Official Title: A Prospective, Pilot Trial to Evaluate Safety and Tolerability of Tacrolimus Extended-Release (Astagraf XL) in HLA Sensitized Kidney Transplant Recipients

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CEDARS-SINAI MEDICAL CENTER

CONSENT FORM FOR RESEARCH

Title: A Prospective, Pilot Trial to Evaluate Safety and Tolerability of Tacrolimus Extended-Release (Astagraf XL) in HLA Sensitized Kidney Transplant Recipients

Study Support Provided By: Astellas

Participating Researchers:

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Study Contact Phone Number at CSMC: 310-423-2641

After Hours Contact (24 hours): 310-423-2641

This research study is sponsored by Astellas. Astellas only reimburses Cedars-Sinai Medical Center for the costs associated with running the study; Astellas is not providing additional compensation to Cedars Sinai Medical Center or the Principal Investigator for their participation in the study.

1. WHAT IS THE PURPOSE OF THIS RESEARCH STUDY?

We are doing this study to determine the safety and tolerability of tacrolimus extended-release (Astagraf XL) in the highly sensitized patient population as measured by the rate of serious adverse events and treatment failure. Treatment failure is defined as a composite of biopsy proven acute rejection, graft failure, or death.

You are being asked to take part in this research study because you are considered to be a highly sensitized kidney transplant recipient. Highly sensitized for this study is defined as having a history of previous transplant, blood transfusions or pregnancies and therefore requiring sensitization to lower your antibodies to allow for transplantation.

The study will enroll up to 20 people in total.

Tacrolimus extended-release is a once daily formulation of tacrolimus and is currently approved for preventing organ rejection in kidney transplant recipients. However, this drug has not been studied in highly sensitized kidney transplant recipients.

In this study, we want to learn what effects, good or bad, Tacrolimus extended-release has on people with your condition. We will give Tacrolimus extended-release to research participants and watch carefully for any side effects.

2. WHAT WILL HAPPEN DURING THE STUDY?

This section provides a general overview of what will happen during your participation in this study. Information included below should be considered along with the flowchart of procedures attached as Appendix A.

The flowchart shows a timeline for research-related or standard of care procedures that are involved in your participation in this study. **Research-related procedures** are those performed solely for the research. They would not be performed if you did not take part in the study. **Standard of care (routine)** procedures would be performed both as part of this study and if you do not participate in this study.

A table describing common medical procedures done solely for the purposes of monitoring and assessing your condition during this study is attached as Appendix B to the end of this consent form. Standard of care procedures that will be repeated or done at greater frequency are listed in the flow chart, attached Appendix A.

Overview of study:
As part of your participation in the research, you will be receiving the study drug, Astagraf. You will be taking this drug daily on a consistent schedule with regard to time of day and relation to meals once daily by oral administration adjusted to target blood levels. Cedars Sinai laboratories will be used to analyze the clinical lab data and viral testing during the study. Please see Appendix A for the flowchart of procedures.

How long will you be in the study?
We think you will be in this study for/until about one year. The total time includes 10 study visits in addition to the two which are of standard of care. The total number of visits include: screening day, Day 0, 2, 4, 7, 14, 30, Month 2, 6, 9 and 12.

We would like to keep track of your medical condition for one year. We would like to review your medical records and collect study labs at each study visit to see how you are doing. Keeping in touch with you and checking on your condition every so often helps us look at long-term effects.

3. WHAT ARE THE POSSIBLE RISKS?

Risks of common medical procedures performed solely for research purposes are described in a table attached to the end of this consent form as Appendix B. Side effects and risks of standard of care procedures are not described in this consent form.

This section describes the possible risks and/or discomforts we anticipate you could experience that are related to the study procedures such as: blood lab draws, urine tests and breach of confidentiality.

Unknown Risks
There also may be other side effects or risks that we cannot predict. Many side effects may go away shortly after the study medication or procedure is stopped. However, in some cases they can be serious, long-lasting, permanent, and/or fatal.

Risks of Tacrolimus extended-release or Astagraf XL:

Common, some may be serious (occurs in greater than 20% of people)	**Occasional, some may be serious** (occurs in 4-20% of people)	**Rare, and serious** (occurs in 1-3% of people)	**Possible, some may be serious** (occurs in less than 1% of people)
• Diarrhea • Constipation • Nausea • Abdominal pain • Hair loss • Headache • Difficulty sleeping • Tremor • fever • Increased blood pressure • Edema (swelling) • Electrolyte abnormalities (may require electrolyte supplements) such as nausea, vomiting, mood changes, excessive thirst • Elevated cholesterol • Elevated blood sugar	• Vomiting • Reduced red blood cells (lead to fatigue) • Reduced platelets (increased risk of bleeding) • Reduced white blood cells (increased susceptibility to infections) • Rash • Itching	• Viral, bacterial and fungal infections • Sun sensitivity • Viral kidney infection • Injury to kidneys	• All immunosuppression treatments increase risk of developing lymphomas and other malignancies particularly skin cancer • Changes in the electrical activity of your heart (QT prolongation) • PRES (see additional information below)

Astagraf XL may interact with other medicines. Be sure to tell your study doctor about all the medicines you take, including prescription and over-the-counter medicine, vitamins and herbal supplements. You should not consume grapefruit or grapefruit juice while taking Astagraf XL. Additionally, you should limit your exposure to sun or UV light by wearing protective clothing and using sunscreen.
Very rarely, Astagraf XL may cause nervous system problems, including posterior reversible encephalopathy syndrome (PRES). Call your doctor or go to the nearest hospital emergency room right away if you get any of these symptoms while taking Astagraf XL. These could be

signs of serious nervous system problems: confusion, changes in alertness, muscle tremors, numbness and tingling, headache, seizures or vision changes.

Reproductive and Lactation Risks
Taking part in this research study can affect an unborn baby. Therefore, you should not become pregnant or father a baby while on this study. If you or your partner is capable of becoming pregnant you will need to use birth control. Check with the researcher about approved birth control methods to use while participating in this study.

Women should not breastfeed a baby while on this study.

Unknown Risks to the Developing Embryo or Fetus (an unborn baby)
If you are pregnant, or become pregnant during participation in this research, the study drug might involve risks to an embryo or fetus, which are currently unknown. It is important that you contact the researcher immediately if you believe you might be pregnant. If pregnancy is suspected, then you will be given both a urine test and a serum pregnancy test to confirm pregnancy.

Collection of Pregnancy Outcomes
If you become pregnant during the study, we will collect information on the outcome of your pregnancy including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, abnormalities, or complications, and the health status of your child. By signing this consent, you are agreeing to have this information about you and your child collected from your medical records in the rare case that you become pregnant during your participation in this research study; however, you are always free to withdraw your consent to participate in any research procedure.

If you are a male participant and your female partner becomes pregnant during the study, we will ask your female partner for consent and authorization to collect information on the outcome of her pregnancy and the status of your child, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, abnormalities, or complications. Your partner is free to decline to consent to provide this information. This information will be collected from your female partner's medical records with her permission.

Follow-up Visit for Discontinuing Participants
While you are free to discontinue your participation at any time, we encourage you to complete a Final Study Visit. During this visit, we will conduct tests to collect safety data, and discuss any information that may be important to share with your treating physician.

Incidental Findings
It is possible that the research procedures could uncover information related to your health that you did not know about before and that is unrelated to the Study. Some of these findings may be too preliminary to share. Cedars-Sinai will carefully consider the research findings and determine if they should be shared with you. Research findings would only be shared with you if such sharing is approved by the Cedars-Sinai IRB and is permitted by applicable law. In some cases, additional clinical testing may be required. The cost of any additional testing and any related treatment will be your responsibility.

4. ARE THERE BENEFITS IN TAKING PART IN THE STUDY?

If you agree to take part in this research study, there may or may not be direct medical benefit to you. The possible benefit of taking part in the research study is that you will be taking Astagraf XL once daily which decreases pill burden. However, no benefit is guaranteed. It is possible that your condition may remain unchanged or even get worse.

We hope the information learned from this research study will benefit other individuals who are highly sensitized kidney transplant recipients in the future by helping us to learn the safety and tolerability of tacrolimus extended-release in these patients.

5. WHY WOULD MY PARTICIPATION BE STOPPED?

Your participation in this study may be stopped at any time by the researcher or the sponsor without your consent for any reason, including:

- The study is stopped or suspended;
- Funding for the study is reduced, stopped or withdrawn;
- If it is in your best interest;
- You do not consent to continue in the study after being told of changes in the research that may affect you;
- You do not follow the study procedures.

You may choose (or you may be required) to withdraw from certain parts of the study, but invited to continue with other parts. For example, you might stop taking a study drug, but continue with follow-up visits or allow us to continue to collect data from your medical records. Separate written consent will be requested if your continued participation will involve procedures not described in this consent form.

6. ARE THERE ANY OTHER OPTIONS?

Your participation is voluntary so you have the right to decline to participate or to withdraw from this research study at any time without any penalty or loss of benefits to which you would be entitled outside of the study. Choosing not to participate will not affect the care you receive at Cedars-Sinai Health System.

If you decide not to take part in this study, you have other choices. For example:

- you may choose to be treated following the usual clinical approach (tacrolimus, mycophenolate mofetil and prednisone).
- you may choose to take part in a different study at CSMC or elsewhere, if one is available
- you could decide not to be treated.

The researcher will discuss these options and their risks and benefits with you.

7. WILL MY INFORMATION BE KEPT CONFIDENTIAL?

We will do our best to make sure that the personal information collected as part of this study is kept private. However, we cannot guarantee total privacy. A copy of your research consent and authorization forms may be filed in your electronic medical record at CSMC. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other identifiable personal information will not

be used. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include: accrediting agencies, government and regulatory groups (such as Food and Drug Administration (FDA), Office for Human Research Protections (OHRP), etc.), safety monitors, companies that sponsor the study, and authorized representatives of the sponsor.

The study team will facilitate any required access to your records by authorized representatives of the Sponsor to verify the information collected for the study.

You may, depending on the circumstances of the study and applicable law, be asked to sign a separate "Authorization Form" that outlines with whom your information may be shared for the purposes of this research and under what circumstances.

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

8. WHAT IF I BECOME ILL OR INJURED BECAUSE OF TAKING PART IN THIS STUDY?

Contact your researcher at once if you feel that you are ill or have been injured because of taking part in this study. If it is a medical emergency, call 911 or go to an emergency room. Promptly notify your researcher of your situation at the phone number listed on page 1 of this consent form.

Who pays for my research related illness or injury?
A research injury or illness is a direct result of the Study Drug, or a procedure performed only as a part of the study and is not part of your standard clinical medical treatment. Injury or illness related to your underlying medical condition or treatment generally provided outside of the study would not be considered research related. If you are being treated for a research injury or illness, you will not pay for the costs of care provided by Cedars-Sinai Health System or in any emergency room provided that you are being treated for a research injury or illness. Cedars-Sinai may, however, ask for reimbursement where allowed from parties such as your health plan. CSMC has no plans to pay for losses such as lost wages. If you choose to obtain non-emergency care elsewhere, you or your health plan may be responsible for the costs of that care.

9. FINANCIAL CONSIDERATIONS

Costs of Participation
Please review the attached Appendix A flowchart for a listing of items, drugs and services that will be billed to you and/or your insurance and those that will be covered by the study sponsor.

Only items, drugs and services that are reasonable and necessary for your medical care throughout the study will be billed to your insurance. You remain responsible for all deductibles, co-pays, and balances under your health benefit plan. If your insurance company does not pay, you will be billed for those charges. You should check with your health benefit plan if you have questions or concerns about your insurance coverage.

Compensation for Participating
You will not be paid for taking part in this research study.

Financial Interest in the Research
The PI and institution have no potential financial conflict of interest with respect to this study.

10. WHAT IF I HAVE QUESTIONS OR PROBLEMS?

Please contact one of the investigators listed on the first page of this form for questions or concerns about the research.

If you have questions, problems, or concerns that you want to discuss with someone who is not associated with this study, or want to offer suggestions or feedback, please contact:

Cedars-Sinai Human Research Protection Program (HRPP) Phone: (310) 423-3783
Email: ResearchConcerns@cshs.org

The Cedars-Sinai HRPP has been established to protect the rights and welfare of research participants. You may also contact the Cedars-Sinai HRPP if you want to offer input or obtain information regarding the study.

11. CONSENT PROVISIONS

If you sign this form below, it means that:

(1) You have taken the time to carefully read and understand the information presented in this informed consent form; you should discuss it with others, and if appropriate seek a second opinion to make an informed decision;
(2) The information concerning the research study and its involved procedures has been fully explained to you and your questions have been answered to your satisfaction;
(3) You have received and understand all of the information you desire regarding your participation in the research study;
(4) You have considered the potential risks, any anticipated benefits and alternatives (and their relative risks and benefits) of participation;
(5) You are voluntarily agreeing to participate in this research study;
(6) You understand that by consenting to participate in the research, you are not giving up any of your legal rights (other than the postponement of your access to certain health information as described in this informed consent form);
(7) You understand that you have the right to be informed of significant new findings related to this research study which may affect your willingness to continue participating in this study; and
(8) You have been provided with a copy of the "Experimental Subject's Bill of Rights", if applicable to this research study, and have been provided with an opportunity to ask questions regarding the Bill of Rights.

We will give you a copy of this signed and dated consent form and a signed copy of the Experimental Subject's Bill of Rights.

SIGNATURE BY THE PARTICIPANT:

Name of Participant (Print)	Signature of Participant	Date of Signature

SIGNATURE BY THE INVESTIGATOR:

I have personally explained the research to the participant in non-technical terms, answered all questions, and attest that he/she freely consents to participate. The participant has been provided with the Experimental Subject's Bill of Rights.

Signature of the Investigator Who Obtained Consent	Date of Signature

SIGNATURE BY THE INTERPRETER/WITNESS

(Signature of an interpreter is only required when a non-English speaking subject is consented with the assistance of an interpreter and an IRB-approved 'short form.' The witness may be any person who is conversant in both English and the language of the Non-English speaking subject, such as the interpreter (the certified hospital interpreter), study staff, a family member, or other person. The witness signs the consent forms to confirm that the oral interpretation occurred.)

Signature of Interpreter/Witness	Date of Signature

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EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

In accordance with California Health and Safety Code 24172, any person who is required to consent to participate as a subject in a research study involving a medical experiment or who is requested to consent on behalf of another has the right to:

1. Be informed of the nature and purpose of the experiment.

2. Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized.

3. Be given a description of any attendant discomforts and risks to the subject reasonably to be expected from the experiment.

4. Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.

5. Be given a disclosure of any appropriate alternative procedures, drugs or devices that might be advantageous to the subject, and their relative risks and benefits.

6. Be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise.

7. Be given an opportunity to ask any questions concerning the experiment or the procedure involved.

8. Be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation in the medical experiment without prejudice.

9. Be given a copy of any signed and dated written consent form used in relation to the experiment.

10. Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject's decision.

_____ _____

Signature of Experimental Subject **Date**

Distribution instruction for researchers:

The signed (i) Consent form, (ii) Authorization for Use and Disclosure of Identifiable Health Information and (iii) "Experimental Subject's Bill of Rights" (the latter required if the research study involves medical interventions)* should be distributed to:

1) Medical Chart
2) Research Participant
3) Pharmacy (if a drug study)
4) Principal Investigator's research records (original)

APPENDIX A: FLOWCHART OF PROCEDURES – Medicare Coverage Analysis (MCA) Review

Study Period	**Screening**										
Visit	**Screening (Pre-op)**	**Day 0 (Kidney Transplant)**	**Day 2 ± 1 days**	**Day 4 ± 2 days**	**Day 7 ± 3 days**	**Day 14 ± 3 days**	**Day 30 ± 7 days**	**M2 ± 7 days**	**M6 ± 14 days**	**M9 ±14 days**	**M12 ±14 days**
Standard of Care Procedures: Items and services that are part of regular care and would be done even if you did not take part in this research study. These will be billed to you and /or your insurance company.											

Full Medical History, Demographics	X										
Physical Exam/Vital Signs (pulse rate, BP, weight)	X	X	X	X	X	X	X	X	X	X	X
Chest X-Ray/EKG[8]	X										
Transplant Serology/Donor Background	X										
Urinalysis (cell count, glucose and protein)				X	X	X	X	X	X	X	X
Blood test: CBC Diff	X	X	X	X	X	X	X	X	X	X	X
Blood test: Complete Metabolic Panel	X	X	X	X	X	X	X	X	X	X	X
Blood test: Liver Function Panel	X	X	X	X	X	X	X	X	X	X	X
Alemtuzumab Administration		X									
Tacrolimus extended-release Trough Level[1]			X	X	X	X	X	X	X	X	X
Viral Testing[2]							X	X	X	X	X
DSA (Donor Specific Antibodies)[3]	X						X	X	X	X	X
Maintenance Immunosuppresion: mycophenolate mofetil and prednisone.			X	X	X	X	X	X	X	X	X
Prophylaxis per SOC: Valganciclovir			X	X	X	X	X	X	X		

Prophylaxis per SOC: TMP/SMX (Trimethoprim/Sulfamethoxasole)			X	X	X	X	X	X	X	X	X
Prophylaxis per SOC: Fluconazole			X	X	X	X	X	X			
Review of: HepB, HepC, HIV blood test results	X										
Research Related Procedures: Items and services done for research purposes only. These will NOT be billed to your insurance company.											
Informed Consent	X										
Inclusion/Exclusion Criteria Review	X										
Serum Pregnancy Test[9]	X										
Maintenance immunosuppression: tacrolimus extended release[6,7]		X[10]	X	X	X	X	X	X	X	X	X
AE/SAE Reporting		X	X	X	X	X	X	X	X	X	X

1. **Tacrolimus extended-release levels will be monitored 4 days after a dose change or stopping of fluconazole.**
2. **Blood tests for: BKV (BK virus), CMV (Cytomegalovirus).**
3. **Performed at time of transplant and quarterly for the first year. For DD (diseased donor) sample will be drawn pre-op. For LD (living donor), sample will be drawn prior to IVIG-2 but patients would already have received IVIG-1 and Ritux 5 weeks prior to the sample drawn**
4. **Will be split over 2 days for peritoneal dialysis pts.**
5. **Pts who are unresponsive to IVIG/Ritux [after 2months for LD and after 6 months for DD] will require PLEX 5-7 sessions followed by IVIG and rituximab.**
6. **Pts will receive acetaminophen, antihistamine and steroid as premedication for all infusions.**
7. **The study drug may be temporarily interrupted if a patient develops a short -term intolerance of oral medication after the initial dose of study medication. Alternatively, administration of tacrolimus twice daily suspension via nasogastric (NG) tube or if more serious, cyclosporine or tacrolimus IV (per SOC) may be used.**
8. **Can be done within 6 months of screening date.**
9. **If subject is of childbearing age [Not required if subject has a history of hysterectomy].**

10. **Depending on when the subject gets transplanted, the investigational drug will either be given same day as transplant (Day 0) OR at the next scheduled dosing after transplantation at 8am.**

APPENDIX B: Detailed Description of Common Medical Procedures Performed for Research Purposes and Associated Risks

The procedures listed below are often performed as part of routine care for a person with your condition. They are being repeated, or performed more frequently as part of this research. However, the risks associated with each procedure should be comparable to what you would experience even if you were undergoing the procedure outside this research study.

Study Procedure	Related Risks
Blood draw: A needle is placed in the vein in your arm to draw blood	Blood drawing may cause some pain and has a small risk of bleeding, bruising, or infection at the puncture site. There is also a small risk of fainting.
Injection: A method for putting fluids into the body using a syringe and a hollow needle that is pierced through the skin	These reactions could include bruising, pain, bleeding, and rarely infection at the injection site, feeling lightheaded and fainting. As with any injection, there may be some irritation at the injection site where the study drug is administered.
Physical Exam: Includes height, weight, vital signs (heart rate and blood pressure)	There are no physical risks associated with these procedures.
Concomitant Medications: You will be asked about your previous and current medications that you take.	There are no physical risks associated with these procedures.
Medical History Review: You will be asked about your medical and surgical history with attention to smoking and alcohol habits and menopausal history (females only).	There are no physical risks associated with this procedure.
Urine Collection:	No risks associated with this procedure.
Pregnancy Test: If you are a woman who is able to become pregnant, [blood/urine] samples will also be used to do a pregnancy test	If your test is positive, you will be told and at that point you should discuss options available with your primary physician.
Demographic Information: You will be asked about your age, gender, race, ethnicity	There are no physical risks associated with these procedures.