CLINICAL TRIALS IN ORGAN TRANSPLANTATION (CTOT)

PROTOCOL CTOT-15

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Optimization of NULOJIX® (Belatacept) Usage as a Means of Minimizing CNI Exposure in Simultaneous Pancreas and Kidney Transplantation

VERSION 7.0/ June 28, 2016

Study Sponsor: The National Institute of Allergy and Infectious Diseases (NIAID)

Corporate Supporter: Bristol-Myers Squibb (BMS)

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INVESTIGATOR SIGNATURE PAGE	
Protocol: CTOT-15	**Version/Date:** 7.0/ June 28, 2016

Title: *Optimization of NULOJIX® (belatacept) Usage as a Means of Minimizing CNI Exposure in Simultaneous Kidney and Pancreas Transplantation*

Study Sponsor: The National Institute of Allergy and Infectious Diseases (NIAID)

INSTRUCTIONS: Please have the Principal Investigator print, sign, and date at the indicated location below. A copy should be kept for your records and the original signature page sent to the NIAID. After signature, please return the original of this form by surface mail to:

DAIT Regulatory Management Center
Pharmaceutical Product Development
3900 Paramount Parkway
Morrisville, NC 27560

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) – 21 CFR Parts 50, 56, and 312, and the International Conference on Harmonization (ICH) document "Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance". Further, I will conduct the study in keeping with local, legal, and regulatory requirements.

As the Site Principal Investigator, I agree to conduct " Optimization of NULOJIX® (belatacept) Usage as a Means of Minimizing CNI Exposure in Simultaneous Kidney and Pancreas Transplantation "

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 written permission of the NIAID.

_____

Site Principal Investigator (Print)

_____ _____

Site Principal Investigator (Signature) **Date**

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PROTOCOL AMENDMENT
Prior Version: Version 6.0, Dated May 14, 2016
Current Version: Version 7.0, Dated June 28, 2016

The following protocol amendment dated June 28, 2016, supersedes all previous versions of the protocol CTOT-15, "Optimization of Belatacept Usage as a Means of Minimizing CNI Exposure in Simultaneous Kidney and Pancreas Transplantation".

A. Rationale for Protocol Amendment
Based upon a recommendation by the NIAID Data Safety Monitoring Board, Dr. Newell, Dr. Stock and the NIH have decided to halt any further protocol directed low dose CNI (Prograf®, tacrolimus) withdrawal. It was observed that there was a higher incidence of acute rejection at/around the time of low dose CNI withdrawal. While the rate of rejection did not meet the study stopping rule, the temporal relationship between the CNI withdrawal and acute rejection warranted sufficient concern to discontinue any further CNI withdrawal.

In addition, any subjects in the experimental arm of the study will transition from a protocol directed study therapy regimen to a physician directed clinical immunosuppressive regimen. The clinical immunosuppressive regimen may include belatacept and if so, the subject may continue to receive the study supply of belatacept until study completion on August 31, 2016.

B. Informed Consent
The investigator at each site must inform all active subjects that any further low dose CNI withdrawal has been halted and that each subject in the experimental arm will be transitioned from a protocol directed study therapy regimen to a physician directed clinical immunosuppressive regimen. The site investigator or designee must explain during the re-consent process the reason for the premature discontinuation of study therapy and describe in lay terms to the subject and/or the subject's legal representative what is involved in the transition from a protocol mandated therapy regimen to a physician directed clinical immunosuppressive regimen as well as the remaining study follow-up. The subject and/or the subject's legal representative, must read, sign, and date the informed consent form prior to any study-specific procedures.

A copy of the informed consent must be given to the subject and/or the subject's legal representative. The subject and/or the subject's legal representative will be informed that participation in the follow-up portion of the study is voluntary and that he/she may withdraw from the study at any time, for any reason.

C. Description of Amendment Modifications
No further subjects in the experimental arm of the study will undergo low dose CNI withdrawal. In addition, subjects in the experimental arm will transition from the protocol directed study therapy regimen to a physician directed clinical immunosuppressive regimen. If the subject, in conjunction with their treating physician,

opts to remain on belatacept after being reconsented regarding the new findings, they may receive the study supply of belatacept until study completion on August 31, 2016.

Subjects will continue to be followed until study completion based on the existing schedule they are following in Appendices 2, 3 or 4.

D. Drug Accountability

Under Title 21 of the Code of Federal Regulations (21 CRF § 312.62) the investigator is required to maintain adequate records of the disposition of the investigational agent, 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. Documentation must be present in the site pharmacy binder to verify the disposition of the study drug, and the institution's procedures for destruction of the study drug.

CTOT-15 Protocol Synopsis

Title	Optimization of NULOJIX® (belatacept) Usage as a Means of Minimizing CNI Exposure in Simultaneous Kidney and Pancreas Transplantation (CTOT-15)
Study Design	This study is a multicenter, prospective, randomized (1:1), open-label, Phase II study to compare a NULOJIX® (belatacept) based immunosuppressive regimen to a CNI-based regimen in recipients of SPK. Subjects will be consented and enrolled until a total of 60 subjects are randomized.
Study Duration	39 months (21 month accrual period, up to 18 month follow-up period). Subjects will be followed for a minimum of 12 months or 60 days post tacrolimus withdrawal.
Accrual Objective	60 Randomize (30 per arm); 1:1 to one of two study therapy arms.
Study Therapy Regimen	**Control Arm:** ❖ Induction: 5 day course of MEDROL® (methylprednisolone) or equivalent; ❖ Induction: Thymoglobulin® (Anti-thymocyte Globulin (Rabbit)); ❖ Maintenance Immunosuppression: Prograf® (tacrolimus), or generic; ❖ Maintenance Immunosuppression: CellCept® (mycophenolate mofetil- MMF), or Myfortic® (mycophenolate sodium), or generic. **Investigational Arm:** ❖ Induction: 5 day course of MEDROL® (methylprednisolone) or equivalent; ❖ Induction: Thymoglobulin® (Anti-thymocyte Globulin (Rabbit)); ❖ Maintenance Immunosuppression: NULOJIX® (belatacept); ❖ Maintenance Immunosuppression: Prograf® (tacrolimus), or generic; ❖ Maintenance Immunosuppression: CellCept® (mycophenolate mofetil- MMF), or Myfortic® (mycophenolate sodium), or generic.
Primary Objective	The primary objective is to evaluate a NULOJIX® (belatacept) based regimen as a means of improving long term graft function without increasing the risks of immunologic graft injury by avoiding both CNI and corticosteroids.
Primary Endpoint	The primary endpoint is mean glomerular filtration rate (GFR) calculated for each treatment group using the CKD-EPI equation at 52 weeks.
Secondary Objective	The secondary objective is to evaluate whether a NULOJIX® (belatacept) based immunosuppression regimen with minimal exposure to CNIs achieves superior renal function, improves cardiovascular and metabolic risk profiles, and preserves protective immunity in recipients of SPK.
Secondary Endpoints	**<u>Measures of Renal Function and Injury</u>** The following secondary endpoints will measure renal function and injury at weeks 52: 1. Proportion of subjects with eGFR < 60 mL/min/1.73 m2 measured by CKD-EPI. 2. Change in CKD stages from baseline. 3. Proportion of subjects with defined CKD stage 4 or 5. 4. Mean calculated eGFR using MDRD 4 variable model. 5. eGFR by CKD-EPI over time based on serum creatinine collected at all visits indicated on the Schedule of Events. 6. Incidence of successful discontinuation of tacrolimus in recipients randomized to the NULOJIX® (belatacept)t treatment arm (Investigational Arm) 7. The incidence of delayed graft function (DGF- refer to study definitions page).

Secondary Endpoints	**Measures of Pancreatic Function and Injury** The following secondary endpoints will measure pancreatic function and injury at week 52, in addition to times of graft dysfunction: 1. Proportion of subjects with full pancreatic graft function (i.e., insulin independent). 2. Partial pancreatic graft function (i.e., fasting c-peptide levels ≥0.3ng.mL (0.1nmol.L), but requiring insulin or oral hypoglycemic agents). 3. Pancreatic loss (i.e., c-peptide value <0.3ng/mL). **Measures of Cardiovascular and Metabolic Parameters** The following will be measured at baseline, days 28, 84, and weeks 28, 36, and 52, unless otherwise stated below. 1. HbA1c. 2. Fasting Blood Sugar (FBS). 3. Standardized blood pressure measurement and use of anti-hypertensive medications. 4. Fasting lipid profile (Total Cholesterol, non-HDL Cholesterol, LDL, HDL, and triglyceride) and the use of lipid lowering medications at baseline, and weeks 28 and 52. **Incidence and Severity of Rejection and Anti- Donor Reactivity** These endpoints will be assessed at 52 weeks post-transplant. Biopsy grading and antibody assessments will be performed at the CTOT-15 Core Laboratories. 1. The incidence and severity of acute cellular rejection defined by the Kidney Banff 2007 criteria and Pancreas Banff 2011 criteria within the first 52 weeks. 2. The severity of first and highest grade of acute cellular rejection in the renal and pancreas biopsies 3. The incidence of humoral rejection in the renal and pancreas biopsies. 4. The prevalence of de novo anti-donor antibodies and anti-HLA antibodies. 5. The type of treatment of rejection. **Safety Outcome Measures** The following safety outcome measures will be assessed: 1. The incidence of death, graft loss, or undetectable c-peptide. 2. The incidence of all adverse events (AEs) and serious adverse events (SAEs). 3. The incidence of selected AEs and SAEs including: o Infections requiring hospitalization or systemic therapy, o BK and CMV viremia (local center monitoring), o EBV Infection (local center monitoring), o Malignancy.
Secondary Endpoints-Mechanistic	Samples for **Mechanistic studies** will be collected as specified on the SOE. **Immune Reactivity and Function** 1. Multiparameter flow cytometric enumeration and phenotyping of peripheral blood leukocyte subsets. 2. Protective immunity a. Viral load monitoring – EBV, CMV, Polyoma BKV & JCV b. Quantity and quality of CMV- and EBV- specific T cells and viral-specific antibody. 3. Anti-donor responses a. Donor-specific antibody. b. Immunohistochemistry of for-cause renal allograft biopsies. c. Gene expression, mRNA profiling in blood, urine and tissue. 4. Serum and urine proteins, selected biomarkers of acute and chronic kidney injury.
Inclusion Criteria	Patients who meet all of the following criteria are eligible for enrollment as study participants: 1. Male or Female, 18-55 years of age at the time of enrollment; 2. Ability to understand and provide written informed consent;

	3. Candidate for a primary simultaneous kidney and pancreas allograft with random c-peptide <0.3 ng/mL. 4. No known contraindications to study therapy using NULOJIX® (belatacept); 5. Female subjects of childbearing potential must have a negative pregnancy test upon study entry; 6. Female and male participants with reproductive potential must agree to use FDA approved methods of birth control during participation in the study and for 4 months following study completion; 7. No donor specific antibodies prior to transplant that are considered to be of clinical significance by the site investigator; ; 8. Negative crossmatch, actual or virtual, or a PRA of 0% on historic and admission sera, as determined by each participating study center. 9. A documented negative TB test within the 12 months prior to transplant. If documentation is not present at the time of transplantation, and the subject does not have any risk factors for TB, a TB-specific interferon gamma release assay (IGRA) may be performed.
Exclusion Criteria	Patients who meet *any* of these criteria are *not* eligible for enrollment as study participants: 1. Need for multi-organ transplantation other than a kidney and pancreas 2. Recipient of previous organ transplant; 3. Active infection with hepatitis B, hepatitis C, or HIV; 4. Individuals who have required treatment with systemic prednisone or other immunosuppressive drugs within 1 year prior to transplant; 5. Individuals previously treated with NULOJIX® (belatacept); 6. Any condition that, in the opinion of the investigator, would interfere with the participant's ability to comply with study requirements; 7. Use of investigational drugs within 4 weeks of enrollment; 8. Known hypersensitivity to mycophenolate mofetil (MMF)or any of the drug's components; 9. Administration of live attenuated vaccine(s) within 8 weeks of enrollment. 10. EBV sero-negative recipients or recipients whose EBV status is unknown or ambiguous prior to the time of transplantation (refer to Section 6.3).

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Glossary of Abbreviations

ACR	Acute Cellular Rejection
AE	Adverse Event
AKI	Acute Kidney Injury
ALP	Alkaline Phosphatase
ALT (SPGT)	Alanine Aminotransferase
AMR	Antibody Mediated Rejection
ANCOVA	Analysis of Covariance
APC	Antigen Presenting Cells
AR	Acute Rejection
AST (SGOT)	Aspartate Aminotransferase
ATG	Thymoglobulin® (Anti-thymocyte Globulin- Rabbit)
AUC	Area Under the Curve
B-CLL	B-cell Chronic Lymphocytic Leukemia
BKV	BK Polyoma Virus
BMS	Bristol-Myers Squibb
BPAR	Biopsy-proven acute rejection
BW	Body Weight
CAN	Chronic allograft nephropathy
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CI	Confidence Intervals
CIT	Clinical Islet Transplantation
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration equation
CKI	Chronic Kidney Injury
CTCAE	Common Terminology Criteria for Adverse Events
CMV	Cytomegalovirus
CNI	Calcineurin Inhibitor
CNS	Central Nervous System
CrCL	Creatinine Clearance
CRF	Case Report Form
CsA	Cyclosporine A
CSBPAR	Clinically suspected and biopsy-proven acute rejection
CTOT	Clinical Trials in Organ Transplantation
CTOT-C	Clinical Trials in Organ Transplantation in Children
DAIT	Division of Allergy, Immunology, and Transplantation
DBP	Diastolic Blood Pressure
DC	Dendritic Cells
DGF	Delayed Graft Function
DM	Diabetes Mellitus
DNA	Deoxyribonucleic Acid
DSA	Donor Specific Antibody

DSMB	Data Safety Monitoring Board
EBV	Epstein Barr Virus
ECD	Extended Criteria Donor
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
ELISPOT	Enzyme Linked Immunospot
FBS	Fasting Blood Sugar
FDA	Food and Drug Administration
FFPE	Formalin Fixed, Paraffin Embedded
FLP	Fasting Lipid Profile
GAD	Glutamic Acid Decarboxylase
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HbA1c	Hemoglobin A1c
HCG	Human Chorionic Gonadotropin
HDL	High Density Lipoprotein
H&E	Hematoxylin and Eosin (pathology stain)
HIV	Human Immunodeficiency Virus
HLA	Histocompatibility Antigen
HUS	Hemolytic Uremic Syndrome
IB	Investigators Brochure
ICH	International Conference on Harmonization
IFTA	Interstitial Fibrosis and Tubular Atrophy
IGRA	TB-specific Interferon Gamma Release Assay
IL	Interleukin
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent to treat
IV	Intravenous
kDa	kilo Dalton
LDL	Low-density Lipoprotein
LI	Less Intensive
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Drug Regulatory Activities
MHC	Major Histocompatibility Complex
MI	More Intensive
MICA	MHC-class I related chain
MMF	Maintenance mycophenolate mofetil
MMRM	Mixed Models Repeated Measures
MOP	Manual of Procedures
MPA	Mycophenolate Acid
mRNA	Messenger Ribonucleic Acid
NCI	National Cancer Institute

NIAID	National Institute of Allergy and Infectious Disease
NIH	National Institutes of Health
NK	Natural Killer cells
OR	Odds Ratio
PAS	Periodic Acid-Schiff (pathology stain)
PBMC	Peripheral Blood Mononuclear Cells
PCP	*Pneumocystis carinii pneumonia*
PCR	Polymerase Chain Reaction
PDT	Protocol Development Team
PHI	Personal Health Identifiers
PI	Principal Investigator
PML	Progressive Multifocal Leukoencephalopathy
PRA	Panel Reactive Antibodies
PRES	Posterior Reversible Encephalopathy Syndrome
PTDM	Post-transplant Diabetes Mellitus
PTLD	Post-transplant Lymphoproliferative Disorder
RNA	Ribonucleic Acid
RR	Risk Ratio
SACCC	Statistical and Clinical Coordinating Center
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SBP	Systolic Blood Pressure
SCr	Serum Creatinine
SOC	System Organ Class
SOE	Schedule of Events
SPK	Simultaneous Pancreas and Kidney Transplantation
SR	Suspected Rejection
SRTR	Scientific Registry of Transplant Recipients
SUSAR	Serious and Unexpected Suspected Adverse Reaction
TB	Tuberculosis
TCR	T-cell receptor
TGs	Triglycerides
TIB	Transplant Immunology Branch
ULN	Upper Limit of Normal
USRDS	United States Renal Data System
UTI	Urinary Tract Infection
WHO	World Health Organization
WOCBP	Women of Child Bearing Potential

Study Definitions

Acute Rejection–Kidney	The endpoint of acute rejection of the kidney allograft will be assessed as in the belatacept phase III studies as histologically confirmed rejection as determined by the central pathologist, in which there are protocol-defined reasons for clinical suspicion of rejection (unexplained rise of serum creatinine ≥25% from baseline, unexplained decrease in urine output; fever and graft tenderness; or serum creatinine that remains elevated within 14 days post-transplantation) or treatment for acute rejection with other reasons for clinical suspicion.
Acute Rejection – Pancreas	Histologic evidence of stage 2 or greater rejection on a biopsy performed for clinical conditions suspicious for rejection such as, but not limited to, a two-fold increase in serum lipase or amylase or suspected rejection with empiric treatment in the absence of a biopsy.
Antibody Mediated Rejection (AMR)	Diffusely positive staining for C4d, presence of circulating anti-donor antibodies, and morphologic evidence of acute tissue injury.
Banff 2007 Scoring Criteria (Kidney)	**1. Normal** **2. Antibody-mediated rejection** (may coincide with categories 3, 4, 5 and 6) Due to documentation of circulating anti-donor antibody, and C4d or allograft pathology C4d deposition without morphologic evidence of active rejection C4d+, presence of circulating anti-donor antibodies, no signs of acute or chronic TCMR or ABMR (i.e., g0, cg0, ptc0, no PTC lamination). Cases with simultaneous borderline changes or ATN are considered as indeterminate. *Acute antibody-mediated rejection:* C4d+, presence of circulating anti-donor antibodies, morphologic evidence of acute tissue injury, such as (Type/Grade): I. ATN-like – C4d+, minimal inflammation II. Capillary and or glomerular inflammation (ptc/g >0) and/or thromboses III. Arterial- v3 *Chronic active antibody-mediated rejection:* C4d+, presence of circulating anti-donor antibodies, morphologic evidence of chronic tissue injury, such as glomerular double contours and/or peritubular capillary basement membrane multilayering and/or interstitial fibrosis/tubular atrophy and/or fibrous intimal thickening in arteries. **3. Borderline changes**: 'Suspicious' for acute T-cell mediated rejection (may coincide with categories 2 and 5 and 6). This category is used when no intimal arteritis is present, but there are foci of mild tubulitis (t1, t2, or t3) with minor interstitial infiltration (i0, or i1) or interstitial infiltration (i2, i3) with mild (t1) tubulitis. **4. T-cell mediated rejection** (may coincide with categories 2 and 5 and 6). *Acute T-cell-mediated rejection (Type/Grade):* IA Cases with significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of moderate tubulitis (t2) IB Cases with significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of severe tubulitis (t3) IIA Cases with mild-to-moderate intimal arteritis (v1) IIB Cases with severe intimal arteritis comprising >25% of the luminal area (v2) III Cases with 'transmural' arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation (v3) *Chronic active T-cell mediated rejection* 'chronic allograft arteriopathy' (arterial intimal fibrosis with mononuclear cell infiltration in fibrosis, formation of neo-intima) **5. Interstitial fibrosis and tubular atrophy**, no evidence of any specific etiology

	(may include nonspecific vascular and glomerular sclerosis, but severity graded by tubulointerstitial features). Grade I Mild interstitial fibrosis and tubular atrophy (<25% or cortical area) Grade II Moderate interstitial fibrosis and tubular atrophy 26-50% of cortical area) Grade III Severe interstitial fibrosis and tubular atrophy/ loss (>50% of cortical area) **6. Other:** Changes not considered to be due to rejection-acute and/or chronic; may include isolated g, cg, or cv lesions and coincide with categories 2, 3, 4, and 5.
Banff 2011 Scoring Criteria (Pancreas)	**1. Normal.** Absent inflammation **or** inactive septal, mononuclear inflammation not involving ducts, veins, arteries or acini. There is no graft sclerosis. The fibrous component is limited to normal septa and its amount is proportional to the size of the enclosed structures (ducts and vessels). The acinar parenchyma shows no signs of atrophy or injury. **2. Indeterminate.** Septal inflammation that appears active but the overall features do not fulfill the criteria for mild cell-mediated acute rejection. **3. Acute T-Cell-mediated rejection** ***- Grade I/Mild acute T-cell-mediated rejection*** Active septal inflammation (activated, blastic lymphocytes, ± eosinophils) involving septal structures: venulitis (sub-endothelial accumulation of inflammatory cells and endothelial damage in septal veins, ductitis (epithelial inflammation and damage of ducts). Neural/peri-neural inflammation. and/or Focal acinar inflammation. No more than two inflammatory foci per lobule with absent or minimal acinar cell injury. ***- Grade II/Moderate acute T-cell-mediated rejection (requires differentiation from AMR)*** Multi-focal (but not confluent or diffuse) acinar inflammation (≥3 foci per lobule) with spotty (individual) acinar cell injury and drop-out. and/or Mild intimal arteritis (with minimal, <25% luminal compromise) ***- Grade III/Severe T-acute cell-mediated rejection*** Diffuse, (widespread, extensive) acinar inflammation with focal or diffuse multicellular /confluent acinar cell necrosis. and/or Moderate- or severe-intimal arteritis. >25% luminal compromise and/or Transmural inflammation-Necrotizing arteritis **4. Antibody-mediated rejection** -Confirmed circulating donor-specific antibody (DSA) -Morphological evidence of tissue injury (interacinar inflammation/capillaritis, acinar cell damage swelling/necrosis/apoptosis/dropout, vasculitis, thrombosis) Grade I/Mild acute AMR Grade II/Moderate acute AMR Grade III/Severe acute AMR -C4d positivity in interacinar capillaries (IAC, ≥5% of acinar lobular surface) **5. Chronic Active Allograft Arteriopathy-** Arterial intimal fibrosis with mononuclear cell infiltration in fibrosis **6. Chronic Allograft Rejection/Graft Fibrosis** ***- Stage I (mild graft sclerosis)*** Expansion of fibrous septa; the fibrosis occupies less than 30% of the core surface but the acinar lobules have eroded, irregular contours. The central lobular areas are normal. ***- Stage II (moderate graft sclerosis)*** The fibrosis occupies 30–60% of the core surface. The exocrine atrophy affects the majority of the lobules in their periphery (irregular contours) and in their central areas (thin fibrous strands criss-cross between individual acin). ***- Stage III (severe graft sclerosis)*** The fibrotic areas predominate and occupy more than 60% of the core surface with only isolated areas of residual acinar tissue and/or islets present.

	7. Islet Pathology -Recurrence of autoimmune DM (insulitis and/or selective beta cell loss) -Islet amyloid (amylin) deposition) **8. Other histological diagnosis.** Pathological changes not considered to be due acute and/or chronic rejection. e.g. CMV pancreatitis, PTLD, etc.
Biopsy Proven Acute Kidney Rejection (BPAR)	Banff grade of greater than or equal to 1A with or without clinical symptoms. • An unexplained rise in serum amylase or lipase • Treatment for acute rejection with other reasons for clinical suspicion.
BKV Infection	A positive BKV infection for the purpose of this study is defined as a level of BKV viremia that causes a change in immunosuppression at the local center.
Clinically Suspected and Biopsy Proven Acute Rejection (CSBPAR) in Kidney	Banff grade of greater than or equal to 1A plus at least one of the following: • Unexplained rise of serum creatinine ≥25% from baseline; • Unexplained decrease in urine output; • Fever and graft tenderness; • Serum creatinine that remains elevated within 14 days post-transplantation; • Treatment for acute rejection with other reasons for clinical suspicion.
Chronic Active Antibody-Mediated Kidney Rejection	By the Banff 2007 criteria, C4d+, presence of circulating antidonor antibodies, morphologic evidence of chronic tissue injury, such as a glomerular double contours and/or peritubular capillary basement membrane multilayering and/or interstitial fibrosis/tubular atrophy and/or fibrous initimal thickening in arteries.
Control Arm	❖ Induction: 5 day course of MEDROL® (methylprednisolone) or equivalent; ❖ Induction: Thymoglobulin® (Anti-Thymocyte Globulin- Rabbit); ❖ Maintenance Immunosuppression: Prograf® (tacrolimus), or generic; ❖ Maintenance Immunosuppression: CellCept® (mycophenolate mofetil- MMF), or Myfortic® (mycophenolate sodium), or generic.
Delayed Graft Function (DGF) in Kidney	Dialysis in the first week on one or more occasions for any indication other than the treatment of acute hyperkalemia in the setting of otherwise acceptable renal function
Donor Specific Antibody Testing	The donor specific antibody testing include: • Class I: A, B, C • Class II: DR, DQ, DP
Graft Failure- Renal	90 consecutive days of dialysis dependency.
Graft Failure- Pancreas	Return to exogenous insulin therapy or initiation of oral hypoglycemic agents for greater than 30 days.
Insulin Independent	Insulin free.
Premature Termination	A subject will be terminated prematurely from the study if: 1) the subject withdraws consent, 2) is lost to follow-up, 3) the investigator or sponsor decision, 4) death, or 5) the subject is found to have a positive TB test.
Protocol Mandated Procedures	Any procedure performed solely for the purpose of this research study, not considered site specific standard of care.
Randomized	A subject who met all eligibility criteria; met with the study investigator or designee to discuss the study purpose, requirements (i.e., time requirements, schedule of events, etc.), discussed all risks and benefits, signed the informed consent document and was randomly assigned to one of the two treatment groups.
Reduced Follow Up	Randomized subjects who are no longer following the assigned study therapy regimen, and do not meet the criteria for early termination, will continue to participate in the study for safety and applicable endpoint assessments.
Renal Dysfunction	Two consecutive readings with an increase in serum creatinine of 25% from baseline.

Sensitizing Event	Defined as a blood transfusion, pregnancy, or an event in the opinion of the Investigator would necessitate repeating the PRA.
Treated Diabetes	Receipt of any oral medication or insulin for the treatment of diabetes for >14 days
Tuberculosis	TB is defined as a positive TB Skin Test (TST/PPD) or a TB-specific interferon gamma release assay, such as a QuantiFERON®-TB, QuantiFERON®-TB in tube, or a T-Spot®.
Withdrawn from Study Therapy	Subjects who prematurely discontinue study treatment will be treated according to the site specific standard of care and followed for safety until 52 weeks post-transplant.
Primary Nonfunction (PNF)	Graft failure that occurs between 3 and 7 days post-transplant.
Women of Child Bearing Potential (WOCBP)	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 level > 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, spermicides) to prevent pregnancy or practicing abstinence or where the partner is sterile (e.g., vasectomy), should be considered to be of child bearing potential.
Humoral Rejection in Kidney	Defined as renal dysfunction, the presence of donor specific anti-HLA antibodies, and diffuse C4d staining as determined by a central pathologist
Investigational Arm	❖ Induction: 5 day course of MEDROL® (methylprednisolone) or equivalent; ❖ Induction: Thymoglobulin® (Anti-Thymocyte Globulin- Rabbit); ❖ Maintenance Immunosuppression: NULOJIX® (belatacept); ❖ Maintenance Immunosuppression: Prograf® (tacrolimus), or generic; ❖ Maintenance Immunosuppression: CellCept® (mycophenolate mofetil- MMF), or Myfortic® (mycophenolate sodium), or generic.

The Stages of Chronic Kidney Disease (CKD)

Stage	GFR*	Description	Treatment stage
1	90+	Normal kidney function but urine findings or structural abnormalities or genetic trait point to kidney disease.	Observation, control of blood pressure.
2	60-89	Mildly reduced kidney function (as for stage 1) point to kidney disease.	Observation, control of blood pressure and risk factors.
3A 3B	45-59 30-44	Moderately reduced kidney function.	Observation, control of blood pressure and risk factors.
4	15-29	Severely reduced kidney function.	Planning for endstage renal failure.
5	<15 or on dialysis	Very severe, or endstage kidney failure (sometimes call established renal failure).	Treatment choices.

*All GFR values are normalized to an average surface area (size) of 1.73m^2.

Suffixes:

p suffix: the addition of **p** to a stage (e.g. 3A**p**, 4**p**) mans that there is a significant proteinuria.

T - the addition of **T** to a stage (e.g. 3A**T**) indicates that the patient has a renal transplant.

D – the addition of **D** to a stage 5 CDK (e.g. 5**D**) indicates that the patient is on dialysis.

1 ESSENTIAL STUDY COMPONENTS

1.1 Hypothesis/Research Question

This study will test the hypothesis that a NULOJIX® (belatacept) based regimen using Thymoglobulin® (Anti-thymocyte Globulin- Rabbit) induction as a means of minimizing and potentially withdrawing calcineurin inhibitors (CNI) will result in comparable rates of rejection and achieve superior renal function as compared with a tacrolimus-based maintenance immunosuppressive regimen in recipients of simultaneous pancreas and kidney transplants (SPK).

1.2 Primary Objective

The primary objective is to evaluate a NULOJIX® (belatacept) based regimen as a means of improving long term graft function without increasing the risks of immunologic graft injury by avoiding both CNI and corticosteroids.

1.3 Secondary Objective

The secondary objective is to evaluate whether a NULOJIX® (belatacept) based immunosuppression regimen with minimal exposure to CNIs achieves superior renal function, improves cardiovascular and metabolic risk profiles, and preserves protective immunity in recipients of SPK.

1.4 Primary Endpoint

The primary endpoint is mean glomerular filtration rate (GFR) calculated for each treatment group using the CKD-EPI equation at 52 weeks.

1.5 Secondary Endpoints

1.5.1 Measures of Renal Function and Injury

The following secondary endpoints will measure renal function and injury at week 52:

1. Proportion of subjects with eGFR < 60 mL/min/1.73 m2 measured by CKD-EPI.
2. Change in CKD stages from baseline.
3. Proportion of subjects with defined CKD stage 4 or 5.
4. Mean calculated eGFR using MDRD 4 variable model.
5. eGFR by CKD-EPI over time based on serum creatinine collected at all visits indicated on the Schedule of Events.
6. Incidence of successful discontinuation of tacrolimus in recipients randomized to the NULOJIX® (belatacept)t treatment arm (Investigational Arm)
7. The incidence of delayed graft function ***(DGF- refer to study definitions page).***

1.5.2 Measures of Pancreatic Function and Injury

The following secondary endpoints will measure pancreatic function and injury at week 52, in addition to times of graft dysfunction:

1. Proportion of subjects with full pancreatic graft function (i.e., insulin independent).
2. Partial pancreatic graft function (i.e., fasting c-peptide levels ≥0.3ng.mL (0.1nmol.L), but requiring insulin or oral hypoglycemic agents).
3. Pancreatic loss (i.e., c-peptide value <0.3ng/mL).

1.5.3 Measures of Cardiovascular and Metabolic Parameters

The following will be measured at baseline, days 28, 84, and weeks 28, 36, and 52, unless otherwise stated below.

1. HbA1c.
2. Fasting Blood Sugar (FBS).
3. Standardized blood pressure measurement and use of anti-hypertensive medications.
4. Fasting lipid profile (Total Cholesterol, non-HDL Cholesterol, LDL, HDL, and triglyceride) and the use of lipid lowering medications at baseline, and weeks 28 and 52.

1.5.4 Incidence and Severity of Rejection and Anti- Donor Reactivity

These endpoints will be assessed at 52 weeks post-transplant. Biopsy grading and antibody assessments will be performed at the CTOT-15 Core Laboratories.

1. The incidence and severity of acute cellular rejection defined by the Kidney Banff 2007 criteria and Pancreas Banff 2011 criteria within the first 52 weeks.
2. The severity of first and highest grade of acute cellular rejection in the renal and pancreas biopsies
3. The incidence of humoral rejection in the renal and pancreas biopsies.
4. The prevalence of *de novo* anti-donor antibodies and anti-HLA antibodies.
5. The type of treatment of rejection.

1.5.5 Safety Outcome Measures

The following safety outcome measures will be assessed:

1. The incidence of death, graft loss, or undetectable c-peptide.
2. The incidence of all adverse events (AEs) and serious adverse events (SAEs).
3. The incidence of selected AEs and SAEs including:
    - Infections requiring hospitalization or systemic therapy,
    - BK and CMV viremia (local center monitoring),
    - EBV Infection (local center monitoring),
    - Malignancy.

1.6 Mechanistic Secondary Endpoints

Samples for **Mechanistic studies** will be collected as specified on the SOE.

Immune Reactivity and Function

1. Multiparameter flow cytometric enumeration and phenotyping of peripheral blood leukocyte subsets. (Emory Cellular Core Laboratory)
2. Protective immunity (Emory Viral Surveillance Core Laboratory)
    a. Viral load monitoring – EBV, CMV, Polyoma BKV & JCV
    b. Quantity and quality of CMV- and EBV- specific T cells and viral-specific antibody.
3. Anti-donor responses
    a. Donor-specific antibody (Emory HLA Clinical Laboratory).
    b. Immunohistochemistry of for-cause renal allograft biopsies (UCSF Pathology Core Lab).
    d. Gene expression, mRNA profiling in blood, urine and tissue (University of Alabama Molecular Core Laboratory).
4. Serum and urine proteins, selected biomarkers of acute and chronic kidney injury (University of Alabama Protein Assay Core Laboratory).

2 BACKGROUND AND RATIONALE

2.1 Background

The overarching aim of CTOT-15 is to investigate a belatacept-based immunosuppressive regimen for the purpose of minimizing the dependence of subjects undergoing simultaneous kidney and pancreas on CNIs and steroids. This study will test the hypothesis that the minimization of CNI exposure and avoidance of steroids will be facilitated by a belatacept-based regimen using thymoglobulin induction. We propose that the minimization of CNIs will lead to superior renal function with comparable rates of rejection compared with a tacrolimus-based maintenance immunosuppressive regimen in recipients of SPK. A second goal is to achieve these ends without an increase in viral infections or virus-associated malignancies.

CTOT-15 is designed to complement the CTOT-16 protocol conducted in renal transplants recipients and extend a comparable line of investigation to recipients of SPK. This group is particularly underserved with respect to trials examining new immunosuppressive regimens. In fact, there have been no multicenter, randomized, prospective trials in combined pancreas and kidney transplantation since the early 1990s. Thus, immunosuppressive protocols in SPK transplantation are largely devised based on experiences with other transplanted organs and reason rather than data. Data from the 2009 Annual Report of the SRTR indicated that in patients transplanted in 2008 immunosuppressive management after SPK transplantation is far from standardized with 16 different regimens reportedly used at the time of discharge following transplantation. Induction was used in 83.4% of transplant procedures and CNI were the backbone of nearly all regimens with > 90% of recipients receiving tacrolimus or cyclosporine at the time of initial discharge.

CTOT-15 is designed to be a first step in providing the potential benefits of an immunosuppressive regimen based on an agent other than a CNI to this underserved patient population. Currently, SPK recipients have no alternatives to CNIs for maintenance immunotherapy. As a result, immunosuppressive protocols remain dependent on these agents despite the long term nephrotoxicity and beta cell toxicity associated with these agents. Furthermore, as abatacept, a precursor of NULOJIX® (belatacept), has been shown effective for treatment of the autoimmune disease psoriasis, we believe that NULOJIX® (belatacept) may offer unique benefits to pancreas transplant recipients with type I diabetes mellitus by acting to control the autoimmune response.

CTOT-15 will also incorporate a battery of mechanistic assays that are designed to be integrated with many of the assays being performed as part of CTOTC-02 and CTOT-16. These assays compare the effects of the belatacept-based regimen on protective antiviral immunity, alloimmunity, and autoimmunity. The study design allows us to focus on how these two different classes of immunosuppressive agents affect memory responses including those that predate the transplant and those arising from homeostatic lymphocyte repopulation.

Over the last two decades, the short-term results of organ transplantation have improved steadily in large part due to the introduction of increasingly potent immunosuppressants. Calcineurin inhibitors (CNI), such as cyclosporine and tacrolimus, form the backbone of the vast majority of all immunosuppressive regimens currently used in abdominal organ transplantation (www.srtr.org). The success of these CNI-based regimens is demonstrated by the ever-decreasing incidence of acute rejection and the ever-improving 1-year graft survival following de novo renal and extra-renal transplantation. Disappointingly, this improvement in short-term outcomes has not resulted in concomitant improvements in long-term outcomes[1,2]. The major factors limiting the long-term survival of transplanted kidneys and kidney transplant recipients are the near universal development of

interstitial fibrosis and tubular atrophy (IFTA)[3] and the extremely high incidence of cardiovascular disease in transplant recipients. This is particularly true for patients with type 1 diabetes undergoing simultaneous kidney and pancreas transplantation.

It is widely recognized that CNIs are major contributors to the principal causes of the poor long-term results that still plague transplantation - death from cardiovascular disease and post-transplant renal failure, be it of the transplant or native kidneys. In the case of renal transplantation, virtually all patients develop lesions of CNI-induced nephrotoxicity and accelerated renal dysfunction [3]. The impact of CNI-induced renal dysfunction is underscored by the well-recognized association between preservation of renal function at one year and long-term graft survival[4,5]. In addition to their nephrotoxic properties, CNIs are associated with a number of toxicities that increase the risk of death from cardiovascular disease, a factor that accounts for 45.7% of all graft losses following renal transplantation (USRDS Annual Report 1999). Most importantly, CNI are major contributors to the development of new onset diabetes mellitus (DM), the incidence of which approaches 30% following renal and 20% following liver transplantation [6,7,8]. These data suggest that CNI would also have a negative impact on beta cell function following pancreas transplantation, although SPK recipients remain largely dependent on these agents to prevent rejection. Strikingly, new onset DM after renal transplantation is associated with more than a 60% increase in risk of graft failure and an almost 90% increase in risk of death[9]. CNI also cause and exacerbate hypertension and dyslipidemia, both of which are known to accelerate cardiovascular disease[10]. Together, these toxicities provide a compelling rationale for the identification of immunosuppressive agents that can replace CNI in maintenance immunosuppressive regimens following SPK.

The importance of developing regimens less dependent upon CNI is reflected in the large number of studies in renal transplantation designed to avoid or replace CNI with less toxic immunosuppressive drugs. That said, until the recent experience with belatacept identifying effective CNI alternatives has proven difficult. For example, attempts to use daclizumab, MMF and prednisone based regimens to spare CNI have been associated with excessive rates of ACR [11, 12]. Similarly, attempts to use sirolimus as a CNI replacement have proven less than ideal. In the recent SYMPHONY trial, low-dose sirolimus in combination with Zenapax® (daclizumab) induction, MMF and prednisone was inferior to low-dose tacrolimus with respect to GFR, the incidence of ACR and the 1-year graft survival. Intermediate results were obtained in patients treated with low-dose CsA[13]. These data suggest that replacement of CNI with Rapamune® (sirolimus), as a means of avoiding the CNI toxicity may not improve the survival or function of renal grafts and likely not provide adequate immunoprotection for SPK subjects.

Corticosteroids, another widely used class of immunosuppressive agents, are also associated with a myriad of metabolic and cardiovascular side effects reported to include weight gain, hypertension, glucose intolerance, abnormalities of lipids, cardiovascular and bone disease to name a few. Several immunosuppressive regimens have been reported that avoid steroids thereby achieving favorable changes in metabolic profiles while simultaneously achieving acceptably low rates of rejection. These have most frequently used either Thymoglobulin® (anti-thymocyte globulin) or Campath® (alemtuzumab) for induction and Prograf® (tacrolimus) and CellCept® (mycophenolate mofetil-MMF) for maintenance immunosuppression.

While the potential advantages of minimizing or avoiding both CNI and corticosteroids are both obvious and significant, to date there are no large randomized, prospective, multicenter studies

demonstrating either the efficacy or the safety of immunosuppressive regimens that avoid both CNI and corticosteroids following kidney and/or pancreas transplantation.

NULOJIX® (BELATACEPT) IN TRANSPLANTATION

One promising approach to avoid chronic therapy with CNI is to use the biologic immunosuppressive drug NULOJIX® (belatacept). Belatacept is a new class of immunosuppressive therapy for transplantation. It is a fusion protein that binds to the B7 molecules on the surface of antigen-presenting cells (APCs) inhibiting the delivery of CD28-dependent co-stimulation for T-cell activation. Belatacept differs from existing immunosuppressants in the restricted distribution of its molecular target and the specificity of its effect. It is administered via intravenous infusion. In the phase II and III, studies it has been given monthly during the maintenance phase for up to six years post-transplant.

Belatacept is a soluble chimeric protein designed to selectively inhibit costimulation of T-cells. T-cells require 2 signals for activation. The first signal, which is antigen specific, is delivered by engagement of the T-cell receptor (TCR) with antigen presented in context with major histocompatibility complex molecules on the APC. The second, or co-stimulatory signal, is delivered by engagement of co-stimulatory ligand on the APC with a receptor on the T-cell. A key co-stimulatory signal is provided by the interaction of B7-1 (CD80) and B7-2 (CD86) on APCs with CD28 expressed on T-cells. In the absence of this second signal, the T-cell becomes anergic (unresponsive) or undergoes apoptosis.

Conversely, if the T-cell becomes fully activated, CTLA4 (CD152) becomes expressed on the cell surface. CTLA4 has a substantially higher avidity than CD28 for CD80 and CD86 (approximately 500- to 2,500-fold). The increased avidity of endogenous CTLA4, in comparison with CD28, affords a homeostatic mechanism to down-regulate T-cell activity.

Belatacept was derived from CTLA4Ig (Abatacept, BMS-188667), a novel fusion protein consisting of the extracellular domain of human CTLA4 fused to a fragment of the Fc domain of a human immunoglobulin (Ig) G1 antibody. By binding avidly to CD80/86, CTLA4Ig blocks the interaction of the T-cell's CD28 with the APCs CD80/CD86, thus preventing T-cells from receiving the required second costimulatory signal. CTLA4Ig has been shown to be efficacious in a wide variety of preclinical models and in participants with psoriasis and rheumatoid arthritis. With respect to transplantation, CTLA4Ig demonstrated efficacy in rodent models of transplantation, but did not demonstrate substantial efficacy in non-human primate models (cynomolgus monkeys). Therefore belatacept, a 2 amino acid variant of CTLA4Ig was developed. This alteration resulted in markedly increased binding avidity for B7 molecules. Belatacept was subsequently shown to have efficacy in non-human primate renal transplant model in which CTLA4Ig was not efficacious[7]. Belatacept was also shown to be efficacious in Phase 2 clinical trial in de novo renal transplant recipients (Study IM103-100).

2.2 Preclinical and Clinical Experience

2.2.1 Preclinical Studies

1. NULOJIX® (belatacept) is a higher avidity CTLA4Ig (abatacept) molecule. The identification of CD28 as a critical costimulatory molecule for T cell activation led to considerable enthusiasm that the fusion protein CTLA4-Ig would prove to be as effective in primate and clinical transplantation studies as it was in initial rodent studies. Unfortunately, the potency of this fusion protein was considerably less effective in non-human primate renal transplantation models as compared to rodent models. Recently, it was shown that the binding affinity of CTLA4-Ig was insufficient to completely block CD28/CD86 interactions in *in vivo* studies. This may be related to the faster dissociation rate of CTLA4-Ig from CD86 as compared to CD80. High avidity CTLA4-Ig molecules were developed at

Bristol Myers Squibb (BMS) using a mutagenesis and screening strategy of over 2,300 fusion proteins. Belatacept was identified as the most potent candidate, as it binds to human CD86 with 4-fold, and to CD80 with 2-fold increased avidity. Belatacept was ten times more potent than CTLA4-Ig at inhibiting T cell proliferative responses in vitro.

2. *NULOJIX® (belatacept) prolongs renal allograft survival and synergizes with conventional immunosuppression in non-human primates*. Given the promising in vitro and in vivo immunosuppressive activity of belatacept, we tested the ability of the molecule to prevent renal allograft rejection in non-human primates. Our initial studies with belatacept monotherapy (> 20 μg/mL for 90 days post-transplant) demonstrated superior efficacy to CTLA4-Ig (median survival time for belatacept group 45d vs. 8d for CTLA4-Ig, p=0.008). These data indicate that the enhanced binding activity of belatacept results in enhanced immunosuppressive activity when compared to the parent molecule CTLA4-Ig.

We found that the combination of belatacept with the chimeric anti-human IL-2R mAb Simulect® (basiliximab) led to potentiation of efficacy, with 5 of 6 recipients demonstrating stable serum Cr and survival for > 100d. However, after cessation of belatacept treatment (day 70), all recipients ultimately rejected their allografts. Importantly, no adverse effects related to the administration of belatacept (e.g., thrombosis, hypertension, hyperglycemia, or hypercholesterolemia) were observed in any of the experimental animals by clinical assessment, by laboratory analysis, or at necropsy[7].

3. *NULOJIX® (belatacept) inhibits the development of anti-donor antibody responses.* Despite progressive improvements in acute rejection rates in recent years the rate of allograft loss per year has remained essentially unchanged. The development of antibodies specific for donor MHC molecules is thought to be an important factor contributing to the process of chronic rejection. In addition to its possible role in the process of chronic rejection the development of antibodies to donor MHC antigens following transplantation has a major impact on the prospect of re-transplantation. To evaluate the potential impact of belatacept treatment on this process we examined the development of anti-donor antibody responses in the various experimental groups. Animals treated with basiliximab alone failed to develop detectable anti-donor antibodies, presumably because the allograft failed before an effective antibody response could be mounted. Animals treated with MMF and CsA generated strong anti-donor antibody responses at the time of rejection (between days 25 and 36). In contrast, none of the animals treated with belatacept developed anti-donor antibodies during therapy, even when rejection occurred during belatacept treatment. Following withdrawal of NULOJIX® (belatacept), however, animals from each of the experimental groups developed anti-donor antibodies at the time of rejection.

These data provide evidence that blockade of T-cell costimulatory pathways is a promising strategy for the development of potentially less toxic immunosuppressive medications.

2.2.2 NULOJIX® (Belatacept) in Clinical Studies

NULOJIX® belatacept has been evaluated as a CNI-alternative in phase II and phase III studies in renal transplantation. In the phase III BENEFIT trial, one of the largest studies in kidney allograft recipients, two NULOJIX® (belatacept) regimens were compared to cyclosporine as the cornerstone of maintenance therapy for standard risk recipients from standard risk donors. All subjects received basiliximab induction and maintenance therapy consisting of mycophenolate mofetil (MMF)and prednisone. At 12 months, both belatacept regimens demonstrated similar patient and graft survival as a composite endpoint compared with cyclosporine (95% MI; 97% LI; 93% cyclosporine). Belatacept was associated with superior renal function compared with cyclosporine as measured by a composite renal

impairment endpoint (defined as CrCl < 60 ml/min/1.73 m2 or a decrease in CrCl of > 10% between months 3 and 12; 55% MI; 54% LI; 78% cyclosporine; P≤ 0.001 MI or LI vs. cyclosporine), and measured glomerular filtration rate at Month 12 (65, 63, and 50 mL/min for MI, LI and cyclosporine, respectively; P≤ 0.001 MI or LI vs. cyclosporine).

However, belatacept-treated patients experienced a higher incidence (22% MI; 17% LI; 7% CsA) and grade (more frequent grade ≥2) of acute rejection episodes. Despite this ostensibly more aggressive rejection profile, belatacept-treated subjects had very low rates of developing donor-specific antibodies that trended toward being lower than the rate observed in the cyclosporine comparison group. Importantly, belatacept-treated patients with acute rejection had better renal function at 12 months than cyclosporine-treated patients without acute rejection. In addition, belatacept-treated subjects showed a trend toward less chronic allograft nephropathy and improved cardiovascular and metabolic profiles (superior blood pressure control and lipid profiles) compared with cyclosporine-treated subjects one year post-transplant, despite the increase in early acute rejection.

Nonetheless, the diagnosis and treatment of acute rejection is associated with morbidity and significant expense. In addition, the higher grades of rejection resulted in more frequent use of T cell depleting therapy for rejection, which is a risk factor the development of viral infections and post-transplant lymphoproliferative disorder (PTLD). Therefore, despite the data that suggest that the short-term consequences of the higher rates and grades of rejection in belatacept-treated subjects are modest, studies designed to optimize the use of NULOJIX® (belatacept) are clearly warranted.

Given that recipients of pancreas transplants are considered to be at higher immunologic risk and that the more than two thirds of SKP recipients transplanted in 2008 were treated with T cell depletion therapy (www.ustransplant.org/annual_reports/current/806a_kp.pdf), it will be important to explore regimens that incorporate potent induction agents. While for individual studies, the overall safety of belatacept and cyclosporine were similar, when data from all phase II and III studies were aggregated, more cases of post-transplant lymphoproliferative disorders were reported in the belatacept groups. Post-hoc analysis indicated the PTLD risk was highest in EBV sero-negative recipients who received kidneys from EBV sero-positive donors. Other risk factors for PTLD included CMV disease and treatment of acute rejection with thymoglobulin. Based on these data, it is apparent that attention to measures aimed at reducing the risk of PTLD in belatacept-based regimens such as the avoidance of high risk subjects (EBV-negative) will be important in the design of future trials using belatacept.

Belatacept in steroid-sparing regimens using lymphocyte depletion: There has been an exploratory phase II study (IM103-034) to evaluate belatacept as a maintenance agent in place of CNI in two steroid avoidance regimens. One regimen evaluated belatacept in combination with mycophenolate mofetil while another examined it in combination with sirolimus. Both regimens included induction therapy with thymoglobulin. Six-month rejection rates were 12 and 4% respectively. Patient and graft survival were high and did not differ between the groups. Eighty-two and 89% of subjects remained steroid-free at six months. This exploratory trial suggests that regimens combining lymphocyte depletional induction using induction polyclonal antibody preparation with belatacept may be safe and effective in appropriately selected populations.

The goal of our proposed exploratory study is to determine the safety and efficacy of a regimen consisting of induction with Thymoglobulin® (Anti-thymocyte Globulin- Rabbit) and perioperative corticosteoids and maintenance with the low intensity regimen of NULOJIX® (belatacept), low dose tacrolimus (starting dose of 0.1mg/kg PO BID, followed by target trough levels of 5-8ng/mL during the first 24 weeks, and then 3-5 ng/mL until week 40), and MMF (1 gm bid). Consideration to withdrawing tacrolimus at week 40 will be given to recipients who have not experienced biopsy-

proven rejection, who have a normal 6 month management kidney biopsy (as is the standard of care at our centers), and who do not develop rejection subsequently. Our comparison group consists of recipients treated with our standard of care regimen. This regimen consists of induction with thymoglobulin and perioperative corticosteoids and maintenance with full-dose tacrolimus (targeting an initial tacrolimus trough level of 8 – 12ng/mL for the first 24 weeks, followed by 5-8ng/mL thereafter) and MMF at 1 gm bid.

Belatacept was also evaluated as a CNI-alternative in the BENEFIT-EXT study, which assessed whether CNI avoidance using belatacept would also benefit recipients of kidneys from extended criteria donors (ECD). As observed in the BENEFIT study, patient and graft survival with belatacept was non-inferior to cyclosporine (86% MI, 89% LI, 85% cyclosporine) at Month 12. Fewer belatacept patients reached the composite renal impairment endpoint compared with cyclosporine (71% MI, 77% LI, and 85% cyclosporine; P=0.002 MI versus cyclosporine; P=0.06 LI versus cyclosporine). The measured glomerular filtration rate was 4–7 mL/min higher in the belatacept group compared to the cyclosporine group at Month 12. Finally, belatacept was associated with an improved cardiovascular risk profile compared to cyclosporine.

While for individual studies, the overall safety of belatacept and cyclosporine were similar, when data from all phase II and III studies were aggregated, more cases of post-transplant lymphoproliferative disorders were reported in the belatacept groups. Post-hoc analysis indicated the PTLD risk was highest in EBV sero-negative recipients who received kidneys from EBV sero-positive donors. Other risk factors for PTLD included CMV disease and treatment of acute rejection with thymoglobulin. Based on these data, it is apparent that attention to measures aimed at reducing the risk of PTLD in belatacept-based regimens such as the avoidance of high risk participants (EBV-negative) and new approaches to avoid the need for thymoglobulin therapy for the treatment of rejection will be important considerations in the design of future trials using belatacept.

Taken together these studies suggest that maintenance therapy with belatacept will provide the best alternative to the long-term use of calcineurin-inhibitors following renal transplantation. Belatacept achieved excellent one-year patient and graft survival, superior renal function, and an improved cardiovascular risk profile. However, unmet needs remain; 1) belatacept-based regimens were associated with higher rates and grades of acute rejection and 2) higher rates of PTLD. Importantly, these adverse events associated with belatacept were observed in patients receiving corticosteroids. This raises the concern that the avoidance of steroids in patients maintained on belatacept may further increase the incidence and severity of rejection and its adverse sequelae.

Belatacept in calcineurin-inhibitor and steroid free regimens: A pilot trial utilizing thymoglobulin induction, and NULOJIX® (belatacept) and sirolimus based maintenance immunosuppression was used to protect pancreatic islet cell transplants following transplantation into Type 1 diabetic recipients. This regimen avoided the use of steroids and calcineurin-inhibitors to minimize both beta cell toxicity as well as nephrotoxicity. All five patients in this trial became insulin independent, and remained insulin independent for greater than one year. No patients developed significant side effects related to the study drugs, and none were sensitized to alloantigen. Furthermore, there was no deterioration in renal function using this regimen which avoided CI (*Transplantation* 2010; 1594-1601).

Belatacept in Steroid-sparing regimens: There has been an exploratory phase II study (IM103-034) to evaluate belatacept as a maintenance agent in place of CNI in two steroid avoidance regimens. One regimen evaluated belatacept in combination with mycophenolate mofetil (MMF) while another examined it in combination with sirolimus. Both regimens included induction therapy with thymoglobulin. Six-month rejection rates were 12 and 4% respectively. Patient and graft survival was

high and did not differ between the groups. Eighty-two and 89% of participants remained steroid-free at six months. These data suggest that belatacept may provide a means to avoid both CNI and corticosteroids but indicate that further investigations designed to optimize the regimen are warranted in order to achieve rates of rejection comparable to those observed in standard of care CNI-based regimens.

SELECTION OF INDUCTION STRATEGIES TO FACILITATE SAFE AND EFFECTIVE STEROID AND CNI-FREE BELATACEPT-BASED MAINTENANCE IMMUNOSUPPRESSIVE REGIMENS

Given the higher rates and grades of rejection associated with the belatacept regimens evaluated in the phase3 studies, it is likely that more potent induction strategies than basiliximab will be required to facilitate regimens that avoid steroids and calcineurin-inhibitors. As outlined above the phase II (IM103-034) study has shown promise that this may be an achievable goal using strategies that include lymphocyte depletion with thymoglobulin.

Since Type I diabetes is an autoimmune disease, immunosuppressive strategies must target both the alloimmune response as well as the recurrent autoimmune response following pancreas transplantation. Since the latter is driven by a memory-cell response, it is imperative that an immunosuppressive regimen must target T-cells with memory for islet autoantigen. Strategies using CTLA4-Ig have been effective in blocking the activation of naïve T-cells, but are less effective in preventing reactivation of memory cells[14,15]. The potential need for immunodepletion prior to the introduction of co-stimulatory/adhesion blockade is further supported by human data suggesting the lack of CD28 expression in effector cells derived from memory CD4+ cells[16]. There are several immunodepleting agents which have been tested and found effective for this specific indication, but the most extensive experience has been with rabbit anti-thymocyte globulin (Thymoglobulin). Rabbit ATG is a polyclonal antibody preparation that depletes T and B cells following IV administration, and has emerged as the superior agent for induction therapy in solid organ transplantation. Thymoglogulin is the current induction agent for all solid organ pancreas transplants performed at UCSF (30/year) and most centers in the US, and is in part responsible for the decrease in early rejection rates from 80% to less than 15 % even in steroid free regimens[17]. An early limited human study with equine anti-thymocyte globulin (ATG) with new onset Type diabetes mellitus suggested efficacy in prolonging the honeymoon phase[18], and has prompted a new trial studying the efficacy of Thymoglobulin in the same scenario sponsored by the NIH Immune Tolerance Network. Thymoglobulin or ATG, either alone or in combination with other agents, has also been used to treat various autoimmune conditions, including Wegner's granulomatosis[19], lupus[20], multiple sclerosis[21] and aplastic anemia[22].
The large clinical experience with Thymoglobulin as a highly effective induction agent for the immunogenic solid organ pancreas transplant, as well as evidence that is effective against multiple autoimmune diseases, make it an ideal induction agent to be used in conjunction with a maintenance regimen focusing on co-stimulatory blockade. In fact, one of the first clinical islet transplantation trials which resulted in long term insulin independence with a single infusion of islets utilized Thymoglobulin induction[23]. Thymoglobulin induction was successfully used in another islet transplant study in conjunction with belatacept in a *steroid and calcineurin free regimen*. This trial also resulted in long term insulin independence following islet transplantation, and provides the most relevant data suggesting that thymoglobulin induction can provide safe and effective immunosuppression following beta cell replacement in the Type I diabetic recipient in a regimen based on costimulation blockade[24].

As a second approach to facilitate steroid-free belatacept-based regimens we will evaluate an 85 day course of induction with low-dose tacrolimus combined with belatacept and mycophenolate mofetil (MMF) maintenance therapy. We have explored a similar approach at the Emory Transplant Center in a clinical islet transplant trial using the anti-CD11a mAb, efalizumab. In this study four patients received one allogeneic islet infusion. The immunosuppressive regimen consisted of daclizumab induction, induction with a tapering dose of tacrolimus (discontinued at six months), belatacept and mycophenolate mofetil. All four participants achieved insulin independence associated with positive determinations of c-peptide and a normalized hemoglobin A1C after a single islet infusion. Rejection-free insulin independent survival of 9, 13, 16, and 29 months was observed until efalizumab was withdrawn from the regimen following Genzyme's decision to withdraw it from the market. Importantly, none of these 4 patients experienced renal dysfunction associated with the short course of tacrolimus (Prograf®). These results suggest that induction using a low dose of tacrolimus may provide protection from acute rejection during the critical early post-transplant period.

Short-term low-dose tacrolimus combined with belatacept and mycophenolate mofetil has potential advantages over T cell depletion approaches with Thymoglobulin® or alemtuzumab. These include 1) the ability to titrate tacrolimus levels and the more rapid reversibility of the immunosuppressive effect of tacrolimus relative to thymoglobulin if over immunosuppression is encountered, 3) fewer long-term effects on the immune system than T cell depletion approaches, and 4) the avoidance of cytokine release-related peri-infusional toxicities. Two potential disadvantages of this approach include the potential for CNI-induced nephrotoxicity and the need for therapeutic drug monitoring. Based on data from the Rapamune Maintenance Regimen Study, the STN study and our observations in our islet trial we anticipate that the renal function benefits of belatacept at one year will not be adversely affected by a 85 day course of low dose (Prograf®) tacrolimus. Assessment of these issues will be an important focus of our trial.

In addition to the studies already discussed, belatacept has been studied in three BMS-sponsored clinical trials protocols: IM103-001 (completed), IM103 002 (completed), and IM103-100 (completed). Protocol IM103-001 was a Phase I, randomized, double blind, placebo-controlled study to assess the safety, pharmacokinetics and immunogenicity of escalating doses of intravenously administered belatacept in healthy volunteers. Protocol IM103-002 was a Phase II, randomized, double blind, placebo-controlled study to evaluate the safety, preliminary clinical activity, immunogenicity and pharmacokinetics of multiple doses of belatacept and CTLA4Ig administered intravenously to participants with active rheumatoid arthritis. IM103-100 was a Phase II, randomized, open-label, controlled study to directly compare the safety and preliminary clinical activity of belatacept with (Neoral®) cyclosporin in kidney transplant recipients.

Results of Phase I studies pharmacokinetics and safety of a single dose, dose escalation study of belatacept in Healthy Volunteers (IM103-001):

A single-dose Phase I study with belatacept was performed in 40 healthy volunteers. Participants received single IV infusions of 0.1, 1, 5, 10, or 20 mg/kg belatacept. At each dose level, 6 participants received active drug and 2 received placebo. Pharmacokinetic sampling and analysis indicated that Cmax values increased in a dose-proportional manner and were in a range similar to that observed with the parent molecule. Both Cmax and AUC (area under the curve) appeared to increase in ratio comparable to the dose increment ratio. The half-life ranged between 176 - 210 hr (~7-9 days) between the 5 and 20 mg/kg dose levels. Overall, the pharmacokinetics of belatacept appears to be linear following intravenous (IV) administration to humans.

Review of the safety data from this trial indicates that single, IV doses of belatacept of 0.1 to 20.0 mg/kg were well tolerated. No deaths or serious adverse events were reported. No histamine-like peri-infusional AEs were reported. No clinically significant changes in vital signs or laboratory parameters were observed. There was no evidence for the development of anti-belatacept antibodies.

Results of a Phase II Study of belatacept in Rheumatoid Arthritis (IM103-002)

Study IM103-002 was a Phase 2 pilot study that assessed the efficacy, safety, and immunogenicity of multiple IV doses of belatacept, CTLA4Ig, and placebo in 214 participants with RA. Eligible participants had a diagnosis of RA for ≤ 7 years, had failed at least 1 disease-modifying anti-rheumatic drug therapy, including etanercept, and had active disease (≥ 10 swollen joints, ≥ 12 tender joints, an erythrocyte sedimentation rate ≥ 28 mm/h, and morning stiffness ≥ 45 minutes). Overall, belatacept demonstrated dose-dependent efficacy in this participant population, as evidenced by American College of Rheumatology scores. With respect to safety, no deaths were reported during the treatment or follow-up period (through Day 169), and 12 participants reported SAEs, although no SAEs were considered drug related by the investigators.

Results of a Phase II Study of belatacept in Solid Organ Transplantation (IM103-100)

Study IM103-100 was a 1-year, partially-blinded, randomized, active-controlled, multiple-dose, multicenter non-inferiority study in de novo renal transplant recipients. All participants received basiliximab induction and background maintenance immunosuppression with MMF and corticosteroids. Participants were randomized in a 1:1:1 ratio to treatment with belatacept (more intensive [MI] or less intensive [LI] regimens) or CsA (open-label dosed twice daily to achieve a specified trough serum concentration range). Belatacept was administered in a double-blind fashion, with the investigator and participant blinded to the identity of the belatacept dose regimen.

Belatacept participants were dosed with 10 mg/kg on Days 1, 5, 15, 29, 43, 57, 71, 85, 113, 141, and 169 (MI regimen) or 10 mg/kg on Days 1, 15, 29, 57, and 85 (LI regimen). Participants were reallocated on Days 85 (LI regimen) and 169 (MI regimen) to a 5 mg/kg dose of the drug every 4 or 8 weeks through Day 365.

The primary efficacy variable was the incidence of clinically-suspected and biopsy-proven acute rejection (CSBPAR) at 6 months post transplantation. CSBPAR was defined as an increase in serum creatinine (SCr) of at least 0.5 mg/dL compared to the baseline value in the absence of other factors known to adversely affect renal function that led the investigator to suspect acute rejection, which was then confirmed by centrally-assessed biopsy. Secondary efficacy variables were the incidence of all biopsy-proven acute rejections (BPARs), including those without an increase in SCr of at least 0.5 mg/dL, as well as the composite endpoints of CSBPAR or presumed acute rejection and BPAR or presumed acute rejection at 6 months and 1 year, and death and/or graft loss at 1 year. 'Presumed acute rejection' was defined as an elevation in SCr (at least 0.5 mg/dL compared to the baseline value in the absence of other factors known to adversely affect renal function) that led the investigator to suspect and treat the participant for acute rejection without a biopsy to confirm the diagnosis, or despite a biopsy that did not confirm acute rejection. All biopsies were assessed in a blinded fashion by a central pathologist. The primary cause of graft loss and death was also adjudicated.

The safety evaluation included AEs (including infections), vital signs, physical examinations, electrocardiograms, and laboratory parameters (hematology, biochemistry, and urinalysis). Topics of special interest were renal function (GFR, as determined by iohexol clearance, SCr, and calculated creatinine clearance or GFR at 1, 6, and 12 months), BP parameters (systolic diastolic pressure [SBP] and

diastolic blood pressure [DBP], presence of hypertension), fasting serum cholesterol and triglycerides (TGs), and the presence of post-transplant diabetes mellitus (PTDM).

The efficacy and safety results for Study IM103-100 study are presented in the following sections. For more detailed information on the efficacy and safety of belatacept, see the Investigator Brochure. Overall, the mean duration of exposure was comparable across all 3 treatment groups. Specifically, mean duration of exposure was 300, 308, and 294 days in the belatacept MI and LI groups and the CsA group, respectively.

Acute Rejection

The primary endpoint, CSBPAR at 6 months, occurred infrequently in all treatment groups. The incidence rate was slightly lower in the belatacept groups than in the CsA group. The criteria for non-inferiority to CsA were easily satisfied for both belatacept groups; however, the number of events was too small to support any further conclusions regarding the relative efficacy of the 3 regimens. The distribution of events by severity (as indicated by histological grade) was similar across the 3 treatment groups. Identical results were observed at 12 months.

The secondary endpoint of BPAR occurred 2 to 4 times more frequently than the primary endpoint of CSBPAR, indicating that most BPAR were subclinical (i.e., not associated with an increase in SCr ≥ 0.5 mg/dL). These episodes of subclinical rejection were observed on biopsies taken to satisfy the protocol requirements, according to local practice, or for other reasons than an increase in SCr ≥ 0.5 mg/dL.

BPAR occurred most frequently in the belatacept LI group. As the rate of CSBPAR was comparable across treatment groups, the difference in the rate of BPAR was due to an increase in the number of subclinical rejection episodes in the belatacept LI arm. In addition, reallocation of participants to an 8-week infusion schedule rather than a 4-week infusion schedule in the maintenance phase was associated with an increased frequency of subclinical rejection.

Overall, the histological severity grade of acute rejection episodes appeared to be similar across the 3 treatment groups. While Grade IIB rejection, as assessed by Banff 97 criteria, occurred more frequently in the belatacept groups, the number of such events was small, and the belatacept LI: 1.1%-13%; and CsA: 0%-6.5%).

Recurrent Acute Rejection

Overall, the average number of rejection episodes per participant (~1.2) was similar among the 3 treatment groups.

Chronic Allograft Nephropathy (CAN)

Biopsy specimens were also examined for CAN by an independent blinded central histopathologist using Banff 97 working classification of kidney transplant pathology[9]. By Month 12, CAN was approximately 30%-50%, in relative terms, less common with belatacept than with CsA.

Participant and Graft Survival

Death and/or graft loss occurred infrequently in all treatment groups, and was least frequently reported in the belatacept LI group. Most graft losses occurred for technical, rather than immunological, reasons.

Five deaths (4 in the CsA group and 1 in the belatacept MI group) occurred and were analyzed according to the intent-to-treat (ITT) principle. Two of these deaths – both in the CsA group – occurred on therapy or within 56 days of the last dose of study therapy. Accordingly, these deaths also are counted under the prespecified safety conventions.

Three other deaths qualify under the ITT principle, but not under the safety conventions because they either never received study drug or the death was an event subsequent to the discontinuation of study drug + 56 days. One death in the CsA group and 1 in the belatacept MI group, occurred > 56 days after the last dose of study therapy. One death in the CsA group occurred in a participant who was randomized, but never treated.

Adverse Events

Overall Adverse Events

The overall incidence of AEs is summarized in Table 1A.

Table 1A: Overall Incidence of Adverse Events Through Day 56 After Double-blind Period (Randomized, Transplanted and Treated Population) - Study IM103-100

	No. (%) of Participants		
	Belatacept MI (N=74)	**Belatacept LI (N=71)**	**CsA (N=71)**
Adverse Events	73 (98.6)	69 (97.2)	68 (95.8)
Discontinued Due to Adverse Events	13 (17.6)	15 (21.1)	14 (19.7)
Related Adverse Events	43 (58.1)	40 (56.3)	50 (70.4)
Serious Adverse Events	50 (67.6)	52 (73.2)	41 (57.7)
Related Serious Adverse Events	20 (27.0)	23 (32.4)	21 (29.6)
Deaths[a]	0	0	2 (2.8)

- [a] Includes all deaths up to 56 days after last dose of study therapy, by therapy received.

CsA = cyclosporine, LI = less intensive, and MI = more intensive.

The rate of AEs, including AEs resulting in discontinuation, was similar across the 3 treatment groups. The rate of SAEs was somewhat higher for both belatacept treatment groups than for the CsA treatment group. As described below, this difference is due to an increased number of reports of AEs of transplant rejection, not subsequently confirmed as transplant rejection, in the belatacept treatment groups.

The incidence of AEs, by Medical Dictionary for Drug Regulatory Activities (MedDRA) system organ class (SOC) and preferred term, is summarized in Table 1B.

Table 1B: Most Frequent Adverse Events (At Least 10% in Any Group) Through Day 56 After Double-blind Period (Randomized, Transplanted and Treated Population) - Study IM103-100

MedDRA System Organ Class Preferred Term	No. (%) of Participants		
	Belatacept MI (N=74)	Belatacept LI (N=71)	CsA (N=71)
Participants with Any Adverse Events	73 (98.6)	69 (97.2)	68 (95.8)
Blood & Lymphatic System Disorders	29 (39.2)	28 (39.4)	40 (56.3)
Leukopenia	14 (18.9)	12 (16.9)	21 (29.6)
Anemia	13 (17.6)	12 (16.9)	21 (29.6)
Cardiac Disorders	10 (13.5)	10 (14.1)	10 (14.1)
Endocrine Disorders	4 (5.4)	8 (11.3)	9 (12.7)
Gastrointestinal Disorders	45 (60.8)	45 (63.4)	42 (59.2)
Nausea	19 (25.7)	18 (25.4)	16 (22.5)
Diarrhea	17 (23.0)	18 (25.4)	17 (23.9)
Constipation	16 (21.6)	22 (31.0)	20 (28.2)
Vomiting	11 (14.9)	14 (19.7)	11 (15.5)
General Disorders & Administration Site Conds.	43 (58.1)	40 (56.3)	42 (59.2)
Edema Peripheral	23 (31.1)	20 (28.2)	21 (29.6)
Pyrexia	15 (20.3)	19 (26.8)	15 (21.1)
Pain	7 (9.5)	6 (8.5)	9 (12.7)
Fatigue	6 (8.1)	6 (8.5)	9 (12.7)
Edema	6 (8.1)	7 (9.9)	11 (15.5)
Immune System Disorders	22 (28.7)	29 (40.8)	16 (22.5)
Transplant Rejection	19 (25.7)	23 (32.4)	11 (15.5)
Infections & Infestations	54 (73.0)	52 (73.2)	53 (74.6)
Urinary Tract Infection	17 (23.0)	17 (23.9)	22 (31.0)
Cytomegalovirus Infection	11 (14.9)	10 (14.1)	13 (18.3)
Nasopharyngitis	9 (12.2)	10 (14.1)	11 (15.5)

Table 1B: Most Frequent Adverse Events (At Least 10% in Any Group) Through Day 56 After Double-blind Period (Randomized, Transplanted and Treated Population) - Study IM103-100

MedDRA System Organ Class Preferred Term	No. (%) of Participants		
	Belatacept MI (N=74)	Belatacept LI (N=71)	CsA (N=71)
Injury, Poisoning & Procedural Complications	44 (59.5)	45 (63.4)	45 (63.4)
Incision Site Complication	17 (23.0)	16 (22.5)	13 (18.3)
Post Procedural Pain	14 (18.9)	17 (23.9)	15 (21.1)
Graft Dysfunction	9 (12.2)	10 (14.1)	10 (14.1)
Investigations	26 (35.1)	22 (31.0)	29 (40.8)
Blood Creatinine Increased	13 (17.6)	10 (14.1)	13 (18.3)
Metabolism & Nutrition Disorders	36 (48.6)	35 (49.3)	42 (59.2)
Hypophosphatemia	14 (18.9)	24 (33.8)	15 (21.1)
Hyperlipidemia	9 (12.2)	8 (11.3)	6 (8.5)
Hypercholesterolemia	6 (8.1)	4 (5.6)	9 (12.7)
Hypokalemia	5 (6.8)	5 (7.0)	9 (12.7)
Musculoskeletal & Connective Tissue Disorders	26 (35.1)	20 (28.2)	20 (28.2)
Arthralgia	8 (10.8)	6 (8.5)	4 (5.6)
Back Pain	8 (10.8)	3 (4.2)	6 (8.5)
Nervous System Disorders	26 (35.1)	20 (28.2)	26 (36.6)
Headache	13 (17.6)	10 (14.1)	8 (11.3)
Tremor	8 (10.8)	10 (14.1)	14 (19.7)
Psychiatric Disorders	18 (24.3)	27 (38.0)	20 (28.2)
Insomnia	12 (16.2)	19 (26.8)	17 (23.9)
Renal & Urinary Disorders	28 (37.8)	27 (38.0)	25 (35.2)
Reproductive System & Breast Disorders	7 (9.5)	12 (16.9)	7 (9.9)
Respiratory, Thoracic & Mediastinal Disorders	23 (31.1)	24 (33.8)	29 (40.8)
Cough	7 (9.5)	8 (11.3)	11 (15.5)

Table 1B: Most Frequent Adverse Events (At Least 10% in Any Group) Through Day 56 After Double-blind Period (Randomized, Transplanted and Treated Population) - Study IM103-100

MedDRA System Organ Class Preferred Term	No. (%) of Participants		
	Belatacept MI (N=74)	Belatacept LI (N=71)	CsA (N=71)
Dyspnea	5 (6.8)	6 (8.5)	9 (12.7)
Skin & Subcutaneous Tissue Disorders	26 (35.1)	18 (25.4)	18 (25.4)
Vascular Disorders	27 (36.5)	29 (40.8)	29 (40.8)
Hypertension	16 (21.6)	17 (23.9)	22 (31.0)

Note: The number of adverse events for transplant rejections includes investigator-reported transplant rejections, often obtained at the time of biopsy, irrespective of central blinded histological evaluation and/or local evaluation.

CsA = cyclosporine, LI = less intensive, MedDRA = Medical Dictionary of Drug Regulatory Activities, and MI = more intensive.

Transplant rejection was reported more commonly with both doses belatacept than with CsA. Subsequent evaluation revealed that these reports reflected episodes of suspected acute rejection later disproved by central biopsy, as well as episodes that resolved spontaneously without treatment. All reported AEs of transplant rejection were subsequently confirmed by biopsy. AEs commonly observed during CsA treatment, such as anemia, leukopenia, hirsutism, tremor, hypomagnesemia, and hypertension, were reported less frequently with belatacept than with CsA in this study. Infectious complications occurred with comparable frequency. Pulmonary edema and proteinuria were reported more frequently with belatacept than with CsA. The significance of these events requires further evaluation.

Serious Adverse Events

SAEs were reported somewhat more frequently in the belatacept treatment groups than in the CsA group (see Table 1C). This difference is accounted for by an increased frequency of reporting acute rejection as an AE in the belatacept groups. Subsequent evaluation revealed that these reports reflected episodes of suspected rejection later disproved by central biopsy, as well as episodes that resolved spontaneously without treatment.

Three participants treated with the belatacept MI regimen developed post-transplant lymphoproliferative disorder (PTLD). One case occurred on treatment and the others occurred 2 months and > 1 year after discontinuation of the study drug. The participant that developed PTLD on treatment was Epstein-Barr virus (EBV) negative and received an EBV positive allograft. This participant was diagnosed with PTLD 9 months after transplantation from a biopsy of a lesion near the basal ganglia, and belatacept was discontinued. The participant died 5 months later from *Pneumocystis carinii* pneumonia and recurrent *Cytomegalovirus* (CMV) infection while receiving dexamethasone and sirolimus. A second participant was diagnosed with PTLD 4 months after transplantation and 2 months after discontinuation of belatacept with initiation of tacrolimus (Prograf®). The diagnosis was based upon a renal allograft biopsy performed for suspected acute rejection. The tumor tissue and urine tested positive for EBV, and retrospective analysis of stored

sera from the recipient tested negative for EBV. This participant underwent a transplant nephrectomy. A final participant received 4 doses of belatacept before discontinuation for a Grade IIB rejection, which was treated with a 10-day course of OKT3®. PTLD was diagnosed from an excisional biopsy of an anterior cervical lymph node 12 months after discontinuation of study drug. Additional information on these cases is provided in the Investigator Brochure.

One participant treated with the belatacept MI regimen developed breast cancer after 12 months of treatment. In retrospect, the baseline mammogram for this participant was abnormal. No participants treated with the belatacept LI regimen developed malignancies. Two participants treated with CsA developed malignancies – squamous cell carcinoma of the skin and thyroid cancer – while a third participant developed a parathyroid nodule not yet confirmed to be malignant.

Table 1C: Most Frequent (At Least 5% in Any Group) Serious Adverse Events Through Day 56 After Double-blind Period (Randomized, Transplanted and Treated Population) - Study IM103-100

	No. (%) of Participants		
MedDRA System Organ Class Preferred Term	**Belatacept MI (N=74)**	**Belatacept LI (N=71)**	**CsA (N=71)**
Participants with Any Serious Adverse Events	50 (67.6)	52 (73.2)	41 (57.7)
Blood & Lymphatic System Disorders	2 (2.7)	3 (4.2)	4 (5.6)
Gastrointestinal Disorders	7 (9.5)	7 (9.9)	5 (7.0)
General Disorders & Administration Site Conds.	5 (6.8)	8 (11.3)	7 (9.9)
Pyrexia	4 (5.4)	8 (11.3)	6 (8.5)
Immune System Disorders	20 (27.0)	23 (32.4)	13 (18.3)
Transplant Rejection	18 (24.3)	20 (28.2)	9 (12.7)
Infections & Infestations	17 (23.0)	12 (16.9)	18 (25.4)
Cytomegalovirus	5 (6.8)	4 (5.6)	7 (9.9)
Pyelonephritis	4 (5.4)	1 (1.4)	2 (2.8)
Urinary Tract Infection	2 (2.7)	0	4 (5.6)
Injury, Poisoning & Procedural Complications	8 (10.8)	6 (8.5)	9 (12.7)
Investigations	8 (10.8)	2 (2.8)	4 (5.6)
Blood Creatinine Increased	8 (10.8)	2 (2.8)	4 (5.6)
Metabolism & Nutrition Disorders	1 (1.4)	2 (2.8)	4 (5.6)
Renal & Urinary Disorders	9 (12.2)	11 (15.5)	9 (12.7)
Respiratory, Thoracic & Mediastinal Disorders	6 (8.1)	3 (4.2)	4 (5.6)
Vascular Disorders	3 (4.1)	5 (7.0)	8 (11.3)

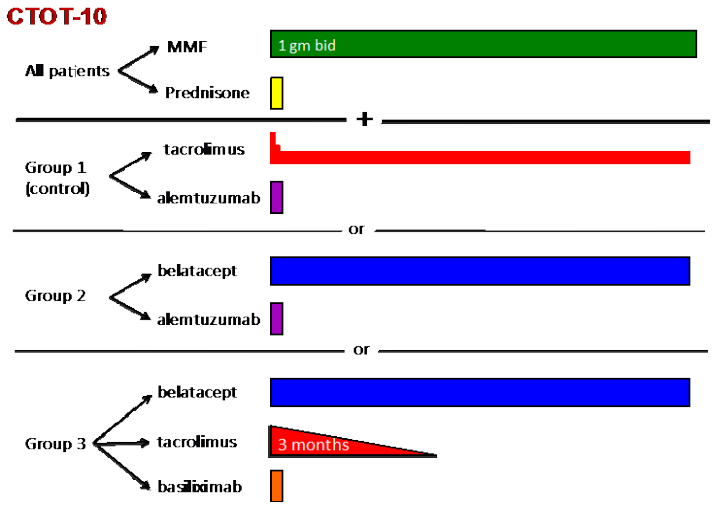
- CsA = cyclosporine, LI = less intensive, MedDRA = Medical Dictionary of Drug Regulatory Activities, and MI = more intensive.

IM103-100 Study Follow-Up

The most recent unpublished analysis of the IM103-100 trial belatacept + CellCept® and low dose steroid (5-10 mg prednisone per day) in clinical renal transplantation shows that there are 75 participants on belatacept and CellCept®-based regimens in long-term extension trials from the original IM103-100 study with no reports of subsequent post-transplant lymphoproliferative disorder in this group.

Nine of these long-term study participants are being followed at Emory University. Out of the 9, one was non-compliant with therapy and had a rejection episode that was successfully reversed. Eight of the 9 Emory participants have excellent, stable renal function (mean Cr = 0.80) with up to 6 years of follow-up.

Preliminary results of a multicenter, phase II study to explore the use of Belatacept as a means of avoiding the long-term use of both calcineurin inhibitors and corticosteroids in renal transplant recipients (CTOT-10)



CTOT-10 was designed as a multicenter, prospective randomized trial to compare maintenance immunosuppressive regimens consisting of belatacept and MMF to a regimen consisting of tacrolimus and MMF. All regimens included a perioperative course of corticosteroids. The details of the three regimens are shown in the adjacent figure. The primary hypothesis was that the use of belatacept in place of tacrolimus would improve renal function and the metabolic profile in patients undergoing a primary renal transplant without increasing episodes of rejection, significant infections, or malignancies. A total of 19 subjects were enrolled in 3 participating centers between 11/10/11 and 4/12/12. The total number of subjects enrolled in each of the 3 groups were Group 1 N = 6, Group 2 N = 6, and Group 3 N = 7. The investigators, after consultation with the NIH Medical Officer, chose to pause enrollment in the spring 2012 to allow review of a number of SAEs that may have been related to the study regimen. The SAEs of concern by group were as follows (reported at the time of this protocol version): Group 1 – one episode of intraoperative renal artery thrombosis that required thrombectomy but had no adverse sequelae. Group 2 – one episode each of renal artery thrombosis, renal vein thrombosis, and renal artery dissection, each of which resulted in graft loss. Three episodes of acute cellular rejection was reported in two patients (Banff grades 1A, 1A and 2B), each episode of rejection responded to therapy with a returned to baseline normal renal function. Group 3 – four episodes of acute rejection in three subjects (Banff grades 2A, 2A, 2A, and 2B). Each of the episodes of rejection responded to therapy with a return of renal function to baseline. Following review by the NIH DSMB and the FDA and further deliberation by the investigators and the NIH Medical Officer, enrollment in CTOT-10 was permanently halted with the enrolled patients transitioned to a protocol designed to gather long-term safety data.

In considering the potential etiologies of the vascular events, it was felt that the renal artery dissection (group 2) that occurred two weeks following the transplant was technical in nature

and likely related to an unappreciated injury caused by the vascular clamp at the time of surgery. The other 3 vascular events were of uncertain etiology but not felt to have a technical component. Each of the three occurred in patients receiving alemtuzumab and was associated with perioperative episodes of relative hypotension and fever.

With regards to the episodes of acute rejection, two of the four episodes in Group 3 occurred shortly after the withdrawal of tacrolimus. With this in mind, the current protocol (CTOT-15) specifies that the administration of tacrolimus in Group 2 be administered to 40 weeks.

3 RATIONALE FOR SELECTION OF STUDY POPULATION

CTOT-15 will study individuals undergoing *de novo* simultaneous pancreas and kidney transplantation (SPK) from a deceased organ donor. This study will test the hypothesis that a regimen of induction with Thymoglobulin® (anti-thymocyte globulin- Rabbit) followed by maintenance with NULOJIX® (belatacept) and minimization or withdrawal of calcineurin inhibitors (CNI) will result in comparable rates of rejection and superior renal function as compared with a tacrolimus-based maintenance immunosuppressive regimen in recipients of SPK.

A transplanted pancreas can elicit both an alloimmune response and an autoimmune response from the recipient. Individuals undergoing SPK transplantation are presumed to be at greater risk of immunologic allograft injury than those that undergo kidney transplant alone; thus, they are treated with more aggressive CNI-based immunosuppressive regimens. However, the population that presents for SPK is also at higher risk for the morbidities associated with CNI due to the consequences of long-standing diabetes. This proposal is an attempt to extend the potential benefits of reduced CNI exposure, facilitated by maintenance therapy with NULOJIX® (belatacept), to recipients of SPK transplantation.

4 RATIONALE FOR INVESTIGATIONAL THERAPEUTIC REGIMEN

Rationale for Co-Stimulation Blockade in Pancreas Transplantation

The potential efficacy of co-stimulation blockade to minimize or eliminate long term CNI should be tested in the setting of pancreas transplantation, as this group is particularly underserved with respect to trials examining new immunosuppressive regimens. As a result of the higher maintenance doses of CNI required to prevent rejection of simultaneously transplanted pancreas and kidney transplants (SPK), long term function of the kidney allograft is compromised by CNI toxicity. In patients experiencing severe CNI induced toxicities, such as neurotoxicity or Hemolytic Uremic Syndrome (HUS), there are no alternative agents for effective immunologic protection. Finally, the calcineurin inhibitors are toxic to beta cells, and the development of strategies to avoid these agents will facilitate long term preservation of metabolic function of the pancreas allografts. For all these reasons, it is important to develop an effective strategy for using non-nephrotoxic and non-beta cell toxic co-stimulation blockade to minimize or eliminate the requirement for CNI. At the same time, the efficacy of lymphodepletion followed by co-stimulation blockade in blocking both the alloimmune and recurrent autoimmune response can be determined.

The design of the study is to compare the safety and efficacy of 2 immunosuppressive regimens, Refer to Section 8 of the protocol for dosing and administration:

1. The Control Arm consists of induction with Thymoglobulin (Anti-thymocyte Globulin (Rabbit)) and solumedrol (or equivalent). Maintenance immunosuppression will consist of CellCept® (mycophenolate mofetil) and Prograf® (tacrolimus). Prograf® (tacrolimus) will not be weaned.
2. The Investigational Arm will receive induction with Thymoglobulin (Anti-thymocyte Globulin (Rabbit)) and solumedrol (or equivalent). Maintenance immunosuppression will consist of NULOJIX® (belatacept), Prograf® (tacrolimus) to week 40, and CellCept® (mycophenolate mofetil).

5 KNOWN AND POTENTIAL RISKS AND BENEFITS TO PARTICIPANTS

Please refer to Manual of Procedures (MOP), study provided Investigator's Brochure (IB), Package Inserts (PI), and to applicable product labeling for known and potential risks to human participants associated with the study medication(s).

All anti-rejection drugs (immunosuppressive medications) may increase the risk of infection, lymphoma, post-transplant lymphoproliferative disorder (PTLD), and cancer. Some of these side-effects may be life-threatening or fatal, and will continue to be closely monitored throughout the study.

5.1 Risks of NULOJIX® (belatacept) Therapy

NULOJIX® (belatacept) is contraindicated in transplant recipients who are Epstein-Barr virus (EBV) sero negative or with unknown EBV serostatus due to the risk of post-transplant lymphoproliferative disorder (PTLD), predominantly involving the central nervous system (CNS)

Potential Risks of belatacept in Renal Transplantation

Post-transplant Lymphoproliferative Disorder
In the combined BMS-sponsored Phase 2 (median exposure 74 to 88 months) and Phase 3 studies (median exposure of approximately 39 months) in *de novo* renal transplantation, post-transplant lymphoproliferative disorder (PTLD) developed more frequently in patients who received belatacept (14 cases out of 949; 1.5% of subjects) than those who received cyclosporine (3 cases out of 476; 0.6%). Of the PTLD cases reported with belatacept, all but 1 occurred during the first 18 months post-transplant. More than half of the PTLD cases in belatacept-treated patients involved the CNS (9 cases out of 14; 65% of belatacept patients). A total of 8 out of 14 patients with PTLD in the belatacept group and 3 out of 3 in the cyclosporine group have died.

The excess risk of PTLD with belatacept was concentrated in EBV negative recipients (approximately 10-fold higher than that observed in EBV positive recipients). While there was also an increased risk in EBV positive subjects with belatacept compared to CsA within the studies, the absolute risk in this population was low. In addition to EBV-negative serostatus, CMV disease, and use of lymphocyte depleting therapy for treatment of AR were also associated with an increased risk of PTLD in the core belatacept studies. Nonetheless, the highest risk of PTLD with belatacept was observed in EBV-negative subjects. Thus, belatacept should not be administered to belatacept naïve patients who are EBV-negative or have unknown EBV serostatus. PTLD should be considered in subjects who develop new neurologic signs or symptoms.

Malignancy
An increased incidence of malignancy is a recognized complication of immunosuppression in recipients of organ transplants. In the Phase 3 studies, overall malignancy rates were similar across all treatment groups, with the exception of PTLD.

Infection
Increased susceptibility to infection, including serious and fatal infections may result from the use of belatacept, as with all immunosuppressive therapies. Overall incidences of infections, including serious fungal and viral infections, were similar across all treatment groups in the Phase 3 studies over the 36 month period of observation. The most common serious infections across treatment groups were urinary tract infection (UTI) and CMV infections.

Progressive Multifocal Leukoencephalopathy (PML)

One (1) case of progressive multifocal leukoencephalopathy (PML) has been reported in the belatacept renal transplantation program, in a subject receiving the MI regimen in study IM103027. PML should be considered in subjects who develop new neurologic signs or symptoms.

Tuberculosis has been more frequently reported in belatacept-treated patients than CsA-treated patients. There were a total of 13 TB cases (12 with belatacept and 1 with CsA) reported in the Phase 3 studies over 36 months. Nearly all cases of TB were reported in subjects who currently or previously resided in countries with a high prevalence of TB.

Other Potential Risks

Other potential risks include graft thrombosis, infusion-related reactions, proteinuria, congestive heart failure, and autoimmune disorders. These events have been observed infrequently in belatacept-treated subjects but are being closely monitored in all belatacept clinical trials.

Potential Risks in Liver Transplantation

A total of 250 subjects who received a liver transplant were randomized and treated in 5 treatment groups (3 belatacept-containing groups and 2 tacrolimus-containing groups): Group 1): Basiliximab + Belatacept MI + MMF; Group 2): Belatacept MI + MMF; Group 3): Belatacept LI + MMF; Group 4): Tacrolimus + MMF; and Group 5): Tacrolimus. Of these patients, 147 received belatacept. All subjects received corticosteroids that could be tapered or discontinued after Month 3 according to institutional practice.

Over the first 12 months of the study, there were 2 cases of post-transplant lymphoproliferative disorder (PTLD) reported in the belatacept groups; 1 patient died due to PTLD. There was 1 fatal case of progressive multifocal leukoencephalopathy (PML) in the belatacept more intensive (MI) group. The overall frequency of serious infections was not different between the groups, but there was an increase in viral and fungal infections in the belatacept groups versus the tacrolimus groups.

During the long-term extension phase of the study (beyond 12 months post-transplant), a higher number of deaths was observed in 2 of the 3 belatacept groups (belatacept MI+MMF and belatacept LI+MMF) when compared to the tacrolimus+MMF group. The frequencies of death were 12%, 21%, and 22% in the basiliximab+ belatacept MI+MMF, belatacept MI+MMF, and belatacept LI+MMF groups, respectively, in comparison to 6% in the tacrolimus+MMF group and 14% in the tacrolimus group. A causal relationship to belatacept could not be clearly established, but likewise could not be rejected. BMS in consultation with the Independent Data Monitoring Committee decided to terminate the study and recommend that all belatacept patients be switched to local standard of care.

5.2 Risks of Thymoglobulin® (Anti-Thymocyte Globulin) Therapy

Contraindications: Thymoglobulin® is contraindicated in patients with history of allergy or anaphylaxis to rabbit proteins or to any product excipients, or who have active acute or chronic infections which contraindicate any additional immunosuppression.

Warnings: Thymoglobulin should only be used by physicians experienced in immunosuppressive therapy for the treatment of renal transplant patients. Medical surveillance is required during Thymoglobulin infusion.

Immune-mediated reactions: Serious immune-mediated reactions have been reported with the use of Thymoglobulin and consist of anaphylaxis or severe cytokine release syndrome (CRS).

Fatal anaphylaxis has been reported. If an anaphylactic reaction occurs, the infusion should be terminated immediately. Medical personnel should be available to treat patients who experience anaphylaxis. Emergency treatment such as 0.3 mL to 0.5 mL aqueous epinephrine (1:1000 dilution) subcutaneously and other resuscitative measures including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated, should be provided. Any further administration of Thymoglobulin to a patient who has a history of anaphylaxis to Thymoglobulin is not recommended.

Severe, acute infusion-associated reactions (IARs) are consistent with CRS which is attributed to the release of cytokines by activated monocytes and lymphocytes. Severe acute CRS can cause serious cardiorespiratory events and/or death.

IARs may occur following the administration of Thymoglobulin and may occur as soon as the first or second infusion during a single course of Thymoglobulin treatment. Clinical manifestations of Infusion-associated reactions IARs have included some of the following signs and symptoms: fever, chills/rigors, dyspnea, nausea/vomiting, diarrhea, hypotension or hypertension, malaise, rash, and/or headache. IARs with Thymoglobulin are generally manageable with a reduction in infusion rates and/or with medications. Serious and fatal anaphylactic reactions have been reported. The fatalities occurred in patients who did not receive epinephrine during the event.

IARs consistent with cytokine release syndrome (CRS) have been reported. Severe and potentially life-threatening CRS have also been reported. Post-marketing reports of severe CRS have included cardiorespiratory dysfunction (including hypotension, acute respiratory distress syndrome, pulmonary edema, myocardial infarction, tachycardia, and/or death).

During post-marketing surveillance, reactions such as fever, rash, arthralgia, and/or myalgia, indicating possible serum sickness, have been reported. Serum sickness tends to occur 5 to 15 days after onset of Thymoglobulin therapy. Symptoms are manageable with corticosteroid treatment.

Infection: Thymoglobulin is routinely used in combination with other immunosuppressive agents. Infections (bacterial, fungal, viral and protozoal), reactivation of infection (particularly cytomegalovirus [CMV]) and sepsis have been reported after Thymoglobulin administration in combination with multiple immunosuppressive agents. Severe acute infections can be fatal.

Infections, reactivation of infection, and sepsis have been reported after Thymoglobulin administration in combination with multiple immunosuppressive agents. Careful patient monitoring and appropriate anti-infective prophylaxis are recommended.

Hematologic Effects: Thrombocytopenia and/or leukopenia (including lymphopenia and neutropenia) have been identified and are reversible following dose adjustments.

Malignancy: Use of immunosuppressive agents, including Thymoglobulin, may increase the incidence of malignancies, including lymphoma or post-transplant lymphoproliferative disease (PTLD).

Special Considerations for Thymoglobulin Infusion: Reactions at the infusion site can occur and may include pain, swelling, and erythema. The recommended route of administration for Thymoglobulin is intravenous infusion using a high-flow vein.

Immunizations: The safety of immunization with attenuated live vaccines following Thymoglobulin therapy has not been studied; therefore, immunization with attenuated live vaccines is not recommended for patients who have recently received Thymoglobulin.

Laboratory Tests: During Thymoglobulin therapy, monitoring the lymphocyte count (i.e., total lymphocyte and/or T-cell subset) may help assess the degree of T-cell depletion (See

Pharmacokinetics and Immunogenicity). For safety, WBC and platelet counts should also be monitored.

Pregnancy- Pregnancy Category C: Animal reproduction studies have not been conducted with Thymoglobulin. It is also not known whether Thymoglobulin can cause fetal harm or can affect reproduction capacity. Thymoglobulin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Thymoglobulin has not been studied in nursing women. It is not known whether this drug is excreted in human milk. Because other immunoglobulins are excreted in human milk, breast-feeding should be discontinued during Thymoglobulin therapy.

Overdosage of Thymoglobulin may result in leukopenia (including lymphopenia and neutropenia) and/or thrombocytopenia. The Thymoglobulin dose should be reduced by one-half if the WBC count is between 2,000 and 3,000 cells/mm3 or if the platelet count is between 50,000 and 75,000 cells/mm3. Stopping Thymoglobulin treatment should be considered if the WBC count falls below 2,000 cells/mm3 or platelets below 50,000 cells/mm3.

5.3 Risks of Medrol® (Methylprednisolone)

Adverse effects of corticosteroid therapy associated with short-term therapy (to three weeks) 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. Please refer to the package insert for a complete listing of risks associated with Medrol® therapy.

5.4 Risks of Maintenance Immunosuppression 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 before, during and for at least 4 months following administration of these agents.

5.4.1 CellCept® (Mycophenolate mofetil - MMF)

CellCept® (Mycophenolate mofetil - MMF) is approved (in combination with cyclosporine and corticosteroids) as an immunosuppressive agent 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, hypercholesteremia, hypokalemia, hyperglycemia, increased creatinine and BUN, cough, hypomagnesaemia, diarrhea, constipation, nausea, vomiting, respiratory infection, dyspnea, lung disorder, pleural effusion, tremor and insomnia.

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 1 - 1.5 mg BID. Severe neutropenia developed in up to 2% of renal transplant recipients receiving MMF 1.5 mg BID. MMF can cause fetal harm 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 1.5 g BID. Additional information about MMF can be found in the package insert.

5.4.2 Prograf® (Tacrolimus)

Side effects of Prograf® (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.

5.5 Risks of Protocol Mandated Procedures

5.5.1 Kidney Biopsy

This protocol requires an additional core of renal tissue during any for cause biopsy. There is a risk of bleeding associated with transplant kidney biopsies. Transient hematuria occurs in 3 to 10% of patients and may prolong hospitalization, require bladder catheterization for clot drainage, or in approximately 1% of patients, require blood transfusion. Ureteral obstruction from blood clot may require percutaneous nephrostomy in <1% of patients. Massive hemorrhage requiring surgical exploration, transplant nephrectomy, or arterial embolization occurs in ~0.1 % of patients. Death from massive hemorrhage is rare.

5.5.2 Blood Draws

The amount of blood that may be drawn from adult subjects for research purposes will not exceed 10.5mL/kg or 550mL, 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.

5.6 Potential Benefits

Potential benefits of a NULOJIX® (belatacept) regimen include avoidance of long term side effects associated with the prolonged use of CNI, such as nephrotoxicity, hypertension, dyslipidemia, and glucose intolerance, and avoidance of sirolimus-related toxicity such as buccal ulcers and dyslipidemia.

Tacrolimus is known to be directly beta-cell toxic in vitro and in vivo, and has been associated with new onset immunosuppression-related diabetes in non-diabetic recipients of solid organ transplants.

Overall, the administration of thymoglobulin to adult renal transplant patients has been safe and effective. Prolonged depletion of T cells has been achieved but has not been accompanied by increased incidence of opportunistic infection or other serious complications. This treatment has generally led to substantial overall reduction in chronic immunosuppression but not tolerance.

6 SELECTION OF PARTICIPANTS

6.1 Selection of Centers

The centers conducting this study have significant experience in SPK transplantation.
Additional centers may be recruited if enrollment is lower than anticipated. The team will evaluate enrollment progress 6 and 12 months after initiation of the study. If enrollment is not satisfactory, we will expand the number of centers involved to accommodate additional participants.

6.2 Inclusion Criteria

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

1. Male or Female, 18-55 years of age at the time of enrollment;
2. Ability to understand and provide written informed consent;
3. Candidate for a primary simultaneous kidney and pancreas allograft with random c-peptide <0.3 ng/mL.
4. No known contraindications to study therapy using NULOJIX® (belatacept);
5. Female subjects of childbearing potential must have a negative pregnancy test upon study entry;
6. Female and male participants with reproductive potential must agree to use FDA approved methods of birth control during participation in the study and for 4 months following study completion;
7. No donor specific antibodies prior to transplant that are considered to be of clinical significance by the site investigator;
8. Negative crossmatch, actual or virtual, or a PRA of 0% on historic and admission sera, as determined by each participating study center.
9. A documented negative TB test within the 12 months prior to transplant. If documentation is not present at the time of transplantation, and the subject does not have any risk factors for TB, a TB-specific interferon gamma release assay (IGRA) may be performed.

6.3 Exclusion Criteria

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

1. Need for multi-organ transplantation other than a kidney and pancreas
2. Recipient of previous organ transplant;
3. Active infection including hepatitis B, hepatitis C, or HIV;
4. Individuals who have required treatment with systemic prednisone or other immunosuppressive drugs within 1 year prior to transplant;
5. Individuals previously treated with NULOJIX® (belatacept);
6. Any condition that, in the opinion of the investigator, would interfere with the participant's ability to comply with study requirements;
7. Use of investigational drugs within 4 weeks of enrollment;
8. Known hypersensitivity to mycophenolate mofetil (MMF)or any of the drug's components;
9. Administration of live attenuated vaccine(s) within 8 weeks of enrollment.
10. EBV sero-negative recipients or recipients whose EBV status is unknown or ambiguous prior to the time of transplantation

Viral Capsid Antigen IgG	Viral Capsid Antigen IgM	EBV Nuclear Antigen	Interpretation	Belatacept
Positive	Negative	Positive	Past Infection (EBV positive)	Eligible
Positive	Positive	Positive	Likely resolved EBV (EBV positive)	Eligible
Positive	Negative	Negative	Recent EBV vs. EBNA negative past infection (EBV positive)	Eligible
Negative	Negative	Negative	Naïve (EBV negative)	**Ineligible**
Negative	Negative	Positive	Possibly a false positive	**Ineligible** [1]
Positive	Positive	Negative	Recent infection	**Ineligible** [2]

1. If on subsequent testing the IgG and/or IgM turn positive the subject is eligible.
2. The subject will be deemed eligible if on subsequent testing the EBNA turns positive or if EBV-PCR testing is negative.

7 STUDY DESIGN

This trial is a prospective, multi-center, open-label, phase II, randomized (1:1) study to compare a NULOJIX® (belatacept) based immunosuppressive regimen to a CNI-based regimen in recipients of SPK. Subjects will be consented and enrolled until a total of 60 subjects are randomized.

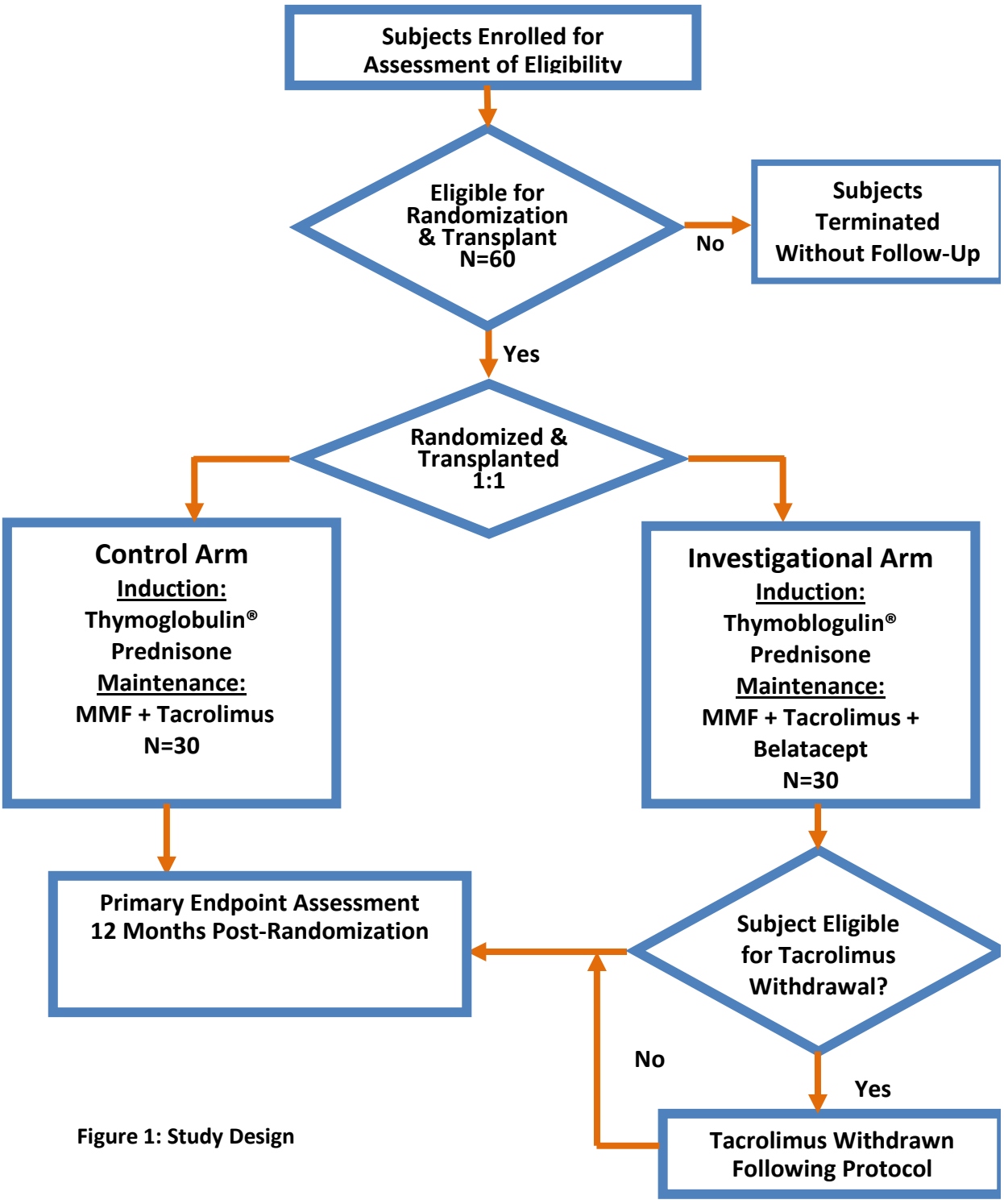


Figure 1: Study Design

8 STUDY THERAPY REGIMEN

The study therapy regimen includes:

Control Arm

- Induction: 5 day course of MEDROL® (methylprednisolone) or equivalent;
- Induction: Thymoglobulin® (Anti-thymocyte Globulin (Rabbit));
- Maintenance Immunosuppression: Prograf® (tacrolimus), or generic;
- Maintenance Immunosuppression: CellCept® (mycophenolate mofetil- MMF), or Myfortic® (mycophenolate sodium), or generic.

Investigational Arm

- Induction: 5 day course of MEDROL® (methylprednisolone) or equivalent;
- Induction: Thymoglobulin® (Anti-thymocyte Globulin (Rabbit));
- Maintenance Immunosuppression: NULOJIX® (belatacept);
- Maintenance Immunosuppression: Prograf® (tacrolimus), or generic;
- Maintenance Immunosuppression: CellCept® (mycophenolate mofetil- MMF), or Myfortic® (mycophenolate sodium), or generic.

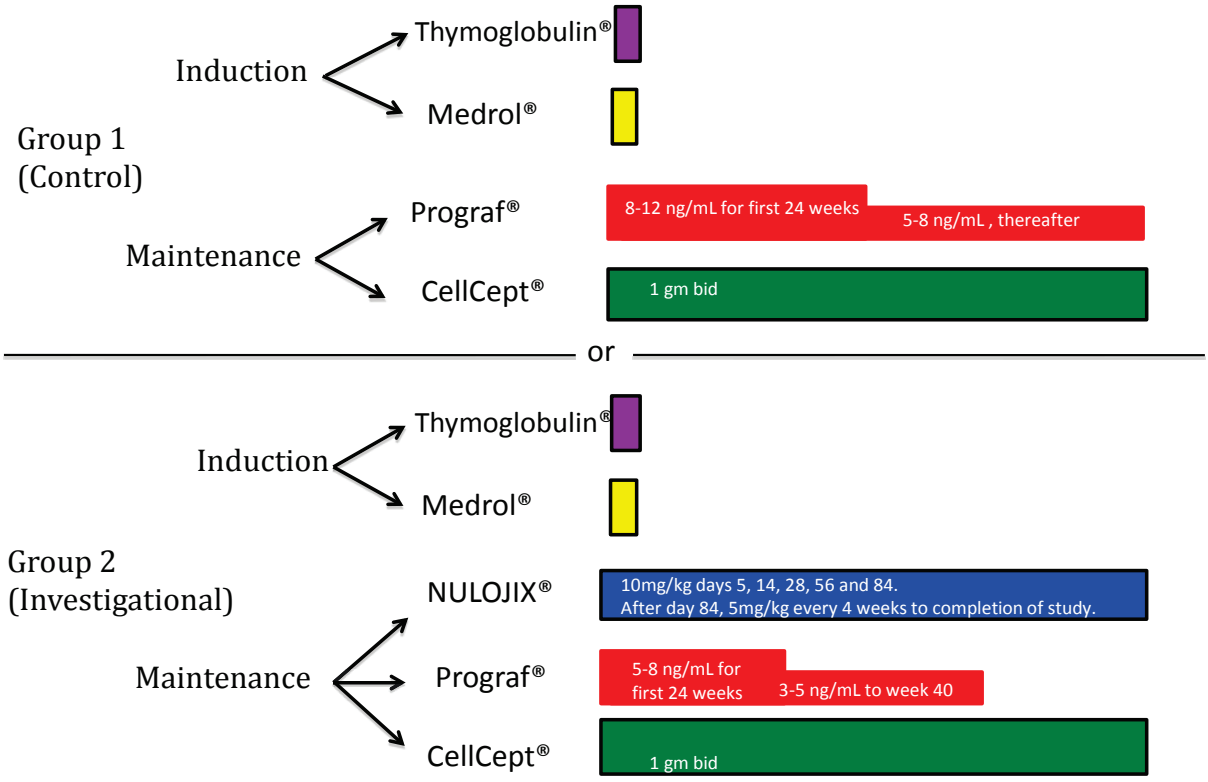


Figure 2. CTOT-15 Study Therapy Regimen

Study Therapy Dosage

CATEGORY	DRUG	DOSING
Investigational Agent	NULOJIX ® (belatacept)	**INVESTIGATIONAL ARM:** Participants will receive NULOJIX® (belatacept) 10mg/kg on days 5, 14, 28, 56 and 84. After 84 days, subjects will receive belatacept at the maintenance dose of 5 mg/kg every 4 weeks until completion of the trial.
Induction Therapy	Medrol® methylprednisolone	**BOTH STUDY GROUPS**: Methylprednisolone will be administered at a target dose of 500 mg beginning on the day of transplant, and tapered to 250 mg day 1 post-transplant, 125 mg day 2 post-transplant, 60 mg day 3 post-transplant, and 30 mg day 4 post-transplant. IV methylprednisolone will be administered over no less than 30 minutes in accordance with the applicable product labeling.
Induction Therapy	Thymoglobulin® (Anti-thymocyte Globulin (Rabbit))	**BOTH STUDY GROUPS:** The Thymoglobulin® target dosage is 6mg/kg total over 3 to 4 days. The recommended route of administration is intravenous infusion using a high-flow vein. Thymoglobulin should be infused over a minimum of 6 hours for the first infusion and over at least 4 hours on subsequent days of therapy. The infusion will be monitored per the center practice/SOPs. Premedication with corticosteroids, acetaminophen, and/or an antihistamine 1 hour prior to the infusion will be given per center practice and may reduce the incidence and intensity of side effects during the infusion. Medical personnel should monitor patients for adverse events during and after infusion.
Maintenance Immunosuppression	Mycophenolate Acid	**BOTH STUDY GROUPS**: CellCept® (Mycophenolate Mofetil- MMF) will be administered at a target dose of 1000 mg PO or IV BID beginning on the day of surgery or post-operative day 1 depending upon when during the day the surgery is completed (maximum MMF dosing is 2G per day). MMF will be adjusted based on clinical complications (such as neutropenia). Myfortic® (mycophenolate sodium) may be used as a replacement for MMF. Mycophenolate sodium will be dosed at 720 mg PO or IV BID. Mycophenolate sodium will be adjusted based on clinical complications.
Maintenance Immunosuppression	Prograf® (tacrolimus)	Tacrolimus may be discontinued or target levels adjusted at the discretion of the Investigator. **CONTROL ARM:** The site investigator will identify a starting tacrolimus dose at their discretion in order to achieve the target trough levels no later than 5 days post-transplantation. Tacrolimus dosing will be initiated on the day of surgery or post-operative day 1 depending upon when during the day the surgery is completed, then adjusted to target trough levels of 8-12 ng/ml during the first 24 weeks post-transplant, then adjusted to target trough levels of 5-8 ng/ml thereafter.
		INVESTIGATIONAL ARM: The site investigator will identify a starting tacrolimus dose at their discretion, in order to achieve the target trough levels no later than 5 days post-transplantation. Tacrolimus dosing will be initiated on the day of surgery or post-operative day 1 depending upon when during the day the surgery is completed. The dosage will be adjusted to achieve the following therapeutic trough levels: 5-8 ng/ml during the first 24 weeks post-transplant and then 3-5 ng/ml until day 280 (week 40). Subjects may be withdrawn if they meet all the criteria defined below. **Tacrolimus Withdrawal:** Subjects participating in the Investigational Arm will be considered eligible for withdraw of tacrolimus once they have reached the week 40 study visit, if all of the following is met: 1. No evidence of cellular or antibody mediated rejection in the first 280 days post-transplant. 2. Stable renal allograft function as measured by serum creatinine over the preceding 90 days.

3. Stable pancreatic function as assessed by levels of fasting blood sugars, HbA1c, and serum amylase/lipase at week 36 post-transplant.
4. The absence of donor specific antibody at week 36 post-transplant.

If eligible for withdrawal, the subject will be weaned off tacrolimus over a 4-8 week period. The chart below should be used as a guide based on the current trough level and tacrolimus dose.

Start of withdrawal tacrolimus dose	Initial dose reduction	4 weeks later dose reduction	4 weeks later
0.5 mg q12h (Prograf level < 5 ng/ml)	0.5 mg daily	Discontinue	--
0.5mg q12h (Prograf level > 5 ng/ml)	0.5 mg daily	0.5mg every other day	Discontinue
1mg daily (Prograf level < 5 ng/ml)	0.5 mg daily	Discontinue	--
1mg daily (Prograf level > 5 ng/ml)	0.5 mg daily	0.5mg every other day	Discontinue
1mg q12h (Prograf level < 5 ng/ml)	1 mg daily	Discontinue	--
1mg q12h (Prograf level > 5 ng/ml)	0.5 mg q12h	0.5 mg daily	Discontinue
2mg q12h (Prograf level < 5 ng/ml)	1 mg q12	1 mg daily	Discontinue
2mg q12h (Prograf level > 5 ng/ml)	1.5 mg q12h	1 mg q12h	Discontinue
3 mg q12h	2 mg q12h	1 mg q12h	Discontinue
4 mg q12h	3 mg q12h	2 mg q12h	Discontinue
5 mg q12h	3 mg q12h	2 mg q12h	Discontinue
6 mg q12h	4 mg q12h	2 mg q12h	Discontinue
7 mg q12h	5 mg q12h	3 mg q12h	Discontinue
8 mg q12h	6 mg q12h	3 mg q12h	Discontinue
9 mg q12h	6 mg q12h	3 mg q12h	Discontinue
10 mg q12h	7 mg q12h	4 mg q12h	Discontinue

Monitoring during Prograf® (tacrolimus) weaning and post withdrawal: During the weaning period and for 6 weeks following complete withdrawal, weekly safety labs will be drawn in order to monitor for early signs of rejection. This includes a serum creatinine, fasting glucose, amylase, and lipase. Labs may be performed by the subject's local physician if they are not able to return to the study center. All results should be reported back to the site investigator and clinical decisions made accordingly. If any signs of rejection are noted, the subject will not continue with tacrolimus withdrawal and treatment will be at the discretion of the site investigator.

Reinstatement of Prograf® (tacrolimus)- Subjects participating in the Investigational Arm may have tacrolimus reinstated, at a dose to be determined by the site investigator, if

		any of the following events occur: 1 - An acute rejection episode 2- Request of the subject or site Investigator.

8.1 Investigational Drug: NULOJIX® (belatacept)

Nulojix® (belatacept), a selective T-cell costimulation blocker, is a soluble fusion protein consisting of the modified extracellular domain of CTLA-4 fused to a portion (hinge-CH2-CH3 domains) of the Fc domain of a human immunoglobulin G1 antibody. Belatacept is produced by recombinant DNA technology in a mammalian cell expression system. Two amino acid substitutions (L104 to E; A29 to Y) were made in the ligand binding region of CTLA-4. As a result of these modifications, belatacept binds CD80 and CD86 more avidly than abatacept, the parent CTLA4-Immunoglobulin (CTLA4-Ig) molecule from which it is derived. The molecular weight of belatacept is approximately 90 kilodaltons.

NULOJIX® (belatacept), along with 1 non-siliconized single-use syringes (Norm-Ject®), will be supplied by Bristol-Myers Squibb (Princeton, NJ). Please refer to section 5.1, and to applicable product labeling for known and potential risks to human participants associated with the study medication(s).

NULOJIX® (belatacept) is indicated for prophylaxis of organ rejection in adult patients receiving a kidney transplant. NULOJIX® (belatacept) is to be used in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids. NULOJIX® (belatacept) should only be used in subjects who are EBV seropositive. Use of NULOJIX® (belatacept) for the prophylaxis of organ rejection in transplanted organs other than kidney has not been established. The current study will investigate the ability of NULOJIX® (belatacept) to facilitate a maintenance regiment that avoids both CNI and corticosteroids following SPK transplantation.

8.1.1 Formulation, Packaging, and Labeling

NULOJIX® (belatacept) is supplied as a sterile, white or off-white lyophilized powder for intravenous administration. Prior to use, the lyophile is reconstituted with a suitable fluid to obtain a clear to slightly opalescent, colorless to pale yellow solution, with a pH in the range of 7.2 to 7.8. Suitable fluids for constitution of the lyophile include SWFI, 0.9% NS, or D5W. Each 250 mg single-use vial of Nulojix also contains: monobasic sodium phosphate (34.5 mg), sodium chloride (5.8 mg), and sucrose (500 mg).

NULOJIX® (NDC 0003-0371-13) will be provided as open-label commercially available supplies. NULOJIX® is packaged in cases of 6 individually boxed vials and syringes. Each case contains the NDC number, lot number, expiration date, product identity and strength, the number of vials, route of administration, and storage requirements. The study label will be affixed to each case and will include the IND number, the protocol number, the Sponsor, the Manufacturer, and the statement "New Drug- Investigational Use Only".

8.1.2 Preparation, Administration, and Dosage

NULOJIX® is for intravenous infusion only. Subjects do not require premedication prior to administration of NULOJIX®. The total infusion dose of NULOJIX® should be based on the actual body weight of the patient at the time of transplantation, and should not be modified during the course of therapy, unless there is a change in body weight of greater than 10%.

The prescribed dose of NULOJIX ®must be evenly divisible by 12.5 mg in order for the dose to be prepared accurately using the reconstituted solution and the *silicone-free disposable syringe* provided. Evenly divisible increments are 0, 12.5, 25, 37.5, 50, 62.5, 75, 87.5, and 100. For example:

A patient weighs 64 kg. The dose is 10 mg per kg.

- Calculated Dose: 64 kg × 10 mg per kg = 640 mg
- The closest doses evenly divisible by 12.5 mg below and above 640 mg are 637.5 mg and 650 mg.
- The nearest dose to 640 mg is 637.5 mg.
- Therefore, the actual prescribed dose for the patient should be 637.5 mg.

INVESTIGATIONAL ARM ONLY: Participants will receive NULOJIX® (belatacept) 10mg/kg through a peripheral vein on days 5, 14, 28, 56 and 84 After 84 days, subjects will receive NULOJIX® (belatacept) at the maintenance dose of 5 mg/kg every 4 weeks until completion of the trial.

Preparation for Administration

1) Calculate the number of Nulojix vials required to provide the total infusion dose. Each vial contains 250 mg of belatacept lyophilized powder.

2) Reconstitute the contents of each vial of Nulojix with 10.5 mL of a suitable diluent using the silicone-free disposable syringe provided with each vial and an 18- to 21-gauge needle. Suitable diluents include: sterile water for injection (SWFI), 0.9% sodium chloride (NS), or 5% dextrose in water (D5W).
Note: If the Nulojix powder is accidentally reconstituted using a different syringe than the one provided, the solution may develop a few translucent particles. Discard any solutions prepared using siliconized syringes.

3) To reconstitute the Nulojix powder, remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of diluent (10.5 mL of SWFI, NS, or D5W) to the glass wall of the vial.

4) To minimize foam formation, rotate the vial and invert with gentle swirling until the contents are completely dissolved. Avoid prolonged or vigorous agitation. Do not shake.

5) The reconstituted solution contains a belatacept concentration of 25 mg/mL and should be clear to slightly opalescent and colorless to pale yellow. Do not use if opaque particles, discoloration, or other foreign particles are present.

6) Calculate the total volume of the reconstituted 25 mg/mL Nulojix solution required to provide the total infusion dose.
Volume of 25 mg/mL Nulojix solution (in mL) = Prescribed Dose (in mg) ÷ 25 mg/mL

7) Prior to intravenous infusion, the required volume of the reconstituted Nulojix solution must be further diluted with a suitable infusion fluid (NS or D5W). Nulojix should be reconstituted with:
   - SWFI should be further diluted with either NS or D5W
   - NS should be further diluted with NS
   - D5W should be further diluted with D5W

8) From the appropriate size infusion container, withdraw a volume of infusion fluid that is equal to the volume of the reconstituted Nulojix solution required to provide the prescribed dose. With the same silicone-free disposable syringe used for reconstitution, withdraw the required amount of

belatacept solution from the vial, inject it into the infusion container, and gently rotate the infusion container to ensure mixing.
The final belatacept concentration in the infusion container should range from 2 mg/mL to 10 mg/mL. Typically, an infusion volume of 100 mL will be appropriate for most patients and doses, but total infusion volumes ranging from 50 mL to 250 mL may be used. Any unused solution remaining in the vials must be discarded.

9) Prior to administration, the Nulojix infusion should be inspected visually for particulate matter and discoloration. Discard the infusion if any particulate matter or discoloration is observed.

10) The entire Nulojix infusion should be administered over a period of 30 minutes and must be administered with an infusion set and a sterile, non-pyrogenic, low-protein-binding filter (with a pore size of 0.2-1.2 μm).

- The reconstituted solution should be transferred from the vial to the infusion bag or bottle immediately. The Nulojix infusion must be completed within 24 hours of reconstitution of the Nulojix lyophilized powder. If not used immediately, the infusion solution may be stored under refrigeration conditions: 2°-8°C (36°-46°F) and protected from light for up to 24 hours (a maximum of 4 hours of the total 24 hours can be at room temperature: 20°-25°C [68°-77°F] and room light).
- Infuse Nulojix in a separate line from other concomitantly infused agents. Nulojix should not be infused concomitantly in the same intravenous line with other agents. No physical or biochemical compatibility studies have been conducted to evaluate the co administration of Nulojix with other agents.

8.1.3 Handling, Dispensing, and Destruction of NULOJIX® (belatacept)

Care should be taken when handling the injectable drug products. Proper aseptic techniques should be used when preparing and administering sterile products such as belatacept. Gloves are recommended during constitution process. If belatacept concentrate or solution comes in contact with skin or mucosa, immediately and thoroughly wash with soap and water.

NULOJIX® (belatacept) vials are single-use vials and do not contain preservatives. Therefore after reconstitution, the vials should be used immediately whenever possible. The belatacept 250 mg vial should be stored under refrigeration (2-8°C), and should be protected from long term exposure to light. Intact vials are stable for at least 1 year under these conditions.

Reconstituted solutions of belatacept at a concentration of 25 mg/mL are stable for 24 hours in the vials if stored at room temperature (15-25°C) and ambient lighting conditions, or under refrigeration. When further diluted with 5% Dextrose for Injection or 0.9% Normal Saline Solution to a belatacept concentration as low as 2 mg/mL, solutions may be stored in plastic, non-siliconized IV bags for up to 24 hours at room temperature and ambient lighting conditions or under refrigeration. The belatacept infusion must be completed within 24 hours of constitution of the lyophilized powder. Storage of reconstituted solutions in syringes is not recommended due to stability and potential bacterial contamination.

Belatacept should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that belatacept is only dispensed to study participants. Belatacept must be dispensed only from official study sites by authorized personnel according to local regulations. The

Investigator should ensure that belatacept is stored in accordance with the environmental conditions (temperature, light and humidity) as determined by the Sponsor and defined in the Investigator Brochure or SmPC/reference label.

If an investigational product is destroyed at the site, it is the investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to applicable regulations and guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused investigational products can only be destroyed after being inspected and reconciled by the responsible study monitor.

8.1.4 Drug Accountability

Under Title 21 of the Code of Federal Regulations (21CFR §312.62) the investigator is required to maintain adequate records of the disposition of the investigational agent, 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 NULOJIX® will be available for inspection by the clinical trial monitor.

8.2 Induction and Maintenance Immunosuppression Medications

The following induction and maintenance immunosuppression medications are considered standard of care post-transplantation and will be supplied by the hospital pharmacy; Medrol® (methylprednisolone), Thymoglobulin® (Anti-Thymocyte Globulin- Rabbit), Mycophenolate Acid, and Prograf® (tacrolimus). Please refer to applicable product labeling for preparation and administration instructions and well as known and potential risks.

8.3 Concomitant Medications

Concomitant medications should be administered according to each centers standard of care. The centers will record immunosuppressive and non-immunosuppressive therapy information on an eCRF in the study electronic data capture system.

8.4 Prophylactic Medications

8.4.1 Viral Prophylaxis

CMV Sero Positive Donor and Sero Positive Recipient (D+/R+)

When tolerating PO or at discharge, subjects will receive Valganciclovir (Valcyte®) PO, 900 mg every day. Dose adjusted according to renal function. Treatment is to continue for 85 days post-transplant for the prevention of CMV.

CMV Sero Positive Donor and Sero Negative Recipient (D+/R-)

When tolerating PO or at discharge, subjects will receive Valganciclovir (Valcyte®) PO, 900 mg QD. Dose adjusted according to renal function. Treatment is to continue for 24 weeks post-transplant for the prevention of CMV.

CMV Sero Negative Donor and Sero Positive Recipient (D-/R+)

When tolerating PO or at discharge, subjects will receive Valganciclovir (Valcyte®) PO, 900 mg QD. Dose adjusted according to renal function. Treatment is to continue for 85 days post-transplant for the prevention of CMV.

CMV Sero Negative Recipient and Negative Donor (D-/R-)

When tolerating PO or at discharge, subjects will receive Valacyclovir (Valtrex®), 1000 mg PO BID. Dose adjusted according to renal function. Treatment is to continue for 85 days post-transplant for the prevention of HSV and VZV.

8.4.2 PCP Prophylaxis

Any of following regimens, at the discretion of the treating medical team, are acceptable for PCP prophylaxis, starting on post-operative day one or when subject is taking oral medications and continuing until 1 year post transplant or later based on your institutional standard of care.

Bactrim ™/Septra ® (Trimethoprim-sulfamethoxazole) single strength (SS; 80/400) administered once daily, if GFR >30. If GFR ≤30), single strength administered once a day on every Monday, Wednesday, and Friday. If patient is on hemodialysis, single strength administered on the day of dialysis after dialysis sessions.

For participants allergic to or intolerant of sulfa compounds or trimethoprim-sulfmethoxazole therapy, and if G6PD level is normal, Aczone ® (Dapsone) 100 mg PO once daily.

For participants allergic to or intolerant of sulfa compounds or trimethoprim-sulfmethoxazole therapy, and is G6PD deficient, Mepron® (Atovaquone) 1500 mg once daily.

8.5 Management of Rejection or Graft Loss

Management of rejection or graft loss is defined by each centers standard of care. The centers will record the treatment information on an eCRF in the study electronic data capture system. Any subject who experiences rejection or graft loss following week 52 will continue to follow the schedule outlined in Appendix 3 [Schedule of Events (Recipient) Post-Transplant (Year 2)].

If a subject experiences rejection either during or after tacrolimus withdrawal, they will complete the remaining visits in Appendix 2 (Schedule of Events (Recipient) Year 1) and continue to be followed based on Appendix 3 [Schedule of Events (Recipient) Post-Transplant (Year 2)].

8.6 Prohibited Medications

Prohibited medications for this protocol, except as specifically indicated in this protocol include:

- Steroid medication (save topicals and prednisone at a dose of ≤ 5 mg daily, or an equivalent dose of hydrocortisone, for physiological replacement only)
- Other investigational products
- Other immunosuppressive agents not defined in the protocol.
- Live vaccines

8.7 Modification or Discontinuation of Study Therapy

Study treatment may be prematurely discontinued at the discretion of the Investigator for any of the following reasons:

1. The subject is unwilling or unable to comply with the protocol.
2. The subject experiences graft failure.
3. Any clinical AE, laboratory abnormality or intercurrent illness, which in the opinion of the site PI indicates that continued treatment with study therapy is not in the best interest.
4. Pregnancy.
5. Two consecutive missed NULOJIX® (Belatacept) infusions.

Subjects who prematurely discontinue study treatment will be treated according to the site standard of care and followed until 52 weeks post-transplant. Please refer to Reduced Follow-Up Schedule (Appendix 4). If subjects discontinue study therapy beyond week 52, they will complete the visits outlined in Appendix 3 [Schedule of Events (Recipient) Post-Transplant (Year 2)]. If the subject is unable to return to the study center, the data associated with these visits may be obtained from the subject's local physician.

9 CRITERIA FOR PREMATURE TERMINATION OF THE STUDY

9.1 Participant Withdrawal Criteria

Participants may be prematurely terminated from study for the following reasons:

1. The subject elects to withdraw consent from all future study activities, including follow-up.
2. The participant is "lost to follow-up" (i.e., attempts to reestablish contact have failed).
3. The participant develops a clinical AE, laboratory abnormality, or intercurrent illness or any other event which, in the opinion of the investigator, indicates that continued treatment with study therapy and further participation in the study (including obtaining vital status of the participant and renal graft) is not in the best interest of the participant.
4. The participant dies.
5. The participant is found to be TB positive.

9.2 Study Stopping Rules

9.2.1 Protocol Suspension and Review

Study enrollment at all participating sites will be suspended pending expedited review of all pertinent data by the institutional review board (IRB), the National Institute of Allergy and Infectious Diseases (NIAID), and the NIAID Data Safety Monitoring Board (DSMB), if any one of the following occurs:

1. Any unexpected fatal or life-threatening AE that is possibly, probably, or definitely related to the study treatment regimen (Section 8);
2. Any event(s) which in the opinion of the Medical Monitor or Protocol Chair indicates the need for DSMB review;
3. Any instance of progressive multifocal leukoencephalopathy (PML).

In the event of any participant death, the study will pause for review of the event by the medical monitor and the protocol chair. Any death that is not clearly due to non-study causes will result in a continued pause in enrollment and DSMB review. "Non-study causes" will include events such as deaths due to motor vehicle accidents.

9.2.2 Continuous Monitoring of Specific Events

In addition, the incidence of specific safety-related events of particular concern will be continuously monitored in each treatment arm throughout the study to determine if any of their observed subject-based incidence rates exceed a threshold incidence rate of concern pre-specified for each particular event. However, since little is known about what incidence rate to expect for graft loss of either pancreas or kidney due to acute or chronic rejection, that rule is based on the incidence of rejection events involving one or both allografts in all subjects randomized.

The following events will be evaluated within each treatment arm, except as noted, and the corresponding thresholds of concern are:

1. Biopsy-proven acute rejection (BPAR) in either pancreas or kidney above 25%.
2. Pancreas rejection above 20%.
3. Post-Transplant Lymphoproliferative Disease (PTLD) above 2% at any time.
4. Incidence of graft loss of either organ due to any rejection above 20% in all randomized subjects.

These rules will be implemented by the SACCC, and continuously monitor the occurrence of any of these events. If any stopping rule is met, enrollment and randomization will be halted pending expedited DSMB review.

The stopping rules for BPAR and PTLD will be considered to be met if the lower one-sided 95% exact confidence limit on the observed incidence rate exceeds the corresponding threshold level of concern for that event. The following two tables describe the minimum numbers of events (n) out of selected numbers of subjects randomized within each treatment arm (N) which, if equaled or exceeded, would satisfy the stopping rule for BPAR and PTLD.

Table 2: Minimum Numbers of Subjects with Events that Meet the Stopping Rule for BPAR in Either Organ in Either Treatment Arm Using a Threshold of 25%

Number of Subjects with Event (n)	Number of Subjects Randomized (N) in Either Arm	Observed Incidence Rate (%)	Lower 95% Confidence Limit (%)
4	5	80.00	34.26
6	10	60.00	30.35
8	15	53.33	30.00
9	20	45.00	25.87
11	25	44.00	26.99
13	30	43.33	27.87

Table 3: Minimum Numbers of Subjects with Events that Meet the Stopping Rule for Pancreas Rejection in Either Treatment Arm Using a Threshold of 20%

Number of Subjects with Event (n)	Number of Subjects Randomized (N)	Observed Incidence Rate (%)	Lower 95% Confidence Limit (%)
4	5	80.00	34.26
5	10	50.00	22.24
7	15	46.67	24.37
8	20	40.00	21.71
9	25	36.00	20.24
11	30	36.67	22.11

Table 4: Minimum Numbers of Subjects with Events that Meet the Stopping Rule for PTLD in Either Treatment Arm Using a Threshold of 2%

Number of Subjects with Event (n)	Number of Subjects Randomized (N) in Either Arm	Observed Incidence Rate (%)	Lower 95% Confidence Limit (%)
2	5	40.00	7.64
2	10	20.00	3.68
2	15	13.33	2.42
3	20	15.00	4.22
3	25	12.00	3.35
3	30	10.00	2.78

The stopping rule for graft loss of either organ due to any rejection will be considered to be met if the lower one-sided 95% exact confidence limit on the observed incidence rate among all study subjects is greater than 20% at any time during the study.

Table 5: Minimum Numbers of Subjects with Events that Meet the Stopping Rule for GRAFT LOSS in All Subjects Randomized at Any Time Using a Threshold of 20%

Number of Subjects with Event (n)	Number of Subjects Randomized (N)	Observed Incidence Rate (%)	Lower 95% Confidence Limit (%)
5	10	50.00	22.24
8	20	40.00	21.71
11	30	36.67	22.11
13	40	32.50	20.41
16	50	32.00	21.21
18	60	30.00	20.37

10 STUDY PROCEDURES

10.1 Enrollment

This research study will be explained in lay terms to each potential research subject. As the part of the informed consent process outlined in CFR Title 21 Part 50, the investigator or physician listed on the FDA 1572 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 screening 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.

10.2 Screening Visit

The pre-transplant visit (visit 1) will begin at the time consent is obtained until all eligibility criteria are available. Subjects can be approached regarding potential study participation while on the organ transplant waiting list, however, the consent process must take place within 60 days of transplant. If the subject is consented on the day of transplant, it is at the discretion of the Investigator to ensure there is sufficient time to appropriately consent the potential subject. If the subject was consented greater than 30 days prior to transplant, the individual obtaining consent must reaffirm the subject's willingness to participate. Refer to Appendix 1, Schedule of Events- Pre-Transplant to Day 4 Post Transplant.

During the screening period the study personnel will review the subject's medical record for previous and current medical history and record the subject's demographic information (age, gender, and race), medications, hematology, chemistry, fasting lipid panel, hemoglobinA1c, and urinalysis. A serum pregnancy test will be conducted on all female subjects of child-bearing potential. Blood, urine and tissue will be collected for research studies.

During the screening visit, data regarding the donor will be collected; this includes demographics (age, gender, and race), cause of death, serum creatinine, HLA, Blood Type, CMV and EBV. Refer to Appendix 5, Schedule of Events – Donor. A sample of spleen will be requested from the local center HLA departments of alloimmune assays.

10.3 Study Assessments

Subjects enrolled in this study will be followed for a minimum of 52 weeks post-transplant in order to assess the primary endpoint. Subjects in the Investigational Arm who are eligible and attempt tacrolimus withdrawal will be followed for at least 60 days following the withdrawal of tacrolimus. Subjects may be followed for up to 18 months (76 weeks) depending upon study completion.

Subjects will have blood, tissue and urine collected for research studies at the following timepoints:

- Visit 1 (Pre-Transplant to Day 4 Post-Transplant)
- Post-Transplant: Days 28, 84 and Weeks 28, 36, and 52.

Clinical safety will be monitored through routine physical examinations and appropriate laboratory assessments every 4 weeks for the duration of the study. During this period, subjects will have repeated clinical/laboratory evaluations, as specified in the Schedule of Events (Appendix 1 through 3, Schedule of Events- Recipient and Appendix 4 – Reduced Follow-Up Schedule of Events - Recipient).

Infusion Supervision
In addition to the study visits and procedures listed in Appendix 1-4, participants assigned to the Investigational Arm will receive a NULOJIX® (belatacept) infusion on days 5, 14, 28, 56 and 84 post-transplant. After 84 days, participants in the Investigational Arm will continue NULOJIX® (belatacept) infusions every 4 weeks throughout the duration of the study. The infusion will be administered in a center where full resuscitation facilities are immediately available and under close supervision of the investigator or infusion center staff. A history of each infusion and any adverse side effects will be recorded and reported to the SACCC using the appropriate case report forms. Vital signs (temperature, blood pressure, pulse, and respiratory rate) will be obtained prior to the start of each infusion and again at the end of the infusion. Additional vital signs will be obtained as clinically indicated. At the discretion of the investigator, the infusion may be discontinued if there is a severe reaction to the infusion.

Clinical Assessments
Assessments for the development of new adverse events, serious adverse events, infections, rejections, graft loss, hospitalizations, new onset diabetes, and malignancies will be completed at each study visit. All events will be reported using a designated electronic case report form (eCRF).

Evaluation of Hemoglobin A1c levels, urinalysis, hematology, chemistry, and pill counts will be obtained at Days 28, 84 and Weeks 28, 36, and 52. Additional time points are also specified during Year 2 of transplant (Appendix 3).

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 recorded at each study visit and reported using a designated case report form. Undocumented, patient-reported infections (e.g. URI) will not be reported. Relationships between test results and clinical endpoints independent of infections will then be determined in secondary analyses.

Pregnancy Testing
Women of child bearing potential (WOCBP) must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized. Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

Pregnancy testing must be performed prior to enrollment and first dose of NULOJIX® (belatacept). The results of all pregnancy tests (positive or negative) recorded on the eCRF. All WOCBP MUST have a negative serum pregnancy test within 72 hours prior to receiving the first dose of the investigational product NULOJIX® (belatacept). The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of Human Chorionic Gonadotropin (HCG). If the pregnancy test is positive, the subject must not receive the investigational product, and must not be enrolled in the study. All WOCBP should be instructed to contact the investigator immediately if they suspect that they might be pregnant (e.g., missed or late menstrual period) at any time during study participation. Subjects who become pregnant will be referred to the National Transplant Pregnancy Registry (http://www.jefferson.edu/ntpr/).

For women who become pregnant while using CellCept® or within 6 weeks of discontinuing therapy, the healthcare practitioner should report the pregnancy to the Mycophenolate Pregnancy Reference Registry (1-800-617-8191) and should strongly encourage the patient to

enroll in the pregnancy registry. The patient should also be apprised of the potential hazard of mycophenolate products to the fetus. The risks and benefits of CellCept/Myfortic should be discussed with the patient. In certain situations, the patients and her healthcare practitioner may decide that the maternal benefits outweigh the risks to the fetus.

If following initiation of study treatment, it is subsequently discovered that a subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 56 days after product administration, the investigational product will be permanently discontinued.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report on the appropriate follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants should be followed for a minimum of 8 weeks. This pregnancy surveillance procedure includes male subjects who fathered a child while receiving study medication; however, male subjects do not need to discontinue study medication.

Viral Monitoring
The local center will monitor all subjects for CMV and BKV infection by quantitative PCR in the blood. This monitoring will take place at days 28 and 84, and at weeks 28, 52 and 76. The local center investigators will make all treatment decisions.

For Cause Biopsies - Renal
The center will perform a biopsy per the discretion of the Investigator in cases of increase in serum creatinine, proteinuria, or other clinical symptoms.

The local center will send the Pathology Core Lab (Dr. Laszik, UCSF) the following:

- 5 original stained slides (1-Trichrome or unstained, 1-PAS, 3 H&E) for histology reading.
- The site will send 1 SV40 and 1- immunohistochemistry C4d stained slides, if collected as standard of care.
- The remaining portion of the FFPE block will be stored at the local center and sent to the Core Pathology when requested for additional immunohistochemistry studies.

The local center will send the Molecular Core Lab (Dr. Mannon, University of Alabama) the following:

- 1 core in RNALater for gene expression, mRNA profiling studies.

Standard of Care or For Cause Biopsies- Pancreas
The center will perform standard of care biopsies which will be read by the local pathologist using Banff criteria. The data generated from the local center reading will be entered in the study database. In addition, once the local pathologist has completed their review of the pathology slides, the site will send the original stained slides (1-Trichrome or unstained, 3 H&E, including a C4d and/or SV40, if collected) used in that reading to the core pathology laboratory. The Pathology Core Laboratory will scan the slides into an Aperio Scan System, and return the slides back to the local center.

Glomerular Filtration Rate (GFR)
Glomerular Filtration Rate (GFR) will be estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and the MDRD 4 variable. Demographic characteristics; gender, age and race are required for calculation in addition to serum creatinine which will be collected as specified in the Schedule of Events (SOE). The equation will be calculated at the SACCC.

Neurological Assessment
All participants will undergo a neurological exam as specified in the SOE. Subjects will be evaluated by their local Neurology consult service for cases with a significantly abnormal exam.

10.4 Study Treatment Assignment Procedures

10.4.1 Blinding and/or Randomization

This is a randomized, open label study. Subjects will be randomized in an unblinded fashion to one of the two study groups in a 1:1 ratio using a web-based randomization system. The randomization schedule will not incorporate stratification variables. However, due to concerns about the potential for un-blinded investigators to be biased in their assessments of endpoints, all data analyses and reports and all data cleaning activities will be blinded with respect to treatment prior to end-of-study database lock, except for safety data reviews by the DSMB. The study treatment assignments will be blinded to all mechanistic core laboratory personnel, including the core pathologist.

11 SAFETY MONITORING

11.1 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 that data. Adverse events that are classified as serious according to the definition of health authorities must be reported promptly (per Section 11.5, *Reporting of Serious Adverse Events*) to the sponsor, DAIT, NIAID. Appropriate notifications must also be made to site principal investigators, Institutional Review Boards (IRBs), and health authorities, as applicable.

Information in this section complies with *ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6: 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 *4.0* (http://ctep.cancer.gov/reporting/ctc.html).

11.2 Definitions

11.2.1 Adverse Event (AE)

An adverse event (AE) is defined as any untoward or unfavorable medical occurrence associated with the use of a drug in humans, whether or not considered drug related (21 CFR 312.32(a)). An adverse event may include any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product (ICH E6, 1.2).

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

- **Study therapy regimen**:
  - Induction: Thymoglobulin® (Anti-thymocyte Globulin- Rabbit);
  - Induction: Medrol® (methylprednisolone) or equivalent;
  - Maintenance Immunosuppression: NULOJIX® (belatacept);
  - Maintenance Immunosuppression: Prograf® (tacrolimus), or generic;
  - Maintenance Immunosuppression: CellCept® (mycophenolate mofetil), or Myfortic® (mycophenolate sodium), or generic.
- **Study mandated procedures**:
  - Renal Transplant Biopsy: Any AE occurring within 24 hours after the additional core (study mandated) was collected from the for cause biopsy.
  - Blood Draw: Any AE occurring within 24 hours after a study mandated blood draw.

11.2.2 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any adverse event for which there is a reasonable possibility that the investigational 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. A 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)).

11.2.3 Unexpected Adverse Event

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, 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 investigator brochure 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)).

11.2.4 Serious Adverse Events

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

1. Death
2. A life-threatening event: An AE or SAR is considered "life-threatening" if, in the view of either the investigator or DAIT/NIAID, 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 or 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.

In addition to the criteria outlined above, all occurrences of drug induced liver injury (DILI) meeting ALL 3 of the defined criteria below must be reported as a SAE:

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)
2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

11.3 Grading and Attribution of Adverse Events

11.3.1 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 Version (CTCAE). 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 Protocol Development Team (PDT) 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 collected and recorded for this study.

11.3.2 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 eCRF. Final determination of attribution for safety reporting will be determined by DAIT/NIAID. The relationship of an adverse event to study therapy regimen or procedures will be determined using the descriptors and definitions provided in the Table below.

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

Table 6. NCI-CTCAE attribution of adverse events

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

11.4 Collection and Recording of Adverse Events

11.4.1 Collection Period

Adverse events will be collected from the time of first dose of study drug, until he/she completes study participation or until 30 days after he/she prematurely withdraws (without withdrawing consent) or is withdrawn from the study.

11.4.2 Collecting Adverse Events

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

- Observing the subject.

- Questioning the subject in an objective manner.
- 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 11.3, *Grading and Attribution of Adverse Events.*

11.4.3 Recording Adverse Events

Throughout the study, the investigator will record adverse events and serious adverse events as described previously (Section 11.2, *Definitions)* on the appropriate eCRF regardless of the relationship to study therapy regimen or study procedure.

Certain adverse events occur commonly in this study population and will not be recorded as an adverse event, unless it meets the definition of a serious adverse event.

- Occurrence of upper respiratory infection, nasopharyngitis, bronchitis, diarrhea, constipation, nausea, vomiting, abdominal pain, hypocalcaemia, hypercalcemia, hypercholesterolemia, hypomagnesemia, hyperuricemia, edema, pyrexia, hematuria, proteinuria, dysuria, cough, dyspnea, arthralgia, back pain, hip pain, fracture, headache, dizziness, tremor, acne, insomnia, anxiety, depression, stomatitis/aphthous ulcers, wound complications, AVF thrombosis, neutropenia, renal impairment, renal artery stenosis, incontinence, hydronephrosis, hematoma, lymphocele, musculoskeletal pain, alopecia, hyperhidrosis, atrial fibrillation.

Elective hospitalizations or hospital admissions for the purpose of conduct of protocol mandated procedures are not to be reported as an SAE unless hospitalization is prolonged due to complications.

All adverse events must be recorded by the site on the appropriate AE/SAE *eCRF* within 5 business days of the site learning of the adverse event(s). Please refer to Section 11.5 for reporting of events meeting serious criteria.

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.

11.5 Reporting of Serious Adverse Events

11.5.1 Reporting of Serious Adverse Events to Sponsor

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

Site investigators must report all serious adverse events (see Section 11.2.3, 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 should be provided to the SACCC. However, unavailable details of the event should not delay submission of the known information. As additional details become available, the AE/SAE eCRF should be updated and submitted.

11.5.2 Sponsor Reporting to Health Authority

After an adverse event requiring 24 hour reporting (per Section 11.5.1, *Reporting of Serious Adverse Events to sponsor)* is submitted by the site investigator and assessed by DAIT/NIAID, there are two options for DAIT/NIAID to report the adverse event to the appropriate health authorities:

11.5.2.1 ANNUAL REPORTING

DAIT/NIAID will include in the annual study report to health authorities all adverse events classified as:

- Serious, expected, suspected adverse reactions (see Section 11.2.1.1, *Suspected Adverse Reaction,* and Section 11.2.2, *Unexpected Adverse Event*).
- Serious and not a suspected adverse reaction (see Section 11.2.2, *Suspected Adverse Reaction*).
- Pregnancies not reported as serious adverse events.

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

11.5.2.2 EXPEDITED REPORTING WITHIN 15 CALENDAR DAYS

The sponsor, DAIT/NIAID, must notify the appropriate health authorities and all participating investigators as soon as possible, or within 15 calendar days if the adverse event is classified as one of the following (21CFR312.32 (c)(1)):

- Serious and unexpected suspected adverse reaction (**SUSAR**) (see Section 11.2.1.1, *Suspected Adverse Reaction* and Section 11.2, *Unexpected Adverse Event*). Expedited reporting of SUSAR's are to include, in an aggregate analysis, specific events that occur more frequently in the investigational drug than in a concurrent or control group.
- Any findings from other studies, whether or not conducted under an IND, and whether or not conducted by DAIT/NIAID that suggest a significant risk in humans exposed to NULOJIX® or Thymoglobulin®. This includes findings from animal or *in vitro* testing that suggest a significant risk in humans exposed to the drug. Ordinarily, such a finding would result in a safety-related change in the protocol, informed consent, investigator brochure or other aspects of the overall conduct of the trial, will be reported.
- Increased rate of occurrence of serious suspected adverse reactions. DAIT/NIAID must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure or package insert.

11.5.2.3 EXPEDITED REPORTING WITHIN 7 CALENDAR DAYS

The sponsor, DAIT/NIAID, must notify the appropriate health authorities and all participating investigators as soon as possible, or within 7 calendar days, of any unexpected fatal or immediately life-threatening suspected adverse reaction.

11.5.3 Reporting of Adverse Events to IRBs

All investigators must report adverse events, including expedited reports, in a timely fashion to their respective IRBs in accordance with applicable regulations and guidelines. All *IND Safety Reports to the FDA* will be distributed by the sponsor, DAIT/NIAID, or designee to all participating institutions for site IRB submission.

11.6 Pregnancy Reporting

The investigator should be informed immediately of any pregnancy in a study subject or a partner of a study subject. *A* pregnant subject should be instructed to stop taking study medication. The investigator should counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the pregnant subject should continue until the conclusion of the pregnancy.

The investigator should report to the SACCC all pregnancies within 1 business day of becoming aware of the event using the Pregnancy eCRF. All pregnancies identified during the study must be followed to conclusion and the outcome of each must be reported. The Pregnancy should be updated and submitted to the *SACCC* when details about the outcome are available. When possible, similar information should be obtained for a pregnancy occurring in a partner of a study subject.

Information requested about the delivery will include:

- Expected delivery date and Actual delivery date;
- Birth weight;
- Outcome of Pregnancy (i.e., full-term, premature, miscarriage, unknown);
- Infant status (i.e., any abnormalities).

Should the pregnancy result in a congenital abnormality or birth defect, an SAE must be submitted to the SACCC using the SAE reporting procedures described above.

11.7 Reporting of Other Safety Information

An investigator should promptly notify the SACCC when an "unanticipated problem involving risks to subjects or others" is identified, which is not otherwise reportable as an adverse event.

11.8 Review of Safety Information

11.8.1 Medical Monitor Review

The DAIT/NIAID Medical Monitor will receive monthly reports from the SACCC compiling new and accumulating information on AEs, SAEs, and pregnancies recorded by the sites on appropriate eCRFs. In addition, the Medical Monitor will review and triage SAE and pregnancy reports received by the *SACCC* (See Sections 11.5.1, *Reporting of Serious Adverse Events to DAIT/NIAID*, and 11.6, *Pregnancy Reporting*).

11.8.2 DSMB Review

The Data and Safety Monitoring Board (DSMB) will review safety data at least yearly during planned DSMB Data Review Meetings. Data for the planned 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.

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 DAIT/NIAID. In addition, the study stopping rules have been established and will be monitored in real-time (Section 9.2, Study Stopping Rules). After careful review of the data, the DSMB will make recommendations regarding study conduct and/or continuation.

11.8.2.1 TEMPORARY HALT FOR EMERGENCY SAFETY REVIEW

A temporary halt in enrollment will be implemented if an *ad hoc* DSMB safety review is required. In the event that the study temporarily halts enrollment, no new subjects will be consented or start on therapy; and subjects already on study therapy will continue on therapy unless they are the focus of the DSMB review. Subjects in the screening phase of the study may continue to undergo minimal risk procedures (e.g. blood tests); all other procedures should be deferred. Randomization will not occur until the DSMB review is complete. The health authorities will be notified of any halt in enrollment.

12 MECHANISTIC ASSAYS

As discussed in other sections of the protocol, we propose that the substitution of belatacept for tacrolimus will result in better preservation of renal function. However, the results of the phase II and phase III studies conducted to date suggest that belatacept, at least as used in those studies, may be associated with a slightly increased risk of acute alloimmune-mediated graft injury and an increased risk of PTLD, which is most commonly a consequence of an active EBV infection. Consequently, our areas of focus include determinations of renal function, viral infections, and alloimmunity. Mechanistic assays will be paired with clinical measurements in an attempt to gain insights into the mechanisms responsible for the hypothesized differences between the 2 treatment groups.

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 or studies 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 grant— approximately 5 years, or longer if the grant is extended.

12.1 Cellular Assays

12.1.1 Intracellular Cytokine Staining Viral Phenotyping

There is ample data to suggest that the number, maturational status and function of virus-specific T cells is affected by treatment with immunosuppressive agents and that these factors are associated with the recipient's ability to prevent de novo viral infections or reactivation of existing latent viruses or control chronic viral infections. The frequency (percent of virus-specific cells for a defined population) as well as the absolute number (using Trucount bead methodology) of virus-specific CD8+ and CD4+ T cells will be determined at each time point. For recipients of the correct HLA type where dominant peptides have been defined and tetramers made, virus-specific cells will be detected by tetramer staining. For those viruses/ MHC combinations where tetramers have yet to be defined or for CD4+ T cells (MHC class II tetramers not being available) the number of virus-specific cells will be determined by stimulating the cells with a pool of overlapping viral peptides and then staining the cells for intracellular expression of IFNγ. Cells producing IFNγ will be considered to be specific for the virus corresponding to the peptide pool used to stimulate the cells. By gating on the virus-specific cells, their phenotype can be determined. Using markers such as CD45RA and CCR7 CD8+ and CD4+ T cells can be differentiated into different subpopulations that may correlate with their maturational status and or functional status including naïve, central memory, effector memory, and effector memory RA cells. Similar characterizations will be performed on the entire population of T cells, CD4+ and CD8+ T cells (irrespective of their specificity) in order to determine global changes in the T cell repertoire following transplantation.

The number, frequency, and phenotype of cells specific for the various viruses listed above will be correlated with the detection of the various viruses in the blood by PCR (described in 12.2.2) and for each of the 2 treatment arms. Similar analyses will be performed to characterize the

number, frequency, and phenotype of other cell populations in the blood including B cells, NK cells, and dendritic cells (DC).

Stimulating recipient T cells with overlapping pools of viral peptides can be used to compare the functional properties of virus-specific T cells as well as to identify them in order to enumerate them. Data derived from viral models suggests that poly-functional T cells are more effective for controlling viral infections than are mono-functional cells. That is, T cells producing both IFNγ and TNFα are more effective in mediating protection from viral infections than are cells that produce only IFNγ. The production of other molecules such as IL-2, MIP1β, CD154, perforin, and granzyme B has also been reported to be associated with increased functionality. By stimulating recipient blood samples with overlapping peptide pools corresponding to the viruses listed above and then performing intracellular cytokine staining for the molecules listed above, we will define the functional status of cells from patients in the different treatment groups and correlate these findings with the results of the viral load monitoring described in 12.9.

12.1.2 Flow Cytometry

Similar to the studies of virus-specific T cells described in 12.2.1, recipient T cells collected at the specified time points will be stimulated with donor cells or cell lysates *in vitro* and the number and frequency (percentage) of CD8+ and CD4+ cells responding to donor antigens determined based on intracellular staining for IFNγ. By gating on the IFNγ-positive population the phenotype of the donor-specific T cell population can be determined. Intracellular staining for IFNγ, TNFα, IL-2, MIP1β, CD154, perforin, and granzyme B will allow for a determination of the functional status of the allo-specific populations. Data will be analyzed for differences in these variables between treatment groups and will be correlated with the development of donor specific antibody (DSA), allograft dysfunction (eGFR) and histologic injury (biopsy).

12.2 Molecular Assays

12.2.1 Gene Expression, mRNA Profiling and miRNA Chip Arrays

Studies to quantify the expression of genes in the urine, blood and tissue that have been reported to correlate with acute kidney injury (AKI) or chronic kidney injury (CKI) will be performed. We will investigate markers of allograft dysfunction including those associated with immune-mediated injury, ischemic/stress injury, as well as non-immunologic injuries including calcineurin inhibitor toxicity and fibrosis targets. A list of the gene targets and their function is outlined in Table 6. Recent studies in transplantation indicate further regulation of both immune injury as well as fibrosis and scarring. Consequently, total RNA will be analyzed for miRNA expression for miR21, miR-29, miR200, miR205, miR124, and further characterization using real-time PCR arrays commercially available.

Table 7. Gene Transcript Array for Kidney Allograft Biopsies

IL-2	CCL2	ACTN4	TLR2	
IL-4	CCL3	AFAP	TLR4	T cell transcripts
IL-10	CCL5	ANGPT2	SOD2	costimulation
IL-17	CXCL9	aSMA	SOD3	B cell
IFNg	CXCL11	BMP7	HIF1A	matrix, fibrosis, EMT
IL-23	CX3CL1	COL1A1	HIG2	CNI toxicity
IL-15	CCR1	COL3A1	HO-1	
CD3e	CCR2	COL4A2	CAPN1	NK, NKT
CD4	CCR5	CTGF	MME	Mac
CD8	CX3CR1	CTNNB1	GPX1	IRI/Stress
CD28	CXCR3	E-cad	HSPB2	apoptosis
CD40	CXCL1	FGF2	CTSG	other immune activation
CD40L	CXCL2	FN1	BAX	Chemokines
CD80	ITGAM	HSP47	BCL2	glomerular injury
CD86	ITGAL	HSPG2	Caspase 3	Antibody/endothelial injury
CTLA4	ITGAX	IGF1	PARP	
ICOS	IGAV	LAMC2	FAS	
ICAM1	ITGB6	MMP2	FASL	
41BB	NFKB1	PAI1	CIDEB	
41BBL	NFKB2	PDGFB	TNFSF10	
CD20	LTA	s100A4	Laminin β2	
BAFF-R	LTB	SPARC	βIG-H3	
CD27	TNF	TGFB1	Thrombospondin-1	
TACI	IL-6	THBS1	PAI-1	
CD127/IL7	IL-13	TIMP1	l-arginase	
IL-5	IL-8	TIMP2	Neph	
SSP1	MMP2	TIMP3	Pod	
DES	SMAD3	TIMP4	Gremlin	
HGF	MMP7	VEGF	C3	
Osteoprotgenrin	SMAD7	VIM	C4	
smad2	MMP9	WNT1	CLU	
b-actin	gapdh	18S	EDN1	

If over time additional markers become of interest, the gene targets may change. Further identification of targets and methods to be used will be determined by the results of cooperative efforts undertaken by the CTOT and CTOT-C consortia funded by a supplemental application for ARRA funding to standardize and cross validate assay methodology and targets, led by Dr. Robert Fairchild at the Cleveland Clinic

12.3 Protein Assays of Allograft Injury

We will evaluate both serum (systemic) and urine (local) protein expression specifically looking at factors associated with acute and chronic injury of the kidneys in patients undergoing kidney allograft transplantation by correlating these putative biomarkers with renal function and biopsy material as described in the statistical plan. The proteins listed include those associated with progressive deterioration of renal function in other settings, specifically kidney allograft dysfunction. Positive control proteins or peptides will be included as appropriate. Urinary results will be normalized to creatinine content. Markers for evaluation, their expected disease association, and method of measurement are shown in Table 8, as the study progresses this panel of markers or the core lab performing the assays may change.

Table 8. Proteins for Analysis of Renal Injury in Kidney Transplantation

Tissue	Protein	AKI	CKI	CNI Toxicity	Methodology
Urine	NGAL	**X**	Unknown	Unknown	ELISA
"AKI"	NAG	**X**	Unknown	Unknown	Colorimetric assay
	IL-18	**X**	Unknown	Unknown	ELISA
	KIM-1	**X**	Unknown	Unknown	ELISA
	IP-10	**AR**	Unknown	Unknown	Luminex
	MIG	**AR**	Unknown	Unknown	Luminex
Urine	CTGF	No association	**X/EMT**	Unknown	ELISA
"IF/TA"	MMP9	No association	**X**	Unknown	ELISA
	Col Iα1	Unknown	**X**	Unknown	Western
	ColIIIα1	Unknown	**X**	Unknown	Western
	ColIVα3	Unknown	**X**	Unknown	Western
	Fibronectin	Unknown	**X**	Unknown	Western
	ICAM-1	Unknown	**X**	Unknown	ELISA
	VCAM-1	Unknown	**X**	Unknown	ELISA
	Laminin β2	Unknown	Unknown	**CNI TOX**	ELISA
	TGFβ	No association	**X/EMT**	**CNI TOX**	ELISA
	βIG-H3	Unknown	Unknown	**CNI TOX**	Western
	Osteoprotogerin	Unknown	**X**	Unknown	Luminex
	MIP-1d	Unknown	**X**	Unknown	Luninex
Urine	S100A4	Unknown	**EMT**	In vitro	ELISA
"EMT"	Vimentin	Unknown	**EMT**	In vitro	ELISA
	BMP-7	Unknown	**EMT**	Unknown	ELISA
Urine	Nestin	Unknown	Unknown	**CNI TOX**	Western
"Tox"	Caspase 1	Unknown	Unknown	**CNI TOX**	Colorimetric assay
	Caspase 3	Unknown	Unknown	**CNI TOX**	ELISA
Serum	Cystatin C	**X**	**Probable**	Unknown	ELISA
	NGAL	**X**	Unknown	Unknown	ELISA
	CTGF	No association	**X**	Unknown	ELISA

Studies to quantify the expression of various cytokines, chemokines and growth factors at the protein level will also be undertaken using a standardized, cross-validated approach that will arise from the collaborative studies between participating CTOT and CTOT-C consortia described in the preceding paragraph. Sequential serum samples additionally may be analyzed for chemokines and cytokines and quantified using the Luminex™ platform. Further target analysis exact assay SOP will be developed by the CTOT mechanistic assays consortia headed by Dr. N. Najafian of Brigham and Women's Hospital for this particular assay.

12.4 Antibody Assays

12.4.1 Anti-HLA Antibody (Alloantibodies) and Non-HLA Antibodies

The presence of antibodies reactive to HLA molecules expressed on the renal allograft as well as non-HLA molecules such as MICA have been associated with both acute and chronic injury to the transplanted kidney. We will determine the presence, and if present the amount, of antibodies specific for HLA-A, B, C, DR, DQα, DQβ, and DPβ. We will use the Luminex™ solid phase testing platform. Serum samples will be collected for analysis at the time of transplantation, days 28 & 84, and weeks 28, 36, and 52. Donor specificity will be assigned based on the HLA type of the donor at the loci listed above.

The frequency and amount of antibodies to MICA will be determined using the approach developed by the CTOT/CTOT-C mechanistic assay consortium for detection of antibodies led by E. Reed at UCLA. The *de novo* development of donor-specific antibodies (DSA) will be compared to functional changes (assessed by eGFR) and histologic changes (as demonstrated by biopsy) for the 2 treatment groups.

12.5 Markers of Autoimmunity

The CTOT-15 study will explore the impact of the autoimmune response on graft function following pancreas transplantation. The hypothesis that is being tested is that markers of recurrent autoimmune disease will correlate with graft loss as defined by a return to insulin dependence. The details of the assay will be worked out at the time of the samples are available based on the needs of the study and technology. The assays for the cellular response against autoantigens are being developed in collaboration with the laboratory of Dr. Gerald Nepom (Benaroya Insititute, Seattle). This work will compliment the current work conducted in the Clinical Islet Transplantation (CIT) consortium.

Whole blood will be collected, and peripheral blood mononuclear cells (PBMCs) and serum will be isolated from CTOT-15 participants at baseline, days 28 and 84, weeks 28, 36, and 52. In addition, these samples will be collected at the time of suspected rejection, prior to initiating therapy. The samples will be stored at the University of California, San Francisco for future analysis of markers of autoimmunity.

12.6 Genomics

We will isolate and save a DNA sample from each consented patient potentially to use in genomic analysis of polymorphisms for cytokine genes. There are several such gene polymorphisms that have been associated with increased risk of poor outcome post-transplant. While our goal is not to test the association between various genetic polymorphisms and graft outcome, it is possible that once our study is complete there may be questions regarding whether our results are independent of such

polymorphisms and that it would be prudent to maintain small samples for analysis should such questions arise.

As already noted, prior studies using belatacept have been associated with acute rejection rates higher than standard therapy and the current study intends to optimize its use to minimize rejection or other toxicities. Analysis of gene polymorphisms in recipients may provide insight into allograft outcomes. Recently, polymorphisms in the CTLA4 gene have been described and associated with transplant outcome[25]. We will analyze these polymorphisms as well as other others related to transplant outcomes[26]. DNA will be isolated from the donor and recipient prior to treatment and subsequently analyzed. These results will be analyzed in terms of the primary and secondary endpoints of the study.

12.7 Pathology

12.7.1 Histology- Renal

Histologic examination will be performed at UCSF Pathology Laboratory. The centers will send 5 original stained slides (1 Trichrome or unstained, 1 PAS and 3 H&E) that were collected at times of for-cause biopsy (i.e., increase in serum creatinine, proteinuria, or other clinical symptoms) at the discretion of the site Investigator.

Fibrosis will be assessed using Trichrome and type III collagen stains in the Aperio digital images. Biopsy results will be reported using the Banff 2007 classification of renal allograft pathology. Furthermore, morphometric techniques performed on whole slide digital images in the central core laboratory will serve as adjunctive data to the routine histologic evaluation. Multivariate analysis will seek correlations with changes in any of the morphological parameters including cellular infiltration, vasculopathy, and fibrosis. C4d stains will also be performed on all biopsies if not performed and/or provided by the participating institution.

Morphological evaluations will be recorded in a standardized format, according to Banff '07 criteria. Primary data will be sent to the Statistical and Clinical Coordinating Center for final analysis. High-resolution images of entire sections of all stains from each biopsy will be acquired and archived in an Aperio Digital database system. Slide images will be stored at the UCSF (PI: Dr. Zoltran Laszik) for additional analysis, if needed.

12.7.2 Immunohistochemistry- Renal

The centers will send the remaining portion of the formalin fixed, paraffin embedded (FFPE) block at times of graft dysfunction/ for cause biopsies.

Immunohistochemical studies will assess collagen III deposition, subsets of inflammatory cell infiltrates, and other molecular markers to be determined in conjunction with genomic, proteomic, chemokine, and cytokine data. Since it is anticipated that the core for immunohistochemistry will be small, immunohistochemical stains will be tailored to biomarkers that show promise in the genomic, proteomic, chemokine, and cytokine studies. Remaining tissue will be stored at the UCSF (PI: Dr. Zoltran Laszik) until the end of the study (no more than 4 years) for additional analysis, if needed.

12.7.3 Histology- Pancreas

Histologic examination will be performed at UCSF. The centers will send stained slides (1- Trichrome or unstained slide and 3- H&E) at the times of standard of care and for cause biopsies, if available. Biopsy results will be reported using the Banff 2011 classification of pancreas allograft

pathology. Slide images will be stored at the UCSF (PI: Dr. Zoltran Laszik) for additional analysis, if needed.

12.8 Viral Testing

Viral infection following renal transplantation remains a significant source or recipient morbidity and mortality as well as a significant cause of allograft dysfunction and loss. We will test and quantify the presence of viremia. These tests will be completed in batch assay runs by a core laboratory, and results will not be available to the clinical centers. Detection of the following viruses will be performed by single assay Quantitative PCR: CMV, BKV, JCV, HHV6 and HHV7. EBV will be performed on serum. In collaboration with the Emory Clinical Laboratories we are developing quantitative viral load assays for HHV3 (varicella zoster), HHV6 (roseola), HHV7 (a potential co-factor for CMV disease), polyoma JC and the recently described polyoma WC and KI viruses. If cost-effective multiplexed or low-density arrays are developed, we will consider extending our studies to map the patterns of reactivation and viremia with these latent/chronic viruses.

12.9 Specimen Repository for Future Studies

An attempt will be made to collect amounts of volumes slightly in excess of the minimal required amount for the studies currently planned in order to allow specimens to be banked for use in new assays that have yet to be optimized of conceived or assays performed by other CTOT members not proposed as part of CTOT-15 such as analysis of miRNA, proteomic analyses, or ELISPOT. Appropriate informed consent will be obtained for both the collection and banking of samples and specimens.

13 STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

13.1 Statistical Analyses

CTOT-15 is a randomized open-label phase II clinical trial in which subjects who have received a SPK transplant are randomized 1:1 to treatment arms receiving (a) Thymoblobulin + methylprednisone induction followed by maintenance with tacrolimus + MMF, or (b) Thymoglobulin + methylprednisone induction followed by initial maintenance belatacept + MMF + gradually declining Tacrolimus so that ultimately they will be maintained entirely on a regime of belatacept and MMF. Analysis of the primary endpoint will be based on outcomes measured at 52 weeks post-randomization, while analyses of most secondary outcomes will be done on measurements taken at day 28, (baseline), day 84, and weeks 28, 36, and 52 post-randomization. The primary study objective is to evaluate the belatacept-based maintenance vs. tacrolimus- only maintenance, as a means of improving long term graft function without increasing the risks associated with the later of immunologic graft injury by avoiding both CNI and corticosteroids associated with the more standard tacrolimus maintenance regimen. In addition, this study has a large number of secondary clinical and mechanistic objectives.

13.2 Endpoint Assessments

13.2.1 Primary Clinical Endpoint

The primary endpoint will be the week-52 eGFR. Mean eGFR of the belatacept group will be compared to the mean eGFR of the tacrolimus reference group within a mixed models repeated measures (MMRM) framework , wherein repeated measures of eGFR at weeks 4, 12, 28, 36 and 52 will be modeled as a linear function of time (and perhaps other baseline covariates) in the 2 treatment groups. At week-52, a contrast will be made between the eGFR mean of the belatacept group and the eGFR mean of the tacrolimus group. ANCOVA assumptions will be evaluated graphically via standard residual analyses. If the assumptions fail, a suitable transformation (e.g., natural logarithms) will be found and the data will be reanalyzed on the transformed scale. Results will be reported with p-values associated with the F-test for each contrast and the corresponding mean treatment differences with two-sided 95% confidence intervals. All tests of significance will be two-tailed at the 0.05 level.

Estimating the contrasts within the repeated measures framework will provide treatment comparisons that are robust to subject dropout bias as long as the dropout pattern is missing at random[27]. Data are missing at random whenever the "missingness" mechanism is a function of observable relationships among the nonmissing responses and covariates. Using the methods of Ma et al.[28] , we will evaluate the MAR assumption in the data prior to implementing the MMRM analysis. If the MAR assumption fails, we will consider more robust alternatives (e.g., pattern mixture modeling)[29].

A number of studies have shown RMANCOVA to be superior to analyses of completers or of data with LOCF imputations[30]. Nonetheless, we will conduct 2 related sensitivity analyses: (1) replace the missing week-52 values with the corresponding nonmissing week 36 values of each subject, dropping anyone who is missing both week-36 and week-52 and perform the ANCOVA as currently specified; (2) include only the completers in the ANCOVA analysis (i.e., exclude all dropouts). The sensitivity analyses will be included as additional secondary analyses.

13.2.2 Secondary Clinical Endpoints

The secondary endpoints are defined in Protocol section 1.5.

The protocol defines 28 secondary clinical endpoints. The endpoints are to be computed and summarized by treatment and, in a few cases, by day/week and treatment. With the exception of specific AEs and lab parameters, proportions or means will be estimated for each treatment arm and tested for treatment differences through the use of a statistical model. The particular model to be used depends on the scale of measurement of the endpoint. The accompanying table lists each endpoint and its measurement scale (continuous, dichotomous, and ordinal). All tests of significance in all analyses will be made at the 0.05 level.

Dichotomous measures of prevalence and incidence will be analyzed with log-binomial regression models, wherein treatment effects will be estimated as relative risk ratios; the reference group will be the tacrolimus-thymoglobulin subjects. The log-binomial model (rather than logistic regression) is applied for prevalence and incidence analyses because model-based estimates of relative risk (RR) are both more desirable and appropriate for non-Poisson events that are expected to occur more commonly than in 10% of the cases. In such cases, logistic regression-based odds ratio (OR) estimates are poor estimators of the relative risk[31,32,33,34]. It may be appropriate to treat some of the dichotomous outcomes as censored data; if this is the case, we will obtain RR estimates by fitting Cox regression models to the data[35].

The single ordinal secondary outcome variable (Banff cell-mediated AR score) will be analyzed in a proportional odds model[36] which may include additional covariates and interaction terms, as appropriate.

For continuous outcomes, we will test for differences in response means among the treatment arms by fitting normal theory analysis of variance (ANOVA) or analysis of covariance (ANCOVA) models to the original scores or to some normalizing-variance stabilizing transformation of them. For some endpoints, these models may be fit separately by month post-randomization (i.e., time will be treated as a by-variable and no repeated measures analysis will be performed). Repeated measures models will be fit to HbA1c data and to the slopes of eGFR vs. time regressions. The latter will be estimated in a mixed effects repeated measures model in which both treatment-group means (with 95% confidence limits) of the individual subject slopes and the individual subject slopes themselves will be estimated and tested for equality. Distributions of the individual slopes will be examined graphically and compared among the treatment groups.

Table 9. CTOT-15 primary and secondary clinical response variables

Response type	Response	Measurement Scale	Summary Statistics	Models to test for treatment effects
Primary Endpoint	Mean GFR at week 52 (based on CKD-EPI Eq.)	continuous	Mean and/or geometric mean + 95% CI	Mixed Effects Repeated Measures ANCOVA
	Week-36 LOCF for missing week-52 eGFR	continuous	Mean and/or geometric mean + 95% CI	Mixed Effects Repeated Measure ANCOVA
	Mean GFR at week 52 (based on CKD-EPI Eq.) For Completers	continuous	Mean and/or geometric mean + 95% CI	Mixed Effects Repeated Measure ANCOVA

Response type	Response	Measurement Scale	Summary Statistics	Models to test for treatment effects
Secondary Endpoints				
Renal Function and Injury Endpoints	Indicator of week 52 eGFR<60 mL/min/1.7 m^2 or day 85 – week 52 eGFR decrease < -10 mL/min/1.7 m^2 (composite endpoint based on CKD-EPI Eq.)	dichotomous	Proportion + 95% CI	Log-binomial or Poisson regression
	Mean GFR at week 52 (based on week 52 MDRD4 values)	continuous	Mean and/or geometric mean + 95% CI	Mixed Effects Repeated Measure ANCOVA
	Slope of GFR vs. time Regression over day 85 – week 52, for each treatment arm	continuous	Slope Mean and Std. Error or mean + 95% CI	Mixed effects Repeated Measures ANCOVA
	Incidence of successful tacrolimus withdrawal	dichotomous	Proportion + 95% CI	Log-binomial or Poisson regression
	Incidence of dialysis at day 5	dichotomous	Proportion + 95% CI	Log-binomial or Poisson regression
	Biopsy-confirmed Incidence of an increase of ≥ 1 CAN/IFTA grade, relative to baseline, at each follow-up assessment	Dichotomous (Banff score <1 vs. ≥ 1)	Proportion + 95% CI	Log-binomial or Poisson regression
	Prevalence of CAN/IFTA grades I, II, III at week 52	Dichotomous (1 outcome for each grade)	Proportion + 95% CI	Log-binomial or Poisson regression (1 model per grade)
Incidence and Severity of Rejection and Anti-donor reactivity	Incidence of Acute Rejection (AR) of renal or pancreatic transplant within the first 52 weeks	dichotomous	Proportion + 95% CI	Log-binomial or Poisson regression
	Banff score of the 1st observed of renal or pancreatic AR within 52 weeks post-transplant	Ordered categories (3 levels)	Proportion + 95% CI	Proportional Odds model
	Highest Banff score observed within 52 weeks post-transplant for either renal or pancreatic transplant	Ordered categories (3 levels)	Proportion + 95% CI	Proportional Odds model

Response type	Response	Measurement Scale	Summary Statistics	Models to test for treatment effects
	Steroid vs. nonsteroidal treatment for renal or pancreatic AR	dichotomous	Proportion + 95% CI	Log-binomial or Poisson regression
	Prevalence of anti-donor HLA antibodies at week 52 for renal or pancreatic transplant subjects	dichotomous	Proportion + 95% CI	Log-binomial or Poisson regression
Cardiovascular + Metabolic	Fasting blood sugar	continuous	Mean and/or geometric mean + 95% CI	Separate ANOVA or ANCOVA at weeks 28 and 52
	HbA1c (baseline through week 52)	continuous	Mean and/or geometric mean + 95% CI	Mixed effects Repeated Measures ANCOVA
	Blood pressure at weeks 28 and 52	Continuous	Mean and/or geometric mean + 95% CI at weeks 28 and 52	ANCOVA at weeks 28 and 52, with use of blood-pressure drugs as a covariate
	Use of BP medications	dichotomous	Proportion + 95% CI	Log-binomial or Poisson regression
	Fasting lipid profiles at weeks 28 and 52	Continuous	Mean and/or geometric mean + 95% CI	Separate ANOVA or ANCOVA at weeks 28 and 52
	Total daily pill count	continuous	Mean + 95% CI tabulated and plotted over time, by trt. group	Separate ANOVA or ANCOVA at day 85 and weeks 28 and 52 (or Poisson Reg)
Safety (for both renal and pancreatic transplant subjects)	Incidence of death or graft loss or undetectable C-peptide separately and as a composite	dichotomous	Proportion + 95% CI	Log-binomial or Poisson regression
	Incidence of any AE	dichotomous	Proportion + 95% CI	Log-binomial or Poisson regression
	Incidence of any SAE	dichotomous	Proportion + 95% CI	Log-binomial or Poisson regression
	Incidence of specific infectious diseases (1 analysis per disease) and/or malignancy	dichotomous	Proportion + 95% CI	Log-binomial or Poisson regression

Response type	Response	Measurement Scale	Summary Statistics	Models to test for treatment effects
	Incidence of specific AEs , by NCI CTC grade and treatment arm	dichotomous	proportion	none
	Specific lab parameters by treatment arm and day/week	continuous	N, min, max, Mean, std. dev	none
	Change from baseline for specific lab parameters by treatment arm and day/week	continuous	N, min, max, Mean, std. dev	none

13.2.3 Mechanistic Assay Analyses

The primary mechanistic objective of CTOT studies is to identify and elucidate pathophysiologic and genetic mechanisms that are associated with allograft rejection and how these associations may evolve over time and/or differ between therapeutic treatments. In this study, the principal objectives of the mechanistic analyses of data from subjects receiving kidney or pancreas transplants will include assessment of the association between treatment (i.e., belatacept vs. tacrolimus maintenance) and renal function, incidence of viral infection and autoimmunity.

Ten mechanistic assays are described in Section 12. There are from 1 to 3 separate correlations or tests desired for each assay category and these are described in Table 8. The analysis numbers in the table refer to the following 10 assays:

1. Intracellular cytokine staining and viral phenotyping
2. Flow cytometry
3. Protein Assays
4. Gene expression, mRNA profiling
5. Anti-HLA alloantibodies and non-HLA antibodies
6. Autoimmunity markers
7. Genomics (gene polymorphisms)
8. Renal histology
9. Renal immunohistochemistry
10. Pancreatic histology
11. Viral testing (viral load determination)

Depending on the scale of measurement of the endpoints, the amount of missing data, and the questions of interest, exploratory data analysis (EDA) and/or statistical hypothesis testing and modeling will used. Given the small sample sizes (n=30 in each of 2 treatment arms), modeling and testing will generally be restricted to the continuous endpoints where the focus will be testing for treatment and time effects on repeated measures of the endpoints. These types of analyses will have sufficient sample sizes to make reasonable inferences; e.g., repeated measures ANCOVA tests for differences in gene expression in the treatment arms, over 5 assessment times would have to following degrees of freedom for the their error terms: treatment df = 58; time df = 238, time × treatment = 238.

Analysis No.	**Effector cells, antibodies, or markers (see Sect. 12)**	**Meas. Scale**	**Assay**	**Objective**	**Analysis Method**[1]
1a	Virus-specific T-cell subpopulations	Continuous. (cell counts)	Cytokine staining + PCR	Correlation with viral loads detected with PCR, by visits and treatment arm	Spearman Rank Correlation Coeff., by visit and treatment group; treatment x time plots; tables of summary stats.
1b	Virus-specific T-cell subpopulations	Binary	Cytokine staining + PCR	Comparison of prevalence of each T-cell type by visits and treatment arm	Contingency tables and Cochran Mantel Haenszel (CMH) tests
1c	Virus-specific T-cell subpopulations	Continuous. (cell counts)	Cytokine staining + PCR	Correlation with B-cell counts, NK cell counts, dendritic cell counts by visit and treatment arm	Spearman Rank Correlation Coeff., by visit and treatment group; treatment x time plots; tables of summary stats.
2a	Donor-reactive T-cell subpopulations	Continuous. (cell counts)	Flow Cytometry	Look for treatment arm differences in counts, over time	Random Effects repeated measures ANCOVA (RMANCOVA); treatment x time plots and random coefficients models and plots; tables of means and standard errors
2b	Donor-reactive T-cell subpopulations	Continuous. (cell counts)	Flow Cytometry	Correlation with eGFR, de novo anti-donor HLA and biopsy findings, by visits and treatment arm	Spearman Rank Correlation Coeff., by visit and treatment group; treatment x time plots; tables of summary stats.
3	Protein Assays				
4a	Gene expression data for > 128 markers	Continuous	Real –time PCR	Identify associations between specific mRNAs and the occurrence of AKI, CHI, CIT, and fibrosis, by visit pooled over trt	EDA: various graphical comparisons and descriptive statistics (by visit if there are enough occurrences of AKI, CKI, CIT, and/or fibrosis

[1] Statistical tests (e.g., t-tests) and statistical models (e.g., ANOVA) will only be performed if sample sizes are adequate

Analysis No.	**Effector cells, antibodies, or markers (see Sect. 12)**	**Meas. Scale**	**Assay**	**Objective**	**Analysis Method**[1]
4b	Gene expression data for > 128 markers	Continuous	Real –time PCR	Look for evidence of treatment differences in the occurrence of each marker over time	Separate RMANCOVAs for each marker; treatment x time plots; tables of means and standard errors by marker, treatment arm, and visit
5a	Anti-HLA and non-Anti-HLA antibodies	Continuous	Luminex	Characterize the occurrence of HLA-A, B, C, DR, DQα, DQβ, DPβ, and anti-MICA, by treatment arm and visit	Separate RMANCOVAs for each ab.; treatment x time plots; tables of means and standard errors by antibody, treatment arm, and visit
5b	Anti-HLA and non-Anti-HLA antibodies	Binary (present absent)	Luminex	Examine prevalence patterns of HLA-A, B, C, DR, DQα, DQβ, DPβ, and anti-MICA	Contingency tables and CMH tests by marker ; treatment x time plots; tables of prevalence means and stderrs by treatment arm and visit
5c	De Novo donor-specific anti-HLA antibodies	Continuous	Luminex	Correlation with eGFR, and biopsy findings (if enough are done), by visits and treatment arm	Spearman Rank Correlation Coeff., by visit and treatment group; treatment x time plots; tables of summary stats.
6	Markers of recurrent autoimmune disease following pancreas transplant	Continuous	TBD	Compare distributions of anti-GAD, anti-insulin and anti-IA2 between subjects with AR and no AR	EDA using graphical and tabular summaries of the data in AR vs. non-AR within and between subjects.
7	Genomic analysis of polymorphisms (SNPs) in cytokine genes	Binary	TBD	Determine if differences in cytokine genetic polymorphisms are associated with AR	Logistic regression analysis for additive and recessive hypotheses; wherein, the predictors are the numbers (0,1,2,) of recessive alleles for each SNP.

Analysis No.	**Effector cells, antibodies, or markers (see Sect. 12)**	**Meas. Scale**	**Assay**	**Objective**	**Analysis Method**[1]
7	Morphological markers in biospsied kidney tissue + CD4 markers	Continuous + binary (present/absent)	Trichrome, H&E, and CD4 staining	Correlation with visit 1 – week 52 changes in Banff scores and corresponding changes in several morphometric features of the grafts	Spearman Rank Correlation Coeff., by visit and treatment group; tables of summary stats.
9	Renal markers of fibrosis and inflammation	Binary (present/ absent)	Immuno-histochemical staining	Compare genomic, proteomic, cytokine profiles in subjects with/without the renal markers	Tables of summary statistics to compare within-subject changes in markers and profiles between visit 1 and week 52.
10	Morphological markers in biospsied pancreatic tissue + CD4 markers	Continuous + binary (present/absent)	Trichrome, H&E	Correlation with visit 1 – week 52 changes in Banff scores and corresponding changes in several morphometric features of the grafts	Spearman Rank Correlation Coeff., by visit and treatment group; tables of summary stats.
11a	Prevalence and intensity (viral load) of several pathogenic viruses	Binary (present/absent)	Quant. PCR	Prevalence of CMV, BKV, JCV, HHV6, HH7, and EBV	Contingency tables and CMH for treatment time differences in prevalence of each viral species
11b	Prevalence and intensity (viral load) of several pathogenic viruses	Continuous	Quant. PCR	Viral loads of HHV6, HHV7,Polyoma JC, Polyoma WC, and KI	Separate RMANCOVAs on each virus; treatment x time plots; tables of means and standard errors by virus, treatment arm and visit

Table 10. Summary of Mechanistic Data Analyses

13.3 Sample Size and Power Calculations

We have used data from the belatacept phase II and DIRECT studies and from the literature (Grewal and Blake 2005) to provide expected values for the GFR standard deviations shown in Table 10 below. Sample size calculations for these analyses were performed using NCSS-PASS software.

In the primary endpoint analysis, we will compare the mean GFR between the study groups at 12 months. With the sample sizes fixed, a priori, at 30 subjects in each of the two treatment arms, the following table shows the smallest treatment mean GFR differences (i.e. effect sizes) we will be able to declare significantly different, with 80% power and Type I error rates of 0.05 and 0.10:

Table 11 – Smallest Detectable Difference in GFR at 12 Months for Different Standard Deviations and Alpha Levels

GFR Standard Deviation	Alpha Level	Smallest Detectable Difference in GFR (mL/min/1.7 m^2)
16	**0.05**	**12.0**
	0.10	**10.5**
20	**0.05**	**15.0**
	0.10	**13.0**
24	**0.05**	**18.0**
	0.10	**16.0**

This study has been powered to be able to detect minimum detectable differences in the primary endpoint at both the 0.05 and 0.10 levels that are clinically relevant as shown in Table 9 above. When reporting results of the primary endpoint analysis, we will report a p-value as significant at the 0.10 level if it is less than 0.10 and as significant at the 0.05 level if it is less than 0.05. As previously stated, all secondary endpoint analyses will be performed at the 0.05 level.

13.4 Safety Analyses

All adverse events (AEs) and serious adverse events (SAEs) will be classified by body system and preferred term according to the *Medical Dictionary for Regulatory Activities* (MedDRA). AEs and SAEs will be summarized as the frequency of each event by treatment group.

Frequency tables by treatment group and category of event (e.g., serious, related to study therapy, causing the discontinuation of study therapy) and by NCI-CTCAE grade will be presented. Selected laboratory values will also be summarized by treatment group using the mean and standard deviation of the change from baseline at scheduled visits.

13.5 Demographic Data

13.5.1 Baseline Characteristics and Demographics

Summary descriptive statistics for baseline and demographic characteristics will be provided for all enrolled participants. Demographic data will include age, race, sex, body weight, and height; these data will be presented in the following manner:

- Continuous data (i.e., age, body weight, and height) will be summarized descriptively by mean, standard deviation, median, and range.

- Categorical data (i.e., sex and race) will be presented as enumerations and percentages.

Statistical presentation for baseline and demographic characteristics will be further defined in the statistical analysis plan (SAP).

13.5.2 Medical History

Medical history will be collected, including the existence of current signs and symptoms and clinical significance for each body system.

13.6 Interim Analyses

No interim analyses are planned for this study. Unspecified interim analyses are only conducted if they will not adversely affect the integrity of the study or for safety reasons.

13.7 Reporting Deviations from Original Statistical Plan

The final study analysis will report the results of the original SAP. Any additional analyses will be identified as ad hoc. Clinical study report will be prepared and submitted to the health authority as specified in the FDA Guideline for Industry - Structure and Content of Clinical Study Reports - ICH E3 July 1996.

13.8 Final Study Analysis

The final study analysis will report the results of the SAP. Any additional analyses will be identified as ad hoc. A final study report will be prepared summarizing the results of analyses of the primary and secondary clinical endpoints and the analyses associated with the 12 mechanistic hypotheses.

14 SOURCE DATA

14.1 Source Data

All study data should be verifiable by source documentation. Most often this will be present in the patient's medical record. Except in rare instances, study documents (CRFs and data collection tools) are not source documents. "Shadow charts"-duplications of material from the medical record are not source documents.

14.2 Access to Source Data

The responsibilities of the study sponsor require that they and their representatives as well as the health authorities have access to (and may when required by applicable law copy) source documents Unless required by the laws that permit copying of records, only the coded identity associated with documents or with other participant data may be copied (and all personally identifying information must be obscured). Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that is linked to identified individuals.

15 QUALITY CONTROL AND QUALITY ASSURANCE

The investigator is required to keep accurate records to ensure that the conduct of the study is fully documented.

The sponsor is responsible for regularly reviewing the conduct of the trial, for verifying adherence to the protocol, and for confirming the completeness, consistency, and accuracy of all documented data.

15.1 Data Handling

The investigator is required to ensure that all CRFs are completed for every participant entered in the trial. All elements of data entry (i.e., time, date, verbatim text, and the name of the person performing the data entry) will be recorded with an audit trail to allow all data changes in the database to be monitored and maintained in accordance with federal regulations.

16 ETHICAL CONSIDERATIONS AND COMPLIANCE WITH GOOD CLINICAL PRACTICE

16.1 Statement of Compliance

This clinical study will be conducted using good clinical practice (GCP), as delineated in *Guidance for Industry: E6 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 an appropriate EC or IRB. Any amendments to the protocol or to the consent materials must also be approved before they are implemented.

16.2 Informed Consent Process

The consent process provides information about the study to a prospective participant and allows adequate time for review and discussion prior to their decision. The principal investigator or designee listed on the 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) must read, sign, and date a consent form before undergoing any study procedures. Consent materials must be presented in participants' primary language. A copy of the signed consent form must be given to the participant. The consent process is ongoing. The consent form must 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.

16.3 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 should not transmit documents containing personal health identifiers (PHI) to the study sponsor or their representatives.

17 PUBLICATION POLICY

The Clinical Trials in Organ Transplantation (CTOT) policy on the publication of study results will apply to this trial. The CTOT Publication Policy is located on the CTOT website at www.ctotstudies.org.

Appendix 1: Schedule of Events – Pre-Transplant to Day 4 Post-Transplant (Visit 1)

Screening Assessments	*Window*
• *Blood Type (A, B, O), Rh Factor* • *HLA Typing (Class I: A, B, C, Class II: DR, DP, DQ)* • *Peak PRA, Current PRA or cPRA (within 12 months prior to transplant),Crossmatch* • *Hepatitis B, Hepatitis C, and HIV test results* • *Last reported CMV (IgG, IgM and/or total CMV Ab) and EBV testing (IgG, IgM)* • *Tuberculosis testing (within 12 months prior to transplant). If documentation is not present at the time of transplant, and the subject does not have any risk factors for TB, a TB-specific interferon gamma release assay (IGRA) may be performed.*	*Retrospective data collection, no time limits, unless specified. Repeat only if not available.*
• *Informed Consent and Assessment of Eligibility* • *Demographics* • *Medical History, Physical exam (BP, Pulse, Temperature, Respiration, Weight)* • *Concomitant Medications* • *Local Labs: Serum Pregnancy Test, Hematology Panel (CBC, differential, platelets), Chemistry 12-Panel / CKD-EPI equation, MDRD 4 variable, Serum Amylase, Serum Lipase, Fasting Lipid Panel (Total, HDL, LDL, Triglycerides), Hemoglobin A1c, Urinalysis*	*Within 30 days prior to transplant, until time of transplant.*
• *Flow Cytometry (20mL blood in Cyto-Chex Tube)* • *Intracellular Cytokine Staining – Viral Phenotyping (32mL blood in CPT Tube)* • *Markers of Autoimmunity – PBMC (30mL blood in Green-top Tube)* • *Markers of Autoimmunity – serum (5mL blood in Red-top Vacutainer)* • *Gene Expression, mRNA profiling in blood (2.5 mL blood in PAXgene RNA tube)* • *Cytokines and Growth Factors- serum (7mL blood in Red-Top Vacutainer)* • *Serum Proteins – CTGF, TGFbeta (4.5mL blood in CTAD)* • *Urine Proteins – CTGF, TGFbeta (supernatant)* • *Gene Expression, mRNA profiling in urine (urine pellet)* • *Non-HLA Ab, Anti-HLA Ab, DSA (5mL blood in Red-top Vacutainer)* • *Genomics- gene polymorphisms (4mL in Lavender-top EDTA Vacutainer)* • *Viral Monitoring by PCR (CMV, BKV, JCV, HHV6, HHV7) and Viral Assay Development (HHV3- varicella zoster, HHV6- roseola, HHV7- cofactor CMV, polyoma JC, WC, KI).(plasma from ICS sample)*	*Within 48 hours prior to transplant*
• *Randomization (RhoRand System)* • *Assessment of Events: AE/SAE* • *Solumedrol®(Methylprednisone) : 500mg – Intraoperatively* • *Thymoglobulin® (Anti-thymocyte Globulin – Rabbit)* • *Prograf® (tacrolimus)* • *CellCept® (mycophenolate mofetil)*	*Day of Transplant*
• *Methylprednisolone 250 mg* • *Thymoglobulin® (Anti-thymocyte Globulin – Rabbit)*	*Day 1 Post-Transplant*
• *Methylprednisolone 125 mg* • *Thymoglobulin® (Anti-thymocyte Globulin – Rabbit)*	*Day 2 Post-Transplant*
• *Methylprednisolone 60mg* • *Thymoglobulin® (Anti-thymocyte Globulin – Rabbit)*	*Day 3 Post-Transplant*
• *Methylprednisolone 30mg*	*Day 4 Post-Transplant*

Appendix 2. Schedule of Events (Recipient) Post-Transplant

		DAYS					WEEKS										FOR CAUSE 2, 3
		5	14	28	56	84	16	20	24	28	32	36	40	44	48	52	
	VISIT NUMBERS	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
	VISIT WINDOWS (+/- DAYS)		2	3	3	3	3	3	3	5	5	5	5	5	5	5	
GENERAL ASSESSMENTS																	
Physical Exam	BP, Pulse, Temperature, Respiration, Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Immunosuppressive Meds	Drug Name and Dose	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Concomitant Medications	Drug Name (Anti-HTN, Prophylaxis, Anti-Viral)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessments of Events	AE/SAE, Infections, Rejections, Hospital, Graft Loss, Malignancies, New Onset Diabetes, Death	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Neurological Assess. for PML	Hx, mini mental, cranial nerve, motor, cerebellar			X		X				X		X				X	
LOCAL LABORATORY ASSESSMENTS																	
Hematology Panel	CBC, differential, Platelet			X		X				X		X				X	X
Chemistry Panel / GFR (CKD-EPI and MDRD)- Renal Function	Serum Creatinine, BUN, glucose, sodium, AST, ALT, ALP, bilirubin, albumin, calcium, phosphate			X		X				X		X				X	X
Chemistry- Pancreatic Function	Serum Amylase, Serum Lipase			X		X				X		X				X	X
Fasting Lipid Panel	Total, HDL, LDL, Triglycerides									X						X	
C-Peptide	C-Peptide															X	X
Hemoglobin A1c	HbA1c			X		X				X		X				X	
Urinalysis	Protein, Glucose, Hematuria, WBC			X		X				X		X				X	X
Trough Levels	Tacrolimus trough levels	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Viral Monitoring	BKV and CMV by PCR in blood			X		X				X						X	
Histology- Renal	Local Read- Banff 2007 Renal																X
Histology – Pancreas	Local Read- Banff 2011 Pancreas																X
NULOJIX® (BELATACEPT) INFUSION DOSING																	
Belatacept Infusion • Investigational Arm	IV, 10mg/kg	X[4]	X	X	X	X											
Belatacept Infusion • Investigational Arm	IV, 5mg/kg						X	X	X	X	X	X	X	X	X	X	
TACROLIMUS DOSING SCHEDULE																	
Tacrolimus Dosing • Control Arm	Dose adjusted to target trough levels of 8-12ng/mL to week 24, then 5-8ng/mL thereafter.	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Tacrolimus Dosing[6,7,8] • Investigational Arm	Dose adjusted to target trough levels 5-8 ng/mL to week 24, then 3-5 ng/mL until week 40.	→	→	→	→	→	→	→	→	→	→	→	→	stop			
MYCOPHENOLATE MOFETIL DOSING SCHEDULE																	
Mycophenolate Mofetil	1gm BID, Adjusted based on clinical complications	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→

		DAYS					WEEKS										
		5	14	28	56	84	16	20	24	28	32	36	40	44	48	52	FOR CAUSE[3]
	VISIT NUMBERS	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
	VISIT WINDOWS (+/- DAYS)		2	3	3	3	3	3	3	5	5	5	5	5	5	5	
CELLULAR CORE LABORATORY- EMORY UNIVERSITY (PI: CHRISTIAN LARSEN, MD																	
Intracellular Cytokine Staining	32 mL Blood CPT Tube									X		X				X	X
Flow Cytometry	20-40 mL Blood Cyto-Chex Tube			X		X				X		X				X	X
MARKERS OF AUTOIMMUNITY CORE LABORATORY- UCSF (PI: PETER STOCK, MD)																	
Markers of Autoimmunity- PBMC	30 mL Blood Green-Top Vacutainer			X		X				X		X				X	X
Markers of Autoimmunity- Serum	5mL Blood- Red-Top Vacutainer			X		X				X		X				X	X
MOLECULAR CORE LABORATORY- UNIVERSITY OF ALABAMA (PI: ROSLYN MANNON, MD)																	
Gene Expression, mRNA Profiling (Blood)	2.5 mL Blood- PAXgene RNA Tube			X		X				X		X				X	X
Gene Expression- mRNA Profiling (Urine)	50-100 mL Urine (Pellet)			X		X				X		X				X	X
Gene Expression- mRNA Profiling (Tissue)	1 renal core in RNALater																X
ASSAYS OF ALLOGRAFT INJURY LABORATORY- UNIVERSITY OF ALABAMA (PI: ROSLYN MANNON, MD)																	
Cytokines and Growth Factors	7 mL Blood - Red-Top Vacutainer			X		X				X		X				X	X
Serum Proteins- CTGF, TGFbeta	4.5mL Blood- Light Blue CTAD			X		X				X		X				X	X
Urine Proteins- CTGF, TGFbeta	50-100 mL Urine (Supernatant)			X		X				X		X				X	X
ANTIBODY CORE- EMORY UNIVERSITY SCHOOL OF MEDICINE (PI: HOWARD GEBEL, PHD)																	
Non-HLA Ab/Anti-HLA Antibodies / DSA[1]	5 mL Blood - Red-Top Vacutainer			X		X				X		X				X	X
PATHOLOGY CORE LABORATORY- UCSF (PI: ZOLTRAN LASZIK, MD)																	
Histology/Immunohistochemistry - Renal	5 slides (1-Trichrome or unstained, 1-PAS, 3-H&E) **AND** FFPE tissue (remaining block) **AND** C4d and SV40 slides (if available)																X
Histology- Pancreas	4 slides (1-Trichrome/ unstain, 3-H&E)																X
VIRAL MONITORING CORE- EMORY UNIVERSITY (PI: ANEESH MEHTA, MD)																	
Viral Monitoring by PCR (EBV) **AND** Viral Monitoring Assay Development: BLOOD	4 mL Blood in EDTA Lavender-top Vacutainer Tube			X		X				X		X				X	X
Viral Monitoring by PCR (CMV, BKV, JCV, HHV6, HHV7) **AND** Viral Monitoring Assay Development (HHV3 (varicella zoster), HHV6 (roseola), HHV7 (cofactor CMV), polyoma JC, WC,KI): PLASMA	5mL PPT Tube OR plasma collected from the CPT tubes for Intracellular Cytokine Staining Viral Phenotyping			X		X				X		X				X	X

1. If a subject develops anti-donor alloantibodies or de novo anti-HLA (PRA >25%), the test must be repeated on a fresh sample and confirmed within 4 weeks.
2. For Cause Biopsy specimens should be collected at times of graft dysfunction, and prior to initiating therapy.
3. If blood samples are collected for a For-Cause biopsy AND are within 2 weeks of a scheduled visit, then the samples will also be used for the scheduled visit.
4. The first dose of NULOJIX® (belatacept) will be administered approximately 24-48 hours after the last dose of Thymoglobulin® (Anti-Thymocyte Globulin- Rabbit).
5. The results of the non-HLA Ab/Anti-HLA Antibodies/DSA drawn at week 36 will be sent back to the clinical sites in order to make a decision regarding tacrolimus withdrawal at week 40.
6. At week 40, subjects eligible for withdrawal will be weaned over a 4-8 week period based on the protocol.
7. Tacrolimus dosing will be collected following week 44 on subjects who were not eligible for withdrawal or failed withdrawal.

8. During tacrolimus weaning and for 6 weeks post tacrolimus withdrawal, subjects will have weekly labs that include serum creatinine, fasting glucose, amylase and lipase.

Appendix 3. Schedule of Events (Recipient) Post-Transplant (Year 2)

		WEEKS						FOR CAUSE 2, 3
		56	**60**	**64**	**68**	**72**	**76**	
	VISIT NUMBERS	17	18	19	20	21	22	
	VISIT WINDOWS (+/- DAYS)	5	5	5	5	5	5	
GENERAL ASSESSMENTS								
Physical Exam	BP, Pulse, Temperature, Respiration, Weight	X	X	X	X	X	X	
Immunosuppressive Meds	Drug Name and Dose	→	→	→	→	→	→	→
Concomitant Medications	Drug Name (Anti-HTN, Prophylaxis, Anti-Viral)	X	X	X	X	X	X	X
Assessments of Events	AE/SAE, Infections, Rejections, Hospital, Graft Loss, Malignancies, New Onset Diabetes, Death	→	→	→	→	→	→	→
Neurological Assess. for PML	Hx, mini mental, cranial nerve, motor, cerebellar			X			X	
LOCAL LABORATORY ASSESSMENTS								
Hematology Panel	CBC, differential, Platelet			X			X	X
Chemistry Panel / GFR (CKD-EPI and MDRD)- Renal Function	Serum Creatinine, BUN, glucose, sodium, AST, ALT, ALP, bilirubin, albumin, calcium, phosphate			X			X	X
Chemistry- Pancreatic Function	Serum Amylase, Serum Lipase			X			X	X
Fasting Lipid Panel	Total, HDL, LDL, Triglycerides			X			X	
C-Peptide	C-Peptide						X	X
Hemoglobin A1c	HbA1c			X			X	
Urinalysis	Protein, Glucose, Hematuria, WBC			X			X	X
Trough Levels	Tacrolimus trough levels	X	X	X	X	X	X	X
Viral Monitoring	BKV and CMV by PCR in blood						X	
Histology- Renal	Local Read- Banff 2007 Renal							X
Histology – Pancreas	Local Read- Banff 2011 Pancreas							X
NULOJIX® (BELATACEPT) INFUSION DOSING								
Belatacept Infusion • Investigational Arm	IV, 5mg/kg	X	X	X	X	X	X	
TACROLIMUS DOSING SCHEDULE								
Tacrolimus Dosing • Control Arm	Dose adjusted to target trough levels of 5-8ng/mL.	→	→	→	→	→	→	→
Tacrolimus Dosing [1] • Investigational Arm	Withdrawn by week 48 or dose adjusted based on Investigator discretion.							
MYCOPHENOLATE MOFETIL DOSING SCHEDULE								
Mycophenolate Mofetil	1gm BID, Adjusted based on clinical complications	→	→	→	→	→	→	→

1. Tacrolimus dosing is only collected on subjects who were not eligible for withdrawal or failed withdrawal.
2. For Cause Biopsy specimens should be collected at times of graft dysfunction, and prior to initiating therapy.
3. If blood samples are collected for a For-Cause biopsy AND are within 2 weeks of a scheduled visit, then the samples will also be used for the scheduled visit.

Appendix 4. Reduced Follow-Up Schedule of Events (Recipient)

		DAYS		WEEKS		
		28	**84**	**24**	**36**	**52**
	VISIT NUMBERS	4	6	9	12	16
	VISIT WINDOWS (+/- DAYS)	3	3	3	5	5
ASSESSMENTS	**DETAILS**					
GENERAL ASSESSMENTS						
Physical Exam	Blood Pressure, Pulse, Temperature, Respiration, Weight	X	X	X	X	X
Immunosuppressive Medications	Drug Name, Dose, Start and End Date	→	→	→	→	→
Assessments of Events	AE/SAE, Infections, Rejections, Hospitalizations, Graft Loss, Malignancies, New Onset Diabetes, Death	→	→	→	→	→
Neurological Assessments for PML	History, mini mental, cranial nerve, motor, cerebellar exam	X	X	X	X	X
LOCAL CLINICAL LAB ASSESSMENTS						
Hematology Panel	CBC, differential, Platelet	X	X	X	X	X
Chemistry Panel	Serum Creatinine	X	X	X	X	X
Urinalysis	Protein, Glucose, Hematuria, WBC	X	X	X	X	X
Viral Monitoring	BKV and CMV by PCR in blood	X	X	X		
Viral Monitoring	CMV by PCR in blood					X

Appendix 5. Schedule of Events (Donor)

		Visit 1
GENERAL ASSESSMENTS		
Demographics	Age, Race, Gender	X
Donor Information	Deceased-Donor, Cause of Death, Serum Creatinine	X
LOCAL LABORATORY ASSESSMENTS		
Blood Type [1]	A, B, O	X
HLA Typing [1]	I (A, B, C), II (DR, DP, DQ)	X
Viral Panel [1]	CMV (IgG, IgM and or total CMV Ab), EBV (IgG, IgM)	X
CORE LABORATORY		
Markers of Autoimmunity	Spleen	X

1. Retrospective data collection. Report results available for center specific transplant for CMV, EBV. If the result is not available/not performed at that center, this is not considered a protocol deviation.

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