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

NCT #: NCT03194321

Document Date: January 25, 2018

Astagraf XL Clinical Study Protocol

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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Document type:	Clinical Study Protocol
Version number:	3
Release date:	25JAN2018

Table of contents

Appendix

List of tables

List of abbreviations

HS	Highly Sensitized
IVIG	Intravenous Immunoglobulin
PLEX	Plasma Exchange
SAEs	Serious Adverse Events
BPAR	Biopsy proven acute rejection
DSA	Donor Specific Antibodies
PRA	Panel reactive antibody
CSMC	Cedars-Sinai Medical Center
TMP/SMX	Trimethoprim/Sulfamethoxazole (Bactrim)
HLA	Human Leukocyte Antigen Antibodies
RIS	Relative Intensity Score
MFI	Mean Fluorescence Intensity
CRF	Case Report Form
SOC	Standard of Care
SAE	Significant Adverse Event
FDA	Federal Drug Administration
WHO	World Health Organization

Glossary of terms (correct format below)

Assessment	A procedure used to generate data required by the study
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
Medication number	A unique identifier on the label of each medication package in studies that dispense medication using an IVR system
Patient number	A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study.
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later
Study drug	Any drug administered to the patient as part of the required study procedures; includes investigational drug and any control drugs
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

Protocol synopsis

Title of study: A Prospective, Pilot Trial to Evaluate the Safety and Tolerability of Tacrolimus Extended-Release in HLA Sensitized Kidney Transplant Recipients

Purpose and rationale:

The purpose of this study is to demonstrate the safety of tacrolimus extended-release in HLA sensitized (HS, defined as panel reactive antibody ≥ 30%), kidney transplant recipients after desensitization with intravenous immunoglobulin (IVIG) and rituximab +/- plasma exchange (PLEX) per the standard of care with alemtuzumab induction.

Objectives:

The primary objective is to determine the safety of tacrolimus extended-release in the HS patient population as measured by the rate of serious adverse events (SAEs) and treatment failure. Treatment failure is defined as a composite of biopsy proven acute rejection (BPAR), graft failure, or death. BPAR is defined as ≥ Banff 1A using the Banff 2007 criteria.

Secondary objectives are to observe the following:

1. Change in donor specific antibodies (DSA) as defined by the DSA relative intensity score[1,2]
2. Tolerability as defined by the number of subjects discontinuing the study medication

Population:

The study population will consist of HS patients (patients who have received desensitization) with end- stage kidney disease undergoing kidney transplantation. The study will begin at the time of transplantation while subjects are inpatients. They will be followed post- transplantation as outpatients.

Inclusion/Exclusion criteria:

Key **inclusion criteria** are as follows:

1. Recipient of a deceased or living donor kidney allograft
2. Patients must have undergone desensitization with IVIG and rituximab with or without plasma exchange prior to transplant or be administered IVIG and rituximab peri-operatively (within seven days of transplant) post-transplant
3. Age 18 and over
4. Able to understand and provide informed consent

5. At transplant, patient must have an acceptable crossmatch (as defined as T-or B- FCMX ≤ 225 MCS) from non-HLA identical donor. Negative crossmatch is Tpronase FCMX <70; T- FCMX <50 and Bpronase FCMX <130; B-FCMX <100.

Key **exclusion criteria** are as follows:

1. Recipients of a dual simultaneous kidney/liver, kidney/heart, kidney/lung, or kidney/pancreas transplant

2. History of hypersensitivity to any of the study drug or to drugs of similar chemical classes

3. Patients being treated with drugs that are strong inducers or inhibitors of cytochrome P450 3A4

4. Patients with a clinically significant systemic infection within 30 days prior to transplant

5. Patients who have any surgical or medical condition that may affect absorption of drug, such as severe diarrhea, active peptic ulcer disease, or uncontrolled diabetes mellitus, which in the opinion of the investigator, might significantly alter the absorption, distribution, metabolism and/or excretion of study medication.

6. Women of childbearing potential who are either pregnant, lactating, planning to become pregnant during this trial, or with a positive serum or urine pregnancy test. Women of childbearing potential must be willing to agree to contraceptive practices.

7. Patients who are PCR positive for Hep B, Hep C, or HIV.

Investigational and reference therapy:

Tacrolimus extended-release starting dose 5mg once daily by oral administration adjusted to target trough level.

Table 1: Target Tacrolimus Extended-Release Trough Levels

Time	Tacrolimus
Day 4 to Month 6	7 – 9 ng/ml
Months 6-12	5 – 8 ng/ml

Study design:

This is a single center, pilot trial. It will be an open label, single-arm, non-controlled design. All HS patients age 18 and older requiring desensitization may be included in the study. Twenty subjects will be enrolled in the study. Subjects will take part in the study until they are one-year post-transplant. All subjects will require informed consent. At the time of screening, subjects will receive a physical exam and undergo lab testing as detailed below in the evaluation schedule. Alemtuzumab (Campath 1H, Lemtrada) will be administered to all subjects for induction immunosuppression immediately post-transplant. Maintenance immunosuppression will consist of tacrolimus extended-release, mycophenolate mofetil, and prednisone. Patients will receive antimicrobial prophylaxis as per Cedars-Sinai Medical Center (CSMC) protocol (valganciclovir x 6 months, TMP/SMX x 12months, and fluconazole x 1 month). Lab tests and physical exams for safety will take place according to the evaluation schedule below. Safety will be assessed by the reporting of serious adverse events as described below. Tacrolimus extended-release trough level, complete metabolic panel, complete blood count with differential, donor specific antibodies, and urinalysis with culture will be assessed according to the evaluation schedule below. Subjects will complete the study at one year post-transplant. Consent may be withdrawn by the study participant at any time. The investigator may also withdraw the study participant at any time if there are any safety concerns.

Efficacy assessments:

This is a pilot study and no efficacy assessments will be made.

Data analysis:

All outcomes will be reported as frequencies. Safety will be assessed by measuring the frequency of serious adverse events at one year post transplant. The frequency of BPAR, graft loss, and death will also be assessed at one year post transplant.

1 Background

Kidney transplantation remains the gold standard for the treatment of end-stage kidney disease. Advances in immunosuppression are integral to the success of kidney transplantation. Current immunosuppression regimens have reduced the number of rejections. However, long-term allograft survival remains a challenge. One limitation of immunosuppression regimens is the pill burden placed upon the recipients. This leads to long-term non-adherence and late rejections that ultimately place the allograft at risk[1,2].

Approximately 30% of the patients currently awaiting a kidney transplant are broadly HLA-sensitized. These preformed HLA-antibodies create a difficult to match phenotype that results in a longer wait time for a kidney transplant and higher rates of rejection

after kidney transplant. Broadly HLA-sensitized patients are often excluded from clinical trials due to their extended length of time on dialysis (associated with increased post-transplant morbidity) and increased rates of rejection.

Tacrolimus twice daily is very effective in preventing allograft rejection and is administered as first line therapy as part of multidrug immunosuppression regimen. Tacrolimus twice daily has a narrow therapeutic index and frequent drug monitoring is necessary to maximize efficacy and prevent adverse effects. There is high intra-individual variability that can place the allograft at risk of deterioration due to rejection or toxicity[3].

Tacrolimus extended-release (Astagraf XL, Astellas Pharma US, Inc., Northbrook, IL) is a once daily formulation of tacrolimus. It is currently approved for the prophylaxis of organ rejection in kidney transplant recipients. Short and long-term data support the efficacy and safety of the once daily formulation[4, 5]. However, patients with a panel reactive antibody > 30% were excluded from the studies. It has therefore, not been studied in this patient population.

2 Purpose and rationale

The purpose of this pilot study is to determine safety and tolerability of tacrolimus extended-release in a population of HS renal transplant patients. Recipients will receive desensitization therapy consisting of IVIG and rituximab +/- PLEX per the standard of care at CSMC. All recipients will receive induction with alemtuzumab. Tacrolimus extended-release has not been studied in this patient population to date.

3 Objectives

3.1 Primary objectives

The primary objective is to determine the safety of tacrolimus extended-release in HS kidney transplant recipients after desensitization with IVIG and rituximab +/- PLEX per the standard of care and alemtuzumab induction.

3.2 Secondary objectives

Secondary objectives are to observe the following:

1. Change in DSA as defined by the DSA relative intensity score (RIS) defined by: 0 points for no DSA, 2 points for each weak DSA (MFI <5,000), 5 points for each moderate DSA (MFI 5,000 -10,000), and 10 points for each strong DSA (MFI >10,000)[1,2].

2. Tolerability as defined by the number of subjects discontinuing the study medication

4 Study design

The study will be a single center, pilot trial. It will be an open label, single-arm, non-controlled design. All HS kidney transplant recipients, age 18 and older, requiring desensitization may be included in the study. Initial desensitization protocol for LD or DD includes Intravenous Immunoglobulin (IVIG) 2g/kg (>70kg max 140g) given on day 0 (split over 2 days for peritoneal dialysis patients), rituximab 375mg/m^2 (rounded to the nearest 100mg vial) given on day 15, and IVIG 2g/kg (>70kg max 140g) given on day 30. Recipients for LD or DD who are unresponsive to IVIG/ritux (after 2 months for LD and after 6 months for DD) will require plasma exchange (PLEX) 5-7 sessions followed by IVIG 2g/kg (>70kg max 140g) and rituximab 375mg/m^2. Patients will be receiving acetaminophen, antihistamine, and steroid as premedication for all infusions.

A total of 20 subjects will be enrolled in the study. Subjects will take part in the study until they are one year post-transplant. All subjects will require informed consent. At the time of screening, subjects will receive a physical exam and undergo lab testing as detailed below in the evaluation schedule. Alemtuzumab (Campath 1H, Lemtrada) 30mg, will be administered subcutaneously to all subjects for induction immunosuppression immediately post-transplant. Maintenance immunosuppression will consist of tacrolimus extended-release, mycophenolate mofetil 500mg twice daily or mycophenolate sodium 360mg twice daily, and prednisone. Patients will receive antimicrobial prophylaxis per CSMC protocol. Lab tests and physical exams for safety will take place according to the evaluation schedule below. Safety will be assessed by the reporting of serious adverse events as described below.

Tacrolimus trough level, complete metabolic panel, liver function panel, complete blood count with differential, DSA, and urinalysis with culture will be assessed according to the evaluation schedule below. Subjects will complete the study at one year post-transplant. Consent may be withdrawn by the study participant at any time. The investigator may also withdraw the study participant at any time if there are any safety concerns.

Desensitization includes Intravenous Immunoglobulin (IVIG) 2g/kg (>70kg max 140g) given on day 0 (split over 2 days for peritoneal dialysis patients), rituximab 375mg/m^2 (rounded to the nearest 100mg vial) given on day 15, and IVIG 2g/kg (>70kg max 140g) given on day 30. Patients will require plasma exchange (PLEX) 5-7 sessions if they have received desensitization in the past. In this case, patients will receive PLEX daily x 5-7 sessions followed by IVIG 2g/kg (>70kg max 140g) and rituximab 375mg/m^2. Patients will be receiving acetaminophen, antihistamine, and steroid as premedication for all infusions.

5 Population

Male and female HS renal transplantation patients, 18 years of age and over, receiving a cadaveric or living donor kidney transplant may enter the study. Patients must

receive desensitization therapy. Twenty patients will be enrolled at CSMC for this pilot study. Patients who discontinue the study prematurely will not be replaced.

5.1 Inclusion Criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria:

1. Recipient of a deceased or living donor kidney allograft
2. Patients must have undergone desensitization with IVIG and rituximab with or without plasma exchange prior to transplant or be administered IVIG and rituximab peri-operatively (within seven days of transplant) post-transplant
3. Age 18 and over
4. Able to understand and provide informed consent
5. At transplant, patient must have an acceptable crossmatch (as defined as T-or B- FCMX ≤ 225 MCS) from non-HLA identical donor. Negative crossmatch is Tpronase FCMX <70; T- FCMX <50 and Bpronase FCMX <130; B-FCMX <100.

5.2 Exclusion criteria

1. Recipients of a dual simultaneous kidney/liver, kidney/heart, kidney/lung, or kidney/pancreas transplant
2. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes
3. Patients being treated with drugs that are <u>strong</u> inducers or inhibitors of cytochrome P450 3A4
4. Patients with a clinically significant systemic infection within 30 days prior to transplant
5. Patients who have any surgical or medical condition that may affect absorption of drug, such as severe diarrhea, active peptic ulcer disease, or uncontrolled diabetes mellitus, which in the opinion of the investigator, might significantly alter the absorption, distribution, metabolism and/or excretion of study medication
6. Women of childbearing potential who are either pregnant, lactating, planning to become pregnant during this trial, or with a positive serum or urine pregnancy test. Women of childbearing potential must be willing to agree to contraceptive practices.
7. Patients who are PCR positive for Hep B, Hep C, or HIV.

6 Treatment

6.1 Investigational drugs

This is a pilot study. All patients will receive tacrolimus extended-release adjusted to target trough levels, mycophenolate mofetil or mycophenolate sodium, and prednisone per CSMC practice. Tacrolimus extended-release will be supplied by Astellas with packs of open-label study drug. A prescription will be filled by the subject for all other drugs.

6.1.1 Patient numbering

Each patient is uniquely identified in the study by a unique subject ID. Upon signing the informed consent form, the patient is assigned a subject ID by the investigator. Once assigned to a patient, a patient number will not be reused.

6.1.2 Dispensing the study drug

Tacrolimus extended-release will be provided free of charge for the duration of the study. Study drug will only be provided up to 12 months post transplant which is the duration of the study. All subjects will be given a prescription for all other drugs to be filled at a local pharmacy after completion of the study.

6.1.3 Study drug supply, storage and tracking

Study drugs must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, all study drugs should be stored according to the instructions specified on the drug labels. Clinical supplies are to be dispensed only in accordance with the protocol.

6.1.4 Instructions for prescribing and taking the study drug

Medication labels will comply with the legal requirements. The investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Patients will be asked to return all unused study drug and packaging at the end of the study or at the time of study drug discontinuation.

The investigator should instruct the patient to take the study drug exactly as prescribed. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Study Drug Administration Record CRF. 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. It will be taken by mouth at the starting dose of 5mg orally or 0.07mg/kg (rounded to the nearest 1mg) daily. A therapeutic drug level will be checked after two doses of the investigational drug and then daily as per SOC. Tacrolimus trough levels will be adjusted to achieve a goal of 7 to 9 ng/ml for the first six months and goal of 5-8ng/ml thereafter (see Table 1).

The investigator and co-investigators are responsible for instructing the patients regarding the exact dose and dosing schedule to be followed. Instructions for taking

the drug will be given at the time of discharge and reinforced at subsequent office visits. Patients will be instructed to take the drug at 8am. They will be instructed to take the drug 2 hours after their last meal or 1 hour before their next meal preferably on an empty stomach and to swallow capsules whole (no crushing or chewing or dividing capsules).

Study Drugs
Patients will take tacrolimus extended-release daily on a consistent schedule with regard to time of day and relation to meals. No grapefruit or grapefruit juice should be taken throughout the study.

6.1.5 Permitted study drug dose adjustments and interruptions

Blood for tacrolimus extended-release trough levels will be obtained from all patients at the time points indicated in Flowchart of Procedures. Therapeutic drug monitoring will be mandatory for all patients throughout the study. For patients who are unable to tolerate the protocol-specified dosing scheme, dose adjustments and interruptions are permitted in order to keep the patient on study drug. PI will follow local practice guidelines for these adjustments and interruptions.

The first tacrolimus level should be drawn after two doses are administered. Tacrolimus extended-release dose adjustments should be made based on results of the trough levels from the local laboratory. Follow-up tacrolimus trough levels should be rechecked after any dose adjustments are made to ensure that the recommended troughs are achieved.

6.1.6 Treatment of Acute Rejection

Rejection episodes will be managed as per local practice. Solumedrol or anti-thymocyte globulin will be administered for cell-mediated rejection. IVIG with or without rituximab may be administered for antibody mediated rejection. Plasma exchange +/- eculizumab may be used for severe antibody mediated rejection.

6.1.7 Treatment of patients unable to tolerate oral medication

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. IV cyclosporine will be preferred due to difficulty checking IV tacrolimus levels (since it is a continuous infusion). Patients should be returned to tacrolimus extended-release oral medication as soon as possible.

7 Visit schedule and assessments

Table 7-1 lists all of the assessments and indicates with an “x” or “SOC” (for standard of care) the visits when they are performed. Patients should be encouraged to attend all visits on the designated day. However, visit windows will be allowed of ± 1day for Day 2, ± 2 days for Day 4, ± 3 days for

Day 7, Day 14, ± 7 days for Day 30, Month 2 and ± 14 days for Month 6, 9, 12.

Table 2 Assessment Schedule

Study Visit	Pre-op	Days						Month			
	Screening	Tx Day 0	2 ±1d	4 ±2 d	7±3d	14±3 d	30±3d	2±3d	6±7d	9±14d	12±14d
Informed Consent	X										
Inclusion/Exclusion	X										
Physical Exam	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC
Chest X-ray/ EKG[5]	SOC										
Transplant Serology / Donor Background	SOC										
Alemtuzumab Administration		SOC									
Safety Lab Tests[1]	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC
Urine Tests[2]				SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC
Tacrolimus extended-release Trough Level[3]			SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC
Viral Testing[4]							SOC	SOC	SOC	SOC	SOC
Serum Pregnancy Test[6]	X										
DSA*	SOC						SOC	SOC	SOC	SOC	SOC
Adverse Events		X	X	X	X	X	X	X	X	X	X

1. CBC and complete metabolic panel
2. Urinalysis
3. Tacrolimus extended-release levels will be monitored 4 days after a dose change or stopping of fluconazole
4. Blood test for: BKV, CMV

* .DSA will be done at time of transplant, and quarterly for the first year.

-For DD (diseased donor), sample will be drawn pre-op, prior to IVIG. Majority of patients would have received desensitization within the past 6-9 months prior to transplant.

-For LD, sample will be drawn prior to IVIG-2, but patient would already have received IVIG-1 and ritux 5 weeks prior to sample drawn.

5. Can be done within 6 months of screening date.
6. If subject is of childbearing age. [Not required if subject has a history of hysterectomy].

7.1 Patient demographics/other baseline characteristics

After informed consent has been signed and the patient's eligibility to participate in the study has been determined, baseline patient information will be obtained, such as date of birth, age, sex, race, full relevant medical history/current medical conditions, information on renal transplantation background of recipient and donor and on transplantation procedure. Results of a full physical examination at baseline, vital signs, blood chemistry and hematology, and serum creatinine.

7.2 Treatment exposure and compliance

All doses of study medication administered during the course of the study will be

recorded on the appropriate Study Drug Dosage Administration CRF. Compliance monitoring will be done during clinic visits via patients' interview and drug levels.

7.3 Safety

7.3.1 Acute Rejection

Renal biopsies will be collected for all cases of suspected acute rejection. Biopsies will be read by the local pathologist according to the Banff 2013 criteria. The results will be used for patient management for acute rejection and for the safety analysis.

7.3.2 Graft Loss

The allograft will be presumed to be lost if the patient requires dialysis for three consecutive months or longer and is not able to subsequently be removed from dialysis. . If the patient undergoes a graft nephrectomy, then the day of nephrectomy is the day of graft loss. Graft loss is considered a Serious Adverse Event and should be reported on the Serious Adverse Event CRF and the SAE form.

7.3.3 Death

In the event of patient death, an SAE form should be completed and reported. The events leading to the death should be entered on the Adverse Event CRF.

7.3.4 Renal function

Renal function will be assessed by measuring serum creatinine and by calculated GFR using the MDRD formula.

7.3.5 Viral PCR

CMV and BKV PCRs will be collected according to the schedule outlined in Table 2.

7.4 Physical examination

A thorough physical examination will be performed during the baseline period and at every subsequent study visit. Significant findings made after the start of study drug which meet the definition of an Adverse Event will be recorded on the Adverse Event monitoring log.

7.4.1 Vital signs

Vital signs (pulse rate, blood pressure and weight (to the nearest 0.1 kilogram [kg]) will be recorded at baseline, prior to the first morning administration of study medication, and at each subsequent visit.

7.4.2 Laboratory evaluations

A local laboratory (Cedars-Sinai Clinical Reference Laboratory) will be used to analyze the clinical laboratory data during the study.

Hematology

Hematology will include platelets, hemoglobin, red blood cell count, white blood cell count to be measured at every study visit.

Clinical chemistry

Biochemistry parameters will include sodium, potassium, chloride, calcium, magnesium, inorganic phosphate, blood urea nitrogen, creatinine, glucose, AST, ALT, alkaline phosphatase, total bilirubin.

Urinalysis
Measurements will be taken for cell count, glucose, and protein.

7.4.3 Pregnancy and assessments of fertility

Any female patient that becomes pregnant after the start of study medication should be discontinued and the patient switched to standard treatment. All pre-menopausal women who are not surgically sterile will have a serum pregnancy test at screening and a urine pregnancy test, if suspected, and at the end of study visit. A positive urine pregnancy test requires immediate interruption of study medication until serum B-hCG is performed and found to be negative. If positive, the patient must be discontinued from the trial. 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 or congenital abnormalities.

8 Safety monitoring

8.1 Adverse events

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Study drug includes the investigational drug under evaluation. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy. The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

8.2 Serious adverse event reporting

An SAE is defined as an event which:
- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization greater than 24 hours unless hospitalization is for:

1. routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
2. elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
3. treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
4. social reasons and respite care in the absence of any deterioration in the patient's

general condition is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

All SAEs that are **serious** and **reasonably or probably related** to tacrolimus extended-release will be reported to FDA and Astellas Pharma using MedWatch 3500A form (Appendix B).

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

All SAEs will be reported to Astellas. Their contact information is listed below:

Email: Safety-US@astellas.com.
Fax: 847.317.1241

Protocol exempted events: Unusually severe rejection episodes
Acute rejections are considered protocol exempted events. They should not be reported simply because they result in hospitalization thus meeting the criteria for SAEs. Acute rejection episodes will therefore not be routinely expedited to health authorities. However, acute rejections should be reported as SAEs if they are unusual in appearance, clinical course and/or are graft threatening.

8.3 Pregnancies
To ensure patient safety, each pregnancy in a patient on study drug must be reported within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

9 Data review and database management

9.1 Data collection
Designated research staff will enter data into a secure electronic database from source documents. Only the PI and designated research staff will have access to the database. All source documents will be kept in a secure, locked cabinet. All data will be reviewed for accuracy. Designated research staff will be trained in the use of the electronic database.

If patients live far from CSMC and are unable to come to their designated study visits within study windows, the study team will try to obtain study labs from the patient's local hospital/clinic. The results will be forwarded to CSMC for analysis.

9.2 Database management and quality control

Designated study staff will validate data on an ongoing basis. Any errors noted will be reviewed, confirmed, and then corrected. A statement noting the correction will be included. This study will be monitored by a formal DSMB. The DSMB will consist of the PI, appointed Co-PIs, and at least one member not part of the investigational group. The DSMB will review safety data quarterly and formulate a letter with recommendations for continuation.

10 Data analysis

A designated statistician will perform the statistical analysis.

10.1 Populations for analysis

All patients enrolled in the study will be included in the analysis.

10.2 Patient demographics/other baseline characteristics

Continuous variables will be summarized by sample size, mean, standard deviation, median, minimum, and maximum. Discrete variables will be summarized by frequencies and percentages.

10.3 Treatments (study drug, other concomitant therapies, compliance)

The average daily dose of tacrolimus extended-release will be summarized within defined time windows. These summaries will apply the following rule: On calculating dosage averages over a time period, zero doses will be used for periods of temporary interruption of study medication regardless of whether this was due to safety reasons, non-compliance or other reasons. The reasons for tacrolimus extended-release dose adjustments will be assessed at these time points. Other immunosuppressive medication will be summarized by WHO drug names. All non-immunosuppressive medications or non-drug therapies will be grouped into prior medications and concomitant medications.

10.4 Analysis of the primary objective(s)

10.4.1 Variable

The primary objective is treatment failure at one year post transplant. Treatment failure is defined as a composite of biopsy proven acute rejection (BPAR), graft failure, or death. BPAR is defined as ≥ Banff 1A using the Banff 2007 criteria. Discrete variables will be summarized by frequencies and percentages. Serious adverse events will be summarized. Categorical variables will be analyzed by Chi square and continuous variables by T-test.

10.4.2 Safety

Safety variables to be assessed include discontinuation from study, discontinuation from treatment, renal function, SAEs, notable events, and laboratory tests. The number of serious adverse events will be reported as an observation since this is a pilot study. Safety data will be reviewed quarterly by a PI and designated Co-PIs.

10.5 Sample size calculation

This is a pilot study therefore sample size calculation is not applicable. Twenty

patients will be enrolled.

11 Ethical considerations

11.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study and 8 weeks after study drug discontinuation. If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.3 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Astellas before study initiation.

11.4 Publication of study protocol and results

The results of this trial will be submitted for publication upon completion of the trial and after all data have been analyzed. The study protocol will be summarized as part of the submission.

12 Protocol adherence

12.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Astellas, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol.

13 References

1. Vo, A.A., et al., *Benefits of rituximab combined with intravenous immunoglobulin for desensitization in kidney transplant recipients.* Transplantation, 2014. **98**(3): p. 312-9.
2. Vo, AA. Sinha, A., Haas, M., et al. Factors predicting risk for antibody mediated rejection and graft loss in highly human leukocyte antigen sensitized patients transplanted after desensitization. Transplantation 2015 (Epub ahead of print).
3. Sapir-Pichhadze, R., A. Young, and S. Joseph Kim, *Living donor age and kidney transplant outcomes: an assessment of risk across the age continuum.* Transpl Int, 2013. **26**(5): p. 493-501.
4. Budde, K., et al., *Novel once-daily extended-release tacrolimus (LCPT) versus twice-daily tacrolimus in de novo kidney transplants: one-year results of Phase III, double-blind, randomized trial.* Am J Transplant, 2014. **14**(12): p. 2796-806.
5. Silva, H.T., et al., *Long-term follow-up of a phase III clinical trial comparing tacrolimus extended-release/MMF, tacrolimus/MMF, and cyclosporine/MMF in de novo kidney transplant recipients.* Transplantation, 2014. **97**(6): p. 636-41.

14 Appendices

A. DSMB Charter

Astagraf DSMB Charter 5.15.15.pdf

B. FDA Med Watch (Form 3500A)

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C. Tacrolimus Extended Release (Astagraf XL) Package Insert

Astagraf package insert.pdf