhibitors *[see Drug Interactions (7)],* or after a change in renal or hepatic function. When interpreting measured concentrations, consider that the time to achieve tacrolimus steady state is approximately 7 days after initiating or changing the ENVARSUS XR dose.

Monitor tacrolimus whole blood trough concentrations using a validated assay [e.g., immunoassays or high-performance liquid chromatography with tandem mass spectrometric detection (HPLC/MS/MS)]. The immunosuppressive activity of tacrolimus is mainly due to the parent drug rather than to its metabolites. Immunoassays may react with metabolites as well as the parent drug. Therefore, whole blood tacrolimus trough concentrations obtained with immunoassays may be numerically higher than concentrations obtained with an assay using HPLC/MS/MS. Comparison of the whole blood tacrolimus trough concentrations of patients to those described in the prescribing information and other published literature must be made with knowledge of the assay method(s) employed.

3 DOSAGE FORMS AND STRENGTHS

Oval, white to off-white uncoated extended-release tablets debossed with “TCS” on one side:

- 0.75 mg extended-release tablet: debossed with “0.75” on the other side.
- 1 mg extended-release tablet: debossed with “1” on the other side.
- 4 mg extended-release tablet: debossed with “4” on the other side.

4 CONTRAINDICATIONS

ENVARSUS XR is contraindicated in patients with known hypersensitivity to tacrolimus.

5 WARNINGS AND PRECAUTIONS

5.1 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 by wearing protective clothing and using a sunscreen with a high protection factor.

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.

5.2 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),
- JC 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 *[see Adverse Reactions (6.1)]*.

5.3 Not Interchangeable with Other Tacrolimus Products-Medication Errors

Medication errors, including substitution and dispensing errors, between tacrolimus capsules and tacrolimus extendedrelease capsules 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 extended-release capsules, tacrolimus capsules or tacrolimus for oral suspension. Instruct patients and caregivers to recognize the appearance of ENVARSUS XR tablet *[see Dosage Forms and Strengths (3)]* and to confirm with their healthcare provider if a different product is dispensed or if dosing instructions have changed. **5.4 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 *[see Adverse Reactions (6.1) and Use in Specific Populations (8.8)]*.

5.5 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) *[see Adverse Reactions (6.1, 6.2), Drug Interactions (7.2)]*. Monitor renal function and consider dosage reduction if nephrotoxicity occurs.

5.6 Neurotoxicity

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 *[see Adverse Reactions (6.1, 6.2)]*. 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.

5.7 Hyperkalemia

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 *[see Adverse Reactions (6.1)]*. Monitor serum potassium levels periodically during treatment.

5.8 Hypertension

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 *[see Drug Interactions (7.2)]*.

5.9 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, 5.10)]*. Therefore, adjust
ENVARSUS XR dose and monitor tacrolimus whole blood trough concentrations when coadministering ENVARSUS XR
with strong CYP3A inhibitors (e.g., including but not limited to telaprevir, boceprevir, ritonavir, ketoconazole, itraconazole, voriconazole, clarithromycin) or strong CYP3A inducers (e.g., including but not limited to rifampin, rifabutin) *[see Dosage and Administration (2.3, 2.5), Drug Interactions (7.2)]*.

5.10 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 *[see Dosage and Administration (2.5), Drug Interactions (7.2)]*.

5.11 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.

5.12 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.

6 ADVERSE REACTIONS

The following clinically significant adverse drug reactions are discussed in greater detail in other sections of the labeling:

- Lymphoma and Other Malignancies *[see Boxed Warning, Warnings and Precautions (5.1)]* • Serious Infections *[see Boxed Warning, Warnings and Precautions (5.2)]* • New Onset Diabetes after Transplant *[see Warnings and Precautions (5.4)]*
- Nephrotoxicity due to ENVARSUS XR and Drug Interactions *[see Warnings and Precautions (5.5)]*
- Neurotoxicity *[see Warnings and Precautions (5.6)]* • Hyperkalemia *[see Warnings and Precautions (5.7)]* • Hypertension *[see Warnings and Precautions (5.8)]* • QT Prolongation *[see Warnings and Precautions (5.10)]* • Pure Red Cell Aplasia *[see Warnings and Precautions (5.12)]*

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. In addition, the clinical studies were not designed to establish comparative differences across study arms with regards to the adverse reactions discussed below.

Study 1- Phase 3 Clinical Study in De Novo Kidney Transplant Recipients

Study 1 (NCT 01187953), was a Phase 3 randomized study in de novo kidney transplant patients that were treated with ENVARSUS XR (N=268) or tacrolimus [immediate-release] capsules (N=275) and concomitant immunosuppressants in a double-blind, randomized, multinational study *[see Clinical Studies (14.1)]*. The proportion of patients who discontinued treatment due to adverse reactions was 8.6% and 9.8% in the ENVARSUS XR and tacrolimus capsules treatment groups, respectively, through 12 months of treatment. The

most common adverse reactions leading to discontinuation of study drug in the ENVARSUS XR treatment group were esophagitis, polyomavirus-associated nephropathy, graft dysfunction, complications of transplanted kidney, and diabetes mellitus, each resulting in 0.7% discontinuations among ENVARSUS XR treatment patients. In Study 1, de novo kidney transplant patients who received a starting dose of 0.17 mg/kg/day, which is higher than the recommended ENVARSUS XR starting dose of 0.14 mg/kg/day, exceeded the recommended target tacrolimus trough concentrations as high as 57 ng/mL during the first 1 to 2 weeks post-transplant *[see Dosage and Administration (2.2)]*.

Infections

The overall incidence of infections, serious infections, and infections with identified etiology reported in de novo kidney transplant recipients treated with ENVARSUS XR or tacrolimus [immediate-release] capsules in Study 1 are shown in **Table 2**.

Table 2 Percentage of Patients with Infections Through 1 Year Post-Kidney Transplant in Study 1 [a]

	ENVARSUS XR ± steroids, IL-2 receptor antagonist induction therapy, MMF/MPS or AZA **N=268**	**Tacrolimus [immediaterelease] capsules ± steroids, IL-2 receptor antagonist induction therapy, MMF/MPS or AZA** **N=275**
All Infections	70%	65%
Urinary Tract Infections	29%	27%
Respiratory Infections	28%	24%
Bacterial Infections	13%	18%
Cytomegalovirus Infections	11%	9%
Fungal Infections	9%	8%
Gastrointestinal Infections	6%	4%
BK virus [b]	6%	9%
Serious Infections	26%	24%

MMF/MPS- Mycophenolate mofetil/mycophenolate sodium; AZA-azathioprin

[a] Study 1 was not designed to support comparative claims of ENVARSUS XR compared to tacrolimus [immediate-release] capsules for the adverse reactions reported in this table.

[b] BK virus-associated nephropathy (BKVAN) occurred in 1.5% (4/268) and 0.7% (2/275) in the ENVARSUS XR and tacrolimus capsules treatment groups, respectively.

New Onset Diabetes After Transplantation

New onset diabetes after transplantation (NODAT) was defined by the composite occurrence of fasting plasma glucose values ≥126 mg/dL, 2-hour post-prandial plasma glucose of at least 200 mg/dL (in oral glucose tolerance test) on two or more consecutive occasions post-baseline, insulin requirement for ≥31 days, an oral hypoglycemic agent use ≥31 days, or HbA_{1c} ≥6.5% (at least 3 months after randomization) among kidney transplant patients with no medical history of diabetes. The incidence of NODAT for Study 1 through one year post-transplant is summarized in **Table 3** below *[see Warnings and Precautions (5.4)]*.

Table 3. Percentage of Patients with NODAT Through 1 Year Post-Kidney Transplant in Study 1 [a]

	ENVARSUS XR ± steroids, IL-2 receptor antagonist induction therapy, MMF/MPS or AZA (N=88)	**Tacrolimus [immediaterelease] capsules ± steroids, IL-2 receptor antagonist induction therapy, MMF/MPS or AZA (N=74)**
Composite NODAT [b]	21%	15%
HbA_{1c} ≥6.5%	13%	8%
Fasting Plasma Glucose Values ≥126 mg/dL on 2 consecutive occurrences	8%	11%
Oral hypoglycemic use	7%	5%
Insulin use ≥31 days	1%	4%

MMF/MPS- Mycophenolate mofetil/mycophenolate sodium; AZA-azathioprin

[a] Study 1 was not designed to support comparative claims of ENVARSUS XR compared to tacrolimus [immediate-release] capsules for the adverse reactions reported in this table. [b] Analyses restricted to patients at risk for NODAT.

Common Adverse Reactions

The incidence of adverse reactions that occurred in ≥10% of ENVARSUS XR-treated patients compared to tacrolimus [immediate-release] capsules through one year of treatment in Study 1 is shown by treatment group in **Table 4**.

Table 4. Adverse Reactions (≥ 10%) in Kidney Transplant Patients Through 1 Year Post-Transplant in Study 1[a]

Adverse Reaction	**ENVARSUS XR N=268**	**Tacrolimus [immediaterelease] capsules N=275**
Diarrhea	31%	34%

Anemia	26%	29%
Urinary Tract Infection	25%	25%
Hypertension	23%	23%
Tremor	19%	17%
Constipation	18%	25%
Diabetes Mellitus	16%	14%
Peripheral Edema	16%	21%
Hyperkalemia	15%	11%
Headache	15%	10%
Hypophosphatemia	13%	15%
Leukopenia	13%	14%
Nausea	13%	15%
Insomnia	13%	11%
Adverse Reaction	**ENVARSUS XR N=268**	**Tacrolimus [immediaterelease] capsules N=275**
Increased Blood Creatinine	12%	14%
Hypomagnesmia	12%	12%
Hypokalemia	12%	12%
Hyperglycemia	11%	12%

[a] Study 1 was not designed to support comparative claims of ENVARSUS XR compared to tacrolimus [immediate-release] capsules for the adverse reactions reported in this table.

Study 2- Phase 2 Clinical Study in De Novo Kidney Transplant Recipients

Study 2 (NCT00765661) was an open-label Phase 2 study conducted in de novo kidney transplant patients randomized to once daily ENVARSUS XR (N=32) or twice daily tacrolimus [immediate-release] capsules (N=31). The study was conducted in the US and patients received an organ from a deceased or living donor. Pharmacokinetics were evaluated during the first 2 weeks with an additional 50-week treatment and follow-up to evaluate safety and efficacy *[see Clinical Studies (14.1)]*.

The starting dosage was 0.14 mg/kg/day (given once daily) for ENVARSUS XR and 0.2 mg/kg/day (given twice daily) for tacrolimus [immediate-release] capsules. On Day 2 predose, the proportion of patients in the

ENVARSUS XR group with tacrolimus trough concentration that were within, above, and below 6 to 11 ng/mL was 53%, 11%, and 37%, respectively. The starting dose of 0.14 mg/kg/day in Study 2 formed the basis of dosing recommendations in de novo kidney transplant patients.

There were no deaths or graft failures in Study 2. Two patients in each arm discontinued due to adverse events. The most common adverse reactions included infections and cardiovascular events, and were generally similar to those reported in Study 1.

Study 3- Phase 3 Clinical Studies in Stable Kidney Transplant Recipients Converted from Tacrolimus Capsules
In Study 3 (NCT00817206) stable kidney transplant patients were treated with ENVARSUS XR (N=162) or tacrolimus [immediate-release] capsules (N=162) and concomitant immunosuppressants in an open-label, randomized, multinational study *[see Clinical Studies (14.2)]*. The proportion of patients who discontinued treatment due to adverse reactions was 7.4% and 1.2% in the ENVARSUS XR and tacrolimus capsules treatment groups, respectively, through 12 months of treatment. The most common adverse reactions leading to discontinuation of study drug in the ENVARSUS XR treatment group was cardiac arrest (2 events).

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 capsules are shown in **Table 5**.

Table 5. Percentage of Stable Patients with Infections Through 1 Year Post-Treatment in Study 3 [a]

	ENVARSUS XR ± steroids, MMF/MPS or AZA **N=162**	**Tacrolimus [immediaterelease] capsules± steroids, MMF/MPS or AZA** **N=162**
All Infections	46%	48%
Respiratory Infections	26%	28%
Urinary Tract Infections	10%	14%
Bacterial Infections	7%	5%
Fungal Infections	4%	4%
Gastrointestinal Infections	4%	5%
BK virus [b]	2%	2%
Cytomegalovirus Infections	2%	1%
Serious Infections	8%	9%

MMF/MPS- Mycophenolate mofetil/mycophenolate sodium; AZA-azathioprine

[a] The stable kidney transplant study was not designed to support comparative claims of ENVARSUS XR compared to tacrolimus capsules 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 capsules treatment groups, respectively.

New Onset Diabetes After Transplantation

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 HbA_{1c} ≥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 6** below *[see Warnings and Precautions (5.4)]*.

Table 6. Percentage of Stable Patients with NODAT Through 1 Year Post-Treatment in Study 3 [a]

	ENVARSUS XR ± steroids, MMF/MPS or AZA (N=90)	**Tacrolimus [immediaterelease] capsules ± steroids, MMF/MPS or AZA (N=95)**
Composite NODAT [b]	10%	11%
HbA_{1c} ≥6.5%	3%	7%
Fasting Plasma Glucose Values ≥126 mg/dL on 2 consecutive occurrences	8%	6%
Oral hypoglycemic use	1%	1%
Insulin use ≥31 days	1%	0%

MMF/MPS- Mycophenolate mofetil/mycophenolate sodium; AZA-azathioprine

[a] The stable kidney transplant study was not designed to support comparative claims of ENVARSUS XR compared to tacrolimus capsules for the adverse reactions reported in this table. [b] Analyses restricted to patients at risk for NODAT.

Common Adverse Reactions

In Study 3, the most common (≥10%) adverse reactions observed with Envarsus XR were diarrhea (14%), and blood creatinine increased (12%).

6.2 Postmarketing Experience

The following adverse reactions have been reported from marketing experience with tacrolimus in the U.S. and outside the U.S. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following reactions have been included due to either their seriousness, frequency of reporting or strength of causal connection to ENVARSUS XR:

- Blood and Lymphatic System Disorders : Agranulocytosis, decreased blood fibrinogen, disseminated intravascular coagulation, hemolytic anemia, hemolytic uremic syndrome, leukopenia, pancytopenia, prolonged activated partial thromboplastin time, pure red cell aplasia *[see Warnings and Precautions (5.12)],* thrombocytopenic purpura, thrombotic thrombocytopenic purpura
- Cardiac Disorders: Atrial fibrillation, atrial flutter, cardiac arrhythmia, cardiac arrest, electrocardiogram T wave abnormal, flushing, myocardial hypertrophy, myocardial infarction, myocardial ischaemia, pericardial effusion, QT prolongation, supraventricular extrasystoles, supraventricular tachycardia, Torsade de Pointes, deep limb venous thrombosis, ventricular fibrillation
- Ear Disorders: Hearing loss including deafness
- Eye Disorders: Blindness, photophobia, optic atrophy
- Gastrointestinal Disorders: Abdominal pain, colitis, dysphagia, gastrointestinal perforation, impaired gastric emptying, intestinal obstruction, mouth ulceration, peritonitis, stomach ulcer
- Hepatobiliary Disorders: Bile duct stenosis, cholangitis, cirrhosis, fatty liver, hepatic cytolysis, hepatic failure, hepatic necrosis, hepatic steatosis, jaundice, hemorrhagic pancreatitis, necrotizing pancreatitis, venoocclusive liver disease
- Hypersensitivity Reactions: Hypersensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria
- Immune System Disorders: Graft versus host disease (acute and chronic)
- Metabolism and Nutrition Disorders: Glycosuria, increased amylase, pancreatitis
- Musculoskeletal and Connective Tissue Disorders: Myalgia, polyarthritis, rhabdomyolysis
- Neoplasms: Lymphoma including EBV-associated lymphoproliferative disorder, PTLD *[see Warnings and Precautions (5.1)]*; leukemia
- Nervous System Disorders: Carpal tunnel syndrome, cerebral infarction, coma, dysarthria, flaccid paralysis, hemiparesis, mental disorder, mutism, nerve compression, posterior reversible encephalopathy syndrome (PRES) *[see Warnings and Precautions (5.6)],* progressive multifocal leukoencephalopathy (PML) sometimes fatal *[see Warnings and Precautions (5.2)],* quadriplegia, speech disorder, status epilepticus, syncope
- Renal and Urinary Disorder: Acute renal failure, hemorrhagic cystitis, hemolytic uremic syndrome, micturition disorder
- Respiratory, Thoracic and Mediastinal Disorders: Acute respiratory distress syndrome, interstitial lung disease, lung infiltration, pulmonary embolism, pulmonary hypertension, respiratory distress, respiratory failure
- Skin and Subcutaneous Tissue Disorders: Hyperpigmentation, photosensitivity, pruritus, rash

7 DRUG INTERACTIONS

7.1 Mycophenolic Acid

When ENVARSUS XR is prescribed with a given dose of mycophenolic acid (MPA) product, exposure to MPA is higher with ENVARSUS XR coadministration than with cyclosporine coadministration with MPA, because cyclosporine interrupts the enterohepatic recirculation of MPA while tacrolimus does not. Monitor for MPA associated adverse reactions and reduce the dose of concomitantly administered MPA products as needed.

7.2 Effects of Other Drugs/Substances on ENVARSUS XR

Table 7. Effects of Other Drugs/Substances on ENVARSUS XR[a, d]

Drug/Substance Class or Name	Drug Interaction Effect	Recommendations
Grapefruit or grapefruit juice[b]	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see Warnings and Precautions (5.6, 5.9, 5.10)]*	Avoid grapefruit or grapefruit juice
Alcohol	May modify the rate of tacrolimus release	Avoid alcoholic beverages
Strong CYP3A Inducers[c,] such as: Antimycobacterials (e.g., rifampin, rifabutin), anticonvulsants (e.g., phenytoin, carbamazepine and phenobarbital), St John's Wort	May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection *[see Warnings and Precautions (5.9)]*	Increase ENVARSUS XR dose and monitor tacrolimus whole blood trough concentrations *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*
Strong CYP3A Inhibitors[c,], such as: Protease inhibitors (e.g., nelfinavir, telaprevir, boceprevir, ritonavir), azole antifungals (e.g., voriconazole, posaconazole, itraconazole, ketoconazole), antibiotics (e.g., clarithromycin, troleandomycin, chloramphenicol), nefazodone	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see Warnings and Precautions (5.6, 5.9, 5.10)]*	Reduce ENVARSUS XR dose (for voriconazole and posaconazole, give one-third of the original dose) and adjust dose based on tacrolimus whole blood trough concentrations *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*
Mild or Moderate CYP3A Inhibitors, such as: antibiotics (e.g., erythromycin), calcium channel blockers (e.g., verapamil, diltiazem, nifedipine, nicardipine), amiodarone, danazol, ethinyl estradiol, cimetidine, lansoprazole and omeprazole, azole antifungals (e.g., clotrimazole, fluconazole)	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see Warnings and Precautions (5.6, 5.9, 5.10)]*	Monitor tacrolimus whole blood trough concentrations and reduce ENVARSUS XR dose if needed *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*

Other drugs, such as: Magnesium and aluminum hydroxide antacids Metoclopramide	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see Warnings and Precautions (5.6 and 5.10)]*	Monitor tacrolimus whole blood trough concentrations and reduce ENVARSUS XR dose if needed *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*
Mild or Moderate CYP3A Inducers, such as: Methylprednisolone, prednisone	May decrease tacrolimus concentrations	Monitor tacrolimus whole blood trough concentrations and adjust ENVARSUS XR dose if needed *[see Dosage and Administration (2.5)]*

[a] ENVARSUS XR dosage adjustment recommendation based on observed effect of coadministered drug on tacrolimus exposures *[see Clinical Pharmacology (12.3)]*, literature reports of altered tacrolimus exposures, or the other drug's known CYP3A inhibitor/inducer status [b] High dose or double strength grapefruit juice is a *strong* CYP3A inhibitor; low dose or single strength grapefruit juice is a *moderate* CYP3A inhibitor

[c] Strong CYP3A inhibitor/inducer, based on reported effect on exposures to immediate-release tacrolimus along with supporting *in vitro* CYP3A inhibitor/inducer data, or based on drug-drug interaction studies with midazolam (sensitive CYP3A probe substrate)

[d] No drug-drug interaction studies were conducted with ENVARSUS XR.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy registry that monitors pregnancy outcomes in women exposed to ENVARSUS XR during pregnancy. The Transplantation Pregnancy Registry International (TPRI) is a voluntary pregnancy exposure registry that monitors outcomes of pregnancy in female transplant recipients and those fathered by male transplant recipients exposed to immunosuppresants including tacrolimus. Healthcare providers are encouraged to advise their patients to register by contacting the Transplantation Pregnancy Registry International at 1-877-955-6877 or https://www.transplantpregnancyregistry.org.

Risk Summary

Tacrolimus can cause fetal harm when administered to a pregnant woman. Data from postmarketing surveillance and TPRI suggest that infants exposed to tacrolimus in utero are at a risk of prematurity, birth defects/congenital anomalies, low birth weight, and fetal distress *[see Human Data]*. Advise pregnant women of the potential risk to the fetus.

Administration of oral tacrolimus to pregnant rabbits and rats throughout the period of organogenesis was associated with maternal toxicity/lethality, and an increased incidence of abortion, malformation and embryofetal death at clinically relevant doses (0.7 to 3.7 times the recommended clinical dose [0.14 mg/kg/day], on a mg/m² basis). Administration of oral tacrolimus to pregnant rats after organogenesis and throughout lactation produced maternal toxicity, effects on parturition, reduced pup viability and reduced pup weight at clinically relevant doses (1.2 to 3.7 times the recommended clinical dose, on a mg/m² basis). Administration of oral tacrolimus to rats prior to mating, and throughout gestation and lactation produced maternal toxicity/lethality, marked effects on

parturition, embryofetal loss, malformations, and reduced pup viability at clinically relevant doses (1.2 to 3.7 times the recommended clinical dose, on a mg/m² basis).

Interventricular septal defects, hydronephrosis, craniofacial malformations and skeletal effects were observed in offspring that died *[see Animal Data]*.

The background risk of major birth defects and miscarriage in the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4 % and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk

Risks during pregnancy are increased in organ transplant recipients.

The risk of premature delivery following transplantation is increased. Pre-existing hypertension and diabetes confer additional risk to the pregnancy of an organ transplant recipient. Pre-gestational and gestational diabetes are associated with birth defects/congenital anomalies, hypertension, low birth weight and fetal death.

Cholestasis of pregnancy (COP) was reported in 7% of liver or liver-kidney (LK) transplant recipients, compared with approximately 1% of pregnancies in the general population. However, COP symptoms resolved postpartum and no long term effects on the offspring were reported.

Maternal Adverse Reactions

ENVARSUS XR may increase hyperglycemia in pregnant women with diabetes (including gestational diabetes). Monitor maternal blood glucose levels regularly *[see Warnings and Precautions (5.4)]*.

ENVARSUS XR may exacerbate hypertension in pregnant women and increase pre-eclampsia. Monitor and control blood pressure *[see Warnings and Precautions (5.7, 5.8)]*.

Fetal/Neonatal Adverse Reactions

Renal dysfunction, transient neonatal hyperkalemia and low birth weight have been reported at the time of delivery in infants of mothers taking ENVARSUS XR.

Labor or Delivery

There is an increased risk for premature delivery (<37 weeks) following transplantation and maternal exposure to ENVARSUS XR.

Data

Human

Data

There are no adequate and well controlled studies on the effects of tacrolimus in human pregnancy.

Safety data from the TPRI and postmarketing surveillance suggest infants exposed to tacrolimus in utero have an increased risk for miscarriage, pre-term delivery (<37 weeks), low birth weight (<2500 g), birth defects/congenital anomalies and fetal distress.

TPRI reported 450 and 241 total pregnancies in kidney and liver transplant recipients exposed to tacrolimus, respectively. The TPRI pregnancy outcomes are summarized in **Table 8**. In the table below, the number of

recipients exposed to tacrolimus concomitantly with mycophenolic acid (MPA) products during the preconception and first trimester periods is high (27% and 29% for renal and liver transplant recipients, respectively). Because MPA products may also cause birth defects, the birth defect rate may be confounded and this should be taken into consideration when reviewing the data, particularly for birth defects. Birth defects observed include cardiac malformations, craniofacial malformations, renal/urogenital disorders, skeletal abnormalities, neurological abnormalities, and multiple malformations.

Table 8. TPRI Reported Pregnancy Outcomes in Transplant Recipients with Exposure to Tacrolimus

	Kidney	Liver
Pregnancy Outcomes*	**462**	**253**
Miscarriage	24.5%	25%
Live births	**331**	**180**
Pre-term delivery (< 37 weeks)	49%	42%
Low birth weight (< 2500 g)	42%	30%
Birth defects	8%†	5%

*Includes multiple births and terminations.

†Birth defect rate confounded by concomitant MPA products exposure in over half of offspring with birth defects.

Additional information reported by TPRI in pregnant transplant patients receiving tacrolimus included diabetes during pregnancy in 9% of kidney recipients and 13% of liver recipients and hypertension during pregnancy in 53% of kidney recipients and 16.2% of liver recipients.

Animal Data

Administration of oral tacrolimus to pregnant rabbits throughout organogenesis produced maternal toxicity and abortion at
0.32 mg/kg (0.7 times the recommended clinical dose based on body surface area). At 1 mg/kg (2.3 times the recommended clinical dose) embryofetal lethality and fetal malformations (ventricular hypoplasia, interventricular septal defect, bulbous aortic arch, stenosis of ductus arteriosus, omphalocele, gallbladder agenesis, skeletal anomalies) were observed. Administration of 3.2 mg/kg oral tacrolimus (3.7 times the recommended clinical dose) to pregnant rats throughout organogenesis produced maternal toxicity/lethality, embryofetal lethality and decreased fetal body weight in the offspring of C-sectioned dams; and decreased pup viability and interventricular septal defect in offspring of dams that delivered.

In a peri/postnatal development study, oral administration of tacrolimus to pregnant rats during late gestation (after organogenesis) and throughout lactation produced maternal toxicity, effects of parturition, and reduced pup viability at 3.2 mg/kg (3.7 times the recommended clinical dose); among these pups that died early, an increased incidence of kidney hydronephrosis was observed. Reduced pup weight was observed at 1mg/kg (1.2 times the recommended clinical dose). Administration of oral tacrolimus to rats prior to mating, and throughout gestation and lactation produced maternal toxicity/lethality, embryofetal loss and reduced pup viability at 3.2 mg/kg (3.7 times the recommended clinical dose). Interventricular septal defects, hydronephrosis, craniofacial malformations and skeletal effects were observed in offspring that died. Effects on parturition (incomplete delivery of nonviable pups) were observed at 1 mg/kg (1.2 times the recommended clinical dose) *[see Nonclinical Toxicology (13.1)]*.

8.2 Lactation

Risk Summary

Controlled lactation studies have not been conducted in humans; however tacrolimus has been reported to be present in human milk. The effects of tacrolimus on the breastfed infant, or on milk production have not been assessed. Tacrolimus is excreted in rat milk and in peri-/postnatal rat studies, exposure to tacrolimus during the postnatal period was associated with developmental toxicity in the offspring at clinically relevant doses *[see Pregnancy (8.1), Nonclinical Toxicology (13.1)]*.

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for ENVARSUS XR and any potential adverse effects on the breastfed child from ENVARSUS XR or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

ENVARSUS XR can cause fetal harm when administered to pregnant women. Advise female and male patients of reproductive potential to speak with their healthcare provider on family planning options including appropriate contraception prior to starting treatment with ENVARSUS XR *[see Use in Specific Populations (8.1), Nonclinical Toxicology (13.1)]*.

Infertility

Based on findings in animals, male and female fertility may be compromised by treatment with ENVARSUS XR *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of ENVARSUS XR in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of ENVARSUS XR did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In Studies 1, 2 and 3, there were 37 patients 65 years of age and older, and no patients were over 75 years *[see Clinical Studies (14)]*. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Impairment

The pharmacokinetics of tacrolimus in patients with renal impairment was similar to that in healthy subjects with normal renal function. However, due to its potential for nephrotoxicity, monitoring of renal function in patients with renal impairment is recommended; tacrolimus dosage should be reduced if indicated *[see Warnings and Precautions (5.5) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

The mean clearance of tacrolimus was substantially lower in patients with severe hepatic impairment (mean Child-Pugh score: >10) compared to healthy subjects with normal hepatic function *[see Clinical Pharmacology (12.3)]*. With greater tacrolimus whole blood trough concentrations in patients with severe hepatic impairment, there is a greater risk of adverse reactions and dosage reduction is recommended *[see Dosage and Administration (2.4)]*.

For patients with moderate hepatic impairment, monitor tacrolimus whole blood trough concentrations. For patients with mild hepatic impairment, no dosage adjustments are needed.

8.8 Race

African-American patients may need to be titrated to higher ENVARSUS XR dosages to attain comparable trough concentrations compared to Caucasian patients. The pharmacokinetics of ENVARSUS XR were evaluated in a study of 46 stable African-American kidney transplant recipients converted from tacrolimus immediate-release to ENVARSUS XR and indicated that an 80% conversion factor is appropriate for African-American patients *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

African-American and Hispanic kidney transplant patients are at an increased risk for new onset diabetes after transplant. Monitor blood glucose concentrations and treat appropriately *[see Warnings and Precautions (5.4)]*.

10 OVERDOSAGE

Postmarketing cases of overdose with tacrolimus have been reported. Overdosage adverse reactions included:

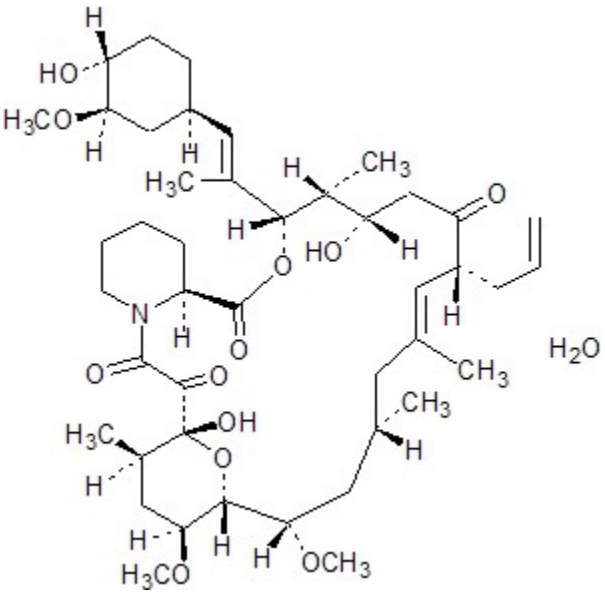
- nervous system disorders (tremor, headache, confusional state, balance disorders, encephalopathy, lethargy, and somnolence)
- gastrointestinal disturbances (nausea, vomiting, and diarrhea)
- abnormal renal function (increased blood urea nitrogen and elevated serum creatinine)
- urticaria
- hypertension
- peripheral edema, and
- infections (one fatal postmarketing case of bilateral pneumopathy and CMV infection was attributed to tacrolimus extended-release capsules overdose).

Based on the poor aqueous solubility and extensive erythrocyte and plasma protein binding, it is anticipated that tacrolimus is not dialyzable to any significant extent; there is no experience with charcoal hemoperfusion. The oral use of activated charcoal has been reported in treating acute overdoses, but experience has not been sufficient to warrant recommending its use. General supportive measures and treatment of specific symptoms should be followed in all cases of overdosage.

11 DESCRIPTION

Tacrolimus is the active ingredient in ENVARSUS XR. Tacrolimus is a calcineurin-inhibitor immunosuppressant produced by *Streptomyces tsukubaensis*. Chemically, tacrolimus is designated as [3*S*-[3*R**[*E*(1*S**,3*S**,4*S**)], 4*S**,5*R**,8*S**,9*E*,12*R**,14*R**,15*S**,16*R**,18*S**,19*S**,26a*R**]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclo-hexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-*c*][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate.

The chemical structure of tacrolimus is:



Tacrolimus has an empirical formula of $C_{44}H_{69}NO_{12}•H_2O$ and a formula weight of 822.03. Tacrolimus appears as white crystals or crystalline powder. It is practically insoluble in water, freely soluble in ethanol, and very soluble in methanol and chloroform.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin (an ubiquitous mammalian intracellular enzyme) is then formed and the phosphatase activity of calcineurin inhibited. Such inhibition prevents the dephosphorylation and translocation of various factors such as the nuclear factor of activated T-cells (NF-AT) and nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB).

Tacrolimus inhibits the expression and/or production of several cytokines that include interleukin (IL)-1 beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, gamma interferon, tumor necrosis factor-alpha, and granulocyte macrophage colony stimulating factor. Tacrolimus also inhibits IL-2 receptor expression and nitric oxide release, induces apoptosis and production of transforming growth factor-beta that can lead to immunosuppressive activity. The net result is the inhibition of T-lymphocyte activation and proliferation as well as T-helper-cell-dependent B-cell response (i.e., immunosuppression).

12.3 Pharmacokinetics

Table 9 summarizes the pharmacokinetic (PK) parameters of tacrolimus following oral administration of once-daily ENVARSUS XR in healthy subjects and in kidney transplant patients, under fasted conditions. Whole blood tacrolimus concentrations in the pharmacokinetic studies were measured using validated HPLC/MS/MS assays.

Table 9. Pharmacokinetic Parameters of ENVARSUS XR by Study Day in Healthy Subjects and Kidney Transplant Patients Under Fasted Conditions

Population	ENVARSUS XR Dose	Day[b]	Pharmacokinetic Parameters of ENVARSUS XR			
			C_{max}[c] (ng/mL)	T_{max}[d] (hr)	AUC_{24c} (ng•hr/mL)	C_{24h} (ng/mL)
Healthy Subjects[a] (n=19)	2 mg 2 mg	Day 1 Day 10	11.9 ± 3.8 8.3 ± 2.9	14.0 [6 - 28] 8.0 [1.0-12.0]	50 ± 14 140 ± 50	1.8 ± 0.6 4.6 ± 1.7
Adult Kidney[a] *De novo*[e] (n=21)	11.8 mg[f] 10 mg 9.5 mg	Day 1 Day 7 Day 14	11.8 ± 7.2 25.1 ± 16.3 27.1 ± 13.4	8.0 [4-24] 6.0 [2-12] 4.0 [1-8]	138 ± 80 335 ± 129 371 ± 104	5.2 ± 2.7 9.9 ± 4.4 11.4 ± 4.1[j]
Adult Kidney[a] *De novo* (n=10)	15.5 mg[g] 11.4 mg 11.1 mg	Day 1 Day 14 Day 28	33.6 ± 21.8 31.1 ± 14.6 35.9± 18.7	6.0 [4-24] 4.0 [1-18] 4.0 [1-14]	377 ± 257 376 ± 140 396 ± 150	11.0 ± 6.1 9.1 ± 3.0 10.5 ± 3.2
Adult Kidney[a] (≥ 6 months posttransplant) (n=47)	5.3 mg	Day 7[i]	13.5 ± 4.8	6.0 [1 - 16]	216 ± 63	7.0 ± 2.3[j]
Adult AfricanAmerican Kidney[k] (≥ 6 months posttransplant) (n=46)	7.8 mg	Day 7[i]	18.4 ± 7.2	5.0 [1 - 16]	272 ± 97	7.8 ± 2.9[j]

a) Healthy adult subjects (administered mg/day dose); Adult *de novo* kidney transplant patients (group average of administered mg/day dose); Adult kidney ≥ 6 months post-transplant (group average of administered mg/day dose of ENVARSUS XR, following conversion to 67% to 80% of the daily tacrolimus immediate -release capsules dose)
b) Day of ENVARSUS XR dosing and PK profiling
c) Arithmetic means ± S.D.
d) Median [range]
e) "*De novo*" refers to immunosuppression starting at the time of transplantation
f) Starting ENVARSUS XR dose = 0.14 mg/kg/day
g) Starting ENVARSUS XR dose = 0.17 mg/kg/day. *De novo* kidney transplant patients who received ENVARSUS XR starting dose of 0.17 mg/kg/day achieved higher than recommended target tacrolimus trough concentrations, as high as 57 ng/mL during the first 1 to 2 weeks posttransplant.
h) Tacrolimus trough concentration before the next dose
i) After 7 days of stable dosing with ENVARSUS XR
j) AUC_{0-24} –to- C_{24} correlation coefficient (r) at steady state was 0.80 or higher
k) Conversion to ENVARSUS XR at a mean dose of 80% of the total daily dose of tacrolimus immediate-release resulted in equivalent exposure with a 30% reduction in C_{max}.

In de novo adult kidney transplant patients, the administration of ENVARSUS XR once daily at a starting dose of
0.14 mg/kg/day results in a tacrolimus systemic exposure (AUC_{24}) on Day 1 post-transplant that is up to 10% lower than that of tacrolimus immediate-release capsules twice daily administered at a starting dose of 0.1 mg/kg/day, while similar tacrolimus trough concentrations (C_{24}) are achieved. As steady state is achieved (typically within 7 days of stable
ENVARSUS XR dosing), the AUC_{24} of ENVARSUS XR is approximately 15% higher than that of tacrolimus immediaterelease capsules, at comparable trough concentrations (C_{24}).

In adult kidney transplant patients ≥ 6 months post-transplant switched to ENVARSUS XR at 67% to 80% of the daily dose of tacrolimus immediate-release capsules, the steady state tacrolimus exposures (AUC_{24}) and tacrolimus trough concentrations (C_{24}) were comparable to the AUC_{24} and C_{24} measured prior to the switch. However, the mean C_{max} estimate was 30% lower and the median T_{max} was more prolonged (6 hours versus 2 hours) following administration of Envarsus XR as compared to that of tacrolimus immediate-release capsules.

Absorption

Absorption of tacrolimus from the gastrointestinal tract after oral administration is incomplete and variable. In de novo kidney transplant patients, the median time to achieve maximum blood concentrations (C_{max}) of ENVARSUS XR was approximately 6 to 10 hours (T_{max}) on day 1 post-transplant; the median T_{max} at steady state was 4 to 6 hours. In healthy subjects, the oral bioavailability of ENVARSUS XR was approximately 50% higher as compared with both tacrolimus immediate-release and extended-release capsule formulations at steady state. In healthy subjects who received single ENVARSUS XR doses ranging from 5 mg to 10 mg, the mean AUC and C_{24} of tacrolimus increased linearly and the elimination half-life did not change with increasing doses.

Food Effects

The presence of a meal affects the absorption of tacrolimus; the rate and extent of absorption is greatest under fasted conditions. In 26 healthy subjects, administration of ENVARSUS XR following a high-fat breakfast reduced the systemic exposure (AUC) to tacrolimus by approximately 55% and the peak plasma concentration of tacrolimus (C_{max}) by 22%, with no effect on the time to reach maximum plasma concentration (T_{max}), compared to when ENVARSUS XR was administered under fasted conditions. ENVARSUS XR tablets should be taken preferably on an empty stomach at least 1 hour before a meal or at least 2 hours after a meal.

Chronopharmacokinetic Effect

In 26 healthy subjects, administration of ENVARSUS XR tablets in the evening resulted in a 15% lower $AUC_{0\text{-}inf}$ and a 20% lower C_{24}, as compared to morning dosing.

Distribution

The plasma protein binding of tacrolimus is approximately 99% and is independent of concentration over a range of 5-50 ng/mL. Tacrolimus is bound mainly to albumin and alpha-1-acid glycoprotein, and has a high level of association with erythrocytes. The distribution of tacrolimus between whole blood and plasma depends on several factors, such as hematocrit, temperature at the time of plasma separation, drug concentration, and plasma protein concentration. In a U.S. trial in which tacrolimus was administered as immediate-release formulation, the ratio of whole blood concentration to plasma concentration averaged 35 (range 12 to 67).

Metabolism

The desired pharmacological activity of tacrolimus is primarily due to the parent drug. Tacrolimus is extensively metabolized by the mixed-function oxidase system, primarily the cytochrome P-450 system 3A (CYP3A). A metabolic pathway leading to the formation of 8 possible metabolites has been proposed. Demethylation and hydroxylation were identified as the primary mechanisms of biotransformation in vitro. The major metabolite identified in incubations with human liver microsomes is 13-demethyl tacrolimus. In in vitro studies, a 31-demethyl metabolite has been reported to have the same activity as tacrolimus.

Excretion

In a mass balance study of orally administered radiolabeled tacrolimus to 6 healthy subjects, the mean recovery of the radiolabel was 94.9 ± 30.7%. Fecal elimination accounted for 92.6 ± 30.7% and urinary elimination

accounted for 2.3 ± 1.1% of the total radiolabel administered. The elimination half-life based on radioactivity was 31.9 ± 10.5 hours, whereas it was 48.4 ± 12.3 hours based on tacrolimus concentrations. The mean clearance of radiolabel was 0.226 ± 0.116 L/hr/kg and the mean clearance of tacrolimus was 0.172 ± 0.088 L/hr/kg.

The elimination half-life of tacrolimus after oral administration of 2 mg ENVARSUS XR once-daily for 10 days was 31.0 ± 8.1 hours (mean ± SD) in 25 healthy subjects.

Specific Populations

Patients With Renal Impairment

Tacrolimus pharmacokinetics following a single administration of tacrolimus (administered as a continuous IV infusion) were determined in 12 patients (7 not on dialysis and 5 on dialysis, serum creatinine of 3.9±1.6 and 12.0±2.4 mg/dL, respectively) prior to their kidney transplant. The mean clearance of tacrolimus in patients with renal dysfunction given IV tacrolimus was similar to that in healthy subjects given tacrolimus IV and in healthy subjects given oral tacrolimus immediate-release *[see Use In Specific Populations (8.6)]*.

Patients With Hepatic Impairment

Tacrolimus pharmacokinetics have been determined in 6 patients with mild hepatic impairment (mean Pugh score: 6.2) following single oral administration of tacrolimus immediate-release. The mean clearance of tacrolimus in patients with mild hepatic impairment was not substantially different from that in healthy subjects. Tacrolimus pharmacokinetics were studied in 6 patients with severe hepatic impairment (mean Pugh score: >10). The mean clearance was substantially lower in patients with severe hepatic impairment *[see Dosage and Administration (2.3) and Use in Specific Populations (8.7)].*

Racial or Ethnic Groups

The pharmacokinetics of ENVARSUS XR were evaluated in a study of 46 stable African American kidney transplant recipients converted from tacrolimus immediate-release to ENVARSUS XR. Approximately 80% of the African American patients were carriers of the active, wild type CYP3A5*1 allele. Regardless of genotype status, the PK results demonstrated similar exposure, lower C_{max}, prolonged T_{max}, and increased bioavailability compared to tacrolimus immediate-release *[see Dosage and Administration (2.3) and Use in Specific Populations (8.8)]*.

Male and Female Patients

A formal trial to evaluate the effect of gender on tacrolimus pharmacokinetics has not been conducted. In a sub-group analysis from the two combined Phase 3 studies in kidney transplant recipients (Study 1 and Study 3) performed with ENVARSUS XR over one year of treatment, no gender-dependent differences in tacrolimus systemic exposures were observed.

Drug Interaction Studies

No drug-drug interaction studies were conducted specifically with ENVARSUS XR.

Because tacrolimus is metabolized mainly by CYP3A enzymes, drugs or substances known to inhibit these enzymes and/or are known CYP3A substrates may increase tacrolimus whole blood concentrations. Drugs known to induce CYP3A enzymes may decrease tacrolimus whole blood concentrations *[see Warnings and Precautions (5.9) and Drug Interactions (7.2)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in male and female rats and mice. In the 80-week mouse oral study and in the 104-week rat oral study, no relationship of tumor incidence to tacrolimus dosage was found. The highest dose used in the mouse was 3mg/kg/day (0.84 times the AUC at the recommended clinical dose of 0.14 mg/kg/day) and in the rat was 5mg/kg/day (0.24 times the AUC at the recommended clinical dose of 0.14 mg/kg/day) *[see Boxed Warning and Warnings and Precautions (5.1)]*.

A 104-week dermal carcinogenicity study was performed in mice with tacrolimus ointment (0.03%-3%), equivalent to tacrolimus doses of 1.1-118 mg/kg/day or 3.3-354 mg/m^2/day. In the study, the incidence of skin tumors was minimal and the topical application of tacrolimus was not associated with skin tumor formation under ambient room lighting. However, a statistically significant elevation in the incidence of pleomorphic lymphoma in high-dose male (25/50) and female animals (27/50) and in the incidence of undifferentiated lymphoma in high-dose female animals (13/50) was noted in the mouse dermal carcinogenicity study. Lymphomas were noted in the mouse dermal carcinogenicity study at a daily dose of 3.5 mg/kg (0.1% tacrolimus ointment; 2.5-fold the human exposure in stable adult renal transplant patients converted from tacrolimus immediate-release product to ENVARSUS XR). No drug-related tumors were noted in the mouse dermal carcinogenicity study at a daily dose of 1.1 mg/kg (0.03% tacrolimus ointment). The relevance of topical administration of tacrolimus in the setting of systemic tacrolimus use is unknown.

The implications of these carcinogenicity studies are limited; doses of tacrolimus were administered that likely induced immunosuppression in these animals, impairing their immune system's ability to inhibit unrelated carcinogenesis.

Mutagenesis

No evidence of genotoxicity was seen in bacterial (*Salmonella* and *E. coli*) or mammalian (Chinese hamster lung-derived cells) *in vitro* assays of mutagenicity, the *in vitro* CHO/HGPRT assay of mutagenicity, or *in vivo* clastogenicity assays performed in mice; tacrolimus did not cause unscheduled DNA synthesis in rodent hepatocytes.

Impairment of Fertility

Tacrolimus subcutaneously administered to male rats at paternally toxic doses of 2 mg/kg/day (2.3 times the recommended clinical dose based on body surface area) or 3 mg/kg/day (3.4 times the recommended clinical dose based on body surface area) resulted in a dose-related decrease in sperm count. Tacrolimus administered orally at 1mg/kg (1.2 times the recommended clinical dose based on body surface area) to male and female rats, prior to and during mating, as well as to dams during gestation and lactation, was associated with embryolethality and adverse effects on female reproduction. Effects on female reproductive function (parturition) and embryolethal effects were indicated by a higher rate of pre- and post-implantation loss and increased numbers of undelivered and nonviable pups. When administered at 3.2 mg/kg (3.7 times the recommended clinical dose based on body surface area), tacrolimus was associated with maternal and paternal toxicity as well as reproductive toxicity including marked adverse effects on estrus cycles, parturition, pup viability, and pup malformations.

14 CLINICAL STUDIES

14.1 Clinical Studies in De Novo Kidney Transplant Recipients

Study 1

Study 1 (NCT 01187953) was a Phase 3, 12-month, randomized, double-blind, multinational study comparing once daily ENVARSUS XR (N=268) to twice daily tacrolimus [immediate-release] capsules (N=275) in patients who received a de novo kidney transplant. Patients received the first dose of the study drug anytime within 48 hours of graft reperfusion. All patients received only IL-2 receptor antagonist induction therapy and concomitant treatment with mycofenolate mofetil (MMF) and corticosteroids. Approximately 97% of all patients received antibody induction therapy with basiliximab and 91% of all patients received corticosteroids and MMF.

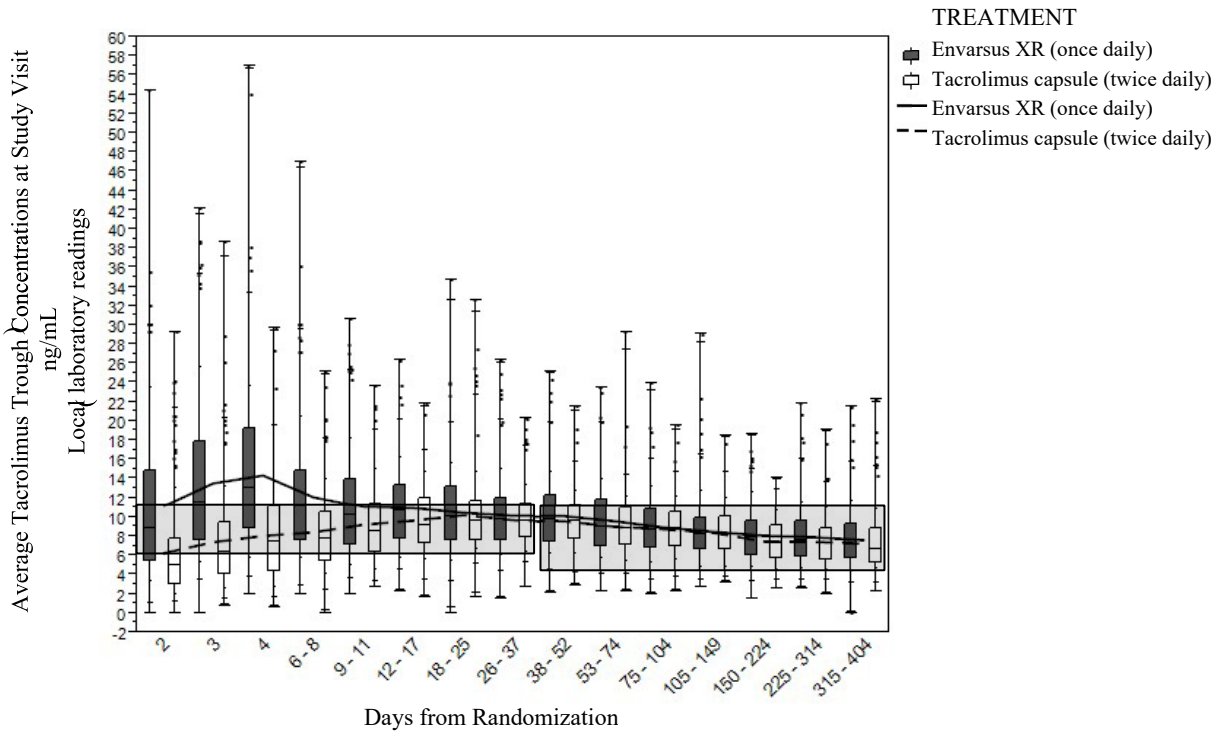
The mean age of the study population was 46 years; 65% were male; 77% were Caucasian, 5% were African-American, 4% were Asian and 14% were categorized as other races. Living donors provided 49% of the organs and 51% of patients received a kidney transplant from a deceased donor. Patients with clinically relevant ECG abnormalities (including QTc prolongation and reversible ischemia) and clinically symptomatic congestive heart failure or patients with documented left ventricular ejection fraction of less than 45% were excluded. Patients with a panel reactive antibody (PRA) >30%, who received a kidney from a non-heart-beating donor or with cold ischemia time >30 hours were also excluded. Premature discontinuation from treatment at the end of one year occurred in 22% of ENVARSUS XR patients and 19% of tacrolimus [immediate-release] capsules patients.

Tacrolimus Therapy

In Study 1, de novo kidney transplant patients were dosed initially at a starting dosage of 0.17 mg/kg given once daily for ENVARSUS XR (approximately 1.2-fold higher than the recommended starting dosage) and 0.1 mg/kg/day (given twice daily) for tacrolimus [immediate-release] capsule, with doses then modified to maintain tacrolimus trough concentrations between 6-11 ng/mL for the first 30 days and then between 4-11 ng/L for the remainder of the study. In the first week of dosing, the tacrolimus doses administered were, on average, ~40% higher in the ENVARSUS XR group compared to the tacrolimus capsule group and were similar in both treatment groups from Day 10 to Week 3. Thereafter, tacrolimus doses were, on average, 10% to 20% lower for ENVARSUS XR than in the tacrolimus capsule group.

Tacrolimus whole blood trough concentrations were monitored on Days 2, 3, 4, 7, 10, 14, 21, 30, 45, 60, 90, 120, 180, 270, and 360. On Day 2 predose, the proportion of patients in the ENVARSUS XR group with tacrolimus trough concentration that were within, above and below the target tacrolimus trough concentration range of 6 to 11 ng/mL was 33%, 39%, and 28%, respectively, compared to 27%, 12%, and 61%, in the tacrolimus [immediate release] capsule group. The average tacrolimus trough concentrations (per local laboratory reading) for the ENVARSUS XR group were above the target range during the first week post-transplant, and higher than in the tacrolimus capsule group during the first 2 weeks post-transplant (see Figure 1). Thereafter, the mean tacrolimus trough concentrations were similar between the treatment groups.

Figure 1. Study 1 Tacrolimus Trough Concentrations by Treatment Group and Visits



Legend: central box represents the 25th to 75th percentile along with the median line (50th percentile); whiskers show the entire range of trough concentrations from minimum to maximum values; line graph connects the mean trough concentration values; shaded gray regions depict the protocol specified target tacrolimus trough concentration ranges

Concomitant Immunosuppressive Drugs

In Study 1, the concomitant use of mycophenolate products was comparable between the ENVARSUS XR and tacrolimus [immediate-release] capsule treatment groups. Patients in both groups started MMF at an average dose of 1 gram twice daily. The MMF daily dose was reduced to less than 2 grams over the course of the study; the mean MMF equivalent total daily dose was approximately 1.5 grams at Month 12 in both treatment groups. Likewise, the average doses of
corticosteroids were comparable between the two treatment groups throughout the 12-month study period. Majority (96% ENVARSUS XR and 99% tacrolimus [immediate-release] capsules) of the patients received two 20 mg doses of basiliximab for antibody induction.

Efficacy Results

The efficacy failure rates including patients who developed biopsy-proven acute rejection (BPAR), graft failure, death, and/or lost to follow-up at 12 months, as well as the rates of the individual events, are shown by treatment group in **Table 10** for the intent-to-treat population.

Table 10. Incidence of BPAR, Graft Loss, Death or Lost to Follow-up at 12 Months in De Novo Kidney Transplant Patients in Study 1

	ENVARSUS XR, MMF, steroids, and IL-2 receptor antagonist induction therapy N=268	**Tacrolimus [Immediate-Release] capsules, MMF, steroids, and IL-2 receptor antagonist induction therapy N=275**
Overall Treatment Difference of efficacy failure compared to tacrolimus immediate-release (95% CI)[a]	-1.0% (-7.6%, 5.6%)	
Treatment Failure	50 (18.7%)	54 (19.6%)
Biopsy Proven Acute Rejection	36 (13.4%)	37 (13.5%)
Graft Failure	9 (3.4%)	11 (4.0%)
Death	8 (3.0)%	8 (2.9%)
Lost to Follow-up	4 (1.5%)	5 (1.8%)

[a] 95% CI was calculated using normal approximation.

Glomerular Filtration Rates

Renal function was assessed as change from Day 30 (baseline) by eGFR calculated using the MDRD7 equation. Baseline eGFR values were 53.8 ml/min/1.73 m^2 and 54.4 ml/min/1.73 m^2, and 12 month eGFR values were 58.6 ml/min/1.73 m^2 and 59.8 ml/min/1.73 m^2 in the ENVARSUS XR and the tacrolimus [immediate-release] capsule groups, respectively, maintaining the small difference of approximately 1ml/min/1.73 m^2 between the treatment groups.

Study 2

Study 2 (NCT 00765661) was an open-label Phase 2 study conducted in de novo kidney transplant patients randomized to once daily ENVARSUS XR (N=32) or twice daily tacrolimus [immediate-release] capsule(N=31). The study was conducted in the US and patients received an organ from a deceased or living donor. Pharmacokinetics were evaluated during the first 2 weeks with an additional 50-week treatment and follow-up to evaluate safety and efficacy.

Study 2 did not have any exclusion criteria based on cardiac disease or ECG findings but patients who received a kidney from a non-heart-beating donor or with cold ischemia time ≥ 36 hours were excluded. Patients were randomized within 12 hours after transplantation and received the first dose of the study drug within 48 hours of graft reperfusion. Induction treatment and concomitant immunosuppressive therapy were allowed per center-specific practices.

The mean age of study population was 47 years (range 23-69); 68% were male; 75% were Caucasian, 21% were AfricanAmerican, 5% were Asian. Two patients in each group withdrew early from the study due to adverse events.

Tacrolimus Therapy

In Study 2, *de novo* kidney transplant patients received a starting dosage of 0.14 mg/kg/day (given once daily) for ENVARSUS XR and 0.20 mg/kg/day (given twice daily) for tacrolimus [immediate-release] capsule. On Day 2 predose, the proportion of patients in the ENVARSUS XR group with tacrolimus trough concentration that were within, above, and below 6 to 11 ng/mL was 53%, 11%, and 37%, respectively. In Study 1, the proportion of de novo kidney transplant patients receiving a starting dose of 0.1 mg/kg/day of tacrolimus capsules that were within, above, and below 6 to 11 ng/mL on Day 2 predose was 27%, 12%, and 61%, respectively.

Concomitant Immunosuppressive Drugs

In Study 2, concomitant therapy with mycophenolate products or azathioprine, corticosteroids, and antibody induction was permitted but not required. The mean daily MMF, prednisone, and antibody induction doses were similar between the ENVARSUS XR and tacrolimus capsules treatment groups.

Efficacy

There were no deaths or graft failures in Study 2. Acute rejection rates at 12 months were 3.1% (1/32) in the ENVARSUS XR group and 6.5% (2/31) in the tacrolimus capsules group and 2 patients (one in each group) were lost to follow-up.

14.2 Conversion Study from Tacrolimus Capsules in Stable Kidney Transplant Recipients

Study 3

The conversion study, Study 3 (NCT00817206), was a Phase 3 randomized, open-label, multinational study evaluating once daily ENVARSUS XR when used to replace tacrolimus [immediate-release] capsules administered twice daily for maintenance immunosuppression to prevent acute allograft rejection in stable adult kidney transplant patients. Patients who received a kidney transplant 3 months to 5 years before study entry and on a stable dose of tacrolimus [immediaterelease] capsules of at least 2 mg per day and tacrolimus whole blood trough concentrations between 4 and 15 ng/mL were randomized to 1) switch from twice daily tacrolimus capsules to once daily ENVARSUS XR (N=163) or 2) continue tacrolimus capsules twice daily (N=163). MMF or mycophenolate sodium (MPS), or azathioprine (AZA) and/or corticosteroids were allowed as concomitant immunosuppressants during the study period according to the standard of care at the participating site.

The mean age of study population was 50 years; 67% were male; 73% were Caucasian, 22% were African-American, 2% were Asian and 3% were categorized as other races. Living donors provided 35% of the organs and 65% of patients received a kidney transplant from a deceased donor. Premature discontinuation from treatment at the end of one year occurred in 13% of ENVARSUS XR patients and 6% of tacrolimus capsule patients.

Tacrolimus Therapy

In Study 3, stable kidney transplant patients converted to ENVARSUS XR at an average daily dose that was 80% of their tacrolimus [immediate-release] capsules daily dose prior to conversion. Mean tacrolimus whole blood trough concentrations were maintained within a relatively narrow range throughout the duration of the study for both the ENVARSUS XR conversion group and the tacrolimus capsules continuation group. At Week 1 (after 7 days of stable dosing), the mean ± SD tacrolimus trough concentrations were 7.2 ± 3.1 ng/mL for the ENVARSUS

XR conversion group and 7.7 ± 2.5 for the tacrolimus capsules continuation group; the baseline values were 7.8 ± 2.3, and 8.0 ± 2.3, respectively.

MMF Therapy

In Study 3, the average daily mycophenolate equivalent doses were comparable between the ENVARSUS XR and tacrolimus capsules treatment groups.

Efficacy Results

The efficacy failure rates including patients who developed BPAR, graft failure, death, and/or lost to follow-up at 12 months, as well as the rates of the individual events, are shown by treatment group in **Table 11** for the modified intent-to treat population.

Table 11. Incidence of BPAR, Graft Loss, Death or Lost to Follow-up at 12 Months in Stable Kidney Transplant

Patients in Study 3

	ENVARSUS XR ± Steroids ± MMF, MPS, or AZA N=162	**Tacrolimus [Immediate-Release] Capsules ± Steroids ± MMF, MPS, or AZA N=162**
Treatment Failure	4 (2.5%)	4 (2.5%)
Overall Treatment Difference of efficacy failure compared to tacrolimus immediate-release (95% CI)[a]	0% (-4.2%, 4.2%)	
Biopsy Proven Acute Rejection	2 (1.2%)	2 (1.2%)
Graft Failure	0%	0%
Death	2 (1.2%)	1 (0.6%)
Lost to Follow-up	0%	1 (0.6%)

[a] 95% CI was calculated using an exact method that is based on the standardized statistic and inverting a 2-sided test *Glomerular*

Filtration Rates

The mean estimated glomerular filtration rates (eGFR), using the Modification of Diet in Renal Disease 7 (MDRD7) formula, were 61.5 ml/min/1.73 m^2 and 60.0 ml/min/1.73 m2 at baseline (Day 0) and 62.0 ml/min/1.73 m^2 and 61.4 ml/min/1.73 m^2 at 12 months in the ENVARSUS XR and tacrolimus capsules treatment groups, respectively.

16 HOW SUPPLIED/STORAGE AND HANDLING

ENVARSUS XR is supplied in round HDPE bottles with twist-off caps (see **Table 12**); the statement 'ONCE-DAILY' appears on its labels.

Table 12. Strengths of ENVARSUS XR

Strength	Description	NDC
0.75 mg	Oval, white to off-white uncoated extended-release tablet, debossed with "0.75" on one side and "TCS" on the other side.	30-count (NDC 68992-3075-3) 100-count (NDC 68992-3075-1)
1 mg	Oval, white to off-white uncoated extended-release tablet, debossed with "1" on one side and "TCS" on the other side.	30-count (NDC 68992-3010-3) 100-count (NDC 68992-3010-1)
4 mg	Oval, white to off-white uncoated extended-release tablet, debossed with "4" on one side and "TCS" on the other side.	30-count (NDC 68992-3040-3) 100-count (NDC 68992-3040-1)

Store and Dispense

Store at 25 °C (77 °F); excursions permitted to 15 °C to 30 °C (59 °F to 86 °F) [see USP Controlled Room Temperature]. **17 PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (Medication

Guide). **17.1 Administration** Advise patients to:

- Inspect their ENVARSUS XR medicine when they receive a new prescription and before taking it. If the appearance of the tablet is not the same as usual, or if dosage instructions have changed, advise patients to contact their healthcare provider as soon as possible to make sure that you have the right medicine. Other tacrolimus products cannot be substituted for ENVARSUS XR [*see Warnings and Precautions (5.3)]*.
- Take once-daily ENVARSUS XR at the same time every day (preferably in the morning) on an empty stomach. at least 1 hour before or at least 2 hours after a meal to ensure consistent and maximum possible drug concentrations in the blood.
- Swallow tablet whole with liquid, preferably water. Do not chew, divide, or crush tablet.
- Avoid alcoholic beverages, grapefruit, and grapefruit juice while on ENVARSUS XR *[see Dosage and Administration (2.1) and Drug Interactions (7.2)]*.
- Take a missed dose as soon as possible but not more than 15 hours after the scheduled time (i.e., for a missed 8 AM dose, take it no later than 10 PM). Beyond the 15-hour timeframe, instruct the patient to wait until the usual scheduled time the following morning to take the next regularly scheduled dose. Do not take two doses at the same time *[see Dosage and Administration (2.1)]*.

17.2 Development of Lymphoma and Other Malignancies

Inform patients that they are at an increased risk of developing lymphomas and other malignancies, particularly of the skin, due to immunosuppression. Advise patients to limit exposure to sunlight and ultraviolet (UV) light by wearing protective clothing and use a sunscreen with a high protection factor *[see Boxed Warning and Warnings and Precautions (5.1)*].

17.3 Increased Risk of Infection

Inform patients that they are at an increased risk of developing a variety of infections, including opportunistic infections, due to immunosuppression and to contact their physician if they develop any symptoms of infection such as fever, sweats or chills, cough or flu-like symptoms, muscle aches, or warm, red, painful areas on the skin *[see Boxed Warning and Warnings and Precautions (5.2)].*

17.4 New Onset Diabetes After Transplant

Inform patients that ENVARSUS XR can cause diabetes mellitus and should be advised to contact their physician if they develop frequent urination, increased thirst, or hunger *[see Warnings and Precautions (5.4)].*

17.5 Nephrotoxicity

Inform patients that ENVARSUS XR can have toxic effects on the kidney that should be monitored. Advise patients to attend all visits and complete all blood tests ordered by their medical team *[see Warnings and Precautions (5.5)* **17.6 Neurotoxicity**

Inform patients that they are at risk of developing adverse neurologic effects including seizure, altered mental status, and tremor. Advise patients to contact their physician should they develop vision changes, delirium, or tremors *[see Warnings and Precautions (5.6)]*.

17.7 Hyperkalemia

Inform patients that ENVARSUS XR can cause hyperkalemia. Monitoring of potassium levels may be necessary, especially with concomitant use of other drugs known to cause hyperkalemia *[see Warnings and Precautions (5.7)]*.

17.8 Hypertension

Inform patients that ENVARSUS XR can cause high blood pressure which may require treatment with anti-hypertensive therapy. Advise patients to monitor their blood pressure *[see Warnings and Precautions (5.8)].*

17.9 Drug Interactions

Instruct patients to tell their healthcare providers when they start or stop taking any concomitant medications, including prescription and non-prescription medicines, natural or herbal remedies, dietary supplements, and vitamins. Some medications could alter tacrolimus concentrations in the blood and thus may require the adjustment of the dosage of ENVARSUS XR. Advise patients to avoid grapefruit, grapefruit juice and alcoholic beverages *[see Warnings and Precautions (5.9) and Drug Interactions (7)].*

17.10 Pregnancy, Lactation, and Infertility

Inform women of childbearing potential that ENVARSUS XR can harm the fetus. Instruct male and female patients to discuss with their healthcare provider family planning options including appropriate contraception. Also discuss with pregnant patients the risks and benefits of breastfeeding their infant *[see Use in Specific Populations (8.1, 8.2, 8.3)].*

Encourage female transplant patients who become pregnant and male patients who have fathered a pregnancy, exposed to immunosuppressants including tacrolimus, to enroll in the voluntary Transplantation Pregnancy Registry International. To enroll or register, patients can call the toll-free number 1-877-955-6877 or https://www.transplantpregnancyregistry.org. Based on animal studies, ENVARSUS XR may affect fertility in males and females *[see Nonclinical Toxicology (13.1)].*

17.11 Immunizations

Inform patients that ENVARSUS XR can interfere with the usual response to immunizations and that they should avoid live vaccines *[see Warnings and Precautions (5.11)]*.

Product of Germany

Manufactured by:
Rottendorf Pharma GmbH
59320 Ennigerloh
North Rhine-Westphalia
Germany

Manufactured for:
Veloxis Pharmaceuticals, Inc.
Cary, North Carolina 27513
United States

MEDICATION GUIDE
ENVARSUS XR® (En var' sus XR**)**
(tacrolimus extended-release tablets)

Read this Medication Guide before you start taking ENVARSUS XR and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment. If you have any questions about ENVARSUS XR, ask your healthcare provider or pharmacist.

What is the most important information I should know about ENVARSUS XR?
ENVARSUS XR can cause serious side effects, including:

1. **Increased risk of cancer.** People who take ENVARSUS XR have an increased risk of getting some kinds of cancer, including skin and lymph gland cancer (lymphoma).
2. **Increased risk of infection.** ENVARSUS XR is a medicine that affects your immune system. ENVARSUS XR can lower the ability of your immune system to fight infections. Serious infections can happen in people receiving ENVARSUS XR that can cause death.
   Call your doctor right away if you have symptoms of an infection such as:
   - fever
   - cough or flu-like symptoms
   - warm, red, or painful areas on your skin
   - muscle aches
   - sweats or chills

What is ENVARSUS XR?

- ENVARSUS XR is a prescription medicine used with other medicines to help prevent organ rejection in people who have had a kidney transplant.
- ENVARSUS XR is an extended-release tablet and is not the same as tacrolimus extended-release capsules, tacrolimus [immediate-release] capsules or tacrolimus for oral suspension. Your healthcare provider should decide what medicine is right for you.

Who should not take ENVARSUS XR?

Do not take ENVARSUS XR if you are allergic to tacrolimus or any of the ingredients in ENVARSUS XR. See the end of this leaflet for a complete list of ingredients in ENVARSUS XR.

What should I tell my doctor before taking ENVARSUS XR?
Before you take ENVARSUS XR, tell your healthcare provider if you:

- plan to receive any live vaccines. Ask your healthcare provider if you are not sure if your vaccine is a live vaccine.
- have or have had liver, kidney, or heart problems.
- have any other medical conditions.
- are pregnant or plan to become pregnant. ENVARSUS XR may harm your unborn baby.
  - If you are able to become pregnant, you should use effective birth control before and during treatment with ENVARSUS XR. Talk to your healthcare provider about birth control methods that may be right for you.
  - Males who have female partners that are able to become pregnant should also use effective birth control before and during treatment with ENVARSUS XR. Talk to your healthcare provider before starting treatment with ENVARSUS XR about birth control methods that may be right for you.
  - There is a pregnancy registry for females who become pregnant and males who have fathered a pregnancy during treatment with ENVARSUS XR. The purpose of this registry is to collect information about your health and of your baby. To enroll in this voluntary registry, call 1-877955-6877.
- are breastfeeding or plan to breastfeed. ENVARSUS XR passes into your breast milk. You and your healthcare provider should decide if you will breastfeed while taking ENVARSUS XR

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, natural, herbal, or nutritional supplements.
ENVARSUS XR may affect the way other medicines work, and other medicines may affect how ENVARSUS XR works.

How should I take ENVARSUS XR?

- Take ENVARSUS XR exactly as your healthcare provider tells you to take it.
- Your healthcare provider may change your dose of ENVARSUS XR if needed. **Do not** stop taking or change your dose of ENVARSUS XR without talking to your healthcare provider.
- Take ENVARSUS XR once daily with fluid (preferably water) on an empty stomach, at least 1 hour before or at least 2 hours after a meal, at the same time each day (preferably in the morning).
- Take ENVARSUS XR tablets whole. **Do not** chew, divide, crush, or dissolve ENVARSUS XR tablets before swallowing. If you cannot swallow ENVARSUS XR tablets whole, tell your healthcare provider.
- If you miss your dose of ENVARSUS XR, it should be taken as soon as possible, but no longer than 15 hours after missing your dose. If the time after missing your dose is more than 15 hours, the missed dose should be skipped and the next dose should be taken the following morning at your regularly scheduled time. **Do not** take 2 doses at the same time.

- If you take too much ENVARSUS XR, call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid while taking ENVARSUS XR?

- Live vaccines such as flu vaccine through your nose, measles, mumps, rubella, polio by mouth, BCG (TB vaccine), yellow fever, chicken pox (varicella), or typhoid.
- Exposure to sunlight and UV light such as tanning machines. Wear protective clothing and use a sunscreen.
- You should not eat grapefruit or drink grapefruit juice while taking ENVARSUS XR.
- You should not drink alcohol while taking ENVARSUS XR.

What are the possible side effects of ENVARSUS XR?

ENVARSUS XR may cause serious side effects, including:

- **See "What the most important information I should know about ENVARSUS XR?"**
- **problems from medication errors such as graft rejection and other serious reactions.** People who take ENVARSUS XR have sometimes been given the wrong medicine because some medicines have the same ingredient (tacrolimus) as ENVARSUS XR. **Check your ENVARSUS XR when you get a new prescription to make sure you have received the right medicine**. ○ Call your healthcare provider right away if you think you were given the wrong medicine.
  - ○ Ask your healthcare provider or pharmacist if you are not sure what ENVARSUS XR should look like.
- **high blood sugar (diabetes)**. Your healthcare provider may do certain tests to check for diabetes while you take ENVARSUS XR. Call your healthcare provider right away if you have:
  - ○ frequent urination ○ increased thirst or ○ blurred vision hunger
  - ○ confusion ○ drowsiness ○ loss of appetite ○ fruity smell on your breath ○ nausea, vomiting, or stomach pain
- **kidney problems**. Kidney problems are serious and common side effects of ENVARSUS XR. Your healthcare provider may do certain tests to check for kidney function while you take ENVARSUS XR. • **nervous system problems**. Nervous system problems are a serious and common side effect of ENVARSUS XR. Call your healthcare provider right away if you get any of these symptoms while taking ENVARSUS XR. These could be signs of serious nervous system problems: ○ confusion ○ coma ○ seizures
  - ○ numbness and tingling ○ headache ○ vision changes ○ muscle tremors
- **high levels of potassium in your blood**. Your healthcare provider may do certain tests to check your potassium level while you take ENVARSUS XR.
- **high blood pressure**. Your healthcare provider will monitor your blood pressure while you take ENVARSUS XR.
- **changes in the electrical activity of your heart (QT prolongation).**
- **severe low blood cell count (anemia)**

The most common side effects of ENVARSUS XR are diarrhea, urinary tract infection, low red blood cell count (anemia), high blood pressure, and constipation.
These are not all the possible side effects of ENVARSUS XR. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ENVARSUS XR?

- Store ENVARSUS XR at room temperature between 68 ºF to 77 ºF (20 °C to 25 ºC).
- Safely throw away medicine that is out of date or no longer needed. **Keep ENVARSUS XR and all medicines out of reach of children.**

General information about the safe and effective use of ENVARSUS XR.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ENVARSUS XR for a condition for which it was not prescribed. Do not give ENVARSUS XR to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about ENVARSUS XR. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about ENVARSUS XR that is written for health professionals. For more information, go to www.ENVARSUSXR.com or call 1-844-Veloxis (1-844-835-6947).

What are the ingredients in ENVARSUS XR?

Active ingredient: tacrolimus USP

Inactive ingredients: hypromellose USP, lactose monohydrate NF, polyethylene glycol NF, poloxamer NF, magnesium stearate NF, tartaric acid NF, butylated hydroxytoluene NF, and dimethicone NF

Manufactured by: **Rottendorf Pharma GmbH**, 59320 Ennigerloh, North Rhine-Westphalia, Germany

Manufactured for: **Veloxis Pharmaceuticals, Inc.**, Cary, North Carolina 27513, United States

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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