Early Substitution of Subcutaneous Abatacept for Belatacept as Costimulation Blockade to Minimize Calcineurin Inhibitors (CNI) Exposure After Kidney Transplantation

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Date: November 6, 2023

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RTB-016

Early substitution of subcutaneous abatacept for belatacept as costimulation blockade to minimize CNI exposure after kidney transplantation

SHORT TITLE Subcutaneous Abatacept in Renal Transplant Recipients

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Confidentiality Statement

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INVESTIGATOR SIGNATURE PAGE	
Protocol: RTB-016	**Version/Date:** Version 1.3 / November 6, 2023
Site Principal Investigator: [redacted]	
Title: Early Abatacept conversion in kidney transplant recipients receiving belatacept as costimulation blockade to minimi CNI exposure after kidney transplantation: A pilot study to assessment feasibility, tolerability, alloimmune events, graft function, and safety.	
Study Sponsor: Emory University School of Medicine	
INSTRUCTIONS: *The site Principal Investigator should print, sign, and date at the indicated location below.*	

I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 45 CFR part 46 and 21 CFR parts 50, 56, and 312, and in the International Conference on Harmonization (ICH) document *Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance* dated April 1996. Further, I will conduct the study in keeping with local legal and regulatory requirements.

As the site Principal Investigator, I agree to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without the written permission of the IRB and NIAID.

_____

Site Principal Investigator (Print)

_____ _____

Site Principal Investigator (Signature) **Date**

Protocol Synopsis

Title	Early substitution of subcutaneous abatacept for belatacept as costimulation blockade to minimize CNI exposure after kidney transplantation
Short Title	Subcutaneous Abatacept in Renal Transplant Recipients
Clinical Phase	Phase I
Number of Sites	Single center- Emory University Hospital, Atlanta, GA, USA
IND Sponsor/Number	Emory University, [redacted] IND number 151377
Study Objectives	• The coprimary objectives of this study are to: o Assess the logistics and feasibility of subcutaneous delivery of abatacept early post-transplant and the accrual and retention of study subjects during the first year after transplant to inform the potential design and conduct of further clinical development including Phase II and/or Phase III trials. o Explore the effectiveness (freedom from rejection) and safety (such as adverse events, serious adverse events, infections, cardiovascular, metabolic side-effects) of a regimen substituting subcutaneous abatacept for belatacept as a means of facilitating the improvement of long-term graft function by reducing exposure to calcineurin inhibitor-based immunosuppression. • Secondary objectives also include: o Additional assessments of effectiveness ▪ Renal allograft graft function: measurement of the levels, stability and trajectory of renal function (eGFR) in abatacept treated patients to inform the design of future prospective, randomized studies ▪ Renal allograft survival ▪ De novo donor-specific antibody formation o Mechanistic and biomarker studies with a focus on pharmacokinetics, pharmacodynamics (target receptor occupancy), T and B cell subsets (eg. Tregs).
Study Design	Phase I, open-label, prospective, single-arm single center study evaluating the feasibility, effectiveness and safety of a regimen substituting subcutaneous abatacept early post-transplant in place of intravenous belatacept as an immunosuppressant in first-time renal transplant recipients. There is a single arm in this study; Investigational (abatacept) group. Participants will be assigned to treatment regimen between 2 and 5 months after transplantation. The study drug will be administered until month 12

	post-transplant; at that point, all participants will be transitioned to a physician directed immunosuppressive regimen post-study. Study endpoints will be assessed at 12 months after transplantation.
Primary Endpoint(s)	**Primary feasibility endpoint** The proportion of subjects who tolerate subcutaneous injections and are compliant with self-administration as measured by abatacept administration logs and autoinjector accountability. **Primary Effectiveness (alloimmunity) endpoint** This primary effectiveness endpoint is the proportion of participants who remain free of biopsy proven acute T-cell mediated rejection (aTCMR) or antibody-mediated rejection (ABMR) as defined by Banff criteria at or before 12 months after transplantation. **Primary Safety Endpoints** • The cumulative incidence of serious adverse events • Incidence of serious infection of special interest (e.g. requiring hospitalization or prolonged therapy, including but not limited to treatment ≥ 20 days) • Incidence of patients with CMV viremia stratified by magnitude (≥35 but <10,000 or ≥10, 000) • Incidence of patients with BK viremia stratified by magnitude (undetected, >0 but < 1,000, ≥ 1,000 but <10,000 or ≥ 10,000 – 100,000, ≥100,000 or stratified by log, which is reported as a result.) • Incidence of any malignancy including PTLD
Secondary Endpoint(s)	**Additional Effectiveness Endpoints** • Proportion of subjects experiencing the composite outcome of death or allograft failure at or before 12 months after transplantation. • Proportion of subjects with biopsy proven acute T-cell mediated cellular rejection (BP-aTCMR) within 12 months of transplantation. • Proportion of subjects treated for rejection with any of the following: i) corticosteroids within 12 months, ii) T-cell depleting therapy within 12 months, iii) any other treatment for rejection within 12 months of transplantation • Proportion of subjects treated for acute rejection due to clinical suspicion rather than BP-aTCMR or BP-aABMR within 12 months of transplantation. • Proportion of subjects with biopsy proven active antibody mediated rejection (BP-aABMR) within 12 months of transplantation. • Proportion of subjects and time to event for the changes in allograft biopsies for the 5 categories of aTCMR specified in the Banff schema. • Proportion of subjects who develop de-novo donor specific antibody by 12 months. • Change in eGFR between abatacepet initiation and 12 months on treatment. • Days to events (TCMR, ABMR, de-novo DSA formation, graft loss).
Exploratory Endpoints	**Clinical** Patient preferences and attitudes toward subcutaneous and intravenous

	route of administration will be assessed based on questionnaires administered at enrollment and at study visits at month 6 and 12 post initiation of abatacept. **<u>Immunologic/Mechanistic</u>** • CD86 receptor occupancy on PBMC will be assessed before the initial dose of abatacept, and prior to abatacept administration at months 9, and 12 months post-transplantation. • The incidence and breadth of anti-HLA antibody (including DSA) development over time (evaluated at screening, , 3, 6 and 12 post-transplant) • Peripheral blood T and B cell subsets will be assessed before initiation of abatacept and on study at 6, 9, and 12 months post - transplant.
Accrual Objective	18 patients will be enrolled into a single, investigational arm receiving abatacept
Study Duration	20 months, with the last new accrual no later than 12/31/2023.
Treatment Description	Participants on qualifying belatacept regimen (with low dose tacrolimus, mmf and prednisone) will have their maintenance regimen changed from i.v. belatacept to s.c. abatacept, which will continue through week 52 (month 12) post-transplant: Costimulation blockade: - Abatacept 125 mg subcutaneous weekly Background maintenance: - Tacrolimus initial trough target 3-5 ng/ml. - Mycophenylate mofetil (MMF), no less than 500 mg bid; comparable dose of mycophenolic acid (MPA) (no less than 360 mg bid) or azathioprine (AZA no less than 2mg/kg daily) may be used instead as maintenance dose. - Prednisone 5 mg po daily.
Inclusion Criteria	1. Must be able to understand and provide informed consent. 2. Male or Female, 18-70 years of age at the time of enrollment (all races and ethnicities. 3. Negative crossmatch (virtual or physical) at time of transplant 4. First dose of Study Drug must be given no less than 8 weeks, no more than 20 weeks post-transplant. 5. First time renal transplant who has been treated with belatacept from the time of transplant, receiving tacrolimus (target trough 3-5 ng/ml), mycophenylate mofetil (or mycophenolic acid or azathioprine), prednisone (also see exclusion criteria). 6. eGFR ≥ 40ml/min/m^2 (using 2021 CKD-EPI equation). 7. Must have prior documented evidence of EBV seropositivity.

	8. Female study participants of childbearing potential must have a negative pregnancy test on Day 0 prior to receiving the first dose of study drug . 9. Agreement to use contraception; according to the FDA Office of Women's Health (http://www.fda.gov/birthcontrol), there are a number of birth control methods that are more than 80% effective. Female study participants of child-bearing potential and men must consult with their physician and determine the most suitable method(s) from this list to be used from the time that study treatment begins until after study completion. 10. Vaccines up to date as per DAIT guidance for patients in transplant trials.(Refer to Appendix 2: DAIT Vaccine Guidance for Patients in Interventional Adult Transplant Trials) 11. Study participants must have a negative purified protein derivative (PPD) or negative testing for tuberculosis using an approved IGRA blood test, such as QuantiFERON®-Gold TB or T-SPOT-TB assay. PPD or IGRA testing must be documented to have been performed within the 52 weeks before enrollment. Patients with latent TB may become eligible according to local or national guidelines following completion of treatment.
Exclusion Criteria	1. Inability or unwillingness of a study participant to give written informed consent or comply with study protocol. 2. Recipient of previous organ transplant of any type. 3. Multi-organ transplant. 4. cPRA >80 at time of enrollment. 5. History of any episode of biopsy-proven Banff rejection (including borderline rejection or any grade of acute TCMR) prior to enrollment. 6. History of any malignancy including lymphoma within 5 years of enrollment. Study participants with curatively treated non-melanomatous skin cancer or curatively treated cervical carcinoma in situ may be enrolled. 7. Any past or current issue which in the opinion of the investigator may pose additional risks to the participant in the study, may interfere with the study participant's ability to comply with the study requirements or that may impact the quality or interpretation of the data obtained from the study. 8. Human immunodeficiency virus (HIV): individuals known to be HIV positive. 9. Hepatitis C virus: any study participant who receives a kidney from a seropositive or HCV RNA PCR positive donor is ineligible. Any study participant who was HCV RNA PCR positive at transplant is ineligible. Any study participant with a history of HCV seropositivity or HCV infection who has not met criteria for sustained spontaneous clearance or sustained viral response to therapy is ineligible. 10. Hepatitis B virus: Individuals with any of the following are NOT eligible: • Recipient or donor positive for hepatitis B surface antigen (HBsAg) • Recipient or donor positive for antibodies to hepatitis B core antigen (anti-HBc) • Recipient or donor known to have had a positive HBV DNA

	PCR 11. Evidence of CMV viremia or clinical CMV infection at any time after transplant. 12. Kidney recipients who were CMV seronegative who received an organ from a CMV seropositive donor. 13. BK viremia of greater than 4.3 DNA log copies/ml (greater than 20,000 copies/ml) at any time post-transplant. 14. Active uncontrolled infection within 1 month of enrollment. 15. Clinically significant proteinuria (urinary protein/Cr ratio >1.0). 16. Receiving belatacept at a dose other than 5 mg/kg body weight. 17. Receiving mycophenolate mofetil at a dose of less than 1000 mg po QD (or mycophenolic acid or azathioprine equivalent). 18. Receiving prednisone at a dose greater than 5 mg po qd. 19. Presence of donor specific antibody by Luminex single antigen bead assay.
Study Stopping Rules	Satisfaction of any of the following stopping rules at any time during the post-transplant follow-up will trigger an ad hoc DSMB Safety Review. • Any unexpected fatal, or unanticipated life-threatening adverse event that is possibly or definitely related to the study treatment regimen or procedures • 2 Deaths • 2 Graft losses • 2 Incidences of BP-aTCMR Banff IIB or Banff III • 2 malignancies or life-threatening infections • 4 rejections in total (biopsy-proven or empirically treated) In addition to the mandated stopping rule thresholds noted, NIAID DSMB, NIAID medical/scientific observer, may pause enrollment after any single death, graft loss, Banff II, Banff III, malignancy or life-threatening infection event.
Participant Stopping Rules	Participants may be prematurely terminated from the study intervention for the following reasons. 1. The participant elects to withdraw consent from all future study activities, including follow-up. 2. The investigator or NIAID medical officer no longer believes that participation or treatment in the trial is in the best interest of the participant. 3. Study therapy may be prematurely discontinued for any participant if the participant has severe injection related hypersensitivity or injection related reaction. 4. Occurrence of Banff grade IIb or higher grade acute rejection 5. The participant dies. For subjects that terminate the study intervention, limited follow-up for safety events and clinical outcomes will continue unless the subject withdraws consent for any further follow-up.

Study Contacts: Participating Centers

SITE PRINCIPAL INVESTIGATOR

[redacted], MD
Associate Professor
Emory University
[redacted]

Study Contacts: Core Laboratories

EMORY TRANSPLANT CENTER
BIOREPOSITORY

[redacted]
Woodruff Memorial Research Bldg.
Emory University
[redacted]

Glossary of Abbreviations

aABMR	Acute antibody-mediated rejection
AE	Adverse Event
ABMR	Antibody mediated rejection
aTCMR	Acute T-cell Mediated Cellular Rejection (Cf Banff 2017 grading/definitions)
BID	Twice Daily
BKV	BK Polyoma Virus
BMS	Bristol Myers Squibb Company
BP-aABMR	Biopsy-Proven aABMR
BP-aTCMR	Biopsy-Proven aTCMR
CD	Cluster of Differentiation (e.g. CD28, CD152, CD4, CD8, etc.)
CFR	Code of Federal Regulations
CRF	Case Report Form
CMV	Cytomegalovirus
CNI	Calcineurin Inhibitor
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4, also known as CD152
DAIT	Division of Allergy, Immunology, and Transplantation
DNA	Deoxyribonucleic Acid
DSA	Donor specific antibody
DSMB	Data Safety Monitoring Board
DVT	Deep vein thrombosis
EAE	Experimental Allergic Encephalitis (Mouse multiple sclerosis model)
EM	Electron microscopy
FDA	Food and Drug Administration
FSGS	Focal Segmental Glomerulosclerosis
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus

HLA	Human Leukocyte Antigen
HUS/TTP	Hemolytic Uremia Syndrome/Thrombotic thrombocytopenic purpura
ICH	International Conference on Harmonization
Ig	Immunoglobulin
IHC	Immunohistochemistry
IND	Investigational New Drug
IRB	Institutional Review Board
KDPI	Kidney Donor Profile Indices
KLH	Keyhole Limpet Hemocyanin
MMF	Mycophenolate Mofetil
MPGN	Membranoproliferative Glomerulonephropathy
NIAID	National Institute of Allergy and Infectious Diseases
PE	Pulmonary Embolism
PI	[Site] Principal Investigator
PRA	Panel Reactive Antibody
PTLD	Post-transplantation Lymphoproliferative Disorder
RA	Rheumatoid Arthritis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
sc	Subcutaneous
SOT	Solid Organ Transplant
SUSAR	Serious Unexpected Suspected Adverse Reaction
PROMIS	Patient-Reported Outcomes Measurement Information System
TCMR	T-cell mediated rejection
TG	Transplant glomerulopathy
TMA	Thrombotic microangiopathy

Study Definitions Page

Acute Rejection	A clinical and histologic event that meets the Banff 2017 revised criteria for acute cellular rejection.
Antibody Mediated Rejection	A clinical and histologic event that meets the Banff 2017 revised criteria for antibody mediated rejection.
Banff 2017 Scoring Criteria (Kidney)	***Reference & further details given in Roufosse C, et al. A 2018 Reference Guide to the Banff Classification of Renal Allograft Pathology. Transplantation 2018; 102: 1795-1814.*** ***https://banfffoundation.org/wp-content/uploads/2019/01/A_2018_Reference_Guide_to_the_Banff_Classification.14-1.pdf*** ***Category 1: Normal biopsy or nonspecific changes*** ***Category 2: Antibody-mediated rejection*** Active ABMR Chronic, active ABMR C4d Staining without Evidence of Rejection ***Category 3: Borderline changes*** Suspicious (Borderline) for acute TCMR ***Category 4: T-cell-mediated rejection (TCMR)*** Acute TCMR (Grade IA, IB, IIA, IIB, III) Chronic Active TCMR (Grade I1, IB, II)
Donor Specific Antibodies	The presence of antibodies against antigens encoded by the HLA (human leukocyte antigen) complex that are expressed on the donor allograft.
Empirically treated rejection	Initiation of any treatment for rejection (e.g. steroids 10mg/kg or Thymoglobulin).
Graft Failure/Loss	Graft loss occurs when a graft is deemed irreversibly nonfunctional and is the earliest of the day that: • dialysis which continues for six consecutive weeks is begun, or • a transplant nephrectomy is performed, or • The participant is re-listed for kidney transplantation, or • Has an eGFR <15 for a period of 8 weeks.
Modified Intent-to-Treat Sample	All enrolled participants who receive at least a single dose of the study intervention (abatacept)
Investigational Agent	Abatacept ORENCIA®
Lost to Follow-up	Missing in-person follow-up visits and cannot be reached by telephone or mail.
NIAID Medical/Scientific Observer	NIAID staff who regularly meets with the protocol director/principle investigator and study team including sponsor-appointed medical monitor, to review the progress of the study, safety events, and reporting.
NIAID Project Manager	NIAID staff who coordinates key study activities, including maintaining versions of protocols and amendments, informed consent templates, study management calls with investigators, coordinators, and other study personnel.
Per Protocol Sample	Completes all study visits and has not had a protocol deviation that impacts the analysis

Principal Investigator	Investigator awarded NIH funding for the grant.
Program Officer	NIAID official who oversees the scientific and budgetary aspects of the grant.
Protocol Mandated Procedures	Any procedure performed solely for the purpose of this research study, not considered site-specific standard of care.
Regulatory Affairs Officer	IND sponsor staff responsible for regulatory aspects of the study, for studies when NIAID is not the IND sponsor.
Principal Investigator	Investigator awarded NIH funding for the grant.
Study Therapy Regimen	The investigational agent and all protocol required medications.
Women of Child-Bearing Potential	WOCBP includes any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥ 12 consecutive months), or women on hormone replacement therapy with documented serum follicle stimulating hormone levels >35 mIU/mL). Even women who are using oral, implanted, or injectable contraceptive hormones or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicide) to prevent pregnancy or practicing abstinence or where the partner is sterile (e.g., vasectomy), should be considered to be of child-bearing potential.

1. Study Hypotheses/Objectives

1.1. Hypotheses

The primary hypothesis of this study is that early substitution of subcutaneous abatacept for belatacept in an immunosuppressive regimen will effectively and safely allow for a minimization of exposure to CNI while preserving renal function and achieving acceptable alloimmune events.

1.2. Primary Objective

The coprimary objectives of this study are to:

- Evaluate the effectiveness (freedom from rejection) and safety (such as adverse events, serious adverse events, infections, cardiovascular, metabolic side-effects) of a regimen substituting subcutaneous abatacept for belatacept as a means of improving long-term graft function by reducing exposure to calcineurin inhibitor-based immunosuppression.
- Assess the logistics of subcutaneous delivery of abatacept and the accrual and retention of study subjects during the first year after transplant to potentially inform the potential design and conduct of further clinical development including Phase II and/or Phase III trials.

1.3. Secondary Objectives

Secondary objectives also include:

- Additional assessment of effectiveness (graft function, DSA).
- Measurement of the levels, stability and trajectory of renal function (eGFR) in abatacept treated patients to inform the design of future prospective, randomized studies.
- Mechanistic and biomarker studies with a focus on pharmacokinetics, receptor occupancy, T cell subsets (Tregs), donor cf-DNA, and blood transcriptomic profiles.

2. Background and Rationale

2.1. Background and Rationale for Investigational Product

Kidney transplantation for end-stage renal disease (ESRD) patients is associated with increased quality of life and reduced mortality compared with dialysis. Approximately 24,000 kidney transplants are performed in the United States annually. In contrast to sustained improvements in early post-transplant outcomes, much less progress has been made with long-term outcomes. Improvement of long-term outcomes remains an important goal. Long-term immunosuppressive therapy is necessary to prevent rejection, but toxicity associated with the most frequently used immunosuppressive drugs - particularly calcineurin inhibitors (CNIs) such as tacrolimus or cyclosporine - can ultimately lead to decreased renal function and result in the need for re-transplantation or return to dialysis. CNIs also increase the rates of serious post-transplant complications through associated metabolic and cardiovascular toxicities, including diabetes mellitus, hypertension, and hyperlipidemia.

Belatacept (Nulojix), a member of a novel class of immunosuppressive medications known as selective T-cell costimulation blocking agents, is an FDA approved alternative to CNI therapy for prophylaxis of kidney rejection in adults with 7-year outcomes data demonstrating significantly improved renal function, reduced risk of patient death, reduced risk of graft loss, and more favorable metabolic profile compared to CNI therapy (1). Additionally, belatacept more effectively blocks humoral responses that can lead to chronic injury and premature renal allograft failure. However, there are clinical and logistical barriers to broad adoption of belatacept. Studies have observed higher rates of early acute rejection (2), although our center has reduced acute rejection rates to standard levels by combining belatacept with transient, short-term CNI therapy (3). The logistical challenges related to the intravenous formulation of Belatacept and the requirement for costly, indefinite – likely life-long – monthly infusions has been problematic for both patients and infusion center capacity planning and scheduling. In the COVID-19 era, the requirement for in-person attendance and social distancing at infusion centers struggling to meet prior clinical demands as well as COVID-19 specific infusion services has intensified these challenges.

A promising approach to address these concerns was noted during periods of belatacept shortage which intensified beginning in 2017. During these periods, our team has utilized abatacept, an earlier selective T-cell costimulation blocking agent which differs from belatacept by only two amino acids. Abatacept is approved for use in rheumatoid arthritis (RA) and other autoimmune conditions, as well as prophylaxis of acute graft-versus-host disease (GVHD). We have reported our experience using abatacept as rescue immunosuppression in nine CNI intolerant kidney transplant recipients (4). There was 100% patient and graft survival after conversion to abatacept. They received abatacept for a median duration of 82 months with stable, long-term renal allograft function, with only a single patient experiencing one cellular rejection episode that responded fully to treatment, and no apparent increase in severity or frequency of infections (4).

Conversion to abatacept during the early post-transplant period will facilitate close monitoring and early detection of infections, rejection, adherence issues, or metabolic or other postoperative complications of the transplant procedure and medications. In contrast, while post-transplant complication rates decrease by 12-24 months after transplant, clinical visits are less frequent for patients who are stable, making early detection and close monitoring more difficult for patients.

2.2 Rationale for Investigational Dose and Regimen

Abatacept and belatacept are both fusion proteins targeting the CD80/CD86 receptor, acting as selective T-cell costimulation blocking agents. The dose of abatacept chosen for this trial follows the maintenance subcutaneous dose administered in rheumatoid arthritis or psoriatic arthritis; this dose was also used for 16 months of the ~21 months of one of the CNI intolerant patients treated at our center (4).

The doses of all other immunosuppressive agents will otherwise follow the early post-transplant Emory belatacept transplant regimen incorporating low-dose tacrolimus (target tacrolimus whole blood trough

between 3-5 ng/ml), mycophenylate mofetil (or mycophenolic acid or azathioprine), and prednisone 5 mg per day.

Specifically, participants on a qualifying belatacept regimen, defined as the Emory standard of care belatacept regimen consisting of Belatacept (iv monthly), tacrolimus (po, trough target 3-5 ng/ml), mycophenolate mofetil (500-1000 mg po bid) and prednisone (5 mg po daily), will have their iv monthly belatacept changed to sc weekly abatacept. They will receive sc abatacept through week 52 (month 12) post-transplant. If stable on the abatacept regimen and the patient prefers to remain on the sc abatacept at the end of study (month 12 post-transplant), then they will be maintained on this regimen. If the patient does not want to continue the sc abatacept regimen, then they will be converted back to belatacept iv monthly and resume our preferred, standard of care regimen of belatacept, tacrolimus, mycophenolate mofetil and prednisone.

3. Study Design

3.1. Description of Study Design

This is a phase I, open-label, prospective, single-arm single center study evaluating the effectiveness and safety of abatacept as a replacement for belatacept early post-transplant in first-time renal transplant recipients. There is a single arm in this study: an Investigational (abatacept) group. Participants will be assigned to treatment regimen for the first 12 months after transplantation.

During periods of belatacept unavailability, our team has utilized its predecessor abatacept, which is available as a subcutaneous formulation, as rescue immunosuppression in 9 CNI intolerant kidney transplant recipients (4). All nine patients experienced successful allograft salvage with 100% patient and graft survival (median 115 months) after conversion to abatacept. They received abatacept for a median duration of 82 months with stable, long-term renal allograft function, a single cellular rejection episode, and no clinically apparent protective immunity concerns. Hence our findings suggest that abatacept as conversion therapy in kidney transplant recipients may be a viable subcutaneous alternative to belatacept for long-term maintenance therapy to overcome logistical barriers derived from belatacept IV infusion requirements and enhance global uptake of costimulation blockade-based immunosuppressive strategies.

The holder of the IND for this study is Idelberto [redacted], MD. The IND number is 151377. Under Title 21 of the Code of Federal Regulations (21CFR §312.62) the investigator will maintain adequate records of the disposition of Abatacept, including the date and quantity of the drug received, to whom the drug was dispensed (participant-by-participant accounting), and a detailed accounting of any drug accidentally or deliberately destroyed. Records for receipt, storage, use, and disposition will be maintained by the study site. A drug-dispensing log will be kept current for each participant. This log will contain the identification of each participant and the date and quantity of drug dispensed. All records regarding the disposition of the investigational product will be available for inspection. The Emory Investigational Drug Services (IDS) will store the drug. They will dispense it to the research team. Our plan is for the research team to give the study drug to the research participant who will then self-administer. The research team will instruct the participant on how to administer the study drug on day of first dose. If they need further teaching, we will provide more instruction. When participant is comfortable with self-injection, we plan to supply the patient with enough study drug to last until Month 6 visit.

- Month 6 patient brings back needle box for drug reconciliation. They will be resupplied with study drug doses up to Month 12.
- Month 12 patient brings back needle box for drug reconciliation.

Schedule may be altered based on par level of study drug in IDS at time of resupply.

Adherence amongst the abatacept group will be monitored by visualization of the used auto-injectors by clinical research staff at designated study visits. Study subjects on abatacept will be asked to bring their used auto-injector syringes between study visits to the next visit to confirm compliance with the study drug. Additionally, a study drug administration diary will be maintained and verified at each study visit. If non-compliance is discovered by the clinical research team, this will be deemed a protocol deviation of medication non-adherence. If the non-adherence is deemed to pose a risk to the study subject or the integrity of the study as determined by the research team, the study subject will be converted back to standard of care with belatacept.

3.2. Primary Endpoint

Primary feasibility endpoint

The proportion of subjects who tolerate subcutaneous injections and are compliant with self-administration as measured by abatacept administration logs and autoinjector accountability.

Primary Effectiveness (alloimmunity) endpoint

This primary effectiveness endpoint is the proportion of participants who remain free of biopsy proven acute T-cell mediated rejection (aTCMR) or antibody-mediated rejection (ABMR) as defined by Banff criteria at or before 12 months after transplantation.

Primary Safety Endpoints

- The cumulative incidence of serious adverse events
- Incidence of serious infection of special interest (e.g. requiring hospitalization or prolonged therapy, including but not limited to treatment ≥ 20 days)
- Incidence of patients with CMV viremia stratified by magnitude (≥35 but <10,000 or ≥10, 000)
- Incidence of patients with BK viremia stratified by magnitude (undetected, >0 but < 1,000, ≥ 1,000 but <10,000 or ≥ 10,000 – 100,000, ≥100,000 or stratified by log, which is reported as a result)
- Incidence of any malignancy including PTLD

3.3. Secondary Endpoints

Additional Effectiveness Endpoint

- Proportion of subjects experiencing the composite outcome of death or allograft failure at or before 12 months after transplantation.
- Proportion of subjects with biopsy proven acute T-cell mediated cellular rejection (BP-aTCMR) within 12 months of transplantation.
- Proportion of subjects treated for rejection with any of the following: i) corticosteroids within 12 months, ii) T-cell depleting therapy within 12 months, iii) any other treatment for rejection within 12 months of transplantation
- Proportion of subjects treated for acute rejection due to clinical suspicion rather than BP-aTCMR or BP-aABMR) within 12 months of transplantation.

- Proportion of subjects with biopsy proven active antibody mediated rejection (BP-aABMR) within 12 months of transplantation.
- Proportion of subjects and time to event for the changes in allograft biopsies for the 5 categories of aTCMR specified in the Banff schema.
- Proportion of subjects who develop de-novo donor specific antibody by 12 months
- Change in eGFR between abatacept initiation and 12 months after transplant.
- Days to events (TCMR, ABMR, de-novo DSA formation, graft loss).

3.4 Exploratory Endpoints

Clinical

Patient preferences and attitudes toward subcutaneous and intravenous route of administration will be assessed based on questionnaires administered at enrollment and at study visits at month 6 and 12 post initiation of Abatacept.

Immunologic/Mechanistic

- CD86 receptor occupancy on PBMC will be assessed before the initial dose of abatacept, and prior to abatacept administration at months 9, and 12 months post-transplantation.
- The incidence and breadth of anti-HLA antibody (including DSA) development over time (evaluated at screening, 3, 6 and 12 post-transplant). <note in the SOE within 30days>
- Peripheral blood T and B cell subsets will assessed at 6, 9, and 12 months post-transplant transplant may fall before inclusion window).

4. Selection of Participants and Clinical Sites/Laboratories

4.1 Rationale for Study Population

As currently practiced, kidney transplantation provides outstanding 1 year patient and transplant survival. However, long term results remain suboptimal. Renal transplantation does not restore normal life expectancy to recipients. While calcineurin-inhibitor based immunosuppression regimens have been pivotal in achieving short-term success their narrow therapeutic window is seen as an impediment to overcoming barriers to long-term success, including cardiovascular-, metabolic- and nephro-toxicities, as well as break-through donor-specific antibody formation. As described in the xx section belatacept, a T cell costimulation-blocker improved GFR, and lowered death and graft loss at seven years. However, post-approval use of belatacept remains low. Barriers to utilization include concern over increased rates of rejection, a gap in drug availability and the challenges associated with short and long-term administration of intravenous medications to transplant recipients. While strategies to reduce rejection rates while preserving the benefits of improved renal function and reduced DSA have been reported, the logistical barriers remain. Abatacept, a similar costimulation blocker has been successfully used as rescue immunosuppression for kidney transplantation. Abatacept has both subcutaneous and intravenous formulations. The goal is to explore the feasibility/efficacy of conversion from intravenous belatacept to subcutaneous abatacept to aid in the design of larger trials to study abatacept as part of an immunosuppression for kidney transplant recipients.

4.2 Enrollment

The study team will approach potential enrollees shortly after transplantation. Study staff will provide information about the trial including the consent form, to interested patients.

4.3 Inclusion Criteria

Individuals who meet all of the following criteria are eligible for enrollment as study participants:

1. Must be able to understand and provide informed consent.
2. Male or Female, 18-70 years of age at the time of enrollment (all races and ethnicities).
3. Negative crossmatch (virtual or physical) at time of transplant.
4. First dose of Study Drug must be given no less than 8 weeks, no more than 20 weeks post-transplant.
5. First time renal transplant who has been treated with belatacept from the time of transplant, receiving tacrolimus (target trough 3-5 ng/ml), mycophenylate mofetil (or mycophenolic acid or azathioprine), prednisone (also see exclusion criteria).
6. eGFR ≥ 40ml/min/m^2 (using 2021 CKD-EPI equation).
7. Must have prior documented evidence of EBV seropositivity.
8. Female study participants of childbearing potential must have a negative pregnancy test on Day 0 prior to receiving the first dose of study drug .
9. Agreement to use contraception; according to the FDA Office of Women's Health (http://www.fda.gov/birthcontrol), there are a number of birth control methods that are more than 80% effective. Female study participants of child-bearing potential and men must consult with their physician and determine the most suitable method(s) from this list to be used from the time that study treatment begins until after study completion.
10. Vaccines up to date as per DAIT guidance for patients in transplant trials.(Refer to Appendix 2: DAIT Vaccine Guidance for Patients in Interventional Adult Transplant Trials)

11. Study participants must have a negative purified protein derivative (PPD) or negative testing for tuberculosis using an approved IGRA blood test, such as QuantiFERON®-Gold TB or T-SPOT-TB assay. PPD or IGRA testing must be documented to have been performed within the 52 weeks before enrollment. Patients with latent TB may become eligible according to local or national guidelines following completion of treatment.

4.4 Exclusion Criteria

Individuals who meet any of these criteria are not eligible for enrollment as study participants:

1. Inability or unwillingness of a study participant to give written informed consent or comply with study protocol.
2. Recipient of previous organ transplant of any type.
3. Multi-organ transplant.
4. cPRA >80 at time of enrollment.
5. History of any episode of biopsy-proven Banff rejection (including borderline rejection or any grade of acute TCMR) prior to enrollment.
6. History of any malignancy including lymphoma within 5 years of enrollment. Study participants with curatively treated non-melanomatous skin cancer or curatively treated cervical carcinoma in situ may be enrolled.
7. Any past or current issue which in the opinion of the investigator may pose additional risks to the participant in the study, may interfere with the study participant's ability to comply with the study requirements or that may impact the quality or interpretation of the data obtained from the study.
8. Human immunodeficiency virus (HIV): individuals known to be HIV positive.
9. Hepatitis C virus: any study participant who receives a kidney from a seropositive or HCV RNA PCR positive donor is ineligible. Any study participant who was HCV RNA PCR positive at transplant is ineligible. Any study participant with a history of HCV seropositivity or HCV infection who has not met criteria for sustained spontaneous clearance or sustained viral response to therapy is ineligible.
10. Hepatitis B virus: Individuals with any of the following are NOT eligible:
    - Recipient or donor positive for hepatitis B surface antigen (HBsAg)
    - Recipient or donor positive for antibodies to hepatitis B core antigen (anti-HBc)
    - Recipient or donor known to have had a positive HBV DNA PCR
11. Evidence of CMV viremia or clinical CMV infection at any time after transplant.
12. Kidney recipients who were CMV seronegative who received an organ from a CMV seropositive donor.
13. BK viremia of greater than 4.3 DNA log copies/ml (greater than 20,000 copies/ml) at any time post-transplant.
14. Active uncontrolled infection within 1 month of enrollment.
15. Clinically significant proteinuria (urinary protein/Cr ratio >1.0).
16. Receiving belatacept at a dose other than 5 mg/kg body weight.
17. Receiving mycophenolate mofetil at a dose of less than 1000 mg po QD (or mycophenolic acid or azathioprine equivalent).
18. Receiving prednisone at a dose greater than 5 mg po qd.
19. Presence of donor specific antibody by Luminex single antigen bead assay.

4.5 Selection of Clinical Sites/Labs

This single center study will be performed at the Emory University Hospital/Emory Transplant Center (ETC). The ETC and our team of investigators has extensive experience and a well-established infrastructure to support the proposed clinical research program. Emory investigators played a lead role in the design, conduct, analysis and interpretation of all phases of the preclinical and clinical development for belatacept, achieving high enrollment in the Phase 2 and 3 studies and maintaining follow-up of subjects for >10 years. Emory is the highest enrolling site (540 patients) in an FDA-mandated post-approval safety study (ENLIST). We have conducted many investigator-initiated studies including trials of alemtuzumab (Campath®) induction with belatacept, randomized trials of q 1 vs q2 month maintenance and belatacept vs conventional management to inhibit sensitization in patients with failing allografts. Further, Emory has conducted research in the NIH consortia (including the Immune Tolerance Network, Clinical Islet Transplantation Study, and Clinical Trials in Organ Transplantation). Emory has well-developed infrastructure to support mechanistic studies having served as a Core in NIH and industry-sponsored trials for flow cytometry and donor-specific antibody assessment.

The ETC is a large volume clinical transplant center performing in excess of 350 kidney transplants each year. When the inclusion and exclusion criteria were applied retrospectively to kidney transplants performed in a recent three-year period (2014-2016) the number of eligible candidates ranged from 105-133.

5 Known and Potential Risks and Benefits to Participants

5.1 Risks of Investigational Product or Intervention as cited in Investigator Brochure or Package Insert

Risks of Abatacept

The package insert for abatacept (ORENCIA®, Bristol Myers Squibb) lists the following adverse effects:[5] Most common adverse events (≥10%) are headache, upper respiratory tract infection, nasopharyngitis, and nausea.

- Serious infection, including sepsis and pneumonia, have been reported in patients treated with the intravenous form of abatacept. Some of these infections have been fatal.
- Serious infections have occurred in patients on concomitant immunosuppressive therapy which in addition to their underlying disease could further predispose them to infection.
- Hypersensitivity observed in <0.1% of patients treated with the intravenous form of the abatacept. Other reactions potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, each occurred in less than 0.9% of treated patients.
- May blunt effectiveness of immunizations.

5.2 Risks of Investigational Product or Intervention cited in Medical Literature

None

5.3 Risks of Other Protocol Specified Medications

5.3.1. Risks of Tacrolimus

Side effects of tacrolimus include hypertension, glucose intolerance, peripheral neuropathy, renal insufficiency, abnormal liver function studies, seizures, nausea, vomiting, confusion, hypomagnesaemia, tremulousness, neurotoxicity, posterior reversible encephalopathy syndrome (PRES), progressive multifocal leukoencephalopathy (PML), interstitial lung disease, BK nephropathy, and increased risk of secondary malignancies. Additional information about tacrolimus can be found in the package insert.

5.3.2. Risks of Maintenance Immunosuppressive Medications

Administration of all immunosuppressive and immunomodulatory therapies used presently to prevent rejection of transplanted tissues carry general risks of opportunistic infection and malignancy, including lymphoma (~1%), and skin cancers. These agents are not recommended for nursing mothers, and it is recommended (and mandated in the current protocol) that women of childbearing potential (WOCBP) use effective contraception throughout the study. For men, the effect of the study drug on sperm in not known. To protect against possible side effects, men should take precautions to prevent pregnancy in all sexual partners while taking the study drug and for 30 days after the last dose. Male subjects and the study doctor will discuss method of birth control to use throughout the study. We intend to monitor for the occurrence of infections and malignancy as described above and will implement appropriate treatment options as necessary.

5.3.3. Risks of Prednisone

Adverse effects of corticosteroid therapy associated with short-term therapy have included sodium retention-related weight gain and fluid accumulation, hyperglycemia and glucose intolerance, hypokalemia, gastrointestinal upset and ulceration, reversible depression of the hypothalamic-pituitary-

adrenal (HPA) axis, and mood changes ranging from mild euphoria and insomnia to nervousness, restlessness, mania, catatonia, depression, delusions, hallucinations, and violent behavior. Long-term use of prednisone may be associated with hypertension, hyperlipidemia, weight gain with Cushingoid features, osteopenia, and skin changes including acne and easy bruisability. We intend to monitor for the occurrence of corticosteroid side-effects and will implement appropriate treatment options as necessary.

5.3.4. Risks of Mycophenolate Acid Derivative (Mycophenolate Mofetil/MMF or enteric coated Mycophenolic Acid/MPA)

Mycophenolate mofetil (MMF) and enteric-coated mycophenolate sodium are approved (in combination with cyclosporine and corticosteroids) as immunosuppressive agents for renal, cardiac, and hepatic solid organ transplantation. Adverse events reported in > 30% of renal, cardiac or liver transplant patients receiving MMF were pain, fever, headache, asthenia, anemia, leukopenia, thrombocytopenia, leukocytosis, urinary tract infection, hypertension, hypotension, peripheral edema, hypercholesterolemia, hypokalemia, hyperglycemia, increased creatinine and BUN, cough, hypomagnesaemia, diarrhea, constipation, nausea, vomiting, respiratory infection, dyspnea, lung disorder, pleural effusion, tremor and insomnia. The side effect profile of enteric-coated mycophenolate sodium is similar to those of MMF.

There is an increased risk of developing lymphomas and other malignancies, particularly of the skin. Lymphoproliferative disease or lymphoma developed in 0.4% to 1% of patients receiving MMF 1000 - 1500 mg twice daily. Severe neutropenia developed in up to 2% of renal transplant recipients receiving MMF 1500 mg twice daily. MMF can cause fetal harm (including spontaneous abortion in the first trimester and can cause congenital malformations in the offspring of women who are treated during pregnancy) when administered to a pregnant woman. Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal and pure red cell aplasia have been reported in patients treated with MMF. Gastrointestinal bleeding (requiring hospitalization) has been observed in approximately 3% of renal, in 1.7% of cardiac, and in 5.4% of hepatic transplant patients treated with MMF 1500 mg twice daily. Additional information about MMF can be found in the package insert. Follow up as specified in the SOE will allow detection of the adverse events specified above. Management of mycophenolate associated adverse events will include dose reduction, conversion to MPA or azathioprine, or discontinuation of MMF.

5.4 Risks of Study Procedures

5.4.1. Kidney Transplant Rejection

All recipients of kidney transplants (except for transplant from identical twins) are at risk for rejection. Most rejection episodes are reversible with additional immunosuppression. All enrolled subjects shall be stringently monitored for empirically treated rejection, biopsy proven acute T cell mediated rejection, and biopsy proven active antibody mediated rejection episodes.

5.4.2. Blood Draws

The amount of blood that may be drawn from adult subjects for research purposes will not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over an eight-week period. All blood samples for the mechanistic study will be obtained at the time of scheduled blood draws, so there will be minimal additional risk associated with obtaining the study samples.

The subject may experience some discomfort at the site of the needle entry, bruising, swelling, redness, fainting, or local infection. The additional amount of blood could contribute to the development of anemia. The subject's clinical condition will be taken into consideration to determine if research blood tests can be performed.

5.4.3. Risks of Coronavirus Disease 2019 (COVID-19)

Early reports indicate an increased risk of critical illness and mortality in kidney transplant recipients infected with SARS-CoV-2, possibly due to chronic immunosuppression and co-existing conditions.[95,96] Given that both immunosuppressive agents including abatacept, mycophenylate mofetil, tacrolimus, and prednisone are associated with increased risk of infection in general, it is possible that study therapy may increase the risk of developing symptomatic severe COVID-19 illness in subjects who would have otherwise been asymptomatic. To limit this risk, potential participants must have received a primary series of COVID-19 vaccination and the most recent recommended booster available prior to transplantation.

5.5 Electronic Data Systems

It is possible that computer/data management systems could be maliciously attacked and personal identifiable information as well as other study documents compromised. There is also the potential of accidental loss of privacy during the consenting and enrollment process. To minimize or prevent this from happening, standard procedures such as using coded forms, locked files, and password protected, encrypted databases will be employed. Investigators and the appropriate study team members will complete training courses in secure data management/privacy. Finally, the Emory University data systems are fully compliant with Federal regulations and have up-to-date virus and malware protection.

5.6 Potential Benefits

This study might not provide direct or immediate benefit to study participants.

In general participants in clinical trials have more intensive follow-up than patients not enrolled in clinical trials, and this may be beneficial independent of study intervention.

6. Investigational Agent /Intervention

6.1 Investigational Agents: / Abatacept (ORENCIA®, Bristol Myers Squibb)

6.1.1. Formulation, Packaging, and Labeling

ORENCIA® (abatacept) ClickJect™ autoinjector is for subcutaneous administration and is clear to slightly opalescent, colorless to pale yellow solutions for subcutaneous administration.

ORENCIA® (abatacept) ClickJect™ autoinjector has a concentration of 125 mg/mL and is supplied as a single-dose disposable prefilled ClickJect autoinjector. The Type I glass syringe contained in the autoinjector has a coated stopper and fixed stainless steel needle (5 bevel, 27-gauge special thin wall,-inch needle) covered with a rigid needle shield. The autoinjector provides 125 mg of abatacept in 1 mL and is provided in a pack of 4 autoinjectors.

6.1.2. Storage

ORENCIA® (abatacept) ClickJect™ autoinjectors are stored at 2°C to 8°C (36°F to 46°F). Protect from light by storing in the original package until time of use. Do not allow the autoinjector to freeze.

6.1.3. Dosage, Preparation, and Administration

6.1.3.1. Dosage

Subjects will receive a weekly dose of 125mg/mL solution of ORENCIA® (abatacept) in a single dose prefilled ClickJect™ autoinjector.

6.1.3.2. Preparation & Labeling

ORENCIA® (abatacept) ClickJect™ autoinjector is a prefilled syringe, it does not require any preparation. Detailed and important information will be provided in the Package Insert regarding labeling, dispensing and accountability prior to dispensing to study subjects.

6.1.3.3. Administration

ORENCIA® (abatacept) ClickJect™ autoinjectors are intended for:

- Subcutaneous use only and are not intended for intravenous infusion.
- Use under the guidance of a healthcare practitioner.

After proper training in subcutaneous injection technique, a patient or the patient's caregiver may administer a subcutaneous injection of ORENCIA® (abatacept) (ClickJect™ autoinjector), if a healthcare practitioner determines that it is appropriate. Study subjects and/or caregivers will be instructed to follow the directions provided in the *Instructions for Use* for additional details on administration. Study subjects and/or caregivers will be specifically instructed to:

- Inject the full amount (which provides the proper dose of ORENCIA® (abatacept).
- Rotate injection sites, and to avoid injections into areas where the skin is tender, bruised, red, or hard.
- Visually inspect for particulate matter and discoloration prior to administration.

NOT to use ORENCIA® (abatacept) ClickJect™ autoinjectors exhibiting particulate matter or discoloration. ORENCIA® should be clear to slightly opalescent and colorless to pale yellow.

6.2 Drug Accountability

Under Title 21 of the Code of Federal Regulations (21CFR §312.62) the investigator will maintain adequate records of the disposition of Abatacept, including the date and quantity of the drug received, to whom the drug was dispensed (participant-by-participant accounting), and a detailed accounting of any drug accidentally or deliberately destroyed.

Records for receipt, storage, use, and disposition will be maintained by the study site. A drug-dispensing log will be kept current for each participant. This log will contain the identification of each participant and the date and quantity of drug dispensed.

All records regarding the disposition of the investigational product will be available for inspection.

The Emory Investigational Drug Services (IDS) will store the drug.

Disposal of ClickJect Autoinjectors

Subjects will be given a puncture-resistant container for disposal of the ClickJect ™ autoinjectors at visits weeks 2 and 24. Subjects will return the used puncture-resistant box to the clinical site at their week 24 and 52 visits.

6.3 Assessment of Participant Adherence with Investigational Agent

Subject adherence will be monitored by scheduled calls from the site's Study Coordinator on the day of injection, and by reviewing doses with patients at scheduled visits

6.4 Toxicity Prevention and Management

Immediate local or systemic reactions to abatacept injection will be monitored for doses given in clinic; i. At each study visit (See Appendix 1: Schedule of Events) subjects will be questioned and have laboratory screening for symptoms and signs of infection. In between study visits, subjects will be instructed to contact their study team in the event of fever or any other signs of infection or illness.

6.5 Premature Discontinuation of Investigational Agent

Study therapy may be prematurely discontinued for any participant if the participant has severe injection related hypersensitivity or injection related-reaction. During or following injection, participants who have severe injection-related hypersensitivity reactions will be discontinued from further abatacept administration. The management of severe injection reactions will be dictated by the signs and symptoms of the reaction.

Study therapy may also be prematurely discontinued for any participant if the investigator believes that the study treatment is no longer in the best interest of the participant, if the subject is judged non-compliant, or due to other safety concerns. Participants that prematurely discontinue the study therapy regimen will remain in the study for endpoint assessment.

7. Other Medications

7.1 Protocol Specified Immunosuppression

Renal transplant recipients will receive FDA-approved, immunosuppressive medications according to standard of care at Emory Transplant Center with or without investigational agent.

7.1.1. Mycophenolate Mofetil (MMF)

Inclusion of maintenance mycophenylate mofetil (minimum dose of 500 mg by mouth twice daily), mycophenolic acid (minimum dose 360 mg by mouth twice daily), or azathioprine (2 mg/kg by mouth daily) is required for study eligibility. The dose and route of MMF or MPA or AZA may be subsequently adjusted based on clinical conditions according to local standard of care.

7.1.2. Tacrolimus (Immediate or Extended-Release)

All study participants will be on tacrolimus at the time of study enrollment; after enrollment, the target whole blood tacrolimus trough level will be between 3-5 ng/ml.

7.1.3. Corticosteroids

The 5 mg maintenance dose will continue throughout the participation of the study. The prednisone dose may be adjusted by the site investigator according to the local standard of care (e.g. a steroid taper) after the treatment of acute rejection or gout flare.

7.1.4. Modification of immunosuppression protocol

If a participant cannot tolerate at least 2 consecutive doses of abatacept or 3 total doses or the site investigator determines that modification of the assigned immunosuppression regimen is in the best interest of the participant, the site investigator will modify the immunosuppression regimen for that participant. This will result in the participant being censored from the Per Protocol analysis of the assigned arm at that point. This would not be considered a protocol deviation.

7.1.5. Other permitted concomitant medications

Other non-immunosuppressive concomitant medications used as standard of care in the management of the kidney transplant subject (e.g., cholesterol lowering medications, blood pressure lowering medications, etc.) not specifically described in Section 7.3 *Prohibited Medications* are acceptable in the study. All immunosuppressive and non-immunosuppressive therapy information will be recorded on an eCRF in the study electronic data capture system.

7.2 Prophylactic Medications

7.2.1.CMV Prophylaxis

Seropositive Donor to Seronegative Recipient- these patients will be excluded from participation in the study.

Seropositive <u>or</u> Seronegative Donor to Seropositive Recipient- when tolerating PO or at discharge, subjects will receive an antiviral prophylaxis regimen with activity against CMV, HSV, and VZV (e.g., Valganciclovir) for 6 months post-transplant. Local standard practice or ID consultation may be used to choose or adjust an appropriate alternative regimen as needed clinically.

Seronegative Donor to Seronegative Recipient- When tolerating PO or at discharge, subjects will receive an antiviral regimen with activity against HSV and VZV (e.g. Valacyclovir) for 3 months post-transplant. Local standard practice or ID consultation may be used to choose or adjust appropriate alternative regimens as needed clinically.

Donor CMV	Recipient CMV	CMV Prophylaxis
+	-	These patients will be excluded from participation in the study
-	+	Subjects will receive antiviral prophylaxis regimen with activity against CMV, HSV, and VZV (e.g. Valganciclovir) 6 **months post-transplant** as per standard of care.
+	+	Subjects will receive antiviral prophylaxis regimen with activity against CMV, HSV, and VZV (e.g. Valganciclovir) **6 months post-transplant** as per standard of care.
-	-	When tolerating PO or at discharge, subjects will receive an antiviral regimen with activity against HSV and VZV (e.g. Valacyclovir) for 3 months post-transplant for HSV and VZV prophylaxis

7.2.2. Pneumocystis pneumonia (PCP) Prophylaxis

When tolerating oral medications, subjects will receive a PCP prophylaxis regimen (e.g. Bactrim™ [Trimethoprim-sulfamethoxazole]). Local standard practice or ID consultation may be used to choose or adjust appropriate alternative regimens as needed clinically. Alternatives include, but are not limited to, Aczone™ (dapsone), Mepron™ (atovaquone), or inhaled pentamidine.

7.3 Prohibited Medications

Prohibited medications for this protocol, except as specifically indicated in this protocol include: Any other investigational medications any time in the 4 weeks prior to study entry and for the duration of participation in the protocol

7.4 Rescue Medications

There are no rescue medications.

7.5 Treatment of Allograft Rejection

Subjects suspected of having a rejection episode on the basis of clinical signs, symptoms or on the basis of laboratory tests will have a transplant biopsy. The local pathologist will make rejection diagnoses. Any rejection diagnosis detected on any biopsy will be treated per local practice taking into account the Banff score, degree of allograft dysfunction (and/or degree or rate of change in function) and recipient co-morbidities and clinical status. If rejection is clinically suspected and treatment for rejection is administered without biopsy confirmation, this will be considered an episode of clinically treated acute rejection (CTAR). CTAR events will be collected in case report forms.

8.0 Study Mandated Procedures

Blood Draws

Since blood draws are necessary after kidney transplantation, additional research blood sample collection has been scheduled to coincide with standard of care testing whenever possible. Study subjects will also have non-standard of care blood draws for research purposes.

9. Study Procedures

9.1 Screening and Baseline Visit

The purpose of the screening period is to confirm eligibility and interest to participate in the study. Study personnel will review the subject's medical record for eligibility. For those meeting enrollment criteria, study personnel may initiate contact with the candidate either in a face-to-face visit or via phone. Study materials will be provided by mail, electronically, or in person. Candidates who are interested in participation, a final review of eligibility criteria will be performed immediately prior to enrollment and initiation of treatment.

A pregnancy test will be conducted on all female subjects of child-bearing potential. Either serum or urine pregnancy test will be acceptable; many subjects may be unable to provide a urine sample due to renal disease.

9.2 Enrollment

The research study will be explained in lay terms to each potential research participant. As the part of the informed consent process outlined in CFR Title 21 Part 50, an investigator or physician listed on the FDA 1572 Investigator of Record form will conduct a face-to-face meeting with the study candidate to review all of the required elements of informed consent. The potential study subject will sign an informed consent form before undergoing any study procedures. Once the informed consent process is complete, the subject is considered enrolled in the study. All enrolled subjects will be assigned a unique subject number and their disposition must be accounted for at the end of the study.

9.3 Study Visits or Study Assessments

Subjects enrolled in this study that initiate study-directed therapy will be followed until 12 months post-transplant. Clinical safety will be monitored through routine physical examinations and appropriate laboratory assessments. During this period, subjects will have repeated clinical/laboratory evaluations, as specified in the Schedule of Events (Appendix 1). Monthly study visits will have a window of +/- 5 days.

Subjects will have blood collected for mechanistic research studies at time points specified in the Schedule of Events (Appendix 1).

Assessment of Participant Adherence with Investigational Agent

Subject adherence will be monitored by the site's Study Coordinator at monthly study visits, at minimum.

<u>Clinical Assessments</u>

Assessments for the development of adverse events, serious adverse events, infections, rejections, graft loss, and hospitalizations will be completed at each study visit. All events will be reported using a designated electronic case report form (eCRF). Clinical evaluation of new onset diabetes will be continuous throughout the study. An updated log of immunosuppressive medications and concomitant medications will be collected at periodic visits or phone calls post-transplant.

Infections could influence results of noninvasive testing. We will therefore record and report hospitalizations for infection. Less serious infections that are diagnosed and treated on an outpatient basis during the interval between visits and confirmed by pertinent cultures or serologic studies as per the local site, will be collected and recorded at each study visit and reported using a designated case report form.

Viral Monitoring

All subjects will be monitored for CMV, and BKV infection by quantitative PCR in the blood per the Emory Transplant Center standard of care protocol (see Appendix 1).

Renal Biopsies (For Cause)

For-cause biopsies may be performed as dictated by the clinical team. A for-cause biopsy (i.e., graft dysfunction) may be performed in cases of increased serum creatinine, proteinuria, or other clinical symptoms at the discretion of the site Investigator. All biopsy reports will be collected, and predefined data elements will be entered into eCRFs. No extra research core will be obtained in this study.

Interpretation and management decisions of "for-cause" biopsies will be performed by the clinical care team and clinical pathologists. The clinical interpretation of the biopsy will be used for clinical management.

Glomerular Filtration Rate (GFR)

Glomerular Filtration Rate (GFR) will be estimated using the 2021 CKD-Epi equation. Demographic characteristics - gender and age - are required for calculation in addition to serum creatinine.

HLA laboratory testing

HLA typing, anti-HLA antibodies, Donor Specific Antibody and cPRA will be assessed by the Emory HLA Lab, a CLIA certified laboratory. cPRA and donor specific values as reported by the clinical lab will be used for secondary endpoints.

9.4 For-Cause Visits

If disease activity increases or other concerns arise between regularly scheduled visits, participants should be instructed to contact study personnel and may be asked to return to the study site for an "unscheduled" visit. Data will be collected from these visits and in some cases, additional research specimens may be collected.

9.5 Visit Windows

Study visits should take place within the visit windows specified in the Schedule of Events (Appendix 1).

10. Mechanistic Assays.

Mechanistic studies will be conducted at the Emory Transplant Center Research Laboratories. Given the focus of this exploratory study on the feasibility, safety and preliminary efficacy of early conversion to subcutaneous abatacept, many of these mechanistic studies will be exploratory in nature. We will look for signals that can be used for hypothesis generation and to design follow-on studies. Samples will be obtained from study participants at the time points indicated in the Table below, and the assays to be conducted.

- Mechanistic and biomarker studies with a focus on pharmacokinetics, receptor occupancy
- T and B cell populations will be assessed phenotypically using high-dimensional flow cytometry with a focus on T cell subsets that have been associated with increased risk of alloimmune events (eg "risky" subsets CD4+CD57+, CD8+ CD28-) and those that might associated with immune quiescence Treg.
- HLA DR/DQ eplet scores will be calculated from high resolution HLA typing.
- Exploration and gene expression profiles as a marker of rejection in the setting of costimulation blockade will be performed.

	Screening	3mo*	6mo	9mo	12mo	For Cause
Serum	~~x~~	x	x	x	x	x
PBMC	~~x~~	x	x	x	x	x

10.1 Pharmacokinetics and Pharmacodynamic monitoring

- CD86 receptor occupancy on PBMC will be assessed before the initial dose of Abatacept, and prior to abatacept administration at months 9, and 12 months post-transplantation.

10.2 Flow Cytometric Immunophenotyping

Peripheral blood T and B cell subsets will be assessed at study entry, 6, 9, and 12 months post-transplant. We will use the Immune Tolerance Network T and B cell panels. These panels will allow our study to assess the phenomena such as those noted above. Additional exploratory characterization of more detailed leukocyte (T, B, NK, monocyte) subsets of interest will also be possible with this approach. We will explore the T and B cell populations that will be assessed phenotypically using high-dimensional flow cytometry with a focus on T cell subsets that have been associated with increased risk of alloimmune events (eg "risky" subsets CD4+CD57+, CD8+ CD28-) and those that might be associated with immune quiescence Treg.

10.3 Assessment of association of HLA DR/DQ eplet scores and alloimmune events.

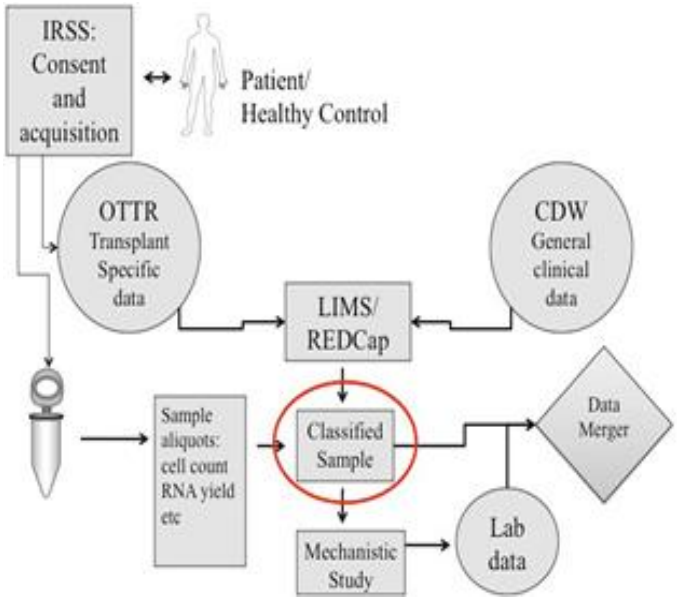
High resolution HLA typing will be used to calculate HLA DR/DQ eplet risk scores. We will explore the association of alloimmune events (rejection and DSA outcomes) with these scores.

10.4 GENE EXPRESSION PROFILES

Gene expression profiles through Immunoknow assay and exploratory RNASeq

Blood transcriptome will be assessed via the Immunoknow assay and by methods described by Orange et al. at baseline, 6, 9, and 12 months and at times of for-cause biopsies. In addition we will assess the feasibility of higher density sampling techniques using the Tasso devise. Patient will obtain ~100 µl of blood from skin using the automated Tasso collection system with q2 week samples and at for-cause to explore the feasibility of this approach in all or a subset of patients. We will explore the association of alloimmune events (rejection and DSA outcomes) with these transcriptomic profiles.

11. Biospecimen Storage



Biobanking will be performed at the Emory Transplant Center Biorepository. This is an established biobank with 290,000 banked specimens from Emory transplant patients including the largest repository of belatacept-treated patients in the world. The biorepository is equipped with pager-based communication with clinical coordinators to facilitate rapid sample transfer and has established SOPs.

Biological specimens (i.e. whole blood, serum, PBMC, and tissue) obtained under this protocol may be used in future assays to reevaluate biological responses as additional research tests are developed over time. These specimens will be collected at time points already scheduled for the core mechanistic studies, in order to allow specimens to be stored for use in new assays that have yet to be optimized or conceived, or assays performed by other investigators for cross-validation studies. Appropriate informed consent will be obtained for both the collection and storing of samples. The specimens from these evaluations may be stored beyond the funding period. During the funding period, samples will be identifiable, which means samples will be coded with a subject ID number that could be directly linked to the subject and the subject's medical record. When the funding period is over, samples will be anonymized, which means a sample that was previously identifiable, will have all identifiers removed and can no longer be linked back to the subject or the subject's medical record by any means.

Study participants will be informed that they may be approached about additional clinical evaluations or studies that have received the full approval of the NIAID as new evaluations are identified. If additional evaluations are determined to be desirable, this protocol (and other appropriate study documents, e.g., the informed consent and the statistical analysis plan) will be amended and submitted to the appropriate regulatory authorities, ethics committees, and IRBs for approval. Each participant's signature will be obtained on the revised informed consent form before additional evaluations are performed. The specimens from these evaluations may be stored up to the end of the contract—approximately 5 years, or longer if the contract is extended.

12. Criteria for Participant and Study Completion and Premature Study Termination

12.1 Participant Completion

At the end of 12 months post-transplant the patient will be converted to appropriate post-transplant immunosuppressive therapy as determined in conjunction with their transplant physician

12.2 Premature Discontinuation of Study Therapy

A subject will be considered as having initiated study-directed therapy once they have started abatacept therapies after consent obtained.

If study therapy is discontinued, the patient will be converted to appropriate post-transplant immunosuppressive therapy as determined in conjunction with their transplant physician.
A participant's study therapy will be discontinued for the following reasons:

1. Pregnancy
2. Patient refusal to continue study therapy
3. Side effect or intolerance of study therapy
4. Non-compliance or inability to comply with study therapy or clinical follow-up sufficient to jeopardize the participant well-being or the integrity of the study
5. Investigator discretion. The investigator may determine that study therapy is no longer in the best interest of the participant

12.2.1. Follow-up for Participants Prematurely Discontinued from Study Therapy

Study subjects who discontinue study therapy will continue to be followed with all scheduled study assessments and sample collection, unless the subject withdraws consent from all future study activities, including follow-up.

12.3 Participant Stopping Rules and Withdrawal Criteria

Participants may be prematurely terminated from the study intervention for the following reasons.

1. The participant elects to withdraw consent from all future study activities, including follow-up.
2. The investigator or NIAID medical officer no longer believes that participation or treatment in the trial is in the best interest of the participant.
3. Study therapy may be prematurely discontinued for any participant if the participant has severe injection related hypersensitivity or injection related reaction.
4. Occurrence of Banff grade IIb or higher grade acute rejection
5. The participant dies.

For subjects that terminate the study intervention, limited follow-up for safety events and clinical outcomes will continue unless the subject withdraws consent for any further follow-up.

12.4 Participant Replacement

Participants who do not start the investigational abatacept treatment will be replaced. Participants who receive even a partial dose of abatacept and subsequently withdraw, or are withdrawn, will not be replaced.

12.5 Follow-up after Early Study Withdrawal

If a participant is withdrawn from the study for any reason, the participant may be asked to complete a final visit and/or final assessments. The final visit will include:

1. An assessment of events including AE/SAE, infections, rejection, death, malignancy, graft loss, etc.
2. Physical Exam
3. List of medications, including immunosuppressive medication doses
4. Collection of blood for standard laboratory values (serum Cr, fasting lipid profile, HbA1c, viral monitoring)
5. HLA antibody assessment
6. Mechanistic Studies

12.6. Study Stopping Rules

Study enrollment will be suspended pending expedited review of all pertinent data by the institutional review board (IRB), the NIAID medical/scientific observer, and the NIAID Data Safety Monitoring Board (DSMB), if any unexpected, fatal, or unanticipated life-threatening AE that is possibly or definitely related to the study treatment regimen or procedures.

Continuous Monitoring of Specific Events

Satisfaction of any of the following stopping rules at any time during the post-transplant follow-up will trigger an ad hoc DSMB Safety Review.

- Any unexpected fatal, or unanticipated life-threatening adverse event that is possibly or definitely related to the study treatment regimen or procedures
- 2 Deaths
- 2 Graft losses
- 2 Incidences of BP-aTCMR Banff IIB or Banff III
- 2 malignancies or life-threatening infections
- 4 rejections in total (biopsy-proven or empirically treated)

In addition to mandated stopping rule thresholds noted, NIAID DSMB, NIAID, or the study NIAID medical/scientific observer may pause enrollment after any single death, graft loss, Banff II, Banff III, malignancy or life-threatening infection event.

13. Safety Monitoring and Reporting

13.1 Overview

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting those data. Adverse events that are classified as serious according to the definition of health authorities must be reported promptly (per Section 13.5, *Reporting of Serious Adverse Events and Adverse Events*) to the funding agency (DAIT/NIAID). Appropriate notifications will also be made to site investigators, Institutional Review Boards (IRBs), and health authorities.

Information in this section complies with *ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6(R2): Guideline for Good Clinical Practice*, 21CFR Parts 312 and 320, and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 : http://ctep.cancer.gov/reporting/ctc.html.

13.2 Definitions

13.2.1 Adverse Event (AE)

Any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in 21 CFR 312.32(a), the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E-6*(R2)* Guidelines for Good Clinical Practice and OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (1/15/07)" http://www.hhs.gov/ohrp/policy/advevntguid.html#Q2)

For this study, an adverse event will include any untoward or unfavorable medical occurrence associated with:

- **Study therapy regimen**:
  Investigational Agent: Abatacept (Orencia)
  Maintenance Immunosuppression: tacrolimus
  Maintenance Immunosuppression: Mycophenolate mofetil (e.g. Cellcept), mycophenolic acid (e.g. Myfortic) or azathioprine (e.g. Imuran)
  Maintenance Immunosuppression: prednisone

- **Study mandated procedures**:
  Blood Draw – any AE occurring within 24 hours after study mandated blood draw.

13.2.2 Suspected Adverse Reaction (SAR)

Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (21 CFR 312.32(a)).

13.2.3 Unexpected Adverse Event

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the package insert or is not listed at the specificity, or severity that has been observed; or, is not consistent with the risk information described in the general investigational plan or elsewhere in the IND.

"Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the package insert as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation (21 CFR 312.32(a)*)*.

13.2.4 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator results in any of the following outcomes (21 CFR 312.32(a)):

1. Death.
2. A life-threatening adverse event: An AE or SAR is considered "life-threatening" if, in the view of the investigator*,* its occurrence places the subject at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
3. Inpatient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. Congenital anomaly/birth defect.
6. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Elective hospitalizations or procedures for health maintenance and/or, hospital admissions for the purpose of conducting protocol mandated procedures are not to be reported as an SAE unless hospitalization is prolonged due to complications.

For this study transmission of an infectious agent via a study drug, whether pathogenic or nonpathogenic, will be considered an important medical event and reported as an SAE.

13.3 Grading and Attribution of Adverse Events

13.3.1 Grading Criteria

The study site will grade the severity of adverse events experienced by the study subjects according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events. The NCI-CTCAE has been reviewed by the *[specify: Protocol Chair(s), Principal Investigator, etc.]* and has been deemed appropriate for the subject population to be studied in this protocol.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

Grade 1 = mild adverse event.

Grade 2 = moderate adverse event.

Grade 3 = severe and undesirable adverse event.
Grade 4 = life-threatening or disabling adverse event.
Grade 5 = death.

Events grade 2 or higher will be recorded on the appropriate AE case report form (eCRF) for this study.

For grading an abnormal value or result of a clinical or laboratory evaluation (including, but not limited to, a radiograph, an ultrasound, an electrocardiogram, etc.), a treatment-emergent adverse event is defined as an increase in grade from baseline or from the last post-baseline value that doesn't meet grading criteria. Changes in grade from screening to baseline will also be recorded as adverse events but are not treatment-emergent. If a specific event or result from a given clinical or laboratory evaluation is not included in the NCI-CTCAE manual, then an abnormal result would be considered an adverse event if changes in therapy or monitoring are implemented as a result of the event/result.

13.3.2 Attribution Definitions

The relationship, or attribution, of an adverse event to the study therapy regimen or study procedure(s) will initially be determined by the site investigator and recorded on the appropriate AE form *(AE/SAE eCRF).* The relationship of an adverse event to study therapy regimen or procedures will be determined using the descriptors and definitions provided in Table 13.3.2.

For additional information and a printable version of the NCI-CTCAE manual, please consult the NCI-CTCAE web site: http://ctep.cancer.gov/reporting/ctc.html.

Table 13.3.2 Attribution of Adverse Events

Code	Descriptor	Relationship (to primary investigational product and/or other concurrent mandated study therapy or study procedure)
UNRELATED CATEGORY		
1	Not Related	The adverse event is clearly not related: there is insufficient evidence to suggest a causal relationship.
RELATED CATEGORIES		
2	Possibly Related	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
3	Related	The adverse event is clearly related.

13.4 Collection and Recording of Adverse Events

13.4.1 Collection Period

Adverse events will be collected from the time of initiation of investigational treatment until a subject completes study participation, or until 30 days after he/she prematurely withdraws (without withdrawing consent) or is withdrawn from the study.

Elective hospitalization or hospital admissions for the purpose of conducting protocol mandated procedures are not to be reported as an AE unless hospitalization is prolonged due to complications and meets an SAE definition.

13.4.2 Collecting Adverse Events

Adverse events (including SAEs) may be discovered through any of these methods:

- Observing the subject.
- Interviewing the subject [e.g., using a checklist, structured questioning, diary, etc.].
- Receiving an unsolicited complaint from the subject.
- In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an adverse event, as defined in Section 13.3, *Grading and Attribution of Adverse Events.*

13.4.3 Recording Adverse Events

Throughout the study, the investigator will record adverse events and serious adverse events as described previously (Section 13.2, *Definitions)* on the appropriate form *(AE/SAE eCRF]* regardless of the relationship to study therapy regimen or study procedure.

Once recorded, an AE/SAE will be followed until it resolves with or without sequelae, or until the end of study participation, or until 30 days after the subject prematurely withdraws (without withdrawing consent)/or is withdrawn from the study, whichever occurs first.

13.5 Reporting of Serious Adverse Events and Adverse Events

13.5.1 Reporting of Serious Adverse Events to the sponsor

This section describes the responsibilities of the site investigator to report serious adverse events to the sponsor via Data coordinating core eCRF. Timely reporting of adverse events is required by 21 CFR 312.32 and ICH E6 guidelines.

Site investigators will report all serious adverse events (see Section 13.2.3, *Serious Adverse Event)*, regardless of relationship or expectedness within 24 hours of discovering the event.
For serious adverse events, all requested information on the AE/SAE eCRF will be provided. However, unavailable details of the event will not delay submission of the known information. As additional details become available, the AE/SAE eCRF will be updated and submitted.

13.5.2 Reporting to Health Authority

After an adverse event requiring 24-hour reporting (per Section 12.5.1, *Reporting of Serious Adverse Events to Sponsor*) is submitted by the site investigator there are two options for the investigator/sponsor to report the adverse event to the appropriate health authorities:

13.5.2.1 Annual Reporting

The sponsor will include in the annual study report to health authorities all adverse events classified as:

- Serious, expected, suspected adverse reactions (see Section 13.2.1.1, *Suspected Adverse Reaction,* and Section 13.2.2, *Unexpected Adverse Event*).
- Serious and not a suspected adverse reaction (see Section 13.2.2, *Suspected Adverse Reaction*).
- Pregnancies.

Note that all adverse events (not just those requiring 24-hour reporting) will be reported in the Annual IND Report.

13.5.2.2 Expedited Safety Reporting
This option, with 2 possible categories, applies if the adverse event is classified as one of the following:

Category 1: **Serious and unexpected suspected adverse reaction** [**SUSAR]** (see Section 13.2.1.1, *Suspected Adverse Reaction* and Section 13.2, *Unexpected Adverse Event* and 21 CFR 312.32(c)(1)i).

The sponsor shall report any suspected adverse reaction that is both serious and unexpected in an expedited manner. The sponsor shall report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

A. A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, or Stevens-Johnson Syndrome);
B. One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
C. An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

Certain SAEs occur commonly in this study population and will not be considered as a SUSAR unless there is evidence to suggest a causal relationship to the study intervention. These events will be captured in the study database but will not be reported as expedited Safety Reports:

Category 2: **Any findings from studies that suggests a significant human risk**
The sponsor shall report any findings from other epidemiological studies, analyses of adverse events within the current study or pooled analysis across clinical studies or animal or *in vitro* testing (e.g. mutagenicity, teratogenicity, carcinogenicity) that suggest a significant risk in humans exposed to the drug that would result in a safety-related change in the protocol, informed consent or package insert or other aspects of the overall conduct of the study.

The sponsor shall notify the appropriate health authorities including the FDA and all participating investigators of expedited Safety Reports within 15 calendar days; unexpected fatal or immediately life-threatening suspected adverse reaction(s) shall be reported as soon as possible or within 7 calendar days.

13.5.3 Reporting of Adverse Events to IRBs/IECs
All investigators shall report adverse events, including expedited reports, in a timely fashion to their respective IRBs/IECs in accordance with applicable regulations and guidelines.

13.6 Pregnancy Reporting

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration the investigator shall be informed immediately of any pregnancy in a study subject or a partner of a study subject. A pregnant subject shall be instructed to stop taking study medication. The investigator shall counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the pregnant subject shall continue until the conclusion of the pregnancy.

All pregnancies identified during the study shall be followed to conclusion and the outcome of each must be recorded. The Pregnancy eCRF shall be updated when details about the outcome are available. When possible, similar information shall be obtained for a pregnancy occurring in a partner of a study subject. Information on this pregnancy will be collected on the Pregnancy [eCRF]. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

Information requested about the delivery shall include:

- Gestational age at delivery
- Birth weight, length, and head circumference
- Gender
- Appearance, pulse, grimace, activity, and respiration (APGAR) score at 1 minute, 5 minutes, and 24 hours after birth, if available
- Any abnormalities

All pregnancy complications that result in a congenital abnormality, birth defect, miscarriage, and medically indicated abortion are considered a SAE and shall be submitted to the FDA using the SAE reporting procedures described above.

13.7 Reporting of Other Safety Information

The investigator shall promptly notify the site IRB as well as the cooperative agreement funding agency (DAIT/NIAID) when an “unanticipated problem involving risks to subjects or others” is identified, which is not otherwise reportable as an adverse event.

13.8 Review of Safety Information

13.8.1 NIAID Medical/Scientific Observer notification

The NIAID Medical/Scientific observer shall be notified within 24 hours of any safety event that is reported expeditiously to the health authority. In addition, the NIAID Medical/Scientific observer shall receive reports no less than monthly to assess new and accumulating information on AEs, SAEs, and pregnancies recorded by the study site(s) on appropriate eCRFs.

In addition, the NIAID Medical/Scientific observer shall be notified of the disposition of the SAE and pregnancy reports, (See Sections 13.5.1, *Reporting of Serious Adverse Events to Sponsor*, and 13.6, *Pregnancy Reporting*).

13.8.2 DSMB Review

13.8.2.1 Planned DSMB Reviews

The Data and Safety Monitoring Board (DSMB) shall review safety data every 6 months during DSMB Data Review Meetings. Data for these safety reviews will include, at a minimum, a listing of all reported AEs and SAEs.

The DSMB will be informed of an Expedited Safety Report in a timely manner.

13.8.2.2 *Ad hoc* DSMB Reviews

In addition to the pre-scheduled data reviews and planned safety monitoring, the DSMB may be called upon for *ad hoc* reviews. The DSMB will review any event that potentially impacts safety at the request of the protocol chair or the sponsor-investigator, or the Medical/Scientific observer from the grant funding agency (DAIT/NIAID). In addition, the following events will trigger an *ad hoc* comprehensive DSMB Safety Review:

- The occurrence of a Grade 4 or higher SAE which is related and unexpected in more than 2 study participants who have received a study treatment
- The occurrence of a Grade 3 or higher SAE which is related and unexpected in more than 4 study participants who have received a study treatment

After review of the data, the DSMB will make recommendations regarding study conduct and/or continuation.

13.8.2.2.1 Temporary Suspension of enrollment for *ad hoc* DSMB Safety Review

See Section 12.2 for Participant Stopping Rules and Withdrawal Criteria
A temporary halt in enrollment *will* be implemented if an *ad hoc* DSMB safety review is required.

Subjects will continue on therapy and protocol specified screening, unless otherwise directed by the DSMB. In the absence of instructions from the DSMB, the site shall discuss any proposed modifications to therapy and protocol directed screening with the NIAID Medical/Scientific Observer .

13.9 Study Ability to Detect Uncommon Safety Events

Adverse Events (AE) include serious infections (COVID-19, CMV disease, pneumonia, BK) and serious disorders (gastrointestinal, cardiac, vascular, PTLD). The table below addresses safety using adverse event probabilities based on the targeted enrollment of 18 patients. The table provides the binomial probabilities of observing 0, 1+, 2+ or 3 or more occurrences of an AE during follow-up.

Adverse Event Probabilities for n=18 treated patients

Event Rate (AE)	Probability [0 / 18 Events]	Probability [1+ / 18 Events]	Probability [2+ / 18 Events]	Probability [3+ / 18 Events]
0.05	0.40	0.60	0.23	0.06
0.10	0.15	**0.85**	0.55	0.27
0.15	0.05	0.95	0.78	0.52

Thus, we can be **85%** sure of observing at least one episode of a rare AE if the true rate of an AE is 10%.

Adverse Events and Laboratory Toxicities: All adverse events will be classified using the Common Terminology Criteria for Adverse Events (CTCAE). Each adverse event and each laboratory toxicity will be counted only once per participant as the most severe level reported during the first year of follow-up. Tabular summaries of the number of participants reporting each AE, for both treatment-related and unrelated AEs as well as just treatment related AEs, respectively will be reported. Adverse events and grade III or higher laboratory toxicities observed during the first year of follow-up will be reported by treatment group.

14. Statistical Considerations and Analytical Plan

14.1 Overview

This is a phase I, open-label, prospective, single-arm, single center clinical trial in which 18 first-time recipients early conversion from a belatacept based regimen to abatacept, after week 8 and prior to week 20. All recipients will receive low dose tacrolimus, MMF (or MPA or azathioprine), and prednisone as a maintenance immunosuppression regimen. The coprimary objective of the study are:

- to assess the logistics and feasibility of subcutaneous delivery of abatacept early post-transplant and the accrual and retention of study subjects during the first year after transplant to inform the potential design and conduct of further clinical development including Phase II and/or Phase III trials,
- and to explore the effectiveness (freedom from rejection) and safety (such as adverse events, serious adverse events, infections, cardiovascular, metabolic side-effects) of a regimen substituting subcutaneous abatacept for belatacept as a means of facilitating the improvement of long-term graft function by reducing exposure to calcineurin inhibitor-based immunosuppression.

14.2 Endpoints/Analysis Plan

All analyses will be detailed in the statistical analysis plan. All analyses will be performed using the SAS System version 9.4 (or higher).

14.2.1 Analysis Populations.

Modified Intent-to-treat (mITT) sample – all enrolled subjects who start abatacept therapy. Subjects who receive drug but who do not remain on the protocol regimen will be used in this population. Enrolled subjects who do not receive any doses of abatacept will be excluded from this population.

Per Protocol (PP) sample – all enrolled subjects who receive abatacept and who remain on the assigned maintenance immunosuppressive regimen without major protocol deviations of concern.

14.2.2 Primary Analysis of Primary Endpoint(s)

Primary feasibility endpoint

The proportion of subjects who tolerate subcutaneous injections and are compliant with self-administration as measured by abatacept administration logs, autoinjector accountability, pharmacokinetics and pharmacodynamic measures of target molecule (CD86) receptor occupancy.

Primary Effectiveness (alloimmunity) endpoint

This primary effectiveness endpoint is the proportion of participants who remain free of biopsy proven acute T-cell mediated rejection (aTCMR) or antibody-mediated rejection (ABMR) as defined by Banff criteria at or before 12 months after transplantation.

Primary Safety Endpoints

- The cumulative incidence of serious adverse events
- Incidence of serious infection of special interest (e.g. requiring hospitalization or prolonged therapy, including but not limited to treatment ≥ 20 days)
- Incidence of patients with CMV viremia stratified by magnitude (≥35 but <10,000 or ≥10, 000)

- Incidence of patients with BK viremia stratified by magnitude (undetected, >0 but < 1,000, ≥ 1,000 but <10,000 or ≥ 10,000 – 100,000, ≥100,000 or stratified by log, which is reported as a result)
- Incidence of any malignancy including PTLD

14.2.3 Analyses of Secondary and Other Endpoint(s)

Additional Effectiveness Endpoints

- Proportion of subjects experiencing the composite outcome of death or allograft failure at or before 12 months after transplantation.
- Proportion of subjects with biopsy proven acute T-cell mediated cellular rejection (BP-aTCMR) within 12 months of transplantation.
- Proportion of subjects treated for rejection with any of the following: i) corticosteroids within 12 months, ii) T-cell depleting therapy within 12 months, iii) any other treatment for rejection within 12 months of transplantation.
- Proportion of subjects treated for acute rejection due to clinical suspicion rather than BP-aTCMR or BP-aABMR) within 12 months of transplantation.
- Proportion of subjects with biopsy proven active antibody mediated rejection (BP-aABMR) within 12 months of transplantation.
- Proportion of subjects and time to event for the changes in allograft biopsies for the 5 categories of aTCMR specified in the Banff schema.
- Proportion of subjects who develop de-novo donor specific antibody by 12 months
- Change in eGFR between abatacept initiation and 12 months on treatment.
- Days to events (TCMR, ABMR, de-novo DSA formation, graft loss)

14.2.4 Analyses of Exploratory Endpoint(s)

Clinical

Patient preferences and attitudes toward subcutaneous and intravenous route of administration will be assessed based on questionnaires administered at enrollment and at study visits at month 6 and 12 months post-initiation of abatacept.

Immunologic/Mechanistic

- CD86 receptor occupancy on PBMC will be assessed before the initial dose of Abatacept, and prior to abatacept administration at months 9, and 12 months post-transplantation.
- The incidence and breadth of anti-HLA antibody (including DSA) development over time (evaluated at screening, 3, 6 and 12 post-transplant).
- Peripheral blood T and B cell subsets will assessed at 6, 9, and 12 months post-transplant.

14.3 Interim Analyses

There is no planned interim analysis for this study.

14.4 Analysis Plan

Binary primary and secondary endpoints that occur at or before 12 months post-transplant will be summarized as a simple fraction and percentage and as a proportion. Confidence intervals (95%) for a one-sample proportion will be calculated for incidence rates using the Wilson score procedure with a correction for continuity.

Primary Effectiveness Endpoint: The cumulative incidence of alloimmunity (or alloimmunity-free survival) during the 12 months after transplantation will be estimated with the Kaplan-Meier method. The standard error of the Kaplan-Meier estimate will be calculated based on Greenwood's formula and used to construct 95% confidence intervals for the time-to-event curve. Patients with follow-up less than 1-year will be censored at last follow-up.

The cumulative incidence of primary safety endpoints during the 12 months after transplantation will be estimated with the Kaplan-Meier method.

A repeated-measures analysis of eGFR will be performed with a means model via the SAS MIXED Procedure (version 9.4; SAS Institute, Cary, NC), providing separate estimates of the mean eGFRs by time on study (between abatacept initiation and 12 months on treatment). The model will include one predictor (time on study as a categorical clinical visit variable). A compound-symmetric variance-covariance form in repeated measurements will be assumed for eGFR and robust estimates of the standard errors of parameters will be used to perform statistical tests and construct 95% confidence intervals (**Reference: Diggle et al**). The model-based means are unbiased with unbalanced and missing data, as long as the missing data are non-informative (missing at random). We will report the estimated mean eGFR and its 95% confidence at each month of follow-up and the time-averaged mean. A baseline-adjusted analysis will also be performed. Serum creatinine, total cholesterol, LDL, HDL, triglyceride and blood pressure plus the exploratory immunologic/mechanistic endpoints (peripheral blood T and B cell subsets) will be analyzed using the same plan described for eGFR.

This phase I trial will provide important estimates of variability (within-subject and between-subject standard deviation) for eGFR. The estimates of variability will be valuable to power future clinical trials since these variability estimates are essential components for sample size calculations.

15. Identification and Access to Source Data

15.1 Source Data

Source documents and source data are considered to be the original documentation where subject information, visits, consultations, examinations and other information are recorded. Documentation of source data is necessary for the reconstruction, evaluation and validation of clinical findings, observations and other activities during a clinical trial.

15.2 Access to Source Data

The site investigators and site staff will make all source data available to the grant funding agency (DAIT/NIAID), as well as to relevant health authorities. Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals.

16. Quality Assurance and Quality Control

The sponsor will review site processes for quality management of the study prior to enrollment at each clinical center, to include processes for data and biological specimen collection. Expectations will be communicated to each site regarding study conduct. In addition, all study staff are required to have GCP, Human Subject Protection, and ICH training. The clinical investigational site will perform internal quality management of study conduct, data collection, documentation and completion.

A quality control plan for electronic data capture and data management will be created by the data center and will be reviewed by the sponsor prior to study onset. Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

The Sponsor will develop a risk-based monitoring plan to direct study monitoring. Sponsor monitors will follow written Standard Operating Procedures (SOPs) to verify that the clinical trial is conducted, data are generated, and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g.).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. (See Appendix 3: Monitoring Plan)

17. Protocol Deviations

17.1 Protocol Deviation Definitions

Protocol Deviation – The investigators and site staff will conduct the study in accordance with the protocol; no deviations from the protocol are permitted. Any change, divergence, or departure from the study design or procedures constitutes a protocol deviation. As a result of any deviation, corrective actions will be developed by the site and implemented promptly.

Major Protocol Deviation (Protocol Violation) - A Protocol Violation is a deviation from the IRB approved protocol that may affect the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. In addition, protocol violations include willful or knowing breaches of human subject protection regulations, or policies, any action that is inconsistent with the NIH Human Research Protection Program's research, medical, and ethical principles, and a serious or continuing noncompliance with federal, state, local or institutional human subject protection regulations, policies, or procedures.

Non-Major Protocol Deviation - A non-major protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that does not have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

17.2 Reporting and Managing Protocol Deviations

The study site principal investigator has the responsibility to identify, document and report protocol deviations as directed by the study Sponsor. However, protocol deviations may also be identified during site monitoring visits or during other forms of study conduct review.

18. Ethical Considerations and Compliance with Good Clinical Practice

18.1 Statement of Compliance

This clinical study will be conducted using good clinical practice (GCP), as delineated in *Guidance for Industry: E6(R2) Good Clinical Practice Consolidated Guidance*, and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by the IRB. Any amendments to the protocol or to the consent materials will also be approved by the IRB before they are implemented.

18.2 Informed Consent Process

The consent process will provide information about the study to a prospective participant and will allow adequate time for review and discussion prior to his/her decision. The principal investigator or designee listed on the Investigator of Record form, FDA 1572, will review the consent and answer questions. The prospective participant will be told that being in the trial is voluntary and that he or she may withdraw from the study at any time, for any reason. All participants (or their legally acceptable representative) will read, sign, and date a consent form before undergoing any study procedures. Consent materials will be presented in participants' primary language. A copy of the signed consent form will be given to the participant.

The consent process will be ongoing. The consent form will be revised when important new safety information is available, the protocol is amended, and/or new information becomes available that may affect participation in the study.

18.3 Privacy and Confidentiality

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a unique identification number and these numbers rather than names will be used to collect, store, and report participant information. Site personnel will not transmit documents containing personal health identifiers (PHI) to the study sponsor or their representatives.

19. Publication Policy

The investigators, NIAID, and BMS agree to a joint publication policy that allows for review by all three parties.

20. References

1. Vincenti, F., et al., *Belatacept and Long-Term Outcomes in Kidney Transplantation.* N Engl J Med, 2016. 374(4): p. 333-43.

2. Heher, E. and J.F. Markmann, *The Clearer BENEFITS of Belatacept*. N Engl J Med, 2016. 374(4): p. 388-9.

3. Adams, A.B., et al., *Belatacept Combined With Transient Calcineurin Inhibitor Therapy Prevents Rejection and Promotes Improved Long-Term Renal Allograft Function*. Am J Transplant, 2017. 17(11): p. 2922-2936.

4. Badell, I.R., et al., *Abatacept as rescue immunosuppression after calcineurin inhibitor treatment failure in renal transplantation.* Am J Transplant, 2019.

5. Diggle PJ, Liang KY, Zeger SL. *Analysis of longitudinal data.* Oxford: Clarendon Press, 1994, pgs. 68-69.

6. Orencia® (abatacept). Package Insert. Princeton, New Jersey: Bristol-Myers Squibb Company; 2021

APPENDIX 1: SCHEDULE OF EVENTS

		Enrollment period is from Week 8 post transplant to week 20 post transplant[1]											
Visit (Months)	**Screen**	**Post Transplant Mth 2**	**Post Transplant Mth 3**	**Post Transplant Mth 4**	**Post Transplant Mth 5**	**Post Transplant Mth 6**	**Post Transplant Mth 7**	**Post Transplant Mth 8**	**Post Transplant Mth 9**	**Post Transplant Mth 10**	**Post Transplant Mth 11**	**Post Transplant Mth 12**	**FC**
Visit (Weeks)		**8-11**	**12**	**16-19**	**20-23**	**24**	**28**	**32**	**36**	**40**	**44**	**52**	
Visit Windows		**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 day**	**+/- 5 day**	
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Pregnancy Testing of WOCB (serum or urine)	X												
Questionnaires		X				X						X	
PRA-HLA Ab Screen	X					X						X	X
SAB I/II (DSA)	X	X (mo 3)				X						X	X
Hemoglobin A1c	X											X	
Hematology (CBC including differentials w/platelets)	X	X				X			X			X	X
Chemistry Panel	X	X				X			X			X	X
Viral Monitoring (BK and CMV)		X				X			X			X	X
Pharmacokinetics (PK) monitoring		X[2]							X			X	X
Assessment of Adverse Events		→				→	→	→	→	→	→	→	X
Concomitant Medications Reviews		X				X	X	X	X	X	X	X	
Abatacept weekly administration		X				→	→	→	→	→	→	→	

		Enrollment period is from Week 8 post transplant to week 20 post transplant[1]											
Visit (Months)	**Screen**	**Post Transplant Mth 2**	**Post Transplant Mth 3**	**Post Transplant Mth 4**	**Post Transplant Mth 5**	**Post Transplant Mth 6**	**Post Transplant Mth 7**	**Post Transplant Mth 8**	**Post Transplant Mth 9**	**Post Transplant Mth 10**	**Post Transplant Mth 11**	**Post Transplant Mth 12**	**FC**
Visit (Weeks)		**8-11**	**12**	**16-19**	**20-23**	**24**	**28**	**32**	**36**	**40**	**44**	**52**	
Visit Windows		**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 day**	**+/- 5 day**	
MMF ≥ 500mg p.o. BID	(X)[4]	→				→	→	→	→	→	→	→	
Prednisone 5mg p.o. daily	(X)[4]	→				→	→	→	→	→	→	→	
Tacrolimus (target trough 3-5ng/mL)	(X)[4]	→				→	→	→	→	→	→	→	
Immunophenotyping		X				X			X			X	X
HLA DR/DQ Eplet Score		X											
Gene Expression		X				X			X			X	X

[1] Subjects will be enrolled no less than 8 weeks post transplant, no more than 20 weeks post-transplant. For subjects enrolled after Month 2, any study visit which occurred prior to subject enrollment does not apply.

[2] Initial PK test only required at first dose of Abatacept.

[3] Collected when enrolled.

[4] Doses required at enrollment.

APPENDIX 2: DAIT Vaccine Guidance for Patients in Interventional Adult Transplant Trials

Vaccine	Verification
Hepatitis B	To be eligible, anybody uninfected AND not immune* must have documentation of having received at least 1 dose of a hepatitis B vaccine (if vaccine series not complete, enrollees will be expected to complete the series after transplant). * Uninfected and Not Immune = HBsAg, anti-HBc, and anti-HBs negative Source: AASLD 2018 Hepatitis B Guidance; Terrault et al Hepatology 2018
Influenza	Study participants must receive the yearly influenza vaccine. Beginning on September 1st of each year, study participants and potential enrollees should be re-evaluated for receipt of the current year influenza vaccine.
Pneumococcal	To be eligible, at least one dose of any licensed pneumococcal vaccine is required. Verification of pneumococcal vaccine is by patient report that he/she has received at least one dose of any licensed pneumococcal vaccine. Potential enrollees who do not recall receiving either pneumococcal vaccine will meet this eligibility upon receiving a single dose of any licensed pneumococcal vaccines.
Varicella (VAR) **"Chickenpox"**	To be eligible, the enrollee must have **prior to transplant** [Varicella is a live vaccine[1], **contraindicated** after transplant]: • a positive Varicella IgG Ab test, **or** • a valid history of varicella disease* (chickenpox) **or** • a history of zoster (shingles) by patient report, **or** • documentation that they have received the varicella (VAR) vaccine (2 doses if born 1980 or later) (*) Valid history: must answer yes to at least one of the following questions: 1- when you had chickenpox, did you know of any nearby person who had chickenpox at the same time (family member, classmate, etc)? 2- were you diagnosed with chickenpox by any medical professional; if testing was done, did the test confirm chickenpox? If the answer to all of these questions is no, the patient must be vaccinated with at least 1 dose of varicella vaccine before they will be considered eligible to enroll.
Zoster (VZV)	To be eligible, the pre-transplant enrollee must have prior to transplant: • **IF >19 years of age**: at least one dose of Shingrix vaccine (RZV: Zoster Recombinant, which is NOT a live vaccine); if both doses of Shingrix are not completed prior to transplant, enrollees will be expected to complete the series after transplant **NOTE**: Hemodynamically unstable heart transplant candidates and ventilated lung transplant candidates, or post-transplant study enrollees can receive their first dose of the Shingrix vaccine once they are stable, post-transplant. In January 2022, CDC modified the age recommendation from >= 50 years of age to >= 19 years of age. To allow time for adoption of this new recommendation, the criteria above for individuals between 19 and 49 years of age (inclusive) will be effective for DAIT studies starting **January 1, 2023.** If a subject is enrolled prior to 19 years of age, the Shingrix vaccine is recommended once they reach their 19th birthday.
MMR	To be eligible, the enrollee must have **prior to transplant** [MMR is a live vaccine[1], **contraindicated** after transplant]: • Documentation that they have received MMR-containing vaccine, **or** • Documentation of Measles titers (IgG, do not test for IgM) NOTE: Documentation of titers to Mumps or Rubella is NOT required.

COVID-19	Completion of a primary COVID-19 vaccination series with a Health Authority-approved or authorized vaccine; (e.g., FDA in US or Health Canada) is an eligibility requirement for all DAIT/NIAID Transplantation Branch Clinical Trials.

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Unless otherwise specified, "documentation" means the vaccine in question is recorded in a formal medical record, military record, school record, state or local vaccine registry, or official vaccination card.

[1] It is usual to postpone transplantation for 4 weeks after receipt of the live attenuated MMR or Varicella (Chickenpox) vaccines; if vaccination is not possible, the patient **cannot be enrolled** in this investigational drug (IND) study.

Reference: https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf