TCD601 (siplizumab)

CLINICAL PROTOCOL TCD601A201

An Adaptive, Regimen Finding, Safety and Tolerability Study of TCD601 (Siplizumab), a Human Anti-CD2 Antibody, Combined with Donor Bone Marrow Cell Infusion and Non-Myeloablative Conditioning, for Tolerance Induction in Living Donor Renal Transplantation (PANORAMA)

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ABO	major human blood group system (Type A, Type B, Type O)
ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
AESI	adverse event of special interest
aGvHD	acute graft-versus-host disease
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMR	antibody-mediated rejection
ANC	absolute neutrophil count
APC	antigen-presenting cell
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATG	anti-thymocyte globulin
BID	twice a day/twice daily
BKV	BK polyomavirus
BMCI	bone marrow cell infusion
BMI	body mass index
BMT	bone marrow transplantation
BPAR	biopsy-proven acute rejection
BUN	blood urea nitrogen
CBC	complete blood count
CDC	complement-dependent cytotoxicity
CKBMT	combined kidney and bone marrow transplantation
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMV	cytomegalovirus
CNI	calcineurin inhibitor
COVID-19	coronavirus disease 2019
CP	cyclophosphamide
CRS	chimeric release syndrome
CS	corticosteroids

Abbreviation	Definition
CsA	cyclosporine
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTS	chimeric transition syndrome
DGF	delayed graft function
DMC	Data Monitoring Committee
DSA	donor-specific antibodies
EBV	Epstein-Barr virus
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOS	End of Study
ESRD	end stage renal disease
[redacted]	[redacted]
FAS	Full Analysis Set
GCP	Good Clinical Practice
GI	gastrointestinal
GvHD	graft-versus-host disease
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HHV	human herpesvirus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HSCT	hematopoietic stem cell transplantation
HSV	herpes simplex virus
HTLV-1	human T-lymphotropic virus type 1
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Abbreviation	Definition
IgG	immunoglobulin G
IGRA	interferon-gamma release assay
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	Intravenous(ly)
IVIG	intravenous immunoglobulin
LLOQ	lower limit of quantitation
LOCF	last-observation-carried-forward
LPD	lymphoproliferative disorder
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MESNA	sodium-2-mercaptoethane sulfonate
MFI	median fluorescence intensity
MHC	major histocompatibility complex
MMF	mycophenolate mofetil
MPA	mycophenolic acid
MRI	magnetic resonance imaging
mTOR	mechanistic target of rapamycin
NAAT	nucleic acid amplification test
NCI	National Cancer Institute
NHP	non-human primate
NK	natural killer
NMA	non-myeloablative
NODAT	new onset diabetes post-transplant
PCP	*Pneumocystis jirovecii* (*Pneumocystis carinii*) pneumonia
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PET	positron emission tomography
PGNF	primary graft non-function
PO	orally

Abbreviation	Definition
PRA	panel reactive antibodies
PT	Preferred Term
PT	prothrombin time
PTLD	post-transplant lymphoproliferative disorder
PTT	partial prothrombin time
PVAN	polyomavirus-associated nephropathy
RIC	reduced intensity conditioning
RNA	ribonucleic acid
SAB	single antigen bead
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
sCr	serum creatinine
SD	standard deviation
SID	subject identification number
SMAC	supramolecular activation cluster
SMQ	standardized MedDRA query
SMZ-TMP	sulfamethoxazole and trimethoprim
SoC	standard of care
SOC	System Organ Class
SOP	standard operating procedure
TAC	tacrolimus
TB	tuberculosis
TBI	total body irradiation
TCMR	T cell-mediated rejection
TEAE	treatment-emergent adverse event
TMA	thrombotic microangiopathy
Tmem	memory T cell
Treg	regulatory T cell
TSH	thyroid-stimulating hormone
ULOQ	upper limit of quantitation
US	United States

Abbreviation	Definition
VL	viral load
VNTR	variable number tandem repeats
WBC	white blood cell(s)
WHO	World Health Organization
WOCBP	women of childbearing potential

PROTOCOL SYNOPSIS

Product Name/Number	TCD601 (siplizumab)
Protocol Number	TCD601A201
Protocol Title	An Adaptive, Regimen Finding, Safety and Tolerability Study of TCD601 (Siplizumab), a Human Anti-CD2 Antibody, Combined with Donor Bone Marrow Cell Infusion and Non-Myeloablative Conditioning, for Tolerance Induction in Living Donor Renal Transplantation (**PANORAMA**)
Investigation Type	Interventional; Drug (biologic)
Purpose and Rationale	Achieving successful withdrawal of all immunosuppression without rejection presents an opportunity for better long term graft and patient survival, fulfilling a significant unmet medical need in solid organ transplantation today. Allogeneic renal tolerance following a combined renal transplant and bone marrow cell infusion (BMCI) from the same donor, following non-myeloablative (NMA) conditioning, has the potential to facilitate immune tolerance of a donor allograft and allow the complete withdrawal of chronic immunosuppression. Prior studies using siplizumab, a humanized anti-CD2 monoclonal antibody in combination with NMA conditioning, living donor renal transplantation and BMCI have achieved this objective of immunosuppression withdrawal in 9/12 (75%) patients enrolled. However, many patients experienced Chimeric Transition Syndrome (CTS) as well as some avoidable graft losses. CTS is an early event characterized by a rise in serum creatinine and transient renal dysfunction that has been associated with the rapid loss of donor chimerism. This study is designed to identify and optimize an allogeneic tolerance-inducing regimen that mitigates CTS symptoms while maintaining the benefits of complete immunosuppression withdrawal. To optimize the peri-transplant conditioning regimen, a 2-arm sequential cohort study using a modified 3+3 enrollment scheme has been designed. This approach will investigate the addition of immunomodulatory therapy to prolong chimerism (e.g., siplizumab, mycophenolate mofetil [MMF]) and mitigate and/or treat CTS symptoms (e.g., tocilizumab).

Objective	**Endpoint**
Primary	
• To determine the optimal regimen for renal allograft tolerance (defined as proportion of recipients off immunosuppression with maintenance of good renal function at Month 24 post-transplant) while minimizing chimeric transition syndrome	• Number and percentage of subjects achieving renal allograft tolerance at Month 24 post-transplant as assessed by: o Immunosuppression dosing o Serum creatinine (estimated glomerular filtration rate [eGFR]) o Incidents of Chimeric Transition Syndrome (CTS) and biopsy proven acute rejection (BPAR) o Renal biopsy

Objective(s)	Endpoint(s)
Key Secondary	
• To determine the composite incidence of BPAR, death and graft loss (with and without lost to follow-up) at Month 24 post-transplant	• Number and percentage of subjects experiencing BPAR, death, and graft loss (with and without lost to follow-up) at Month 24 post-transplant.
• To determine the incidence and mean fluorescence intensity (MFI) of donor-specific antibody (DSA) at Month 24 post-transplant	• Number and percentage of subjects of DSA positivity at Month 24 post-transplant. • MFI of DSA at Month 24 post-transplant.
Secondary	
• Incidence, duration, severity of CTS	• Number and percentage of subjects experiencing CTS by severity • Time from onset of CTS to resolution
• Proportion of recipients with transient mixed chimerism without CTS	• Number and percentage of subjects with transient mixed chimerism without CTS
• Proportion of recipients off immunosuppression for at least 12 Months	• Number and percentage of subjects off immunosuppression for at least 12 months
• Incidence of BPAR and treated BPAR (with Banff classification)	• Number and percentage of subjects experiencing BPAR • Number and percentage of subjects treated for BPAR (with Banff classification)
• Incidence of de novo DSA presentation	• Number and percentage of subjects with positive, semi-quantitative, DSA assay results
• Incidence of death and graft loss	• Number and percentage of subjects experiencing death and graft loss
• Incidence of chronic rejection	• Number and percentage of subjects with chronic rejection
• Renal function (eGFR) and change of eGFR over time	• eGFR and change in eGFR
• Incidence of AEs and SAEs	• Number and percentage of subjects with treatment-emergent AEs/SAEs by system organ class (SOC) and preferred term (PT)
• Incidence of severe and clinically significant opportunistic infections	• Number and percentage of subjects with clinically significant opportunistic infections.
• Incidence of BK viremia, infection, and nephropathy	• Number and percentage of subjects with BK viremia, infection, and nephropathy.
• Incidence of malignancies	• Number and percentage of subjects with malignancies.

• Incidence and severity of graft-versus-host disease (GvHD) • Incidence of new onset diabetes post-transplant (NODAT)	• Number and percentage of subjects with GvHD by severity • Number and percentage of subjects with NODAT
Exploratory	
• [redacted]	[redacted]
Study Design	TCD601A201 is a 60-month, adaptive, multi-center, 2-arm, safety, tolerability, and regimen finding study of siplizumab combined with NMA conditioning and donor BMCI for tolerance induction in living donor renal transplantation. The primary endpoint is assessed at 24 months and twice- yearly assessments thereafter (see Study Schema and Schedule of Assessments [Appendix 1]). This 2-arm design is amended from the 3-arm design employed in the original protocol. The rationale for this change is included in the full protocol.

The study will evaluate 2 siplizumab-based treatment regimens in a sequential manner with up to 18 recipients planned. Subjects in both arms will receive the same background conditioning and immunosuppression.

As shown below, Arm 1 subjects will receive 4 doses of siplizumab; Arm 2 subjects will receive 5 doses of siplizumab. In either arm, if CTS occurs, tocilizumab will be administered as treatment.

Dosing Regimens

Arm	Subjects (N)	Product	Dosing Regimen
Arm 1	12	Siplizumab	[redacted] mg/kg (Days [redacted], -1, 0, and 1)
		Tocilizumab	8 mg/kg IV if CTS occurs
Arm 2	6	Siplizumab	[redacted] mg/kg (Days [redacted], -1, 0, 1, and [redacted])
		Tocilizumab	8 mg/kg IV if CTS occurs

Abbreviations: CTS = chimeric transition syndrome; IV = intravenous; N = number of subjects.

Subjects will be enrolled using a modified 3+3 study methodology with the regimens investigated sequentially following a 'learning' and 'confirming' design. The first 3 subjects in each study arm will be enrolled one at a time. Acceptable safety and tolerability through Week 4 must be demonstrated before the next subject can be enrolled. After the first 3 subjects have been enrolled and completed assessments at Week 4, the remaining subjects in that arm will be enrolled simultaneously across centers to 'confirm' the initial response. If any subject in Arm 1 presents with severe CTS, the arm will be closed to further recruitment and the study will progress to Arm 2. A severe case of CTS in Arm 2 would constitute a stopping rule for further enrollment to that arm.

No formal interim analysis will be conducted. The decision to proceed to Arm 2 will be made in close contact with all Principal Investigators (PIs) and the Data Monitoring Committee (DMC) based on reports of AEs, SAEs, and clinical data captured in the clinical study database.

The study periods are shown below.

Study Periods	
Day -37 to Day -10	**Screening Period**
Day -9 to Day 12	**Conditioning Period**
Day 0 to Month 12 [a]	**Immunosuppression Period** [b]
Month 12 to Month 60	**Immunosuppression-Free Period**

a. As rituximab is administered on Day 12, the Conditioning Period and Immunosuppression Period overlap by 13 days (including day of transplant on Day 0).

b. Immunosuppression weaning Month 6 to Month 12.

During the screening period (from Day -37 to Day -10) and after informed consent has been obtained, baseline information will be obtained from the donor and recipient, including date of birth (month and year), age, sex, race, and ethnicity. In addition, relevant medical history, including current medical conditions, cause of end stage renal disease (ESRD), dialysis, and medication history for the recipient will be reviewed.

Pre-transplant screening procedures will include donor/recipient HLA typing (molecular), CDC lymphocyte crossmatch (or virtual crossmatch), qualitative DSA by single antigen bead (SAB) assay, and donor/recipient viral serology. Standard of

care procedures performed prior to consent may be considered in the determination of subject eligibility (e.g., HLA/ABO typing, specific laboratory results).

Refer to the Schedule of Assessments (Appendix 1) for a comprehensive list of all assessments and procedures performed during screening.

Subjects confirmed to meet all inclusion and none of the exclusion criteria, recipients, and their respective donors, will be enrolled in the study.

The study design overview is presented below.

Study Design Overview	
Day -9	Recipients will initiate pre-transplant conditioning with outpatient administration of rituximab (375 mg/m^2).
Day [redacted]	Administration of siplizumab ([redacted] mg/kg).
Day -5	Recipients will be admitted to the hospital and continue as an inpatient until discharge from the hospital post-transplant (discharge will vary based on the clinical status of the donor and recipient and will be determined at the discretion and judgment of the clinical team and Principal Investigator [PI]).
Days -5, -4	Administration of cyclophosphamide (60 mg/kg).
Day -2	Administration of rituximab (375 mg/m^2).
Day -1	Thymic irradiation (700 cGy). Administration of siplizumab ([redacted] mg/kg).
Day 0	Administration of siplizumab ([redacted] mg/kg) perioperatively. Concentration-controlled background immunosuppression will start with administration of tacrolimus (TAC; target trough concentration of 4–11 ng/mL) and mycophenolate mofetil (MMF; 2.0 g/day), perioperatively. Combined renal transplant and donor bone marrow cell infusion (BMCI) will be performed.
Day 0 to ~Day 4	On the day of transplant (Day 0) and post-operatively through approximately Day 4, intravenous (IV) corticosteroids will be administered based on dose and tolerability. Note: During the first week post-transplant, subjects will transition from IV to oral corticosteroids then taper until stopping at Day 20.
Day 1	Administration of siplizumab ([redacted] mg/kg).
Day 5	Administration of rituximab (375 mg/m^2).
Day [redacted]	Arm 2 only: Administration of siplizumab ([redacted] mg/kg).
Day 12	Administration of rituximab (375 mg/m^2).
Week 8	At Week 8 post-transplant, if MMF weaning criteria continue to be met, MMF will be discontinued.
Month 6	A biopsy will be conducted, and if the a priori defined immunosuppression weaning criteria are met, TAC dose reduction based on guidelines provided in the weaning schedule will begin.
Month 12	At Month 12 post-transplant, if the weaning criteria continue to be met (based on assessment of the scheduled Month 12 biopsy and allograft function), TAC will be withdrawn completely.

	<table><tr><th colspan="2">Study Design Overview</th></tr><tr><td>Month 12 to Month 24</td><td>Following the Month 12 visit, subjects will return for study visits on a quarterly basis through Month 24 for overall health and laboratory assessments and for evaluation of adverse events (AEs).</td></tr><tr><td>Month 24 to Month 60</td><td>Following completion of the Month 24 visit, subjects will enter a long-term follow-up period with study visits every 6 months until the final study visit at Month 60.</td></tr></table> Note: In addition to the procedures above, subjects will be administered broad infectious disease prophylaxis, as well as infusion premedication to minimize signs and symptoms of infusion/medication reactions. Details on conditioning and immunosuppression management, including associated premedication and infection prophylaxis are provided in the full protocol. During the conduct of this study ITB-MED and an independent DMC will review safety results of the study on an ongoing and periodic basis. Considering the open-label nature of this study, ITB-MED will also conduct a regular review of cumulative safety data, including a near real-time assessment of CTS, BPAR, graft losses, deaths, key safety endpoints, AEs, and SAEs. In the event any of the other predefined Stopping Rules outlined in the full protocol are met, enrollment will be suspended to allow for DMC review. If the DMC determines the benefit/risk is unacceptable, early termination of the arm or study will occur. Refer to the Schedule of Assessments (Appendix 1) for a complete listing and timing of study assessments and procedures.
Population	It is planned that up to 18 transplant recipients (and their respective donors) will be enrolled in the study.
Planned Study Sites	Study sites are planned within the United States.
Inclusion Criteria	Subjects who meet ALL the following inclusion criteria will be eligible to participate in the study: **Recipient Subjects:** 1. Recipients are able to understand the study requirements and provide written informed consent before any study assessment performed. 2. Male or female recipients aged 18–65 years. 3. Undergoing a renal transplant/retransplant. 4. Recipient of a renal transplant from an ABO compatible living donor who is at least human leukocyte antigen (HLA) haploidentical. 5. Capable of complying with the schedule of study visits, especially after discontinuation of immunosuppression. 6. Stable cardiopulmonary status per the judgement of the Investigator, with ejection fraction >40% within 3 months of transplant, and eligible for transplantation. 7. Epstein-Barr virus (EBV) seropositive during screening (Day -37 to Day -10). Seropositive results up to 12 months prior to Day -37 are acceptable.

	8. Recipient free from any other locally endemic infections that would be contraindications to solid organ or bone marrow transplant (BMT)/ hematopoietic stem cell transplantation (HSCT) according to applicable guidelines. 9. Male subjects must agree to maintain barrier contraception (condom) and further agree not to father a child for at least 4 months after the last dose of cyclophosphamide and 3 months after the last dose of MMF. 10. Women of childbearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, must agree to use highly effective methods of contraception during dosing and for at least 12 months after the last dose of cyclophosphamide. **Donor Subjects:** 1. Donors are able to understand the study requirements and provide written informed consent before any study assessments are performed. 2. Male or female donors aged 18–65 years. 3. Be in excellent health per conventional pre-donor history (medical, laboratory, and psychosocial evaluation). 4. Negative for hepatitis B surface antigen (HBsAg), human immunodeficiency virus (HIV), hepatitis C virus (HCV) ribonucleic acid (RNA), and human T-lymphotropic virus type 1 (HTLV-1) during screening (Day -37 to Day -10). 5. Negative for latent tuberculosis (TB) infection, as detected by QuantiFERON Gold Plus interferon-gamma release assay (IGRA; or current standard interferon-gamma release assay for TB) during screening (Day -37 to Day -10), unless treated per US Centers for Disease Control and Prevention (CDC), World Health Organization (WHO), and/or institutional guidelines within 6 months prior to Day -9. 6. Free from any other locally endemic infections that would be contraindications to solid organ or BMT/HSCT transplantation according to applicable guidelines.
Exclusion Criteria	Subjects who meet ANY of the following exclusion criteria will be excluded from participation in the study: **Recipient Subjects:** 1. Use of other investigational drugs (or enrollment in another investigational drug study) within 30 days of the start of screening (Day -37) or 5 half-lives of the medication, whichever is longer. 2. History of hypersensitivity to any of the study treatments or excipients or to drugs of similar chemical classes (e.g., MEDI-507 [siplizumab], tacrolimus, mycophenolate mofetil [MMF], cyclophosphamide, or rituximab). 3. Recipient with end stage renal disease (ESRD) due to primary focal segmental glomerulosclerosis (FSGS) or membranoproliferative glomerulonephritis (MPGN)/complement 3 (C3) glomerulopathy. 4. Recipient with anti-HLA donor-specific antibody (DSA) as measured by single antigen bead (e.g., Luminex) assay(s) during screening (Day -37 to Day -10). 5. Recipient with a positive donor crossmatch result (assayed according to local practice) during screening (Day -37 to Day -10).

	6. Recipient with >85% panel reactive antibodies (PRA) during screening (Day -37 to Day -10). Results up to 2 months prior to Day -37 are acceptable. 7. Subjects with leukopenia (white blood cell [WBC] count <2,000/mm^3) or thrombocytopenia (platelet count <75,000/mm^3) at baseline. 8. Seropositive for HIV-1, HBsAg, or HCV during screening (Day -37 to Day -10). Subjects who are seropositive for HCV are excluded without proof of sustained viral response (SVR) after anti-HCV treatment. Results within 6 months prior to screening (Day -37) are acceptable. 9. Subjects with latent TB infection as detected by QuantiFERON Gold Plus IGRA (or current standard interferon-gamma release assay for TB) during screening (Day -37 to Day -10), unless treated per US CDC, WHO, and/or institutional guidelines within 6 months prior to starting the conditioning regimen on Day -9. 10. Subjects with a history of cancer other than basal cell carcinoma of the skin or carcinoma in situ of the cervix. 11. Subjects with a clinically significant laboratory abnormality that would preclude participation in the study. For example, values >2.5 × upper limit of normal (ULN) for: - Liver function chemistries (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP]). - Bilirubin. - Coagulation studies (prothrombin time [PT]/International Normalized Ratio [INR], activated partial thromboplastin time [aPTT]). 12. Subjects who, in the opinion of the Investigator, are not capable of giving informed consent for the study or who are unable or unwilling to adhere to the study requirements outlined in the protocol. 13. Subjects with any other clinically significant medical condition or laboratory abnormality that would, in the judgment of the Investigator, interfere with the subject's ability to participate in the study. 14. Subjects who have received any live-attenuated vaccine within 1 month prior to starting the conditioning regimen on Day -9. 15. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.
Investigational Product	Siplizumab is a humanized IgG1κ class monoclonal antibody supplied in 6 mL vials containing 60 mg at a concentration of 10 mg/mL.

Conditioning Regimen

Conditioning Regimen		
Product/Treatment	**Dose**	**Study Day(s)**
Siplizumab (Arm 1)	[redacted] mg/kg	Days [redacted], -1, 0, and 1
Tocilizumab (Arm 1/2)	8 mg/kg	When required for CTS
Siplizumab (Arm 2)	[redacted] mg/kg	Days [redacted], -1, 0, 1, and [redacted]
Rituximab	375 mg/m^2	Days -9, -2, 5, and 12
Cyclophosphamide	60 mg/kg	Days -5 and -4
Thymic Irradiation	700 cGy	Day -1

Abbreviation: CTS = chimeric transition syndrome.

Background Immuno-suppression

Background Immunosuppression	
Product	**Dosing Regimen**
Tacrolimus	Target trough concentration 4–11 ng/mL
Corticosteroids	Intravenous (IV) bolus on the day of transplant (Day 0) and post-operatively through approximately Day 4; switch to oral during first week post-transplant, then taper until stopping at Day 20.
MMF	2.0 g per day

Abbreviation: MMF = mycophenolate mofetil.

Other Concomitant Treatments

- **Premedication prior to siplizumab infusions:**
  Methylprednisolone sodium succinate (8 mg/kg; first dose only), along with acetaminophen/paracetamol (650–1000 mg) and antihistamine (e.g., 25 mg diphenhydramine or 4 mg chlorpheniramine)
- **Premedication prior to rituximab infusions:**
  Acetaminophen/paracetamol (650–1000 mg), antihistamine (e.g., 25–50 mg diphenhydramine or 4 mg chlorpheniramine), and hydrocortisone sodium succinate (e.g., Solu-Cortef 100 mg)
- **Premedication prior to cyclophosphamide:**
  Pretreatment for nausea, vomiting, and prophylaxis for infusion reaction (e.g., a glucocorticoid, antihistamine, anxiolytic, and/or antiemetic) per local institutional standard; prophylaxis for hemorrhagic cystitis (i.e., MESNA)
- **Infection prophylaxis:**
  Prophylaxis for cytomegalovirus (CMV), human herpesvirus (HHV), *Pneumocystis jirovecii* pneumonia (PCP), hepatitis B (at discretion of the Investigator), fungal/yeast, and other infectious agents per local practice.

Safety Assessments

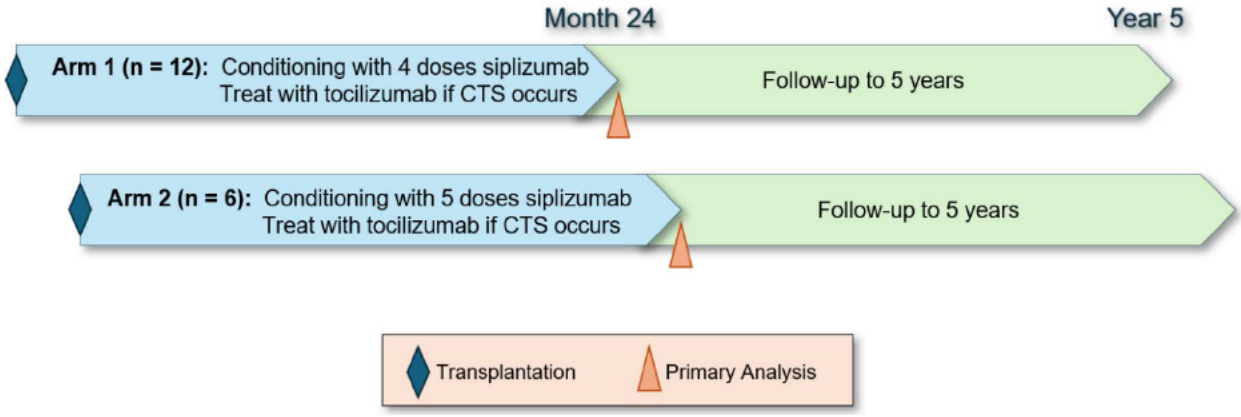
- AEs and SAEs
- Clinically significant changes in clinical chemistry, hematology, vital signs, and serology
- Renal function

Data Analysis

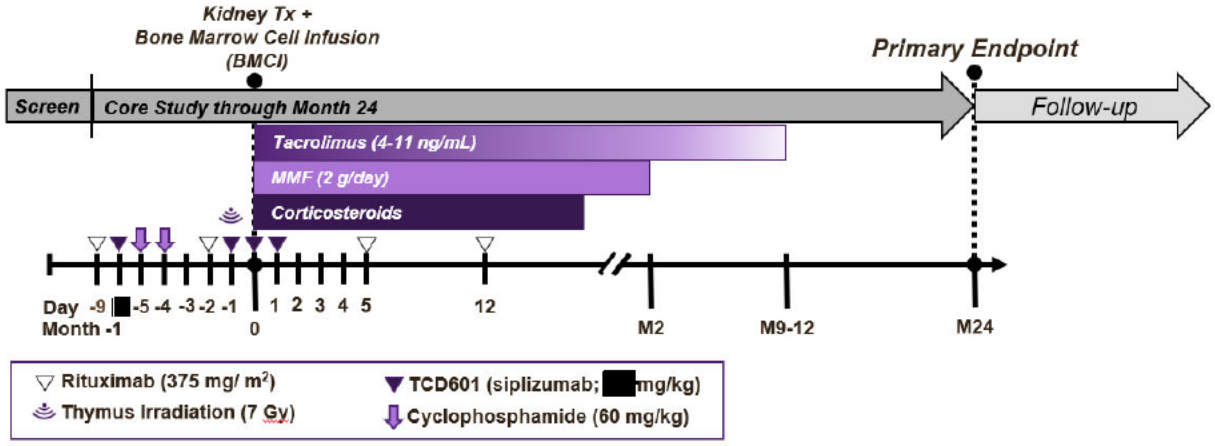
No formal statistical testing will be performed. AE/SAE data will be coded and displayed by System Organ Class (SOC) and Preferred Term (PT) with incidence. Laboratory data will be analyzed by visit with summary statistics and change from baseline.

Sample Size Determination	No formal sample size and power analysis has been performed. A sample size of 18 subjects (Arm 1 = 12; Arm 2 = 6) was chosen to characterize the incidence and severity of CTS in the immediate post-transplant time period while balancing the overall risk-benefit in a regimen finding study.
Study Duration	All subjects will participate in screening for up to 28 days prior to the start of conditioning. Post-screening, all transplant recipient subjects will be followed to Month 60; all donor subjects will be followed to Week 4.

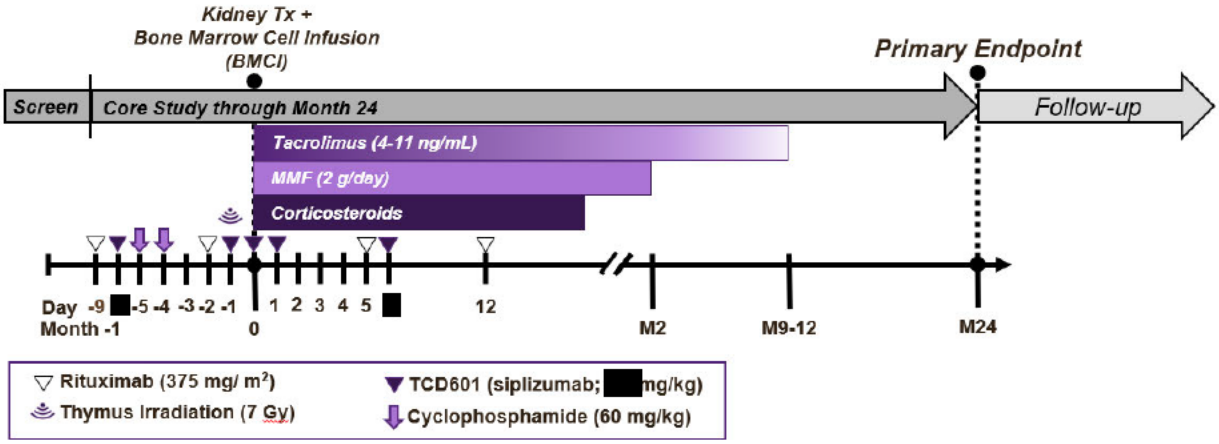
STUDY SCHEMA



Arm 1: Siplizumab (Days [redacted], -1, 0, and 1); Tocilizumab Treatment for CTS



Arm 2: Siplizumab (Days [redacted], -1, 0, 1, [redacted]); Tocilizumab Treatment for CTS



1. INTRODUCTION

1.1. Background

Since the first successful human kidney transplantation by Murray et al. in 1954 (Murray 1954) numerous immunosuppressive regimens have been developed for clinical application.
The ultimate goal of immunosuppression in kidney transplantation is to prevent acute rejection and maintain allograft function while balancing the risk of adverse effects (Tanriover 2015). Immunosuppressive agents are categorized as (1) induction therapy that is administered in the perioperative period and (2) maintenance therapy that transplant recipients require for lifelong use (KDIGO 2009). To maximize efficacy and minimize adverse effects, current immunosuppressive regimens are typically based on combinations of 2 or 3 immunosuppressive drugs with or without induction. Optimal combinations of therapies must be individualized based on the risk and benefit for each individual recipient (Bia 2010).

The contemporary standard of care (SoC) maintenance regimen is based on a calcineurin inhibitor (CNI), such as cyclosporine (CsA, Neoral) or tacrolimus (TAC, Prograf) which inhibits T-cell activation, in combination with a T-cell proliferation inhibitor. CNIs are generally considered the primary immunosuppressant or “corner stone” of the immunosuppressive regimen. Immunosuppressive drugs which are typically paired with CNIs include antiproliferative agents such as mycophenolic acid (MPA)-based drugs (mycophenolate mofetil [MMF], CellCept or Myfortic) which block inosine monophosphate dehydrogenase (IMPDH) or mechanistic target of rapamycin (mTOR) inhibitors such as sirolimus (rapamycin, Rapamune) or everolimus (Certican/Zortress). In addition to a CNI (e.g., TAC) and an antiproliferative agent (e.g., MMF), corticosteroids (CS) are usually started in the peri-transplant period and continued post-transplant in a triple therapy SoC regimen.

Calcineurin inhibitor-based SoC regimens have resulted in high 1-year patient and graft survival rates of 94.7% for deceased donor kidneys and 98.1% for living donor kidneys in the United States (US), with low (7–8%) 1-year acute rejection rates (Hart 2020). However, long-term graft and patient survival is still limited by mechanism-based side effects of currently available immunosuppressive drugs. Death with functioning graft occurs in 18% of living donor kidney recipients at 10 years post-transplant. The most common cause of mortality in renal transplant patients, accounting for 30–48% of post-transplant deaths is cardiovascular disease (Marcén 2009). Infections remain the second most common cause of post-transplant mortality (Alangaden 2006). Moreover, the risk of malignancies in transplant patients has been reported to be as high as 40% after 20 years of immunosuppressive therapy with the incidence of skin cancers (both non-melanoma and melanoma) reported at rates up to 30-fold higher, and leukemias 3-fold higher, compared to the general population (Rama 2010).

1.1.1. CD2 Biology

Human CD2 (also known as leukocyte function-associated antigen-2 [LFA-2]) is a monomeric transmembrane glycoprotein of 45–50 kDa. CD2 is expressed early during human thymocyte development and is found on about half of thymocytes, thymic B-cells, natural killer (NK) cells and almost all mature peripheral T-cells. CD2 functions as an intercellular adhesion molecule, binding to its ligand LFA-3 (CD58) in humans with high affinity. Human LFA-3 is a surface

glycoprotein that contains 2 extracellular immunoglobulin (Ig)-like domains and is expressed on B-cells and antigen-presenting cells (APCs); particularly macrophages.

The CD2-CD58 complex functions as an intercellular adhesion complex, forming a conjugate and supporting the development of an immune synapse or supramolecular activation cluster (SMAC). The formation of the SMAC gives the T-cell receptor (TCR) a longer interval to scan the various major histocompatibility complex (MHC) combinations presented by the APC, determine if a match has been made, and, if so, complete the intracellular signaling and co-stimulation necessary for T-cell activation (Seed 1987, Springer 1987, Davis 1996). The interaction of CD58 with CD2 has been found to be essential for the activation of cellular immunity, such as $CD8^+$ cytotoxic T-lymphocytes and NK cell-mediated cytotoxic reactions (Leitner 2015, Rölle 2016). In addition, CD2 is upregulated on both activated and memory T cells (Tmems) while CD58-ligation to CD2 activates NK and dendritic cells, lowers the threshold for T-cell activation and enhances T-cell responsiveness to pro-inflammatory cytokines such as interleukin (IL)-12 (Lo 2011). Furthermore, CD2-ligation of B-cell specific CD58 induces the upregulation of CD40 expression, suggesting that CD2 may also play a role in the stimulation and/or delivery of T-cell help to B-cells.

1.1.2. Siplizumab Mechanism of Action

Siplizumab (TCD601; previously known as MEDI-507) is a non-agonistic, humanized, anti-CD2 monoclonal antibody of the IgG1κ class. Siplizumab binds to a unique epitope on human CD2, distinct from the CD58 binding site, with high affinity (Kd = 5 nM), inhibiting co-stimulation and T-cell activation. In addition, the fragment crystallizable (Fc) portion of the siplizumab antibody binds to fragment crystallizable gamma receptors (FcγR) on NK cells resulting in antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP)-mediated depletion of CD2+ lymphocytes. Siplizumab also demonstrates selective immunomodulatory activity with depletion of Tmems (high CD2 expression) and sparing of regulatory T cells (Treg; low CD2 expression) in vitro and in vivo due to the differential expression of CD2. Considering this activity, siplizumab is expected to modulate T-cell memory and immune reactivity in the setting of transplantation. All these mechanisms of siplizumab are key contributors of tolerance induction.

For complete information on the mechanism of action (MoA) please refer to the current TCD601 Investigator's Brochure (IB).

1.2. Immunological Tolerance in Renal Transplantation

Immunological or allogeneic tolerance, defined as the absence of a destructive immune response to a transplanted tissue without ongoing immunosuppression (Sachs 2011), is one strategy that may improve the long-term results of organ transplantation; avoiding the morbidity associated with chronic immunosuppression and graft dysfunction.

In conventionally treated kidney transplant recipients, allogeneic tolerance is very rare. Massart and colleagues investigated the incidence of spontaneous operational tolerance in a large survey of 256 European transplant centers including 218,913 kidney recipients. Overall, 61 patients were found to be completely free of chronic immunosuppression giving a spontaneous frequency of only 0.028% (Massart 2016). Nevertheless, these patients demonstrated excellent long-term outcomes; superior to patients remaining on chronic immunosuppression. Dugast and colleagues

recently conducted a prospective, randomized, multicenter, double-blind, placebo-controlled study aimed at prospectively weaning calcineurin inhibitors in a stable renal transplant population to assess spontaneous allogeneic tolerance. Eligible patients were 4 years or greater post-transplant, low-immunological risk of rejection, and receiving SoC immunosuppression. Of the 1500 patients screened, 10 recipients of deceased donor kidneys were eligible for randomization (1:1) to remain on treatment or taper the CNI over 6 months. All 5 patients in the CNI tapering arm experienced either acute rejection or formation of anti-human leukocyte antigen (HLA) donor-specific antibodies (DSAs) and were returned to SoC (Dugast 2016).

Allogeneic tolerance in kidney transplant recipients who had previously undergone a full bone marrow transplant (BMT) from the same donor was first reported by Sayegh and colleagues (Sayegh 1991). Other clinicians have reported on similar successes with combined kidney and bone marrow transplantation (CKBMT) with long-term follow-up (Chen 2016). Patients with a concomitant hematological malignancy who have undergone CKBMT generally present with full chimerism and have no need for chronic immunosuppressive therapy. Presumably, if tolerance could be induced consistently across HLA barriers, chronic rejection could be eliminated. Similarly, the risks of cardiovascular disease, infection, malignancy, and other immunosuppressive related morbidity would be minimized (Massart 2016).

However, full allogeneic BMT requires myeloablative conditioning. In the absence of a hematological malignancy, the increased patient morbidity associated with fully myeloablative conditioning and risk of acute and chronic graft-versus-host disease (GvHD) following BMT is not acceptable in the setting of living donor renal transplantation. Hence, a regimen that facilitates the establishment of mixed chimerism, while balancing the risk to the recipient, is needed. Studies of non-myeloablative (NMA) conditioning regimens that use bone marrow-derived stem cells have resulted in the induction of allogeneic tolerance in a number of rodent models (Sharabi 1989, Sykes 2001) and miniature swine (Fuchimoto 2000); where stable mixed chimerism is essential for allograft survival. In nonhuman primates (NHPs), Kawai and colleagues demonstrated allogeneic tolerance in fully MHC mismatched cynomolgus monkeys (Kawai 1995, Kawai 1999, Kawai 2004). Murakami and colleagues further explored the induction of tolerance in NHPs noting that renal allograft tolerance can be induced with transient chimerism, in contrast to the results in mice where stable mixed-chimerism is required to induce skin allograft tolerance (Murakami 2009).

In patients, similar success with allogeneic tolerance has been demonstrated with a cyclophosphamide (CP)-based, reduced intensity conditioning (RIC) regimen combined with a simultaneous, donor-specific, allogeneic bone marrow transplant. Spitzer and Bühler first reported on the successful induction of transient mixed-chimerism and tolerance in patients with advanced multiple myeloma and renal failure through simultaneous bone marrow and renal transplantation from HLA-matched donors using a RIC regimen (Spitzer 1999, Bühler 2002). Busque and colleagues recently reported on tolerance induction in 29 HLA-matched kidney transplant patients who were given a donor cell infusion of highly enriched CD34+ progenitor cells mixed with CD3+ T-cells, following a conditioning regimen of total lymphoid irradiation (TLI) and post-transplant anti-thymocyte globulin (ATG). Patients with mixed chimerism for 6 months were completely withdrawn from immunosuppression. In the Busque study, 23 patients participating have been immunosuppression-free for up to 8 years without evidence of rejection (Busque 2019). However, when a similar regimen was investigated in 6 HLA-mismatched

patients, using increased radiation doses and total CD3/CD34+ cell infusion, only 2 patients achieved the per protocol criteria for immunosuppression withdrawal. These 2 patients rejected their allografts between 4–6 months after immunosuppression withdrawal and were later returned to maintenance immunosuppression (Scandling 2012).

Kawai and colleagues have reported on their experience using siplizumab as a component of an NMA conditioning regimen in 10 HLA-mismatched (haploidentical) renal transplant recipients. Patients were enrolled in 2 open-label, investigator-initiated trials; NKD03/ITN010ST (NCT00063817; n = 5) and ITN036ST (NCT00801632, n = 5). In these studies, a siplizumab and CP-based conditioning regimen facilitated the establishment of mixed chimerism following a bone marrow cell infusion (BMCI) at the time of kidney transplantation. In all patients, chimerism was transient without any signs of acute GvHD. Of the 10 patients, 7 were able to discontinue all immunosuppressive therapy for at least 5 years post-transplantation (Kawai 2014). Furthermore, mechanistic studies in 5 patients from study ITN036ST (NCT00801632) demonstrated enrichment of Tregs in the circulation and kidney without infiltrating cytotoxic T cells in renal biopsy specimens (Kawai 2008, Sprangers 2017). It was noted that in vivo, generated Tregs are donor-specific (Savage 2018, Podestà 2020) suggesting early tolerance is supported by expansion of donor-specific Tregs, whereas long-term operational tolerance relies on the central deletion of donor-reactive T cells. The 2 prior studies using this approach have achieved the objective of withdrawal of immunosuppression in 70% (7/10) of patients, however there were some avoidable cases of graft loss. In addition, several patients experienced a transient, early engraftment syndrome-like condition (Farris 2011) termed chimeric transition syndrome (CTS).

In a follow-up tolerance study (NCT01780454) in 2 subjects utilizing siplizumab with total body irradiation (TBI) in place of cyclophosphamide there was no CTS, however only 1 subject was ultimately able to discontinue immunosuppression.

Overall, there were no deaths reported during the 3 studies in 12 subjects or during long-term follow-up. Furthermore, in quality-of-life analysis, the subjects enrolled in the 2 initial tolerance studies presented with significantly better overall scores on many of the assessment domains as comparted to SoC controls (Madariaga 2016).

Achieving successful withdrawal of all immunosuppression without rejection would fulfill a significant unmet medical need in solid organ transplantation and presents a potential opportunity for better quality of life as well as longer-term graft and patient survival. Building on past experience, this study uses a sequential approach to investigating changes in the conditioning regimen and post-transplant care to identify and select an optimized allogeneic tolerance regimen in a limited number of subjects.

1.3. Study Purpose

The purpose of this study is to determine the optimal siplizumab regimen, in combination with non-myeloablative conditioning and donor bone marrow cell infusion with living donor renal transplantation, for allogeneic tolerance induction.

2. OBJECTIVES AND ENDPOINTS

Table 1: Objectives and Endpoints

Objective	Endpoint
Primary	
• To determine the optimal regimen for renal allograft tolerance (defined as proportion of recipients off immunosuppression with maintenance of good renal function at Month 24 post-transplant) while minimizing chimeric transition syndrome	• Number and percentage of subjects achieving renal allograft tolerance at Month 24 post-transplant as assessed by: o Immunosuppression dosing o Serum creatinine (estimated glomerular filtration rate [eGFR]) o Incidents of Chimeric Transition Syndrome (CTS) and biopsy proven acute rejection (BPAR) o Renal biopsy
Key Secondary	
• To determine the composite incidence of BPAR, death and graft loss (with and without lost to follow-up) at Month 24 post-transplant	• Number and percentage of subjects experiencing BPAR, death, and graft loss (with and without lost to follow-up) at Month 24 post-transplant.
• To determine the incidence and mean fluorescence intensity (MFI) of donor-specific antibody (DSA) at Month 24 post-transplant	• Number and percentage of subjects of DSA positivity at Month 24 post-transplant. • MFI of DSA at Month 24 post-transplant.
Secondary	
• Incidence, duration, severity of CTS	• Number and percentage of subjects experiencing CTS by severity • Time from onset of CTS to resolution
• Proportion of recipients with transient mixed chimerism without CTS	• Number and percentage of subjects with transient mixed chimerism without CTS
• Proportion of recipients off immunosuppression for at least 12 Months	• Number and percentage of subjects off immunosuppression for at least 12 months
• Incidence of BPAR and treated BPAR (with Banff classification)	• Number and percentage of subjects experiencing BPAR • Number and percentage of subjects treated for BPAR (with Banff classification)
• Incidence of de novo DSA presentation	• Number and percentage of subjects with positive, semi-quantitative, DSA assay results
• Incidence of death and graft loss	• Number and percentage of subjects experiencing death and graft loss
• Incidence of chronic rejection	• Number and percentage of subjects with chronic rejection

Objective	Endpoint
• Renal function (eGFR) and change of eGFR over time	• eGFR and change in eGFR
• Incidence of AEs and SAEs	• Number and percentage of subjects with treatment-emergent AEs/SAEs by system organ class (SOC) and preferred term (PT)
• Incidence of severe and clinically significant opportunistic infections	• Number and percentage of subjects with clinically significant opportunistic infections.
• Incidence of BK viremia, infection, and nephropathy	• Number and percentage of subjects with BK viremia, infection, and nephropathy.
• Incidence of malignancies	• Number and percentage of subjects with malignancies.
• Incidence and severity of graft-versus-host disease (GvHD)	• Number and percentage of subjects with GvHD by severity
• Incidence of new onset diabetes post-transplant (NODAT)	• Number and percentage of subjects with NODAT
Exploratory	
• [redacted]	[redacted]

3. STUDY DESIGN

TCD601A201 is a 60-month, adaptive, multi-center, 2-arm, safety, tolerability, and regimen finding study of siplizumab combined with NMA conditioning and donor BMCI for tolerance induction in living donor renal transplantation. The primary endpoint is assessed at 24 months and twice-yearly assessments thereafter (see Study Schema and Schedule of Assessments [Appendix 1]).

This 2-arm design is amended from the 3-arm design employed in the original protocol. The rationale for this change is provided in Section 4.1.

The study will evaluate 2 siplizumab-based treatment regimens in a sequential manner with up to 18 recipients planned. Subjects in both arms will receive the same background conditioning and immunosuppression.

Arm 1 subjects will receive 4 doses of siplizumab; Arm 2 subjects will receive 5 doses of siplizumab. In either arm, if CTS occurs, tocilizumab will be administered as treatment (Table 2).

Table 2: Dosing Regimens

Arm	Subjects (N)	Product	Dosing Regimen
Arm 1	12	Siplizumab	[redacted] mg/kg (Days [redacted], -1, 0, and 1)
		Tocilizumab	8 mg/kg IV if CTS occurs
Arm 2	6	Siplizumab	[redacted] mg/kg (Days [redacted], -1, 0, 1, and [redacted])
		Tocilizumab	8 mg/kg IV if CTS occurs

Abbreviations: CTS = chimeric transition syndrome; IV = intravenous; N = number of subjects.

Subjects will be enrolled using a modified 3+3 study methodology with the regimens investigated sequentially following a 'learning' and 'confirming' design. The first 3 subjects in each study arm will be enrolled one at a time. Acceptable safety and tolerability through Week 4 must be demonstrated before the next subject can be enrolled. After the first 3 subjects have been enrolled and completed assessments at Week 4, the remaining subjects in that arm will be enrolled simultaneously across centers to 'confirm' the initial response. If any subject in Arm 1 presents with severe CTS, the arm will be closed to further recruitment and the study will progress to Arm 2. A severe case of CTS in Arm 2 would constitute a stopping rule for further enrollment to that arm (see Section 9.1.2).

No formal interim analysis will be conducted. The decision to proceed to Arm 2 will be made in close contact with all Principal Investigators (PIs) and the DMC (see Section 11) based on reports of AEs, SAEs, and clinical data captured in the clinical study database.

The study periods are shown below in Table 3.

Table 3: Study Periods

Study Periods	
Day -37 to Day -10	**Screening Period**
Day -9 to Day 12	**Conditioning Period**
Day 0 to Month 12 [a]	**Immunosuppression Period** [b]
Month 12 to Month 60	**Immunosuppression-Free Period**

a. As rituximab is administered on Day 12, the Conditioning Period and Immunosuppression Period overlap by 13 days (including day of transplant on Day 0).
b. Immunosuppression weaning Month 6 to Month 12.

During the screening period (from Day -37 to Day -10) and after informed consent has been obtained, baseline information will be obtained from the donor and recipient, including date of birth (month and year), age, sex, race, and ethnicity. In addition, relevant medical history, including current medical conditions, cause of end stage renal disease (ESRD), dialysis, and medication history for the recipient will be reviewed.

Pre-transplant screening procedures will include donor/recipient HLA typing (molecular), CDC lymphocyte crossmatch (or virtual crossmatch), qualitative DSA by single antigen bead (SAB) assay, and donor/recipient viral serology. Standard of care procedures performed prior to consent may be considered in the determination of subject eligibility (e.g., HLA/ABO typing, specific laboratory results).

Refer to the Schedule of Assessments (Appendix 1) for a comprehensive list of all assessments and procedures performed during screening.

Subjects confirmed to meet all inclusion and none of the exclusion criteria, recipients, and their respective donors, will be enrolled in the study.

The study design overview is presented in Table 4 below.

Table 4: Study Design Overview

Study Design Overview	
Day -9	Recipients will initiate pre-transplant conditioning with outpatient administration of rituximab (375 mg/m^2).
Day [redacted]	Administration of siplizumab ([redacted] mg/kg).
Day -5	Recipients will be admitted to the hospital and continue as an inpatient until discharge from the hospital post-transplant (discharge will vary based on the clinical status of the donor and recipient and will be determined at the discretion and judgment of the clinical team and Principal Investigator [PI]).
Days -5, -4	Administration of cyclophosphamide (60 mg/kg).
Day -2	Administration of rituximab (375 mg/m^2).
Day -1	Thymic irradiation (700 cGy). Administration of siplizumab ([redacted] mg/kg).

Study Design Overview	
Day 0	Administration of siplizumab ([redacted] mg/kg) perioperatively. Concentration-controlled background immunosuppression will start with administration of tacrolimus (TAC; target trough concentration of 4–11 ng/mL) and mycophenolate mofetil (MMF; 2.0 g/day), perioperatively. Combined renal transplant and donor bone marrow cell infusion (BMCI) will be performed.
Day 0 to ~Day 4	On the day of transplant (Day 0) and post-operatively through approximately Day 4, intravenous (IV) corticosteroids will be administered based on dose and tolerability. Note: During the first week post-transplant, subjects will transition from IV to oral corticosteroids then taper until stopping at Day 20.
Day 1	Administration of siplizumab ([redacted] mg/kg).
Day 5	Administration of rituximab (375 mg/m^2).
Day [redacted]	Arm 2 only: Administration of siplizumab ([redacted] mg/kg).
Day 12	Administration of rituximab (375 mg/m^2).
Week 8	At Week 8 post-transplant, if the weaning criteria in Table 7 continue to be met, MMF will be discontinued.
Month 6	A biopsy will be conducted, and if the a priori defined immunosuppression weaning criteria are met, TAC dose reduction based on guidelines provided in the weaning schedule will begin (Table 9).
Month 12	At Month 12 post-transplant, if the weaning criteria continue to be met (based on assessment of the scheduled Month 12 biopsy and allograft function), TAC will be withdrawn completely.
Month 12 to Month 24	Following the Month 12 visit, subjects will return for study visits on a quarterly basis through Month 24 for overall health and laboratory assessments and for evaluation of adverse events (AEs).
Month 24 to Month 60	Following completion of the Month 24 visit, subjects will enter a long-term follow-up period with study visits every 6 months until the final study visit at Month 60.

Note: In addition to the procedures above, subjects will be administered broad infectious disease prophylaxis, as well as infusion premedication to minimize signs and symptoms of infusion/medication reactions.

Full details on conditioning and immunosuppression management, including associated premedication and infection prophylaxis are provided in Section 6.

During the conduct of this study ITB-MED and an independent DMC will review safety results of the study on an ongoing and periodic basis. Considering the open-label nature of this study, ITB-MED will also conduct a regular review of cumulative safety data, including a near real-time assessment of CTS, BPAR, graft losses, deaths, key safety endpoints, AEs, and SAEs. In the event any of the other predefined Stopping Rules outlined in Section 9.1.2 are met, enrollment will be suspended to allow for DMC review. If the DMC determines the benefit/risk is unacceptable, early termination of the arm or study will occur.

Refer to the Schedule of Assessments (Appendix 1) for a complete listing and timing of study assessments and procedures.

4. STUDY DESIGN RATIONALE

The purpose of the TCD601A201 study is to investigate the hypothesis that an extension of the transient chimerism induced with a siplizumab-based conditioning regimen and combined renal transplant and BMCI will mitigate CTS while facilitating long term immunosuppression withdrawal. This protocol was designed in close collaboration with the clinicians and renal pathologist who developed and conducted the initial trials utilizing siplizumab-based conditioning in the setting of living donor renal transplantation (See Section 1.2).

Within each study arm, this protocol introduces key changes in the peri-transplant conditioning designed to treat and mitigate CTS while facilitating immunosuppression withdrawal.

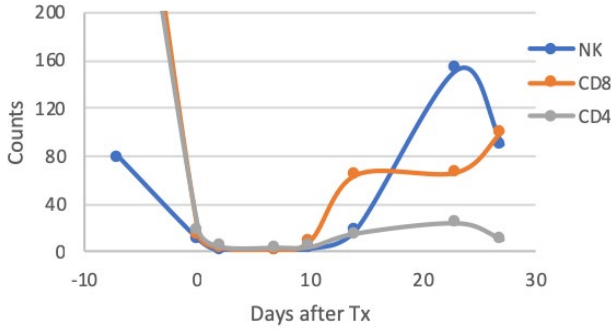
4.1. Dose/Regimen and Treatment Duration Rationale

Building on the final conditioning regimen in the ITN036ST protocol discussed in Section 1.2, the [redacted] mg/kg Day [redacted] dose of siplizumab has been moved earlier to Day [redacted] (prior to transplant) and the dose increased to [redacted] mg/kg. Each of the 4 siplizumab doses (and a fifth dose in Arm 2) are now equal (at [redacted] mg/kg) in this study. This earlier increased dose is intended to induce immunomodulation and lymphodepletion earlier (prior to transplant), akin to TBI, with the objective of mitigating CTS. In addition, the activity of siplizumab administered on study Day [redacted] in hematopoietic stem cell transplantation (HSCT) patients was associated with increased donor chimerism in the setting of host T cell depletion (Spitzer 2003). The adjustment of the initial rituximab administration from Day -7 to Day -9 was made for consistency with the labeling and a minimum 7-day inter-dose interval. Otherwise, the remaining conditioning is consistent with the ITN036ST protocol.

The NCT01780454 pilot study (n = 2) also discussed in Section 1.2 utilized TBI and appeared promising in preventing CTS. However, the outcomes did not suggest that TBI could substitute for cyclophosphamide in the conditioning regimen.

Post-transplant mycophenolic acid (2.0 g/day in divided doses) for the first 8 weeks has been added to the conditioning regimen to further mitigate CTS. This hypothesis is based on the recovery of host lymphocytes, especially CD8+ T cells and NK cells around the time of CTS onset and loss of donor chimerism in the ITN036ST study (Figure 1). Innate immunity, specifically NK-cell activity may be associated with CTS pathology and is supported by the observation that CD8 cells are specifically activated, as judged by CD25 upregulation, in the first week post-transplant (Farris 2011).

Figure 1: Study ITN036ST Pooled Host Lymphocyte Recovery (Mean; N = 5)



Furthermore, Ohata and colleagues have reported that a combination of MMF and a CNI effectively suppress NK cell function (87 ±18%), in contrast to 31 ±19% by CNI alone, or 14 ±6% by MMF alone (Ohata 2011). It is therefore theorized, that the addition of immunosuppression with a CNI- and MPA-based regimen can synergistically suppress NK function and moderate or eliminate CTS. In addition, MMF is known to suppress B cell activation and proliferation, so it is possible that the addition of MPA will also mitigate DSA formation and antibody-mediated rejection (Lederer 2005). In addition, in vivo and in vitro data show that anti-CD2 therapy with siplizumab can effectively deplete CD2+ NK (LoCascio 2010) cells while sparing $CD2^{LOW}$ regulatory T cells (Podestà 2020), further supporting the establishment of allogeneic tolerance and potentially mitigating the onset and severity of CTS. Moreover, NK cells recovering initially in siplizumab-treated patients demonstrated a lack of cytotoxic activity and an absence of surface CD2 expression (Koenecke 2003)

While the addition of increased peri-transplant siplizumab exposure and MMF is anticipated to mitigate CTS, tocilizumab, an anti-IL-6 monoclonal antibody (mAb), may be administered therapeutically to treat CTS. In Arm 2, an additional dose of siplizumab on Day 6 post-transplant will be administered. It is expected that by administering this additional dose of siplizumab, both donor and recipient T cell activity will be further suppressed and reactive cells will be depleted; prolonging chimerism similar to early NHP models described by Kawai and colleagues. In these primate models, loss of chimerism occurred over a 2 to 3 month period without CTS (Kawai 1995).

4.2. Purpose and Timing of Analyses

The primary analysis will be conducted after all enrolled subjects have completed the study to 24 months or discontinued from the study, having met one of the safety or stopping endpoints. If subjects are weaned from immunosuppression after post-transplant Month 12 then the analysis may be adjusted to allow for inclusion of data from subjects with at least 12 months off immunosuppression. The approach and precise timing of the primary analysis will be defined in the Statistical Analysis Plan (SAP).

4.3. Risks and Benefits

The below sections list the possible benefits and risks related to treatment with this regimen, including siplizumab. For further details please refer to Section 7 of the current IB.

4.3.1. Benefits

Combined renal transplantation with BMCI from the same donor, using non-myeloablative conditioning, may allow for the establishment of allogenic tolerance and facilitate the withdrawal of chronic immunosuppression.

Potential benefits to subjects participating in this study may include freedom from dialysis without the morbidity associated with long -term immunosuppressive therapy. These morbidities include increased risk of cataracts, osteoporosis, opportunistic infections, (NODAT, atherosclerosis, hypertension, malignancies, peripheral neuropathies/central neurological disorders, serious cardiovascular events, chronic allograft rejection, and death. There is no benefit to the donor.

4.3.2. Risks

Participation in this study is associated with certain risks for both the recipient and the donor. These risks are summarized below.

4.3.2.1. Conditioning Regimen Risks to the Recipient:

The safety and tolerability of the approved immunosuppressive components of the conditioning regimens have been characterized in the setting of different studies and patient populations, with doses and exposures that differ from those planned in this study. Therefore, the identified risks for the other components of the treatment regimen reflect the approved labeling.

4.3.2.1.1. Siplizumab Risks

Based on the clinical experience to date, risks of siplizumab administration include those generally associated with administration of a monoclonal antibody in humans. These include the possibility of a hypersensitivity reaction characterized by acute or delayed allergic reaction, anaphylaxis, urticaria, rash, dyspnea, hypotension, fever, chills, and immunogenicity.

The most common clinical symptoms reported are chills, headache, myalgia, changes in hematological parameters, including decreased lymphocyte count, and changes in vital signs. These events were generally transient, temporally associated with dosing, and resolved without sequelae or need for therapy. See Table 5 below for identified and potential risks of siplizumab.

Table 5: Identified and Potential Risks of Siplizumab

Identified Risks of Siplizumab May Include:	
Infusion Reactions	Infusion-related reactions (e.g., chills, pyrexia, fatigue) have been commonly seen in siplizumab-treated subjects with cancer, GvHD, psoriasis, and following organ transplantation. Events have been mild to moderate in severity, transient in nature, and have not recurred with re-challenge. Other associated events included nausea, vomiting, and hypotension.
Infections	T-cell depleting antibodies, such as siplizumab, may be immunosuppressive and prolonged immunosuppression may increase the risk of infection, including opportunistic infections. Administration of multiple siplizumab doses is expected to result in general immunosuppression due to T- and NK-cell depletion when full receptor occupancy has been achieved. Siplizumab-treated subjects may present with an increase in the overall degree of immunosuppression from days to weeks depending on the dose and regimen and during this time may be at a higher risk for infection. In completed clinical trials with siplizumab there was no clear evidence for a higher rate of infections associated with treatment administration. Infections were common in a siplizumab study in post-hematopoietic stem cell transplantation (HSCT) patients with Grade II–IV acute graft-versus-host disease (aGvHD), where increased risk of immunosuppression related opportunistic infections, including viral reactivation, is common. In a study conducted in subjects with CD2+ T-cell lymphoma, there was no dose-related increase in infection rates between arms, although there was an increase in Epstein-Barr virus (EBV)-related events. EBV-associated lymphoproliferative disease (EBV-LPD) was reported in 9 patients treated across the T-cell lymphoma and aGvHD populations; see Lymphoproliferative Disorders and other Malignancies. Vaccination of human subjects during treatment with siplizumab and prior to clearance of the antibody is likely to result in therapeutic failure (i.e., non-protective antibody titers). No studies on the combination with, or effectiveness of, vaccination during siplizumab therapy have been conducted.
Potential Risks of Siplizumab May Include:	
Chimeric Transition Syndrome (Renal Dysfunction)	A transient, acute kidney injury (AKI)-like syndrome was reported in a majority (9/10) of recipients early in the post-transplant course of prior allogenic renal tolerance trials with siplizumab (Kawai 2014). The syndrome was associated with recovery of host hematopoietic cells and rapid loss of donor chimerism at ~2 weeks post-transplant and is now described as chimeric transition syndrome (CTS; Farris 2011). Subjects in these trials received siplizumab ([redacted] mg/kg on Day -2, and [redacted] mg/kg on Days -1, 0, 1) in combination with a non-myeloablative, cyclophosphamide-based conditioning regimen including thymic irradiation. In the majority of subjects, rituximab was also administered. All subjects received a combined haploidentical bone marrow cell infusion to induce transient chimerism and a renal allograft from the same donor on Day 0. Those with CTS presented with an increase in serum creatinine (sCr) with onset around post-transplant Days 10–14 that peaked (range 3.5–15.4 mg/dL) between Days 10–20; resolving by Day 30. Renal biopsies taken during the CTS event were negative for T-cell mediated rejection (TCMR) but showed capillary endothelial injury with cellular infiltrates ($CD8^+/CD68^+$ cells) in the peritubular and glomerular capillaries. In subjects with CTS, 78% (7/9) recovered renal function between 2–3 weeks post event onset. Three subjects recovered spontaneously with minimal intervention (corticosteroid pulse) while 4 subjects received treatment with intravenous immunoglobulin (IVIG), anti-thymocyte globulin (ATG), and/or plasma exchange. The remaining 2 subjects failed to recover full renal function; including 1 who lost their graft at Day 10 due to antibody mediated rejection (AMR). The AMR was subsequently considered an avoidable loss due to pre-transplant work-up failure as the subject was pre-sensitized (retrospective analysis). The second graft loss was in a subject who presented with CNI toxicity subsequent to CTS and later progressed to graft loss associated with thrombotic microangiopathy (TMA) at Month 7. Since the effect of replacing ATG with siplizumab in the Lee et al (Lee 2020) regimen and has not been fully characterized, CTS remains a potential risk.

Potential Risks of Siplizumab May Include:	
Cytokine Release Syndrome	Cytokine release syndrome (CRS) is an acute clinical syndrome and has been temporally associated with the administration of certain T-cell depleting antibodies, particularly the murine anti-CD3 antibody, muromonab-CD3 (Orthoclone-OKT3). Similar effects are noted with B-cell depleting antibodies such as rituximab (Rituxan). This syndrome has been attributed to the release of cytokines by activated lymphocytes or monocytes. No severe CRS events have been reported in any subjects receiving siplizumab alone or in combination with other immunosuppressants to date. Siplizumab is a non-activating humanized monoclonal antibody (mAb) that binds to CD2+ immune cells and rapidly eliminates them via antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). As a result, any CRS events would not be related to direct T cell activation but rather to depletion of CD2-expressing cells. Across all patients that have received siplizumab, self-limiting infusion reactions have been observed, including fever and chills, which although not meeting the full presentation of CRS could be associated with a milder release of cytokines during ADCC and ADCP.
Inflammatory Reactions	Allergic reactions may present as mild pruritic rashes or they may be severe such as erythroderma, Stevens-Johnson syndrome, vasculitis, delayed hypersensitivity, or anaphylaxis. Anaphylactic reactions (anaphylaxis) are serious and occasionally fatal hypersensitivity reactions. Allergic reactions including anaphylaxis may occur when any foreign protein is injected into the body. They may range from mild manifestations such as urticaria or rash to lethal systemic reactions. Anaphylactic reactions occur soon after exposure, usually within 10 minutes. Subjects may experience paresthesia, hypotension, laryngeal edema, mental status changes, facial or pharyngeal angioedema, airway obstruction, bronchospasm, urticaria and pruritus, serum sickness, arthritis, allergic nephritis, glomerulonephritis, temporal arteritis, or eosinophilia.
Lymphoproliferative Disorders and other Malignancies	Prolonged and sustained immunosuppression post renal transplantation may result in an increased risk of developing certain types of cancer. In patients at a high risk of lymphoproliferative disorders participating in studies with siplizumab, specifically patients with CD2+ T-cell lymphoma or aGvHD following a bone marrow transplant (BMT), EBV-LPD, post-transplant lymphoproliferative disease (PTLD), and lymphoma have been reported. The rate of EBV-LPD is known to be higher in patients who are EBV-seronegative with a relative risk up to 33-fold that of EBV+ recipients (Marks 2011). Therefore, all recipients will be screened prior to administration of siplizumab, and EBV-seronegative subjects excluded from participating in the TCD601A201 clinical study. In the studies of renal transplant patients, one patient experienced a basal cell carcinoma of the skin on an area of actinic exposure reported during long-term follow-up. Two patients in psoriasis studies had secondary malignancies (squamous cell carcinoma of the skin and myelodysplastic syndrome) following treatment with siplizumab. Both patients had a prior history of these respective conditions and were entered into a siplizumab psoriasis study in violation of protocol entry criteria that excluded patients with a history of cancer (although in the latter case the condition was not disclosed at study enrollment).

4.3.2.1.2. Cyclophosphamide Risks

Cyclophosphamide may cause bone marrow suppression, immune suppression, nausea, vomiting, hemorrhagic cystitis, anaphylactic reactions, and hair loss. Malignancies have developed in some subjects treated with cyclophosphamide used alone or in association with other antineoplastic drugs and/or modalities. Cardiotoxicities, including myocarditis, myopericarditis, pericardial effusion with cardiac tamponade, and congestive heart failure, which may be fatal, have been reported with cyclophosphamide therapy. A small fraction of subjects may have prolonged bladder injury and bleeding.

Malignancies have developed in some subjects treated with cyclophosphamide alone or in association with other antineoplastic drugs or treatments. In non-clinical testing, cyclophosphamide was mutagenic and clastogenic in vivo and in vitro and was genotoxic in male and female germ cells. Cyclophosphamide may also result in sterility, cause genetic damage to future offspring, or interfere in normal wound healing. Due to the risk of genetic damage, all women of childbearing potential (WOCBP) will have a pregnancy test before starting the treatment. Furthermore, WOCBP should use highly effective contraception during and for up to 1 year after completion of cyclophosphamide treatment. Male subjects who are sexually active with female partners who are or may become pregnant should use a condom during and for at least 120 days (4 months) after treatment.

Cyclophosphamide administration results in prolonged, irreversible, inhibition of plasma cholinesterase activity and may potentiate the effects of succinylcholine. Reductions in cholinesterase activity of 35–70% have been reported, resulting in decreased metabolism of some neuromuscular blockers. The anesthesiologist should be alerted that the subject has been treated with cyclophosphamide prior to the transplant.

Please refer to the approved labeling for further details.

4.3.2.1.3. Rituximab Risks

The anti-CD20 receptor monoclonal antibody rituximab is approved for the treatment of B-cell malignancies and autoimmune conditions. The most common adverse events (AEs) reported in clinical trials with rituximab (non-Hodgkin lymphoma patients) included infusion reactions, fever, lymphopenia, chills, infection, and asthenia. In patients with rheumatoid arthritis (RA) the most frequent AEs were hypertension, nausea, upper respiratory tract infection, arthralgia, pruritus, and pyrexia. Other important adverse reactions include infusion reactions, serious infections, and cardiovascular events.

Serious adverse events (SAEs) associated with use of rituximab are tumor lysis syndrome (in lymphoma patients), severe mucocutaneous reactions, progressive multifocal leukoencephalopathy (PML), hepatitis B reactivation with fulminant hepatitis, cardiac arrhythmias and angina, and bowel obstruction and perforation.

Please refer to the approved labeling for further details. It is important to note that most of the SAEs were related to tumor lysis in the treatment of cancer patients and are therefore not expected to be relevant to the renal transplant patient population.

4.3.2.1.4. Tocilizumab Risks

The anti-IL-6 receptor monoclonal antibody tocilizumab is approved for treatment of chimeric antigen receptor T-cell therapy-induced cytokine release syndrome (CRS), as well as for several autoimmune indications. In the pooled analysis of patients treated for CRS, no adverse reactions to tocilizumab were reported.

In the broader patient experience of more chronic administration in autoimmune diseases (rheumatoid arthritis, giant cell arteritis, polyarticular juvenile idiopathic arthritis, and systemic juvenile arthritis) serious infections were reported including tuberculosis, fungal infections, bacterial infections, and viral infections.

Please refer to the approved labeling for further details.

4.3.2.1.5. Thymic Irradiation Risks

Irradiation of the thymus gland may cause nausea, vomiting, mild skin irritation, and inflammation of the esophagus (causing mild, temporary dysphagia). Occasionally pericarditis or pneumonitis may occur. Hypothyroidism and secondary malignancies are additional theoretical risks.

4.3.2.1.6. Bone Marrow Cell Infusion Risks

Acute and/or chronic GvHD are common complications of allogeneic bone marrow/stem cell transplantation usually performed in the setting of hematological malignancy. In those settings the risk of aGvHD (30–90%) or chronic GvHD (30–50%) depend on the degree of HLA mismatch and subject age. However, the risk of GvHD in the patients receiving combined BMCI and renal transplantation, following the non-myeloablative regimens used in the prior studies (Kawai 2014, Lee 2020), appear to be lower than reported for conventional BMT/HSCT, although the sample size remains limited.

4.3.2.2. Renal Transplant Immunosuppression Risks

Please refer to the approved labeling information for summaries of risks for the immunosuppressive drugs.

4.3.2.2.1. Tacrolimus

Side effects include renal insufficiency, abnormal liver function studies, seizures, nausea, vomiting, confusion, hypomagnesemia, tremulousness, and increased risk of secondary malignancies. Co-administration with methylprednisolone will decrease hepatic metabolism and thus increase TAC plasma concentrations; convulsions have been reported with concomitant high doses of methylprednisolone. Please refer to the approved labeling for further details.

4.3.2.2.2. Mycophenolate Mofetil

Side effects include bone marrow suppression (thrombocytopenia, leukopenia, neutropenia, pure red cell aplasia), gastrointestinal (GI) symptoms (constipation, nausea, diarrhea, vomiting and abdominal pain, GI bleeding), hypertension, and peripheral edema. Please refer to the approved labeling for further details.

4.3.2.2.3. Corticosteroids

Side effects include convulsions, headache, vertigo, mood swings, psychosis, congestive heart failure (CHF), hypertension, Cushing's syndrome, menstrual irregularities, hyperglycemia, GI irritation, peptic ulcer, and weight gain. Dermatologic effects may include thin skin, petechiae, ecchymoses, facial erythema, poor wound healing, hirsutism, and urticaria. Muscle weakness, loss of muscle mass, and osteoporosis may also occur. Ophthalmologic complications may include increased intraocular pressure, glaucoma, exophthalmos, and cataracts. Other complications may include immunosuppression and increased susceptibility to infection.

4.3.2.3. Procedural Risks

4.3.2.3.1. Renal Biopsies

A wedge or needle biopsy is to be performed on the explanted allograft prior to transplant, with post-transplant percutaneous biopsies performed at Month 6, Month 12, and at any time for cause. Complications of renal biopsy include hemorrhage, renal infarction, infection, retention cysts, urinary fistula, and hydronephrosis.

Biopsies will only be performed in subjects with platelet counts >50,000 mL. The most frequent complication of temporary, self-limited, bleeding occurs in approximately 2% of allograft recipients. In the case of a rare but significant bleeding event resulting from the renal biopsy, transfusion with packed red blood cells may or may not become medically necessary.

4.3.2.3.2. Hemodialysis

Hemodialysis is performed 3 times in this study (Day -6, Day -5, Day -4) to mitigate against the cumulative risks of cyclophosphamide toxicity. The risks of dialysis include low blood pressure (hypotension), high blood pressure (hypertension), fluid overload, high potassium levels (hyperkalemia), inflammation of the membrane surrounding the heart (pericarditis), muscle cramps, itching, sleep problems, anemia, bone diseases, access site complications, amyloidosis, and depression.

4.3.2.4. Risks to the Donor

4.3.2.4.1. Bone Marrow Donation

Risks of bone marrow donation are related to either the administration of anesthesia or the operative procedure itself.

Risks of anesthesia include, but are not limited to, post-operative nausea, vomiting, fatigue, and rare life- threatening allergic reactions or hemodynamic instability. Most donors experience post-operative discomfort at the sites of bone marrow procurement. On average, the soreness and bruising last for approximately 2–3 weeks. A small percentage of donors (less than 10%) experience prolonged (weeks or months) pain or sciatic-type pain, likely as the result of inflammation of the nerve roots from local bleeding or edema. Rare complications of bone marrow procurement include local infection (including reports of osteomyelitis), pelvic fracture, phlegmon formation, pancreatitis, ileus, and fat embolism. Fatal complications are exceptionally rare and have been related to cardiopulmonary complications secondary to anesthesia or other catastrophic events such as pulmonary embolism.

4.3.2.4.2. Kidney Donation

Risks of kidney donation include the same anesthesia-related complications described above.

The major post-operative morbidity associated with donor surgery includes pneumonia, wound infection, hematoma, phlebitis, pulmonary embolism, and urinary tract infection. The surgical complication rate for living kidney donation is approximately 2%. The perioperative mortality for a living kidney donor is estimated to be 0.033%. Although uni-nephrectomy of living donors has been associated with proteinuria and hypertension 6–10 years following nephrectomy, careful study of long-term outcome in kidney donors (up to 23 years) and army personnel who lost kidneys due to trauma during World War II (45 years follow up) did not indicate an increased risk of hypertension or renal failure.

4.3.2.4.3. Combined BMCI and Kidney Donation

The major risk to the donor is that of general anesthesia. The nephrectomy procedure takes 2–2.5 hours under general anesthesia. The simultaneous procurement of kidney and bone marrow requires approximately an additional hour of anesthesia as compared to a nephrectomy alone. This modestly increased operative time does not add any significant risk for the donor. Support for this conclusion is provided from observations of donors undergoing laparoscopic nephrectomy.

4.3.2.5. SARS-CoV-2 (COVID-19) Risks

The novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can spread rapidly within healthcare settings and communities and poses a special challenge for organ transplantation. Coronavirus disease 2019 (COVID-19) is a respiratory illness caused by the SARS-CoV-2 virus with variable presentation from asymptomatic to severe. Shedding of high viral titers has been documented from the respiratory tract, including shedding before the onset of symptoms, and results in droplet transmission of SARS-CoV-2 (Zou 2020). Transmission via droplet spread can occur from both symptomatic and asymptomatic individuals (Arons 2020) and it appears that patients with COVID-19 have the highest viral loads early in the course of their infection. Thus, a reliance on symptom-based screening strategies alone is not sufficient to prevent or diagnose infection; consideration of symptoms and exposure history, including PCR-based testing per local practice, may be employed.

4.3.3. Risk Mitigation Strategy

4.3.3.1. MMF and Cyclophosphamide Risk Mitigation

This protocol includes the use of NMA conditioning and donor BMCI with low exposure MMF and cyclophosphamide. Due to the known genotoxic and embryotoxic effects of these conditioning treatments, WOCBP are to avoid becoming pregnant for at least 12 months after the last dose of cyclophosphamide. Male subjects are to avoid fathering a child for at least 4 months after the last dose of cyclophosphamide and 3 months after the last dose of MMF.

In addition, per protocol hemodialysis as well as MESNA for non-anuric subjects will be used to mitigate known systemic and bladder toxicities, respectively, of cyclophosphamide.

4.3.3.2. Infection Risk Mitigation

Considering the expected immunomodulatory nature of siplizumab in combination with the pretransplant conditioning and post-transplant immunosuppression, subjects will be screened for both active and a history of latent infections including tuberculosis (TB), hepatitis C, hepatitis B, cytomegalovirus (CMV), and Epstein-Barr virus (EBV) and excluded based on their serology and treatment status. EBV serology will also serve as a key inclusion criterion, where EBV-sero*negative* subjects will be excluded from participation. Post-transplant viral reactivation will be assessed with longitudinal and quantitative surveillance to assess EBV, CMV, and BK polyomavirus (BKV) viral loads.

To profile the immune status of all subjects, a complete blood count (CBC) with differential will be assessed in all subjects during the study. At select centers, [redacted]

In addition, infection prophylaxis and monitoring will be mandatory as described in Section 6.7. During the study, subjects will be regularly evaluated while hospitalized, and upon return to the clinic, for signs and symptoms which might indicate a severe infection (e.g., fever, nausea, myalgia, headache, arthralgia, chills, diarrhea, stiff neck, malaise) and will be treated as appropriate per local practice depending on the infectious agent. Subjects will be informed to report any of the aforementioned symptoms to the clinical staff to assure proper assessment and care can be administered in a timely manner.

4.3.3.3. SARS-CoV-2 (COVID-19) Risk Mitigation

Despite the availability of vaccines and therapies to treat SARS-CoV-2 infections, local infections represent a continued challenge for all renal transplant candidates and recipients. Based on current vaccination guidelines, it is recommended that all transplant candidates and their household members receive SARS-CoV-2 vaccination. Ideally, transplant candidates should be vaccinated while they are awaiting transplant. Within the clinical study setting, subjects will be required to attend in-person study visits in excess of those based on SoC for clinical laboratory assessments, as well as chimerism, DSA, and pharmacodynamic (PD) sample collection; this may increase their risk of SARS-CoV-2 exposure. To minimize the time subjects spend indoors and within the clinic for these assessments, phone contact or virtual/telehealth technology will be utilized where appropriate by the site staff.

To mitigate the risk of peri-transplant, community acquired infections, including COVID-19 which could result in a loss of study eligibility, subjects will be hospitalized for approximately 1 week pre- and several weeks post-transplant. Following discharge from the hospital, subjects will return to the clinic for weekly visits through Week 11, monthly visits from Month 3 through Month 12, quarterly visits up until Month 24, and then visits every 6 months until the end of study (EOS)/Month 60. Throughout these visits, safety and PD assessments will be collected according to the Schedule of Assessments (see Appendix 1).

4.3.3.4. Renal Toxicity/Rejection Risk Mitigation

Enhanced safety monitoring will include more frequent assessment of vital signs, physical examinations, clinical laboratory evaluations (hematology, blood chemistry, urinalysis), and AE/SAE monitoring. In addition to standard clinical laboratory assessments, subjects will be

monitored regularly for coagulopathies as well as signs and symptoms of inflammatory, hematologic, or renal toxicity/rejection. Subjects' serum creatinine (sCr) and serum cytokines will be collected post-transplant with a focus on renal dysfunction, acute rejection, and CTS. This will include weekly serum creatinine sampling through Month 3, monthly from Month 3 through Month 6, and every other week from Month 6 to Month 18. Changes in renal function will be assessed via serial assessment of sCr. All biopsies (protocol and for cause) will be evaluated per the Banff classification of renal allograft pathology guidelines (Appendix 7) by a trained renal pathologist.

4.3.3.5. Infusion Reaction(s) Risk Mitigation

As indicated in the siplizumab risks (Section 4.3.2.1.1), siplizumab administration may result in a 'first-dose-effect' that presents as mild and transient pyrexia with chills, nausea, and fatigue. These infusion reactions generally present with the first infusion, are self-limiting and respond well to premedication with acetaminophen and histamine blockade (e.g., diphenhydramine). Subjects will receive their first dose of siplizumab on Day -6 under the close supervision of clinical staff in a hospital environment. Any infusion-related reactions can be managed at that time in accordance with local protocols. All subjects will receive premedication prior to the first dose of siplizumab to mitigate any infusion reactions. Subjects will be receiving CS as part of their peri-transplant immunosuppression at the time of all subsequent siplizumab doses.

4.3.3.6. GvHD Risk Mitigation

To mitigate the risks of GvHD, this protocol will be carried out by solid organ transplant investigators in close collaboration with co- or sub-investigators who are experienced in hematological transplantation and the diagnosis and management of subjects with aGvHD.

In addition, GvHD risk increases in the setting of prolonged, mixed chimerism, therefore the level of donor chimerism will be assessed frequently in the first 3 months with a focus on total chimerism as well as lineage specific chimerism when possible. Further, in the setting of prolonged chimerism, chimerism and GvHD assessments will continue until chimerism is lost, defined as less than 5%.

4.3.3.7. Overall Risk Mitigation Strategy

Finally, in addition to the clinical opinion of the Investigator and biopsy results noted above, a priori defined stopping criteria (Section 9.1.2) will be used to protect individual subject safety during the study. All subjects will be informed of the aforementioned risks and ITB-MED and an independent DMC will review the individual and cumulative study data regularly and on an ad hoc basis.

In consideration of the strategies and monitoring described above, the risk of administering siplizumab to a recipient of a living donor renal allograft with TAC, MMF, and CS immunosuppression in combination with a peri-transplant conditioning regimen of rituximab, cyclophosphamide, and thymic irradiation prior to a donor BMCI is manageable and the benefit-risk assessment in the intended patient population remains positive.

5. POPULATION

The study will enroll adult renal transplant candidates and their respective donors.

The Investigator must ensure that all subjects being considered for the study meet the following eligibility criteria. Subject selection is to be established by checking all inclusion/exclusion criteria at screening/baseline. A relevant record (e.g., checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from **any** entry criterion excludes a subject from enrollment into the study.

5.1. Inclusion Criteria

Subjects who meet ALL the following inclusion criteria will be eligible to participate in the study:

Recipient Subjects:

1. Recipients are able to understand the study requirements and provide written informed consent before any study assessment performed.
2. Male or female recipients aged 18–65 years.
3. Undergoing a renal transplant/retransplant.
4. Recipient of a renal transplant from an ABO compatible living donor who is at least human leukocyte antigen (HLA) haploidentical.
5. Capable of complying with the schedule of study visits, especially after discontinuation of immunosuppression.
6. Stable cardiopulmonary status per the judgement of the Investigator, with ejection fraction >40% within 3 months of transplant, and eligible for transplantation.
7. Epstein-Barr virus (EBV) seropositive during screening (Day -37 to Day -10). Seropositive results up to 12 months prior to Day -37 are acceptable.
8. Recipient free from any other locally endemic infections that would be contraindications to solid organ or bone marrow transplant (BMT)/hematopoietic stem cell transplantation (HSCT) according to applicable guidelines.
9. Male subjects must agree to maintain barrier contraception (condom) and further agree not to father a child for at least 4 months after the last dose of cyclophosphamide and 3 months after the last dose of MMF.
10. Women of childbearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, must agree to use highly effective methods of contraception during dosing and for at least 12 months after the last dose of cyclophosphamide.

Donor Subjects:

1. Donors are able to understand the study requirements and provide written informed consent before any study assessments are performed.

2. Male or female donors aged 18–65 years.
3. Be in excellent health per conventional pre-donor history (medical, laboratory, and psychosocial evaluation).
4. Negative for hepatitis B surface antigen (HBsAg), human immunodeficiency virus (HIV), hepatitis C virus (HCV) ribonucleic acid (RNA), and human T-lymphotropic virus type 1 (HTLV-1) during screening (Day -37 to Day -10).
5. Negative for latent tuberculosis (TB) infection, as detected by QuantiFERON Gold Plus interferon-gamma release assay (IGRA; or current standard interferon-gamma release assay for TB) during screening (Day -37 to Day -10), unless treated per US Centers for Disease Control and Prevention (CDC), World Health Organization (WHO), and/or institutional guidelines within 6 months prior to Day -9.
6. Free from any other locally endemic infections that would be contraindications to solid organ or BMT/HSCT transplantation according to applicable guidelines.

5.2. Exclusion Criteria

Subjects who meet ANY of the following exclusion criteria will be excluded from participation in the study:

Recipient Subjects:

1. Use of other investigational drugs (or enrollment in another investigational drug study) within 30 days of the start of screening (Day -37) or 5 half-lives of the medication, whichever is longer.
2. History of hypersensitivity to any of the study treatments or excipients or to drugs of similar chemical classes (e.g., MEDI-507 [siplizumab], tacrolimus, mycophenolate mofetil [MMF], cyclophosphamide, or rituximab).
3. Recipient with end stage renal disease (ESRD) due to primary focal segmental glomerulosclerosis (FSGS) or membranoproliferative glomerulonephritis (MPGN)/complement 3 (C3) glomerulopathy.
4. Recipient with anti-HLA donor-specific antibody (DSA) as measured by single antigen bead (e.g., Luminex) assay(s) during screening (Day -37 to Day -10).
5. Recipient with a positive donor crossmatch result (assayed according to local practice) during screening (Day -37 to Day -10).
6. Recipient with >85% panel reactive antibodies (PRA) during screening (Day -37 to Day -10). Results up to 2 months prior to Day -37 are acceptable.
7. Subjects with leukopenia (white blood cell [WBC] count <2,000/mm^3) or thrombocytopenia (platelet count <75,000/mm^3) at baseline.
8. Seropositive for HIV-1, HBsAg, or HCV during screening (Day -37 to Day -10). Subjects who are seropositive for HCV are excluded without proof of sustained viral response (SVR) after anti-HCV treatment. Results within 6 months prior to screening (Day -37) are acceptable.

9. Subjects with latent TB infection as detected by QuantiFERON Gold Plus IGRA (or current standard interferon-gamma release assay for TB) during screening (Day -37 to Day -10), unless treated per US CDC, WHO, and/or institutional guidelines within 6 months prior to starting the conditioning regimen on Day -9.
10. Subjects with a history of cancer other than basal cell carcinoma of the skin or carcinoma in situ of the cervix.
11. Subjects with a clinically significant laboratory abnormality that would preclude participation in the study.

    For example, values >2.5 × upper limit of normal (ULN) for:

    - Liver function chemistries (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP]).
    - Bilirubin.
    - Coagulation studies (prothrombin time [PT]/International Normalized Ratio [INR], activated partial thromboplastin time [aPTT]).
12. Subjects who, in the opinion of the Investigator, are not capable of giving informed consent for the study or who are unable or unwilling to adhere to the study requirements outlined in the protocol.
13. Subjects with any other clinically significant medical condition or laboratory abnormality that would, in the judgment of the Investigator, interfere with the subject's ability to participate in the study.
14. Subjects who have received any live-attenuated vaccine within 1 month prior to starting the conditioning regimen on Day -9.
15. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.

6. TREATMENTS, CONCOMITANT MEDICATIONS, AND PROCEDURES

6.1. Method of Treatment Assignment

The study is open label and non-randomized so each subject (donor and recipient) will be assigned a sequential subject identification number (SID) in the clinical database system at screening (see Section 8.1). After a subject is assigned a number, that number will not be reused even if the subject screen fails or withdraws before receiving any Investigational Product (IP).

6.2. Investigational Product

6.2.1. Identification of Investigational Product

Siplizumab is a humanized IgG1κ class monoclonal antibody, supplied [redacted] for infusion. Siplizumab will be supplied in [redacted] mL vials containing [redacted] mg and supplied at a concentration of [redacted] mg/mL.

6.2.2. Management of Investigational Product

Investigational product (IP) will be provided as open-label, bulk medication. Detailed instructions for the receipt, storage, accountability, and return or destruction will be described in the Pharmacy Manual, as well as expectations for reporting temperature excursions to ITB-MED.

Investigational product must be received at the study site by the Investigator or his/her designee. Confirmation of product receipt and condition will be logged into the Interactive Response Technology (IRT) system and any documentation of receipt maintained in the site's study file.

Following confirmation of receipt, all IP must be stored in an appropriate secure area (e.g., a locked room or a locked refrigerator) and within an adequately monitored 2–8°C refrigerator. Temperature logs must be maintained to document the daily minimum, maximum, and actual temperature to confirm the absence or presence of a temperature excursion. Access to the storage area and/or storage refrigerator must be limited to those persons authorized by the Investigator.

The Investigator must maintain an accurate record of the dispensing of all IP in a drug accountability log. A copy of the log(s) must be maintained by the Investigator, pharmacy staff, or designee. ITB-MED will retrieve copies of the logs periodically or at the end of the study for maintenance in the electronic Trial Master file (eTMF). Additionally, IP accountability will be noted by the Monitor during site visits and/or at the completion of the study.

All IP supplies are to be used only for this protocol and not for any other purpose. Unless specifically instructed by ITB-MED, the Investigator must not destroy any drug labels, or any partly used or unused IP supply.

Only after receiving a written authorization by ITB-MED, the Investigator/designee will:

- Send all the unused and partly used drug supplies (as well as the empty containers) to the address provided at the time of authorization for destruction,

  OR

- Destroy the unused and partly used drug supplies (as well as the empty containers) by the site's pharmacist or designee, who will provide a drug destruction certificate.

6.2.3. Investigational Product Treatment Regimen

The dose of siplizumab will be [redacted] mg/kg at each administration.

The planned duration of treatment with siplizumab is 4 doses over a period of 8 days for subjects assigned to Arm 1 and 5 doses over 13 days for those assigned to Arm 2. All subjects will receive siplizumab on Days [redacted], -1, 0 (perioperatively), and Day 1, with an additional dose provided to subjects in Arm 2 on Day [redacted].

Siplizumab dose adjustments (other than for weight) and/or interruptions of the dosing schedule for a given subject are not permitted. The siplizumab infusion rate may be changed in the event of an infusion reaction. Subjects may be discontinued from treatment earlier at the discretion of the Investigator or upon request of the subject.

6.2.4. Investigational Product Dose Calculation and Preparation

The Investigator or his/her designee will obtain the IP to be administered to the subject. The siplizumab infusion must be prepared and administered either by the Investigator or designee(s) properly trained in the handling and aseptic preparation of IV infusions. The subject should be weighed within 24 hours of each infusion administration and this weight will serve as the basis for final dose calculations and admixture procedures.

Detailed instructions on the preparation and administration of the IP will be provided in the Pharmacy Manual and must be referenced prior to administration of IP to any study subject.

6.3. Reporting of Study Treatment Errors

Medication errors are defined as potential, intercepted, or unintentional errors in the prescribing, dispensing, administration, or monitoring of a medicine while under the control of a healthcare professional, subject, or consumer.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded in the appropriate electronic case report form (eCRF) whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE; however, the ITB-MED study team should be notified immediately.

6.4. Concomitant Medications and Procedures

All treatments, concomitant medications, and procedures, including SoC surgical prophylaxis, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject is enrolled into the study must be recorded in the appropriate eCRF. The subject should be reminded to notify the Investigator and/or site staff of any new medications or treatments or changes to existing medications or treatments, throughout the study. ITB-MED will provide eCRF completion guidelines with additional detail for recording concomitant medications.

All concomitant medications must be individually assessed against all exclusion criteria/ prohibited medication. If in doubt, the Investigator should contact the ITB-MED Medical

Monitor or designee before randomizing a subject or allowing a new medication to be started. If the subject is already enrolled, ITB-MED should be contacted to determine if the subject should continue participation in the study.

6.5. Conditioning Regimen Treatment and Procedures

6.5.1. Siplizumab

Siplizumab Premedication
Prior to each infusion of siplizumab, subjects should receive premedication with 650–1000 mg acetaminophen/paracetamol and an H_1-antagonist (antihistamine; e.g., 25 mg diphenhydramine or 4 mg chlorpheniramine) to minimize signs and symptoms of an infusion reaction. Additionally, for the first dose of siplizumab ONLY (Day [redacted]), 8 mg/kg methylprednisolone sodium succinate (SoluMedrol) should be given prior to starting the infusion. Administration of required premedications should occur no less than 30 minutes and no more than 3 hours prior to the start of the infusion.

Siplizumab Administration (Days [redacted] -1, 0, and 1; also Day [redacted] for Arm 2 only)
Siplizumab will be administered over 60 (±5) minutes by IV infusion (using a syringe pump) to the subject by authorized site personnel. The first dose of siplizumab ([redacted] mg/kg) will be administered on Day [redacted]. Siplizumab doses should be administered approximately 20–24 hours apart. Premedication (see above) should precede administration of siplizumab on Days [redacted] -1, and 1 (also Day [redacted] for Arm 2 only). On Day 0, the infusion should be administered pre- or intra-operatively. The [redacted] minute infusion may be administered during a 4 hour window that results in completion of the infusion prior to revascularization and reperfusion of the allograft. Practically, the infusion may be started between [redacted] hour and [redacted] hours prior to reperfusion of the allograft. Premedication should be coordinated with any pre-operative medications to avoid therapeutic duplication in consultation with the anesthesiologist. When administered intra-operatively, the infusion must be completed prior to revascularization and administration of the BMCI (see Section 6.5.6). This ensures both donor and alloreactive T-lymphocytes are suppressed and depletion is initiated in the hours post-transplant. Subjects should be carefully monitored (a minimum of 2 hours) after each dose for infusion reactions. The infusions may be given directly into a peripheral vein or a separate lumen in an indwelling, multi-lumen, central catheter. The compatibility of siplizumab with other IV medications is not known and must not be combined with other infusions or medications in the same syringe or line. The date, start time, completion time, and total dose of siplizumab administration must be recorded in the subject's source documentation and applicable eCRF. No dose adjustments beyond changes based on the subject's actual body weight are permitted to the siplizumab dose during the study.

6.5.2. Rituximab

Rituximab Premedication

Acetaminophen (650–1000 mg PO), an H_1-antagonist (antihistamine; e.g., 25–50 mg diphenhydramine or 4 mg chlorpheniramine), and hydrocortisone sodium succinate (Solu-Cortef 100 mg IV) should be administered to subjects 2 hours prior to each dose of rituximab or per local institutional standards and documented in the concomitant medications eCRF.

Rituximab Administration (Days -9, -2, 5, and 12)

Rituximab (375 mg/m^2/dose) will be administered on Days -9, -2, 5, and 12. In those subjects receiving ongoing renal replacement therapy with hemodialysis, rituximab should be administered several hours after a dialysis session.

The first rituximab solution for infusion should be administered IV at an initial rate of 50 mg/hour. The rate may be escalated by 50 mg/hour every 30 minutes to a maximum of 400 mg/hour. Subsequent infusions may be started at 100 mg/hour and titrated by 100 mg/hour every 30 minutes to a maximum of 400 mg/hour if the subject tolerated the first infusion.

Subjects should be carefully monitored (a minimum of 1 hour) for infusion reactions. In the event the subject did not tolerate the first infusion, the initial infusion guidelines should be followed. If hypersensitivity or an infusion-related event develops, the infusion should be temporarily slowed or interrupted. The infusion can then be continued at one-half the previous rate upon improvement of symptoms. The start and stop times and total dose for rituximab administration should be recorded.

6.5.3. Cyclophosphamide

Cyclophosphamide Premedication

Prior to administration of cyclophosphamide on Days -5 and -4, the subject should receive pretreatment for nausea, vomiting, and infusion reaction prophylaxis (e.g., a glucocorticoid, antihistamine, anxiolytic, and antiemetic) per local institutional standards.

Subjects will also undergo prophylaxis against hemorrhagic cystitis with MESNA (see also hemodialysis Section 6.5.4) as follows:

- Oliguric subjects: MESNA, 4 mg/kg administered via 4 bolus IV injections 15 minutes before, and 3, 6, and 9 hours after cyclophosphamide administration.
- Non-oliguric subjects: MESNA as above, plus IV hydration (e.g., with 5% dextrose, 1500 mL/m^2/24 hours as tolerated) beginning 4 hours prior to cyclophosphamide. If the subject is oliguric, bladder washout may also be performed.

Cyclophosphamide Administration (Days -5 and -4)

Subjects will receive hemodialysis as prophylaxis against cyclophosphamide toxicity as indicated in Section 6.5.4.

Subjects will receive cyclophosphamide 60 mg/kg/day (based on lesser of ideal or actual body weight). Cyclophosphamide is dissolved in 250 mL of 5% dextrose and administered via IV infusion over approximately 1 hour.

6.5.4. Hemodialysis

All subjects will require hemodialysis treatment as prophylaxis against cyclophosphamide toxicity during the conditioning period.

Within 24 hours prior to the first administration of cyclophosphamide subjects will undergo hemodialysis. Recipients with no existing vascular access will be seen by a nephrologist on or prior to Day -6 for vascular access and insertion of a catheter in preparation for hemodialysis during conditioning, as required.

Hemodialysis should be performed as indicated in Table 6.

Please note that if the subject's eGFR was <10 mL/min and the subject was on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) at study entry, an additional hemodialysis will be performed on Day-1.

Dialysis date, time and duration should be recorded on the appropriate eCRF.

Table 6: Hemodialysis Timing and Duration

Day	Duration [a]	Timing
Day -6	4 hours	Within 24 hours prior to Day -5 cyclophosphamide administration
Day -5	4 hours	14 (±2) hours after cyclophosphamide administration
Day -4	4 hours	14 (±2) hours after cyclophosphamide administration

a. As close to 4 hours in duration as possible or per local nephrologist recommendation to assure adequate removal of cyclophosphamide metabolites.

Post-transplant hemodialysis (renal replacement therapy) should be performed as clinically indicated.

6.5.5. Thymic Irradiation (Day -1)

Thymic irradiation 700 cGy will be administered in a single dose on Day -1. The field size and dose rate will be calculated and administered per local institutional standards.

6.5.6. Donor Nephrectomy and Bone Marrow Procurement

The donor will undergo nephrectomy and bone marrow cell procurement under general anesthesia on Day 0 (day of transplant). Unfractionated donor bone marrow cells (intended minimum of 2×10^8 TNC/kg of recipient body weight) are prepared for infusion according to institutional standard procedures (See procedure guidance in Appendix 3).

6.5.7. Recipient Transplantation and Bone Marrow Cell Infusion

On Day 0, transplant recipients will receive the allograft per each site's institutional practice. A baseline wedge or needle biopsy will be obtained from the allograft pre-implantation.

Following revascularization of the allograft and upon confirmation that no bleeding or leakage from the vascular anastomoses is present, the recipient may receive the BMCI. The cells will be infused IV, at a rate of approximately 300–500 mL/hr. The infusion should begin no later than 4 hours following reperfusion.

If bleeding is excessive, a partial thromboplastin time (PTT) should be considered half-way through and following completion of the BMCI. Protamine 25 mg may be given IV for a PTT of >60 seconds or for an elevated PTT due to heparin, if that is believed to be the cause of bleeding.

6.5.8. Tocilizumab Preparation and Administration

Tocilizumab use is ONLY permissible as treatment for the presentation of CTS. If CTS occurs, tocilizumab may be initiated at any time and, if warranted, a further dose given approximately one week later.

Tocilizumab should be prepared and administered according to approved labeling at a dosage of 8 mg/kg IV over approximately 60 minutes.

6.5.9. Management of First Dose (Infusion) Reactions

"First dose" or infusion reactions may occur upon the initial administration of rituximab, siplizumab, or tocilizumab. These have the potential to be severe. Prophylaxis against first dose reactions is described above in Section 6.5.1 and Section 6.5.2.

In addition, the following procedures or local equivalent are to be followed in assessing the occurrence and management of any such reactions.

Qualified personnel should observe each subject periodically for a period of 2 hours after the administration of the first dose of siplizumab. A physician who is a member of the transplant team and who is familiar with this protocol must be available throughout this time period. Additionally, an emergency cart must be available and personnel who are qualified to administer advanced cardiac life-support (ACLS) must be on call, in the facility and available for 2 hours after the first and second doses of rituximab, siplizumab, and tocilizumab in each subject. If these monoclonal antibodies are administered in an outpatient or ambulatory clinic, it must be given in a clinical setting equipped for the administration of antibodies, and subjects must remain under observation for at least 2 hours after completion of the infusion of the first 2 doses of antibody.

Although premedications are given prophylactically prior to administration of rituximab and siplizumab, further doses of acetaminophen and antihistamine may be administered if fever or chills occur post-study drug administration. Temperature and other physical symptoms of the subject must be documented prior to administration of either medication. Corticosteroids (e.g., 250 mg IV methylprednisolone) may be administered if a severe reaction occurs. All symptoms of drug reactions and treatment for drug reactions must be recorded in the appropriate eCRFs.

Subjects who develop hypersensitivity to rituximab, tocilizumab, or siplizumab, as evidenced by type I reaction or anaphylaxis, will be withdrawn from study drug and managed per local practice and as outlined in Section 9.1.3.

As described in Section 6.9 "Prohibited Concomitant Treatment," if a subject receives any immunosuppressant other than rituximab, tocilizumab, and siplizumab (or others specified in this protocol) during the conditioning regimen, further infusions of rituximab, tocilizumab, or siplizumab will not be given and the subject will revert to management per SoC. Procedures following withdrawal of study drug are described in Section 9.1.3.

6.6. Background Immunosuppression

The following background immunosuppression medications will be used in this study, supplied locally, and administered in accordance with this protocol, SoC practices at the institution, and where applicable, approved labeling:

- Immediate-release tacrolimus (TAC): 0.5 mg, 1.0 mg, or 5.0 mg capsules or IV
- Mycophenolate mofetil (MMF): 500 mg tablets, 250 mg capsules or IV
- Corticosteroids (CS): oral and IV administration

The use of immediate release generic TAC and MMF are permitted in this study. It is preferred that subjects remain on the same type, brand, and manufacturer of immunosuppressive medication through complete withdrawal (or long-term maintenance if the subject is unable to complete immunosuppression withdrawal). As such, if a subject starts with branded drug they should remain on branded medication and not switch to a generic during the study. Likewise, if the subject starts with generic, the subject should remain on the same generic throughout the study.

In the case of intolerance to the immunosuppressive regimen, symptomatic treatment should be considered first. However, for subjects who are still unable to tolerate the protocol-specified study treatment, dose adjustments, route adjustments, and interruptions of study drugs may be permitted to keep the subject on study treatment.

While subjects are receiving TAC, special attention must be taken to avoid concomitant administration of drugs, food, or beverages which are known to be a strong inducer or inhibitor of CYP3A4 (see Appendix 4). In the case where drug-drug interactions are anticipated (e.g., with viral and fungal prophylaxis), careful attention should be made to actively manage immunosuppression concentrations at the time of introduction or discontinuation of the interacting therapies until the immunosuppression concentrations have stabilized.

6.6.1. MMF Administration (Day 0 through Week 8)

MMF (2.0 g/day) will be administered orally (PO) as 2 × 500 mg tablets or 4 × 250 mg capsules twice per day (BID). Intravenous administration (1000 mg; 2 × 500 mg vials) may be considered for subjects who remain intubated >24 hours post-transplant and/or who are otherwise unable to swallow oral medications, until oral conversion is possible.

The first dose of MMF will be administered at the time of transplant, but no later than 24 hours after reperfusion of the allograft. Dose adjustment/interruption guidance for MMF is provided in Appendix 5. All MMF doses and changes must be recorded in the applicable eCRF. US-specific pregnancy guidance for MMF (CellCept®) is contained in Appendix 6.

6.6.1.1. MMF Weaning Criteria for Discontinuation

Once the weaning criteria in Table 7 below are met, MMF should be discontinued after Week 8.

Table 7: MMF Weaning Criteria

MMF Weaning Criteria
1. Stable renal function (serum creatinine [sCr] <2.0 mg/dL) under immunosuppression, unless a transient rise in creatinine is related to an alternative cause of renal dysfunction.
2. No evidence of antibody mediated rejection (AMR) or Banff grade IA or greater T cell-mediated rejection (TCMR).

If renal function criteria are not met at Week 8 due to an alternative cause, MMF discontinuation may be delayed until the excursion in serum creatine is corrected and renal function is considered stable. However, any biopsy confirmed rejection will be considered a treatment failure and subjects will be managed as outlined in Section 9.1.3.

6.6.2. TAC Administration

TAC will be administered as capsules or tablets orally (PO) twice a day (BID) and adjusted to maintain serum trough (C_0) concentrations within the target range of 4–11 ng/mL. If oral administration is not feasible or practical, administration of TAC by continuous IV infusion can be substituted per label. Controlled release/once-a-day TAC is not permitted in this study.

TAC should be started as soon as possible in the peri-transplant period and may follow local practice but must be initiated no later than 24 hours after reperfusion of the allograft. The lowest permitted dosing of TAC in this study is 0.5 mg daily (QD) or IV equivalent. If TAC is discontinued for more than 14 consecutive days, and the study regimen cannot be maintained, the new immunosuppressive regimen must be documented in the relevant medication eCRF, including dose and trough concentrations where applicable. Subjects who discontinue their study regimen are expected to remain in the study on the local SoC until Month 12.

TAC dosing will be modified by Investigators as needed and dosing, trough concentrations, and details for any dose changed will be recorded in the applicable eCRF at each visit. In the event of TAC intolerance (e.g., nephrotoxicity, neurotoxicity) dose reduction of TAC may be necessary.

On days when trough concentrations are monitored, the subject will be instructed to record the time of the last dose on the day prior to the blood draw and to bring the morning dose to the visit so it may be administered after the blood sampling is completed.

6.6.2.1. Tacrolimus Weaning (Starting at Month 6)

Once all weaning criteria listed in Table 8 below are met, the dose of TAC should be reduced as suggested in Table 9.

Table 8: Tacrolimus Weaning Criteria

Tacrolimus Weaning Criteria
1. Stable renal function (serum creatinine [sCr] < 2.0 mg/dL) under immunosuppression, unless a transient rise in creatinine is related to an alternative cause of renal dysfunction.
2. Detectable multilineage white blood cell chimerism (any level) in the early post-transplant period.
3. No current or prior donor-specific antibodies (DSAs).
4. No current evidence of graft-versus-host disease (GvHD).

Tacrolimus Weaning Criteria
5. No evidence of antibody-mediated rejection (AMR) or Banff Grade IA or greater T cell-mediated rejection (TCMR) on the Month 6 (or most recent) renal biopsy. History of borderline changes do not disqualify a subject from complete immunosuppression withdrawal, provided that the biopsy result is normal at Month 12.

Tacrolimus Weaning Schedule (Starting at Month 6–9)

Tacrolimus trough concentration should be measured throughout TAC dose reduction. The schedule in Table 9 below is a guideline and dose reduction may be delayed or paused based on the overall clinical considerations:

Table 9: Tacrolimus Weaning Schedule

Time Period	TAC Dose Level
Months 6–7	75% of Month 6 dose
Months 7–9	50% of Month 6 dose
Months 9–11	25% of Month 6 dose
Month 11	12.5% of Month 6 dose
Month 12+	Undetectable

In the event a reduction in dose alone results in an over-proportional reduction in TAC exposure (i.e., trough concentrations decrease more than anticipated), the same titration scheme can be applied to a reduction in exposure (TAC trough concentrations) and doses should be adjusted accordingly. When TAC trough concentrations decrease below the assay limit of quantification, a reduction in the total daily dose by percentage alone should be used to complete the tapering.

TAC should only be stopped completely after a **second biopsy** (nominally at Month 12, but may be earlier or later depending on the schedule and subject's clinical presentation) demonstrates the allograft is rejection-free as described in criterion #5 above. In addition, all other weaning criteria must continue to be met.

TAC is a substrate for CYP3A metabolism and therefore susceptible to drug-drug interactions that can raise or lower systemic concentrations, leading to toxicity or therapeutic failure. The co-administration of drugs known to interfere with TAC metabolism (Appendix 4) should be avoided if possible. If these drugs are required, the Investigator should carefully monitor TAC trough concentrations and adjust the TAC dose accordingly during and after the use of the interacting treatment.

All TAC doses and changes must be recorded in the applicable eCRF.

6.6.3. Corticosteroid Administration

Corticosteroids (CS) are given at several times in the study for different purposes and the prespecified dosing is as follows below.

- Premedication for rituximab (see Section 6.5.2).
- Premedication for siplizumab (see Section 6.5.1).

- Transplant immunosuppression:
  - IV methylprednisolone sodium succinate (SoluMedrol):
    - Day 0 (250 mg)
    - Day 1 (125 mg)
    - Day 2 (100 mg)
    - Day 3 (80 mg)
  - Steroid route of administration can be switched from IV to oral on approximately Day 4 per local practice and subject status:
    - Prednisone 2 mg/kg/day starting Day 4 through Day 12 and rapidly tapering off completely by Day 20.

If CTS is observed CS should be considered in first line treatment (see Section 6.8.2).

If rejection is observed CS should be used as first line treatment (see Section 6.8.1).

6.7. Infection Prophylaxis

During period(s) of mild neutropenia (ANC < 500 cells/µL), oral levofloxacin 500 mg daily should be administered as infection prophylaxis. Prophylaxis should continue until ANC >500 cells/µL, or as dictated by local practice.

6.7.1. CMV Prophylaxis

Cytomegalovirus (CMV) prophylaxis is central to the successful outcome of BMCI and organ transplantation. CMV antiviral prophylaxis will be adjusted to each subject's expected risk of viral activation.

All subjects should receive seronegative or CMV "Safe" blood (leukofiltered). The greatest risk for CMV infection in solid organ transplantation is for the donor seropositive (D+) into recipient seronegative (R-) combination.

For all CMV positive combinations- (**D+/R-, D-/R+ and D+/R+**) subjects will:

- Have weekly monitoring by quantitative CMV DNA nucleic acid amplification test (NAAT) assay while neutropenic and PCR following engraftment.
- Receive ganciclovir or the locally approved CMV prophylaxis regimen. This will be initiated prior to renal transplantation (Day -1) until 6 months post-transplant. Note that during neutropenia, in CMV+ recipients, ganciclovir should not be used and letermovir should be considered for up to 100 days as available.

Provided CMV pedigreed blood products are utilized, there is essentially no risk of CMV disease in the D-/R- population, other than via sexual contacts and no additional prophylaxis or treatment is required.

6.7.2. Human Herpes Virus (HHV)

All subjects will receive acyclovir or famciclovir for human herpes virus (HHV) infection prophylaxis for at least 3 months, or according to standard guidelines and local practice. Subjects receiving ganciclovir for CMV prophylaxis should be sufficiently protected against herpes

simplex virus (HSV), varicella-zoster virus (VZV), HHV6, and HHV7 infection and do not require additional treatment.

6.7.3. *Pneumocystis jirovecii* (*Pneumocystis carinii*) Pneumonia (PCP)

All transplant recipients should receive sulfamethoxazole and trimethoprim (SMZ-TMP), one single strength tablet daily starting on Day -9 and continuing through post–transplant Month 6. This prophylaxis may be interrupted, starting on Day 0 (day of transplant) and during the perioperative period until ANC >500 cells/μL. Consideration should be given to extending the period of prophylaxis for an additional 6 months if it is felt by the Investigator to be clinically indicated.

In the event of allergy or intolerance to the components of SMZ-TMP, atovaquone and/or inhaled pentamidine may be used in its place for PCP prophylaxis.

Due to the potential for bone marrow suppression with SMZ-TMP, subjects must be monitored carefully during treatment and the alternative regimen used in the case of possible SMZ-TMP-related bone marrow suppression.

6.7.4. Hepatitis B Virus (HBV)

Prophylaxis for HBV reactivation (e.g., Hepatitis B Immunoglobulin; HBIg) during the course of this study is allowed and will be administered at the discretion of the Investigator.

6.7.5. Fungal/Yeast Infection Prophylaxis

Local practice for fungal/yeast prophylaxis will be followed. For example, itraconazole or fluconazole may be started on Day 1 and continued for 2 months or at least until resolution of neutropenia.

For oral thrush (*Candida*), Nystatin may be used in a swish and swallow regimen; alternatively, clotrimazole (Mycelex®) lozenges/troches may be used. Routine use of systemic agents (e.g., itraconazole, voriconazole, and fluconazole) will not be allowed except as above in the immediate post-transplant period or if subjects are systemically infected. Attention should be paid to the drug-drug interaction of azole antifungal agents which may increase blood concentrations of TAC.

Systemic therapy will be based on center practice and at the Investigator's discretion.

6.7.6. Immunization

Immunization of transplant candidates for vaccine preventable diseases is recommended more than 2 weeks prior to transplantation or starting at 1–6 months after transplantation. If given prior to transplantation, the full immunization series should be completed before the transplant procedure. In certain situations, it may be appropriate to wait until 3 or more months after transplantation to vaccinate following T- or B-cell depleting therapy. Waning vaccine titers to other routine immunizations have been well documented after transplantation. Lower seroconversion rates to influenza vaccination are well documented in the setting of mycophenolate mofetil and tacrolimus use (Danziger-Isakov 2019).

Vaccination during treatment with siplizumab and prior to clearance of the antibody and pharmacodynamic effects are likely to result in therapeutic failure (i.e., non-protective antibody

titers). Administration of live attenuated agents should be avoided while receiving siplizumab treatment and for up to 6 months thereafter, depending on the dose and time for reconstitution of immune function.

6.8. Treatment of Adverse Events

Medications used to treat AEs must be recorded in the appropriate eCRF.

6.8.1. Treatment of Acute Rejection Episodes

For all suspected acute rejection episodes, regardless of initiation of anti-rejection treatment, a renal biopsy should be performed within 48 hours.

Acute rejections should be treated with bolus methylprednisolone (other CS are acceptable at an equivalent dose) according to local practice. Recommended treatment is at least 3 boluses of IV methylprednisolone with a minimal dose of 250 mg/bolus or at least 2 boluses of IV methylprednisolone with a minimal total dose of 750 mg.

Subjects who experience steroid-resistant rejections, vascular rejections, or rejections with a Banff Grade ≥2B (Appendix 7) may be treated with other anti-rejection therapies (i.e., antibody therapy).

It is important to note that limited information is available on the combination of siplizumab and other T-cell depleting antibodies (e.g., ATG), immunosuppressants (e.g., mTOR inhibitors [sirolimus or everolimus]) or costimulatory blockade (belatacept) and intravenous immunoglobulin (IVIG) and may result in overlapping pharmacology. In the setting of an acute rejection episode, the selection and use of one or more of these agents in combination with siplizumab is at the Investigator's discretion based on their experience and immune status of the subject.

All episodes of acute rejection, and any medications used for suspected or confirmed acute rejections, must be entered in the corresponding eCRF, preferably within 24 hours.

6.8.2. Diagnosis, Treatment of Chimeric Transition Syndrome (CTS)

The diagnosis of CTS will be made by the Investigator based on the overall clinical presentation of the subject which may include acute fluid retention, fever, loss of or reduction in chimerism, and increased sCr.

A diagnosis of CTS is made following biopsy confirmation and the exclusion of alternative causalities for renal dysfunction. CTS must be reported as an SAE, and designated per the severity criteria outlined below:

Mild:	Elevation ≤2× baseline serum creatinine
Moderate:	>2 and ≤4× baseline serum creatinine
Severe:	>4× baseline serum creatinine or need for any dialysis

Suspected CTS is any increase in sCr >2× baseline, where baseline is the lowest sCr observed post-transplant. In a case where renal function has not recovered (e.g. delayed graft function

[DGF]) ultrasound will first be used to evaluate blood flow to the graft with any DGF treated according to local practice.

It is anticipated that some subjects' coagulation status may preclude biopsy so there may be cases of "clinical CTS" and "biopsy-proven CTS" similar to T cell-mediated rejection. Pathological features of CTS include graft endothelial inflammation, interstitial edema/swelling, and acute tubular injury. Note that a severe case of CTS would constitute a stopping rule for further enrollment to the study.

Treatment for CTS may be initiated without biopsy per Investigator judgment and may include pulse steroids and dialysis. Depending on CTS symptoms (renal function), IV methylprednisolone sodium succinate 500 mg for 2–3 days should be considered for first line therapy. In the case of rapid deterioration of renal function in combination of reduced renal blood flow, plasma exchange may be considered.

If any subject in an Arm 1 presents with severe CTS, the arm will be closed to further recruitment and the study will progress to Arm 2. A severe case of CTS in Arm 2 would constitute a stopping rule for further enrollment to that arm (see Section 9.1.2). All other cases of CTS (mild and moderate) including the time to onset, course, and response to treatment will be reviewed individually and in aggregate to assure the risk-benefit assessment remains positive and study documentation reflect the risks within a given arm. Any significant updates and amendments will be approved following local and national requirements.

6.8.3. Management of CMV

The SoC for treating symptomatic CMV disease is a minimum of 2–3 weeks of IV ganciclovir (with dosage adjustment recommended for renal dysfunction per local labeling), oral valganciclovir, or other approved antiviral medication per local practice. CMV immunoglobulin G (IgG) can be added for seronegative subjects with viral activation. Intravenous therapy is discontinued once clearance of the virus from the blood occurs, as demonstrated by CMV antigenemia assay (or quantitative assay).

In subjects with relapsing infection, CMV IgG can be administered in conjunction with the IV ganciclovir therapy in seronegative recipients. Treatment is maintained in the setting of active GvHD.

6.8.4. Management of BKV Viremia

BK polyomavirus (BKV) screening generally utilizes plasma (or whole blood) viral load (VL) molecular assays. Urine studies (cytology for "decoy cells," BKV DNA or VP-1 mRNA) are less specific. Decoy cells are shed infected tubular and ureteric epithelial cells with an enlarged nucleus with a large basophilic intranuclear inclusion by urine cytology. Cytology cannot distinguish BKV from adenovirus and false negative tests also occur. A urinary test for BKV (cytology for decoy cells or urine BKV loads over 7-log geq/mL) is adequate for screening; if negative, the risk for polyomavirus-associated nephropathy (PVAN) is low.

Quantitative cutoffs for presumptive diagnosis of BKV nephropathy include:

- Plasma DNA VL >10,000 copies/mL
  (whole blood PCR VL >1500–3500 copies/mL)

- Urine VP1 mRNA load >6.5×10^5 copies/ng total RNA, **or**
- Urine DNA load >10^7 copies/mL

Higher viral loads are increasingly predictive of PVAN

World Health Organization (WHO) standards should be utilized in the performance of BKV quantitative nucleic acid testing (QNAT) to ensure minimization of interlaboratory variability.

Biopsy is suggested for confirmation if creatinine is elevated. Renal histopathology provides definitive diagnosis of PVAN (Fishman 2017).

If a subject is found to have BKV viremia or PVAN, the event should be recorded in the appropriate eCRF as an AE or SAE, and should be managed per local center practice.

6.8.5. Management of Delayed Graft Function (DGF)

Delayed graft function (DGF) for this study is defined as the need for dialysis performed within 7 days of transplant.

> NOTE: Subjects who require dialysis (up to 2 sessions), with the purpose of correcting electrolyte abnormalities in the immediate post-transplant time period (first 36 hours), would not meet the definition of DGF for purposes of this study.

In the event DGF is reported as an AE, and dialysis is also reported, the end of DGF is the date the last dialysis session ends. For all other subjects, the end of DGF is the date renal dysfunction is considered resolved by the Investigator.

If a subject experiences DGF, the DGF is by definition starting at reperfusion after the transplantation procedure. If the graft dysfunction starts later according to the Investigator, the condition is considered secondary graft dysfunction.

DGF treatment will be according to local practice. DGF treatments must maintain sufficient immunological coverage for the graft and may include maintaining, interrupting, or reducing the dose of study treatment and use of a polyclonal antibody. If a polyclonal antibody is used, the subject will be placed on SoC and managed per local practice.

6.8.6. Primary Graft Non-Function (PGNF)

Primary graft non-function (PGNF) is defined as dialysis starting after transplantation with a continuous record of post-transplant dialysis until either transplantectomy, retransplantation, or death. PGNF should be reported on the Graft Loss eCRF.

If a subject is placed on permanent dialysis (or re-transplanted), the Graft Loss and AE eCRFs should be completed, and an SAE of graft loss reported.

6.8.7. Epstein-Barr Virus-Post-Transplant Lymphoproliferative Disorder (EBV-PTLD)

Epstein-Barr virus (EBV)-post-transplant lymphoproliferative disorder (PTLD) is a serious disease. Transplant clinicians managing suspected and confirmed PTLD should follow local institutional guidance on the diagnosis and management of EBV-PTLD, including consulting with transplant infectious disease and hematology-oncology clinicians where relevant.

In subjects diagnosed with EBV-PLTD, therapy must be individualized. Siplizumab doses planned for this study are expected to result in T- and NK-cell depletion and minimal to no modulation of the B-cell compartment, respectively. However, B-cell compartment coverage is expected from concomitant, per-transplant rituximab. Clinicians should refer to the siplizumab IB when considering therapeutic options for the treatment of EBV-PTLD.

Consensus guidelines on the diagnosis and management of EBV-LPD and PTLD in the setting of solid organ transplantation have been published and may be referenced (Parker 2010, Allen 2013).

6.8.8. Treatment of GvHD (acute or chronic)

Acute GvHD is a serious possible complication following bone marrow cell infusion. In case of aGvHD, the applicable local treatment guidelines, typically using high dose steroids as first line therapy (e.g., Martin 2012), should be followed.

Calcineurin inhibitor therapy should continue if the subject is already receiving it. Second line treatment is variable and depends on the severity of the GvHD and organ(s) involved but may include ruxolitinib, mycophenolate mofetil, and/or sirolimus.

Treatment of chronic GvHD is also variable but is generally steroid-based, for which second line glucocorticoid sparing agents such as ibrutinib or ruxolitinib may be considered.

6.9. Prohibited Concomitant Treatment

Immunosuppressants and induction treatment other than those specified in the protocol are NOT permitted from the signing of informed consent through end of study (EOS).

If the use of any of these medications or other non-protocol immunosuppressants is discovered prior to enrollment, the subject must not be enrolled and will be recorded as a screen failure. If discovered after enrollment, no further doses are to be given, and the subject should continue on the assigned treatment regimen, noting the protocol deviation. The exception is for the treatment of an acute rejection not responding to corticosteroids.

The use of concomitant medications that may influence TAC concentrations should be avoided. Please refer to Appendix 4 and local prescribing information.

6.10. Study Treatment Exposure and Compliance

Drug accountability and compliance with the subject's treatment regimen will be assessed by the Investigator and/or designed site personnel at each study visit and information captured in the source documentation and relevant eCRF. The Investigator should promote compliance of immunosuppressive therapy by instructing the subject to take study medication exactly as prescribed and emphasize that compliance is necessary for the subject's safety and the validity of the study. The subject should be instructed to contact the Investigator if he/she is unable for any reason to take their study medication as prescribed.

Drug trough concentrations assessed in this study (TAC) will be measured as indicated in the Schedule of Assessments (Appendix 1) and samples will be analyzed locally.

The exact time and the date of sampling, together with the exact time and date of the last study medication dose prior to the sampling **must** be accurately recorded in the study chart (TAC), and then transcribed into the applicable eCRF. TAC will be measured in whole blood.

On the day of a scheduled sampling, the subject will be instructed not to take his/her morning dose of immunosuppressant medications, to record the medication dosage and time of last dose on the day prior to the blood sampling, and to bring all study drugs to the visit so that a dose may be administered upon completion of blood sampling.

6.11. Lifestyle Considerations/Contraception

To reduce the risk of pregnancy in the study, women of childbearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, are not allowed to participate unless they are using highly effective methods of contraception (Table 10) during dosing and for at least 12 months after the last dose of cyclophosphamide.

Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks prior to screening. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of childbearing potential.

Male subjects must agree to maintain barrier contraception (condom) and further agree not to father a child for at least 4 months after the last dose of cyclophosphamide and 3 months after the last dose of MMF.

Table 10: Highly Effective Contraception Methods

Highly Effective Contraception Methods
• **Total abstinence (when this is in line with the preferred and usual lifestyle of the subject).** Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
• **Male sterilization (at least 6 months prior to screening).** For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
Any of the following: • Use of oral, injected, or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%); for example, hormone vaginal ring or transdermal hormone contraception. • Placement of long-acting reversible contraceptives, an intrauterine device, or intrauterine system. • In case of use of oral contraception, women should have been stable on the same brand (or generic equivalent) for a minimum of 3 months before taking study treatment.

7. INFORMED CONSENT PROCEDURES

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation) Institutional Review Board (IRB)-approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written Informed Consent Form (ICF).

Informed consent must be obtained before conducting any study-specific procedures. The process of obtaining informed consent must be documented in the subject source documents.

ITB-MED will provide to investigators in a separate document a proposed ICF that complies with the International Council for Harmonisation Good Clinical Practice (ICH GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the Investigator must be agreed by ITB-MED before submission to the IRB.

A copy of the approved version of all consent forms must be provided to ITB-MED after IRB approval.

8. STUDY PROCEDURES AND ASSESSMENTS

While COVID-19 disease remains a risk, efforts to minimize the time a subject spends indoors at the clinic may be considered. These efforts could include use of virtual or telehealth technology, where appropriate, to remotely capture applicable study data (e.g., overall health status, assessment of medication compliance, review of AEs). The intent is to allow centers to minimize in-person onsite clinic visit activities for those assessments that require the subject to be physically present (e.g., laboratory collections or physical assessments), while conducting other study assessments virtually. In the event virtual or telehealth technology is utilized to facilitate data collection, it should be conducted per institutional practice and local regulations. Detailed documentation of all contact and information collected virtually is to be recorded in the study records.

This protocol defines 7 days to a week and 4 weeks (or 28 days) to a Study Month. For example, Week 2 is considered to start on Day 7 and Study Month 2 is considered to start on Week 5/ Day 28.

The full Schedule of Assessments is located in Appendix 1 and lists all study assessments and timing of when they are to be performed. All data obtained from these assessments must be supported in the subject's source documentation.

8.1. Study Periods

8.1.1. Screening Period (Day -37 to -10)

All donor and recipient subjects who have provided written informed consent will have up to 28 days to complete the screening assessments and procedures.

Refer to Screening Assessments (Section 8.2) and the Schedule of Assessments (Appendix 1) for required screening assessments and procedures.

8.1.1.1. Subject Identification Number (SID)

Each subject is identified in the study by a subject identification number (SID) that is automatically assigned by the IRT system once the subject has signed informed consent and has at least 1 study assessment or procedure completed. The SID is retained as the primary identifier for the subject throughout his/her entire participation in the study. The SID consists of the site number (assigned by ITB-MED to the investigative site) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database. A SID will be assigned for all donor and recipient subjects.

8.1.1.2. Screen Failures

All recipients who sign an ICF, have at least 1 study assessment or procedure, and are subsequently found to be ineligible prior to initiation of study treatment on Day -9, will be considered screen failures. The reason for screen failure should be recorded in the appropriate eCRF. Demographic information, informed consent, eligibility criteria, and any AEs/SAEs should be recorded in the appropriate eCRF for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures.

It is permissible to rescreen a recipient if s/he fails the initial screening; however, each case must be discussed and agreed with ITB-MED on a case-by-case basis.

8.1.2. Conditioning Period (Day -9 to Day 12) †

The conditioning regimen in this study is a specific set of treatments and procedures (see Section 6.5) that should be executed in a precise and timely manner. Refer to the Schedule of Assessments (Appendix 1) for required assessments and procedures during the Conditioning Period.

Note: Baseline clinical laboratory results for recipients must be available prior to initiation of the conditioning regimen.

† As rituximab is administered on Day 12, the Conditioning Period and Immunosuppression Period overlap by 13 days (including day of transplant on Day 0).

8.1.2.1. Day -9 (Outpatient)

The conditioning regimen will commence with the recipient receiving their first dose of rituximab (+ premedication) on Day -9. Administration of this first dose of rituximab will occur on an outpatient basis, but subjects should be informed of the lengthy time required at the clinic to accommodate premedication administration, infusion, and post-infusion evaluation. Refer to Section 6.5.2 for details on rituximab administration.

For complete details regarding administration of study treatments and all required assessments and procedures, refer to:

- Study Design Overview (Table 4)
- Schedule of Assessments (Appendix 1)
- Infection prophylaxis (Section 6.7)

8.1.2.2. Day [redacted] (Outpatient)

Administration of the first dose of siplizumab will occur on an outpatient basis, but subjects should be informed of the lengthy time required at the clinic to accommodate premedication administration, infusion, and post-infusion evaluation. Refer to Section 6.5.1 for details on siplizumab administration. The first per protocol hemodialysis will also be performed during this visit.

For complete details regarding administration of study treatments and all required assessments and procedures, refer to:

- Study Design Overview (Table 4)
- Schedule of Assessments (Appendix 1)
- Infection prophylaxis (Section 6.7)
- Hemodialysis (Section 6.5.4)

8.1.2.3. Day -5 through Day -1

Starting on Day -5, recipient subjects will be hospitalized and will remain domiciled for the remainder of the conditioning regimen, until discharge following transplantation. For complete details regarding administration of study treatments and all required assessments and procedures, refer to:

- Study Design Overview (Table 4)
- Schedule of Assessments (Appendix 1)
- Rituximab administration (Section 6.5.2)
- Infection prophylaxis (Section 6.7)
- Cyclophosphamide administration (Section 6.5.3)
- Hemodialysis (Section 6.5.4)
- Thymic irradiation (Section 6.5.5)
- Siplizumab administration (Section 6.5.1)

8.1.2.4. Day 0 (Day of Transplant)

The donor nephrectomy/bone marrow procurement and recipient renal transplant will be performed in coordination with the BMT team and executed per the surgeon's clinical judgment, expertise, and local guidelines.

- Donor Surgical Procedures (Section 6.5.6)
- Recipient Surgical Procedures (Section 6.5.7)

For complete details regarding Day 0 administration of study treatments and all required assessments and procedures, refer to:

- Study Design Overview (Table 4)
- Schedule of Assessments (Appendix 1)
- Siplizumab administration (Section 6.5.1)
- Tacrolimus (TAC) administration (Section 6.6.2)
- Corticosteroid (CS) administration (Section 6.6.3)
- Mycophenolate mofetil (MMF) administration (Section 6.6.1)

8.1.3. Immunosuppression Period (Day 0 to Month 12)

As rituximab is administered on Day 12, the Conditioning Period and Immunosuppression Period overlap by 13 days (including day of transplant on Day 0).

- Starting on Day 1, subjects will initiate broad infection prophylaxis against fungal/yeast, CMV, and HSV infection (see Section 6.7).
- Subjects will remain hospitalized, treated, and discharged per local and institutional guidelines. While hospitalized, the subject will have daily CBC and comprehensive

metabolic panel (chemistry) assessments, weekly CMV DNA NAAT surveillance, and assessments for graft loss, rejection, and GvHD. Following discharge, recipient subjects will return for weekly clinic visits through Week 12 (Month 3) and then monthly visits to the clinic through Month 12.

- Siplizumab administration on Day 1 for both arms; on Day [redacted] for Arm 2 only (Section 6.5.1).
- Rituximab administration on Days 5 and 12 (Section 6.5.2).
- Tocilizumab will be administered if CTS occurs (Section 6.5.8).
- Subjects will be administered TAC through Month 12 with concentrations managed via therapeutic drug monitoring using the local laboratory per local policy in agreement with the target concentration range (see Section 6.6.2).
- Corticosteroids will be tapered to stop at Day 20; if all weaning criteria are met, TAC will be tapered from Month 6 to complete withdrawal at Month 12 (see Section 6.6.2.1).
- Subjects will be administered MMF (see Section 6.6.1) until the weaning criteria are met, then discontinued at Week 8 (see Section 6.6.1.1).
- From Month 6 through Month 12, sCr testing will be performed every other week. On visit dates that include a comprehensive metabolic panel, an additional sample for sCr will not need to be drawn during the visit, as it is included in the panel.
- All donor subjects will have a telehealth assessment at 4 weeks post-nephrectomy to assess general well-being and to assess for any adverse events.

For complete details regarding all required assessments and procedures during the Immunosuppression Period, refer to the Schedule of Assessments (Appendix 1).

8.1.4. Immunosuppression-Free Period (Month 12 to Month 60)

Following the Month 12 visit, subjects will return for study visits on a quarterly basis through Month 24 for overall health and laboratory assessments and for evaluation of AEs. Month 24 is the study endpoint and a critical visit.

From Month 12 through Month 18, sCr testing will continue to be performed every other week. On visit dates that include a comprehensive metabolic panel, an additional sample for sCr will not need to be drawn during the visit, as it is included in the panel

Following completion of the Month 24 visit, subjects will enter a long-term follow-up period with study visits every 6 months until the final study visit at Month 60.

For complete details regarding all required assessments and procedures during the Immunosuppression-Free Period, refer to the Schedule of Assessments (Appendix 1).

8.1.5. Subject Study Completion

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them (as applicable based on local regulations).

Subjects who prematurely discontinue the study prior to Month 24, should have all Month 24 (M24) assessments and procedures performed. Subjects terminating after the Month 24 time point should have all assessments and procedures noted under the M60/EOS visit performed.

Subjects who are prematurely withdrawn from the study should be treated according to local SoC per the Investigator's judgment.

8.2. Screening Assessments

Pre-transplant screening procedures will include donor/recipient HLA typing (high resolution), crossmatch (flow, complement-dependent cytotoxicity [CDC], or virtual), DSA by single antigen bead (SAB) assay, PRA, and donor/recipient viral serology. Standard of care procedures performed prior to consent may be considered in the determination of subject eligibility (e.g., HLA/ABO typing, specific laboratory results).

8.2.1. Donors

All donors will be evaluated to confirm they are medically approved for allograft donation. Evaluation will follow SoC and local guidelines/institutional practice and should include donor demographics; histocompatibility testing; infectious disease screening; and medical, physical, and psychosocial evaluation (see Schedule of Assessments Appendix 1).

Laboratory assessments for donors may be performed as required per local practice and may omit assessments listed in the table of clinical laboratory evaluations (Section 8.4.3) including thyroid panel, coagulation studies, and immunogenicity if not required per local SoC.

8.2.2. Recipients

Refer to the Schedule of Assessments for all required assessments and procedures for recipients (Appendix 1).

See Section 8.4.3 for a comprehensive list of required laboratory evaluations.

8.2.3. Donors and Recipients

Refer to the Schedule of Assessments for all required assessments and procedures for donors and recipients (Appendix 1).

Histocompatibility Testing (HLA/ABO typing)

High-resolution HLA typing pre-transplant and HLA class I and class II antigens (including HLA A, B, C, DR, DP, and DQ) will be performed. In addition, serological testing of blood groups as well as B- and T-cell crossmatch tests will also be performed.

In addition to providing information on the quality of the match, the high-resolution HLA results will ensure capability of detecting hematopoietic cells of donor origin by [redacted] and by immunohistochemistry. HLA results will be recorded on the Recipient HLA Typing eCRF. Exploratory assessments of [redacted] will be calculated and reported out in the clinical study report (CSR) in combination with the [redacted] typing.

History of Sensitization (PRA, DSA)

The potential subject's serum is screened prior to transplant for reactivity against the proposed donor as well as against a panel of HLA specificities (PRA). The screening for anti-donor HLA antibodies (DSA) will utilize single antigen bead assays (e.g., Luminex).

Infectious Disease Screening

- CMV IgG antibody within 12 months of Day 0 (if no historical positive result)
- CMV IgM antibody within 12 months of Day 0 (if no historical positive result)
- Epstein-Barr virus nuclear antigen IgG antibodies
- Hepatitis B core antibody
- Hepatitis B surface antibody
- Hepatitis B surface antigen
- Hepatitis C antibody
- TB QuantiFERON
- HIV I/II screen
- HTLV-1 antibody
- Syphilis serology

8.3. Efficacy Assessments

The assessment of induction of renal allograft tolerance as the primary objective will rely on a composite of renal function as measured by the changes in serum creatinine and eGFR (Modification of Diet in Renal Disease [MDRD] and Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]) over time, as well as incidence and severity of acute rejection based on per protocol and for cause renal biopsies (Section 8.4.6), and immunosuppression dosing. In addition to standard safety assessments, the incidence of graft loss (Section 8.4.9), death, biopsy-proven acute rejection (Section 8.4.7), and lost to follow-up (Section 9.1.5) will be included as a key secondary composite endpoint.

8.4. Safety Assessments

8.4.1. Physical Examination

A complete physical examination (as per the Schedule of Assessments Appendix 1) will include a comprehensive assessment of the subject's general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen (including spleen and liver), back, lymph nodes, extremities, and vasculature. The examination will also include a thorough neurological evaluation.

If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant findings discovered after the start of study procedures, which meet the definition, must be recorded as an AE.

8.4.2. Electrocardiogram (ECG)

A standard 12-lead electrocardiogram (ECG) will be conducted with the subject in a supine position at screening, Month 24, and EOS. The ECG will be evaluated for potential contraindication for transplantation at screening and/or changes from baseline at the Month 24 and Month 60 visits. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Any abnormalities at baseline should be recorded as medical history in the subject's source documentation and entered into the medical history in the eCRF. Subsequent ECGs will be compared to baseline and when changes are present, the clinical significance evaluated by the Investigator or qualified designee, with relevant findings noted in the AE eCRF. The original tracing, or a copy, must be maintained and available for review.

8.4.3. Laboratory Evaluations

Unless indicated otherwise, all laboratory assessments will be processed and analyzed by the local laboratory and instructions for handling, processing, and storage of samples should be per institutional guidelines and procedure.

The Investigator must document in the source the clinical considerations and medical relevance of any values outside of the reference range. (i.e., result was/was not clinically significant and/or medically relevant) for all laboratory values.

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with ITB-MED personnel. The results should be evaluated for criteria defining an AE and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant.

Samples for the following local laboratory assessments (Table 11) will be performed at the time points noted in the Schedule of Assessment (Appendix 1) and as clinically indicated.

Table 11: Laboratory Assessments

Laboratory Panel	Analytes	
Complete Blood Count (CBC) with differential	Red blood cells (RBCs) Hemoglobin Hematocrit Mean corpuscular volume (MCV)	Mean corpuscular hemoglobin (MCH) White blood cells (WBCs) with differential (percent and absolute) Platelet count
Coagulation studies	Prothrombin time (PT)/ International Normalized Ratio (INR)	Activated partial thromboplastin time (aPTT)
Comprehensive metabolic panel	Albumin Total protein Sodium Potassium Bicarbonate (CO_2) Chloride Total calcium Blood urea nitrogen (BUN) Creatinine	Alanine aminotransferase (ALT)/ serum glutamic-pyruvic transaminase (SGPT) Aspartate aminotransferase (AST)/ serum glutamic-oxaloacetic transaminase (SGOT) Alkaline phosphatase Total bilirubin Glucose
Lipid panel	Total cholesterol Triglycerides	Low-density lipoprotein (LDL) High-density lipoprotein (HDL)
Thyroid panel	T3/ T4/Thyroid-stimulating hormone (TSH)	
Urinalysis	Leukocytes Nitrites Urobilinogen Protein pH Blood	Specific Gravity Ketones Bilirubin Glucose Microscopic, as indicated
Pregnancy testing (urine or serum)	A negative serum pregnancy test for women of childbearing potential (WOCBP) required during screening; negative urine pregnancy test prior to treatment on Day -9 (if anuric, serum test on Day -9).	
Donor-specific antibodies (DSA)	Blood samples (antibodies directed against antigens expressed on donor organs) will be processed and analyzed locally.	
[redacted]	Site dependent: panel to be defined by local laboratories (Refer to Section 8.6)	
[redacted]	Site dependent: panel to be defined by local laboratories (Refer to Section 8.6)	
Chimerism	[redacted]	

8.4.4. Infection Surveillance

8.4.4.1. Infections

Due to the increased likelihood of infections in transplant recipients and the use of peri-transplant conditioning, the assessment of all infections are important in quantifying the effects of the study treatment in this patient population. The clinical symptoms experienced by

the subject, along with the severity, source/causative organism, and seriousness of the event will be assessed by the Investigator or qualified designee and reported as an AE or SAE in the eCRF. Opportunistic infections will be treated as adverse events of special interest (AESIs) and reported as noted in Section 10.1.3.

8.4.4.2. Viral Surveillance

All subjects will be screened/monitored for TB, HBV, HCV, HIV, EBV, CMV, and BKV as outlined in Appendix 1 and per Section 6.8.3, Section 6.8.4, and Section 6.8.7 when more rigorous testing is indicated.

8.4.4.2.1. CMV DNA PCR

All subjects will have quantitative CMV viral load measured locally by a NAAT-based method, preferably calibrated in IU/mL. The CMV titer in blood should be recorded in the applicable eCRF. No specific viral load cutoffs are proposed for the initiation of antiviral therapy. However, persistent low-level viremia (<2500 IU) suggests excess immunosuppression or stimulation by other infections or processes (e.g., rejection).

If positive, treatment should be initiated per local practice. Where quantitative CMV is not available locally then CMV antigenemia may be measured for surveillance.

8.4.4.2.2. EBV DNA PCR

All subjects will have quantitative EBV viral load measured in serum (or whole blood) by a standardized PCR-based method. All measurements will be conducted by a laboratory utilizing World Health Organization (WHO) EBV international reference standards.

There are currently no consensus guidelines on thresholds for EBV DNAemia or viral load in adult renal transplant recipients; therefore, any PCR positive result that is increasing from baseline or a previous assessment should be flagged to the investigator for local follow-up per protocol, including a full physical and neurological exam with careful attention to the liver, spleen, allograft, and lymph nodes. In addition, ad hoc abdominal and allograft ultrasound to screen for signs and symptoms of potential PTLD lesions will be conducted.

Suspicion of PTLD in the setting of increasing EBV viral load should be further evaluated as outlined in Section 8.4.5.

8.4.5. EBV-PTLD Surveillance

Clinical manifestations of EBV infection range from asymptomatic infection to clinically significant and potentially life-threatening disease in transplant recipients. EBV infection can be either primary (new infection occurring in an immunologically naïve subject) or secondary due to either reactivation of latent EBV in the transplant recipient under the pressure of immune suppression or reinfection with a new EBV strain. In general, secondary infection tends to be mild or even asymptomatic. Histologic evaluation is important in defining disease status of a subject with suspected PTLD; manifestations can evolve in individual subjects.

The World Health Organization has provided standardized criteria for the pathologic evaluation of lesions associated with EBV in solid organ transplant recipients.

The following signs and symptoms should guide the clinician in assessing the risk of, and for, EBV-PTLD:

EBV Signs and Symptoms		
Signs:	Pallor Lymphadenopathy Subcutaneous nodules Tonsillar enlargement / inflammation	Hepatosplenomegaly Focal neurologic signs Mass lesions found on imaging obtained for other reasons
Constitutional and Systemic Symptoms:	Unexplained fever or night sweats Malaise Weight loss and/or anorexia	Sore throat Swollen glands Headache or focal neurological symptoms
Allograft-specific symptoms:	Liver: jaundice, abdominal pain Intestine: abdominal pain, gastrointestinal bleeding, nausea, and vomiting Heart/Lung: shortness of breath, cough, decreased lung function (lung alone) Renal: kidney dysfunction	
Lab Tests:	Serial increase in EBV viral load from peripheral blood	

Abbreviation: EBV = Epstein-Barr virus.
Source: Green 2013.

The following assessments may be considered as part of the diagnostic work-up for suspected EBV-PTLD):

EBV Diagnostic Evaluation	
Routine Laboratory Assessments:	CBC with differential Platelets Serum electrolytes (inc. BUN/creatinine, calcium) Liver function test Uric acid Lactate dehydrogenase Quantitative immunoglobulins EBV serologies (anti-Epstein-Barr nuclear antigen (EBNA), viral capsid antigen (VCA) and early antigen (EA) EBV viral load from peripheral blood Stool: occult bleeding
Routine Procedures:	Chest radiograph (anteroposterior and lateral) CT or PET scan of neck/chest/abdomen/pelvis Core needle or excisional biopsy of lesion(s) with flow cytometry of lymphocytes (when feasible) EBER, CD20 histochemistry studies of pathologic samples
Procedures based on S/Sx:	Bone marrow biopsy Bone scan Brain CT/MRI Gastrointestinal endoscopy Lumbar puncture Ultrasound (abdomen and allograft)
Lab Tests:	Serial increase in EBV viral load from peripheral blood

Abbreviations: BUN = blood urea nitrogen; CBC = complete blood count; CT = computed tomography; EBV = Epstein-Barr virus; MRI = magnetic resonance imaging; PET = positron emission tomography; S/Sx = signs and symptoms.
Source: Green 2013.

Any diagnostic procedures or additional laboratory assessments that result in the diagnosis of EBV-PTLD must be captured in the relevant eCRFs.

8.4.5.1. Imaging: PTLD Surveillance

When warranted based on physical examination findings and/or EBV surveillance, subjects should have an ultrasound performed of the abdominal cavity and allograft to rule out nodal and/or extra-nodal EBV-LPD lesions. Computed tomography (CT), magnetic resonance imaging (MRI) and/or positron emission tomography (PET) imaging may be considered for staging and monitoring of biopsy-confirmed PTLD.

8.4.6. Renal Biopsy

Protocol biopsies are required at the time of transplant (Day 0); nominally at Month 6 and Month 12 (to allow the weaning of immunosuppression); and at Month 24 to support the primary analysis. Renal allograft biopsies for the assessment of weaning and primary analysis should fulfill the 'minimal sample' thresholds and criteria for specimen adequacy as defined by the Banff Foundation for Allograft Pathology. Biopsies will be stained and processed according to local practice and the 2018 Banff criteria (Appendix 7). The biopsy is to be read by the local pathologist and results, including component scores and final assessment, recorded in the applicable eCRF. In the event a biopsy result is inconclusive, central pathology and an independent adjudication committee may be convened on an ad hoc basis.

For all suspected rejection episodes, regardless of initiation of anti-rejection treatment, a renal biopsy must be performed within 48 hours. The results will be used for subject management for acute rejection.

All biopsy results (for cause, per protocol, local practice) should be recorded in the applicable eCRF.

8.4.7. Treated Biopsy-Proven Acute Rejection

Treated biopsy proven acute rejection (tBPAR) is any condition in which the subject receives anti-rejection treatment and is histologically diagnosed as acute rejection according to the 2019 Banff criteria, including borderline rejections, as outlined in Appendix 7.

All rejection episodes will be documented with final clinical diagnosis and outcome on the Allograft Rejection eCRF.

8.4.8. Graft-versus-Host Disease (GvHD)

It is expected that study subjects will present with transient mixed chimerism post conditioning and BMCI infusion. The intent of the ongoing screening and aGvHD surveillance is to monitor subjects for signs and symptoms of GvHD while they remain chimeric. GvHD assessments will be carried out regularly according to the Schedule of Assessments (Appendix 1) and aGvHD Assessment scoring and staging per Appendix 8.

Surveillance for aGvHD in subjects with persistent chimerism, defined as chimerism >5%, beyond Month 3, may require additional weekly visits to check liver function tests (LFTs; for liver GvHD), rash for skin GvHD, and stool volume for GI GvHD, if diarrhea is present. This extended (greater than Month 3) surveillance can be conducted using a tiered approach per the

clinical judgment of the Investigator and clinical team. At a minimum, the subject should be contacted by phone by the Investigator or their designee to ascertain any new signs or symptoms consistent with aGvHD (i.e., rash, intermittent or persistent nausea, vomiting, anorexia, or diarrhea). If there is no clinical suspicion based on the telehealth visit with the study subject, no further testing is required at that time. A repeat telehealth assessment should be conducted a week later. If the Investigator suspects the possibility of aGvHD, the subject should be seen for a more comprehensive in-person assessment consistent with the protocol, current clinical guidelines, and institutional policies. Any phone or telehealth visit with the study subject should be recorded in the source. In addition, relevant AEs and SAEs pursuant to any telehealth screening and assessment should be captured as required.

Biopsies of skin, gut, and/or liver should be performed as clinically indicated to confirm a diagnosis of GvHD. Acute GvHD will be diagnosed, staged, and graded (I–IV) according to current hematology/oncology practice guidelines (e.g., Harris 2016). Similarly, chronic GvHD will be assessed according to applicable consensus guidelines for diagnosis and staging of chronic GvHD (Jagasia 2015). Any cases of acute or chronic GvHD will be recorded as AEs/SAEs, noting organ involvement and severity grading.

8.4.9. Graft Loss

The allograft will be presumed to be lost on the day the subject starts dialysis and is not able to subsequently be removed from dialysis. If the subject undergoes allograft nephrectomy prior to starting permanent dialysis, then the day of nephrectomy is the day of graft loss. The reason for graft loss will be recorded in the applicable eCRF. Graft loss is considered an SAE and should be reported on the AE eCRF (as serious) and the SAE reported to ITB-MED Safety within 24 hours.

8.4.10. Death

In the event of subject death, the SAE leading to death should be reported to ITB-MED Safety within 24 hours.

8.5. Pharmacodynamic (PD) Assessments

All pharmacodynamic (PD) blood samples will be taken by either direct venipuncture or an indwelling cannula.

8.5.1. Chimerism Assessment

The nature and level of donor hematopoietic chimerism post-transplantation will be monitored.

Flow cytometric analysis of blood after the donor cell infusion will be performed for the assessment of chimerism. Testing of percent chimerism may be done for multiple lineages. These analyses may be performed to determine distinct donor/recipient profiles. The frequencies of recipient and donor-derived leukocytes and their subsets will be measured by [redacted] until donor chimerism (via donor MHC class I expression) becomes undetectable. The frequencies of recipient leukocytes and their subsets recovered in the blood of subjects using [redacted] will also be evaluated every month after transplantation through Month 12 and then quarterly through Month 24.

[redacted]. This assay is generally capable of detecting approximately 0.1% donor-type cells (Foissac 1997). Assays on separated PBMC cell fractions (T cells: when present at >30 cells/mm^3, B cells: when present at >30 mm^3, granulocytes and monocytes) will be used to assess chimerism in different lineages.

8.6. Exploratory Assessments

[redacted] per protocol and will be conducted by select centers with the laboratory capabilities. Separate exploratory or mechanistic assessments may also be conducted under the setting of an approved sub-study protocol by centers who have enrolled subjects in the core TCD601A201 study (see Section 13.4.4).

8.6.1. [redacted]

Serum blood samples will be collected during the study for [redacted] Details of exploratory biomarker sample collection, handling, processing, storage, shipment, and analysis will be described in a separate Laboratory Manual.

8.6.2. [redacted]

At clinical center's with capabilities, the effect of siplizumab and conditioning on circulating [redacted]

9. STUDY DISCONTINUATION AND COMPLETION

9.1. Discontinuation

9.1.1. Vital Signs, Height, Weight, and Body Mass Index (BMI)

Vital signs (radial pulse rate, blood pressure, respiratory rate, body temperature), along with height and weight will be recorded as indicated in the Schedule of Assessments (Appendix 1). Attempts should be made to assess the blood pressure and pulse on the same arm each time of determination and after the subject has rested in the sitting position (may be supine if during hospitalization) for at least 5 minutes. Body temperature should be measured as per local practice; the same method to be used consistently for all subjects at each site.

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg]); in indoor clothing, but without shoes will be measured.

Body mass index (BMI) will be calculated using the following formula:

$$BMI = \frac{Body\ Weight\ (kg)}{Height\ (m)^2}$$

9.1.2. Safety Stopping Rules

The following stopping rules based on potential toxicities will serve as the basis for pausing enrollment.

Although the stopping criteria do not incorporate an absolute requirement for causality, the potential relationship between an AE(s) and siplizumab will be evaluated carefully on a case-by-case basis between ITB-MED and the Investigator. Following a review of the AE(s), a decision to permanently discontinue enrollment or re-initiate dosing will be made by the DMC.

- One (1) subject death or graft loss within the first month with the exception of technical failures.
- One (1) subject presents with histologically† confirmed EBV-PTLD.
- One (1) subject with Grade 3 or higher cytokine release syndrome within 24 hours of any siplizumab administration.
- One (1) subject with any Grade 4 toxicity (except neutropenia), considered siplizumab related as determined by the Investigator within the first 28 days.
- One (1) subject with failure to recover from Grade 4 neutropenia (ANC <500 mm^3; $<0.5 \times 10^9$/L) by Day 28.
- Two (2) subjects with sustained (>21 days) Grade 3 neutropenia (ANC of 500 to <1000/mm^3; 0.5 to $<1.0 \times 10^9$/L) considered related to siplizumab.
- Two (2) or more subjects presenting with Grade 3 or higher toxicity considered study drug related as determined by the Investigator, including infusion reactions, within 24 hours of any siplizumab administration.

- Two (2) or more subjects presenting with Grade IIA or higher BPAR (T-cell mediated rejection [TCMR]; central pathology) during the first 6 months post-transplant.

  † NOTE: In the event of suspected PTLD lesions where a biopsy is not possible (e.g., central nervous system symptoms), radiographic and imaging (MRI) studies may be used to stage and assess the disease.

9.1.3. Discontinuation of Study Treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration. Discontinuation can be initiated by the subject, the investigator, or by ITB-MED.

9.1.3.1. Possible Reasons for Study Treatment Discontinuation

Possible reasons for study treatment discontinuation are:

- AE (e.g., cytokine release syndrome, prolonged neutropenia, PTLD, CTS)
- Lack of Efficacy
- Technical problem during transplant surgery
- Primary non-function
- Subject/Guardian Decision
- Lost to follow-up
- Pregnancy
- Death
- Graft Loss

9.1.3.2. Other Discontinuation Scenarios

Due to the nature of the pre-transplant NMA conditioning regimen and combined renal transplant and BMCI, there are several situations that could occur, requiring a shift in the treatment and care of the recipient, should the subject terminate from the study prematurely.

The following scenarios provide initial guidance on the management of subjects under such conditions. Please note, these are to be implemented in consultation with ITB-MED.

9.1.3.3. Discontinuation Pre-transplant: During Conditioning

In the unlikely event that a recipient initiates the conditioning regimen but is unable to complete the entire conditioning treatment course prior to receiving the BMCI, the subject will be deemed a treatment failure, terminated from the study, and treated per institutional practice and SoC. The BMCI will not be administered in this scenario and the living-donor transplant procedure should proceed per standard practice. Any myelosuppression following the partial conditioning should be managed per institutional practice under the supervision of the hematology and renal transplant team assigned to this study. Any SAEs experienced by the subject over the 12-month period following transplant, should be evaluated and reported to ITB-MED when felt to be related to the treatment regimen under study.

9.1.3.4. Discontinuation Post-transplant/BMCI

In the event a recipient is unable to complete the conditioning regimen following their transplant and BMCI, the subject should continue in the study.

9.1.3.5. Discontinuation Prior-to/During Immunosuppression Withdrawal

In the event a recipient presents with Banff Grade IA or higher biopsy proven acute rejection (BPAR) or AMR or is unable to meet the weaning criteria (see Table 8) the subject will be considered a treatment failure and immunosuppression weaning will not be attempted. The subject should continue on SoC immunosuppression and be followed per protocol to assess safety and outcomes.

These subjects, in addition to those who complete the conditioning regimen and terminate prematurely, should NOT be considered withdrawn from the study UNLESS they withdraw their consent to participate. These subjects should remain in the study, and receive SoC immunosuppression, according to local practice, and return for all study visits through Month 60.

To assure adequate monitoring of safety and outcomes while reducing the study burden, subjects meeting the criteria of a treatment failure may adopt an abbreviated visit schedule as outlined below.

- Prior to Month 12: Every 3 months through Month 12
- Between Month 12 and 24: Every 6 months through Month 24
- After Month 24: Annually through Month 60

When local SoC visits occur between the study visits noted above, collection and subsequent entry into the eCRF of SoC data (e.g., serum creatinine, tacrolimus trough concentrations, laboratory results, DSA rejection) is encouraged to provide a more comprehensive assessment of safety and activity.

All enrolled subjects are expected to continue in the study up to Month 60. If they refuse to return for planned assessments or are unable to do so, every effort should be made to contact them to determine their health status, evaluate safety (SAEs) and to request a final study visit. Subjects who prematurely discontinue the study prior to Month 24, should have all Month 24 (M24) assessments and procedures performed. Subjects terminating after the Month 24 time point should have all assessments and procedures noted under the M60/EOS visit performed. Documentation of attempts to contact the subject should be recorded in the source documentation. If the subject is unable to return for a final study visit, every effort to obtain the subject and graft status should be made and documented within the subject chart.

9.1.4. Withdrawal of Informed Consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject no longer wishes to participate in the study and does not allow further collection of personal data.

In this situation, the Investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information. Study treatment must be discontinued, and no further assessments

completed. Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up. ITB-MED will continue to maintain, and use collected study information (including any data resulting from the analysis of a subject's samples until the time of withdrawal) according to applicable law.

All biological samples collected at the time of withdrawal, but not yet analyzed for subjects enrolled within the US, may still be used for further testing/analysis in accordance with the terms of this protocol and the ICF.

Prior to withdrawing consent, subjects should be given the option for the Investigator to collect limited safety data, either from personal subject account or via health records. In the event the subject is willing, an informed consent document that has been reviewed and approved by the local IRB must be obtained from the subject prior to entry of data into the eCRF.

9.1.5. Lost to Follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the Investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, (e.g., dates of telephone calls, registered letters). A subject should not be considered as lost to follow-up until due diligence has been completed or until the EOS.

9.1.6. Early Study Termination by the Sponsor

The study can be terminated by ITB-MED at any time. Should this be necessary, the subject should be seen as soon as possible and treated as a prematurely withdrawn subject. The Investigator may be informed of additional procedures to be followed in order to ensure adequate consideration is given to the protection of the subject's interests. The Investigator will be responsible for informing IRBs of the early termination of the study.

9.2. Study Completion

Study completion is defined as when the last subject finishes their final study visit (Month 60) and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that termination and the end of study (EOS) assessments.

10. SAFETY MONITORING AND REPORTING

10.1. Definition of Adverse Events and Reporting Requirements

10.1.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered an investigational product which does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including a new, clinical important abnormal laboratory finding), symptom, or disease, temporally associated with the product, whether or not related to the product.

Pre-existing diseases or conditions will not be considered an AE unless there is an increase in the frequency or severity, or a change in the quality of the disease or condition (worsening of a pre-existing condition is considered an AE).

The occurrence of AEs must be sought by non-directive questioning of the subject at each visit during the study. AEs also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

AEs must be recorded under the signs, symptoms, or diagnosis associated with them, and accompanied by the following information: Assessment and grade according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

- Relationship to the study treatment

  If the event is due to lack of efficacy or progression of underlying illness (i.e., progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the event is not caused by the study drug itself, but due to the symptoms as a result of lack of efficacy or a progression of the disease under study.

- Duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved
- Whether it constitutes a SAE and which seriousness criteria have been met
- Action taken regarding with study treatment
- Outcome

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for the duration of the study. In the event a subject does not complete the study for any reason, AE monitoring should continue for 6 months after the last administration of IP.

Once an AE is detected it must be followed until resolution or until it is judged to be permanent (e.g., continuing at the EOS). An assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat the AE, and the outcome.

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study medication or their clinical significance. Given the potential for protracted time between a subject providing informed consent and organ transplant, AE collection will commence once a subject has provided consent and has at least one invasive study procedure completed and/or performed (e.g., blood draw).

Information about adverse drug reactions for the investigational drug can be found in the IB.

Abnormal laboratory values or test results constitute AEs only if they are considered clinically significant and/or require therapy or active management.

10.1.2. Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that:

- Results in death
- Is life-threatening
    - Note: The term “life-threatening” in the definition of ‘serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization
    - Note: Inpatient hospitalization is defined as 24 hours in a hospital or an overnight stay. An elective hospital admission to treat a condition present before exposure to the study drug, or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE. Further, an overnight stay in the hospital that is only due to transportation, organization, or accommodation problems and without medical background does not need to be considered an SAE. Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition that has not worsened since the signing of consent is not considered an SAE.
- Is an important medical event

In this study, hospitalization is expected during the Conditioning Period starting on Day -5 until post-transplant discharge and this pre-specified hospitalization would not be considered an SAE. In addition, hospitalization solely for renal biopsy per protocol or for cause would not itself be considered an SAE.

All reports of intentional misuse and abuse of the product are also considered SAEs irrespective if a clinical event has occurred.

10.1.3. Adverse Events of Special Interest (AESIs)

The following AEs are selected as adverse events of special interest (AESIs) for surveillance and follow-up, both serious and non-serious, based on previous experience with siplizumab:

- CTS
- Opportunistic Infections
- Malignancies

10.1.4. SAE Reporting

Every SAE, regardless of causality, occurring after the subject has provided informed consent and had at least 1 invasive study procedure performed and continuing until the final study visit, must be reported to the ITB-MED Safety Department or its designee. Reporting must take place within 24 hours of learning of its occurrence and is done by entering the SAE into the eCRF within 24 hours of awareness. Additionally, all AESIs, whether serious or not should also be reported following the same procedure.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This information must be submitted within 24 hours of the Investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information on all SAEs (either initial or follow up) is collected and entered into the eCRF(s). Information may also be submitted in writing to pharmacovigilance@klifo.com when important information or clinical updates are required that may not be feasible to provide within the eCRFs. Please refer to the Site Study Manual for detailed instructions on the reporting of SAEs.

If the SAE is not previously documented in the IB or Prescribing Information (new occurrence) and is thought to be related to the study treatment, ITB-MED Safety may urgently require further information from the Investigator for health authority reporting. ITB-MED may need to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with national regulatory requirements in participating countries.

Any SAEs experienced in subjects who terminate from the study prematurely should be reported if a causal relationship is suspected.

10.1.5. Pregnancy Reporting

To ensure subject safety, each pregnancy occurring while the subject is on study treatment must be reported to ITB-MED Safety within 24 hours of learning of its occurrence. The pregnancy should be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy follow-up should be reported to ITB-MED Safety and should include an assessment of the possible relationship to the investigational treatment to pregnancy outcome. Any AE or SAE experienced during pregnancy must also be reported.

10.2. Enhanced Safety Monitoring – First Month

The Investigator will monitor AEs in an ongoing manner and inform ITB-MED of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel between ITB-MED or its designee and the Investigator. Criteria pertaining to stopping the study/treatment or adapting the study design are presented in Section 9.1.

ITB-MED will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if life threatening) of any new, clinically relevant safety information during the conduct of the study in a timely manner.

11. DATA MONITORING COMMITTEE

This study will include a Data Monitoring Committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical study, including the site investigators participating in the study. The DMC will assess at defined intervals the progress of the clinical study, safety data including the incidence and severity of CTS as well as critical efficacy variables and recommend to ITB-MED whether to continue, modify, or terminate the study.

Specific details regarding composition, responsibilities, data monitoring and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between ITB-MED and the DMC.

12. DATA ANALYSIS AND STATISTICAL METHODS

The final analysis plan will be documented in a formal statistical analysis plan (SAP) that must be finalized before database lock. The SAP will include details on how variables will be derived, how missing data will be handled, and how data will be presented, as well as the details on statistical methods to be used for safety and efficacy analyses. The final clinical study report (CSR) will discuss deviations from the final SAP, if any.

Any data analysis carried out independently by the Investigator must be conducted in accordance with this protocol, contract and/or ITB-MED publication policies. Any ad hoc analysis that complies with these requirements is be submitted to ITB-MED before publication or presentation.

12.1. Analysis Sets

The Full Analysis Set (FAS) comprises all subjects to whom study treatment has been assigned. According to the intent-to-treat principle, subjects will be analyzed according to the treatment they have been assigned during the procedure.

The Safety Set includes all subjects who received at least 1 dose of study treatment. Subjects will be analyzed according to the study treatment received, where treatment received is defined as the randomized/assigned treatment if the subject took at least 1 dose of that treatment (or the first treatment received if the randomized/assigned treatment was never received).

The PD Analysis Set [redacted] will include all subjects in the FAS with available PD data and no protocol deviations with relevant impact on PD data.

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

12.2. Subject Demographics and other Baseline Characteristics

All data for background and demographic variables will be listed by arm and subject. Summary statistics will be provided by arm.

Subject demographics will include age, sex, race, ethnicity, height, weight, and BMI.
Other baseline disease characteristics include relevant medical history, current medical conditions, results of laboratory screens, transplant history, donor characteristics (e.g., age, sex, race, type, warm ischemia time [WIC]/cold ischemia time [CIT]) and any other relevant information.

Summary statistics will be presented for the subjects in the FAS. Continuous variables will be presented with mean, median, 25th percentile, 75th percentile, standard deviation (SD), minimum and maximum, and the number of non-missing observations.

Categorical data will be displayed via absolute and relative frequencies for each category (including a category labeled as “missing” when appropriate).

12.3. Treatments

The duration (days) of study medication administration will be summarized. This will be calculated by subtracting the date of the last administration of study medication from the date of first administration and then adding the dosing interval for siplizumab, TAC, MMF, or CS.

In calculating the duration of treatment, days of temporary interruption of study medication for any reason will be included. Further, the frequency of dose changes (including temporary dose interruptions) will be presented by reason for the change.

Average daily doses will be presented by dose levels. “Zero” will be used for periods of temporary interruption of study medication for any reason.

The number and percentage of subjects who prematurely discontinued study medication will be summarized by reason for discontinuation.

Study treatment errors, including uses outside of what is foreseen in the protocol, will be summarized. Adverse events as a result of study treatment error will also be summarized.

12.3.1. Background Immunosuppressants and Conditioning

The average daily dose of TAC, MMF, and CS will be summarized by arm for subjects on study medication. Where concentrations are measured, trough concentrations will be summarized by subject and treatment arm. The dose of antibodies used for the treatment of acute rejection episodes will be recorded as well. The time to complete weaning of immunosuppression and the number of days off immunosuppression will be calculated for each subject and summary statistics prepared. Resumption of immunosuppression after complete discontinuation will be recorded as a failure. The status of the subject as “off immunosuppression” will be derived from the dose administration records.

For rituximab and cyclophosphamide, presentation will include the total calculated dose (per kg) and number of doses. Similarly, the dose of thymic irradiation will be given.

12.3.2. Other Concomitant Treatments

Concomitant medications, other than immunosuppressants and conditioning agents mentioned above, will be summarized by therapeutic class and Preferred Term (PT) by presenting the number and percentage of subjects using each medication for each treatment arm. For infectious prophylaxis the medications used will be tabulated separately.

12.4. Analysis of the Primary Endpoint(s)

12.4.1. Definition of Primary Endpoint(s)

The primary objective is to determine the optimal regimen for renal allograft tolerance (proportion of recipients off immunosuppression with maintenance of good renal function at Month 24 post-transplant) while minimizing CTS.

This will be assessed using the endpoints of immunosuppression dosing, renal function [assessed as eGFR using sCr (eCFR)], CTS (assessed by renal biopsy and serum creatinine), rejection (also assessed by renal biopsy), and the overall AE/SAE data.

Number and percentage of subjects achieving renal allograft tolerance will be summarized for the FAS.

12.4.2. Statistical Model, Hypothesis, and Method of Analysis

All data will be summarized and presented descriptively, no formal statistical analysis or hypothesis testing will be conducted on the analysis sets.

12.4.3. Handling of Missing Values/Censoring/Discontinuations

The analysis will be made on the FAS population. The following imputation method will be applied for subjects with missing data:

- Subjects that lose their graft will be assigned a value of zero for their missing estimated glomerular filtration (eGFR) value.
- Subjects that die or are lost to follow-up with a functioning graft will have an imputed value using the last-observation-carried-forward (LOCF) method.
- For subjects that discontinue treatment, the eGFR will be considered missing after applying the windows defined in the SAP.

Graft loss subjects do not have a functioning graft; hence the lowest possible GFR value (zero) will be assigned to such subject. Subjects who die for other reasons (e.g., suicide, car accident, cancer), but with a functioning graft, will be imputed with the most recent GFR value.

Subjects who are lost to follow-up and have measurable renal function, but missing values for various reasons (e.g., moving from the area, not being able to make the site visit during the Month 6 or Month 12 visit window), or subjects who have a functioning graft at the time of death or are lost to follow-up with a functioning graft will be analyzed via an imputation method that employs LOCF.

12.5. Analysis of Key Secondary Endpoints

Key secondary endpoints include:

- Number and percentage of subjects experiencing BPAR, death, and graft loss (with and without lost to follow-up) up to Month 24 post-transplant.
- Number and percentage of subjects of DSA positivity up to Month 24 post-transplant.
- MFI of DSA up to Month 24 post-transplant.

Incidence data will be summarized by number and percentage of subjects with the incidence. MFI of DSAs at Month 24 post-transplant will be presented with mean, median, 25th percentile, 75th percentile, SD, minimum and maximum, and the number of non-missing observations.

12.6. Analysis of Other Secondary Endpoints

Other secondary endpoints include:

- Number and percentage of subjects experiencing CTS by severity
- Duration of CTS defined as time from onset of CTS to resolution
- Number and percentage of subjects with transient mixed chimerism without CTS
- Number and percentage of subjects off immunosuppression for at least 12 months

- Number and percentage of subjects experiencing death and graft loss.
- Number and percentage of subjects experiencing BPAR
- Number and percentage of subjects treated for BPAR (with Banff classification)
- Number and percentage of subjects with positive, semi-quantitative DSA
- eGFR and change in eGFR
- Number and percentage of subjects with treatment-emergent AEs/SAEs by System Organ Class (SOC) and PT
- Number and percentage of subjects with clinically significant opportunistic infections
- Number and percentage of subjects with BK viremia, infection, and nephropathy
- Number and percentage of subjects with malignancies
- Number and percentage of subjects with GvHD by severity
- Number and percentage of subjects with NODAT

Incidence data will be summarized by number and percentage of subjects with the incidence.

Continuous variables will be presented with mean, median, 25th percentile, 75th percentile, SD, minimum and maximum, and the number of non-missing observations.

Categorical data will be displayed via absolute and relative frequencies for each category (including a category labeled as "missing" when appropriate).

12.6.1. Safety Endpoints

For all safety analyses, the Safety Set will be used. All listings and tables will be presented by dose levels.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g., change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for AEs will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent adverse events [TEAEs]).

The on-treatment period lasts from the date of the first administration of study treatment through the last administration of immunosuppression (e.g., Month 12, or end of study [EOS] for recipients who are unable to discontinue therapy).

12.6.1.1. Adverse Events

Adverse events which will be counted for a specific treatment period are those which are treatment-emergent. These events are those with an onset after the start of the treatment period, or which were present prior to the start of the treatment period but increased in severity, changed from being not suspected to being suspected of study drug relationship, or developed into SAEs after the start of the treatment period. All information obtained on TEAEs will be displayed by arm.

The number (and percentage) of subjects with TEAEs (events started after the first dose of study medication or events present prior to start of treatment but increased in severity based on PT) will be summarized in the following ways:

- TEAEs by primary SOC and PT
- TEAEs rated to have relationship to study drug by SOC and PT
- TEAEs by primary SOC, PT, and maximum severity
- SAEs by SOC and PT
- SAEs rated to have relationship to study drug by SOC and PT
- Deaths by SOC and PT
- TEAEs leading to discontinuation of a study drug by SOC and PT
- TEAEs leading to dose adjustment or interruptions of a study drug by SOC and PT
- Infections by type of infection (viral, bacterial, fungal, and others) and microorganism of infection
- Serious infections by type of infection and micro-organism of infection
- TEAEs by standardized Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) levels (broad and narrow search)
- TEAEs by SMQ and PT (broad and narrow search)

Separate summaries will be provided for study medication related TEAEs, death, SAEs, other significant TEAEs leading to discontinuation and TEAEs leading to dose adjustment.

The number (and proportion) of subjects with AESIs/related to identified and potential risks (i.e., CTS, opportunistic infections, malignancies) will be summarized by dose levels.

Multiple Occurrences for Tables

In all tables about incidence rates of TEAEs/infections, if a subject has multiple occurrences of a TEAE, the subject will be counted only once in the corresponding TEAE category. A subject with multiple TEAEs within an SOC will be counted only once for that class. A subject with multiple severity ratings for a TEAE while on treatment is only counted under the maximum rating.

Treatment-emergent adverse events will be listed by subject, verbatim term given by the Investigator, MedDRA PT and SOC, start and end date, causality, National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade, and relationship to study drug (as assessed by the Investigator).

12.6.1.2. Vital Signs

All vital sign data will be listed by arm, subject, and visit/time; if ranges are available, abnormalities will be flagged. Summary statistics will be provided by arm and visit/time.

12.6.1.3. Clinical Laboratory Evaluations

Abnormalities according to clinically notable criteria will be identified. A by-subject listing of individual subject laboratory data will be generated. Values outside of the clinically notable limits will be flagged. Shift tables describing changes from baseline based on the clinical notable criteria will be presented.

Descriptive statistics (mean, SD, minimum, median and maximum) of quantitative laboratory variables, including change from baseline, will be generated by visit.

12.6.1.4. Other Safety Evaluations

BK-polyoma viremia and nephropathy**; t**he following variables will be analyzed descriptively:

- Occurrence of BK-polyoma viremia any time post-transplantation
- Occurrence of BK-polyoma virus nephropathy any time post-transplantation

12.6.1.4.1. EBV and CMV Surveillance

All EBV and CMV surveillance data will be listed by arm, subject, and visit/time; if normal ranges are available, abnormalities will be flagged. Summary statistics will be provided by arm and visit/time.

12.6.2. Estimated GFR (eGFR)

Renal function as assessed by eGFR (CKD-EPI and MDRD formulae) will be evaluated at Months 3, 6, 12, 24, and yearly thereafter. Observed value and change from baseline of eGFR will be summarized by arm and visit.

12.6.3. Chimerism Assessment

All data will be listed by arm, subject, and visit/time. Summary statistics will be provided (mean, median, SD, minimum and maximum) by arm and visit and time.

12.7. Exploratory Endpoints

All exploratory assessments (e.g., [redacted]) will be listed by arm, subject, and visit/time. Summary statistics will be provided (mean, median, SD, minimum and maximum) by arm and visit/time.

In summary tables of [redacted] data, the frequency (n, %) of values below the lower limit of quantification (LLOQ) and above the upper limit of quantification (ULOQ), respectively, will be included. For censored values (values below the LLOQ and/or values above the ULOQ), the summary statistics (arithmetic mean, SD, geometric mean, and percent coefficient of variation [CV%] of geometric mean) will be calculated as the maximum likelihood estimates using a parametric model for data that can be right-censored and left-censored assuming the data is normally or log-normally distributed.

12.8. Interim Analyses

Additional ad hoc interim analyses may be performed. Results of such interim analyses will be communicated to the DMC for information, consulting and/or decision purposes as well as to participating investigators for information as deemed appropriate.

12.9. Sample Size Calculation

No formal sample size or power analysis has been performed. A sample size of 18 subjects (Arm 1 = 12; Arm 2 = 6) was chosen to characterize the incidence and severity of CTS in the

immediate post-transplant time period while balancing the overall risk-benefit in a regimen finding study.

13. STUDY CONDUCT

13.1. Sponsor Responsibilities

ITB-MED is obligated to conduct the study in accordance with strict ethical principles. ITB-MED will take action to ensure the accuracy and reliability of study data by selecting qualified investigators and sites, reviewing protocol procedures with the Investigator and relevant study personnel prior to study initiation, conducting routine monitoring visits and by utilizing robust data management standards.

13.2. Investigator Responsibilities

The Investigator agrees to conduct this study in accordance with all laws, regulations, and guidelines of the pertinent regulatory authority. While delegation of certain aspects of the study to sub-investigators and research personnel is appropriate, the Investigator will remain personally accountable for closely overseeing the study and for ensuring compliance with the protocol and all applicable regulations and guidelines. Investigators should ensure that all persons who have been delegated study-related responsibilities are adequately qualified and informed about the protocol, study drugs and their specific duties within the context of the study.

Before initiating a study, the Investigator/institution must obtain approval/favorable opinion from the IRB for the study protocol, written ICF, consent form updates, subject recruitment materials (e.g., advertisements) and any other written information to be provided to subjects.

Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to ITB-MED monitors, auditors, ITB-MED Quality Assurance representatives, designated agents of ITB-MED, IRBs, and regulatory authorities as required.

If an inspection of the clinical site is requested by a regulatory authority, the Investigator must inform ITB-MED immediately that this request has been made.

13.3. Site Initiation

Study personnel may not screen or enroll subjects into the study until after receiving notification from ITB-MED or its designee that the study can be started.

The regulatory documents must be received from the Investigator and reviewed and approved by ITB-MED or its designee before the study site can begin screening procedures and before ITB-MED can authorize shipment of IP to the site. Copies of the Investigator's regulatory documents must be retained at the study site in a secure location. It is the Investigator's responsibility to ensure that copies of all required documents are organized, current, and available for inspection.

13.4. Data Quality Control

13.4.1. Data Collection

Designated Investigator staff will enter the data required by the protocol into the eCRFs as soon as possible. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements and Investigator site staff will not be given access to the electronic data capture (EDC) system until they have been trained.

The investigator/designee is responsible for assuring that the data entered into the eCRF is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate. All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation, and verification.

Collection and handling of data collected in the setting of a sub-study will be defined in separate sub-study protocol(s).

After final database lock, the Investigator will receive copies of the subject and relevant sub-study data for archiving at the investigational site.

13.4.2. Data Management

ITB-MED personnel or its designee will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated Investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Randomization/treatment codes and data about all study treatment(s) dispensed to the subject and all dosage changes will be tracked using an IRT. The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to ITB-MED (or a designee) at specific timelines.

13.4.3. Monitoring Procedures

Before study initiation, ITB-MED or its designee will review the protocol and data capture requirements with the investigators and their study personnel. During the study, ITB-MED employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of subject records, the accuracy of data capture/data entry, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits. Continuous remote monitoring of each site's data may be performed by ITB-MED or its designee.

The Investigator must maintain source documents/data for each subject in the study. Source data is defined in International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH GCP §1.51) as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a

clinical study necessary for the reconstruction and evaluation of the study. Source data should be accurate, legible, contemporaneous, original, attributable, complete and consistent.

All information within the eCRFs must be traceable to these source documents in the subject's file. Any data not requiring a separate written record will be defined before study start and will be recorded directly within the eCRFs. The investigator must also keep the original ICF signed by the subject (a signed copy is given to the subject).

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

13.4.4. Protocol Adherence and Amendments

This protocol defines the study objectives, study procedures, and data to be collected on study subjects. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case-by-case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study or approved sub-study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to ITB-MED and not use it for any purpose other than the study, except for the appropriate monitoring on study subjects.

Investigators should exercise due diligence to avoid protocol deviations; however, should a deviation occur, the Investigator or his/her designee, must document the deviation from the approved protocol and include an explanation for the deviation, including mitigation plans to avoid future occurrences.

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by ITB-MED, health authorities where required, and the IRB prior to implementation.

Only deviations to the protocol that are required for subject safety may be implemented immediately. ITB-MED and the applicable health authorities must be subsequently notified of the protocol deviation(s). Additionally, the Investigator must notify the reviewing IRB per the IRB's protocol deviation reporting requirements.

Exploratory or mechanistic sub-study(s) on data as well as blood, urine or tissue samples from donors and/or recipients may be conducted by centers participating in the TCD601A201 study. Only subjects who have been enrolled in the core study will be eligible to participate in a sub-study. Sub-studies may be sponsored by a core study investigator or ITB-MED and require a separate protocol and, when applicable, separate informed consent document(s). All investigator-sponsored sub-studies must be approved by ITB-MED prior to conduct. In addition, all sub-studies must be conducted in compliance with ICH-GCP guidelines and following IRB and health authority approval where applicable. Participation in sub-studies is voluntary. Subjects may consent to all, none or part of the sub-study without impacting their participation in the core study.

13.4.5. Quality Assurance

ITB-MED maintains a Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures (SOPs) as well as applicable global/local GCP regulations and ICH Guidelines.

This study will be subject to audit by ITB-MED or its designee. Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs.

The Investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with direct access to source documents and other necessary study files as necessary to conduct the audit. In the event a regulatory authority notifies the site of an upcoming inspection, the Investigator shall notify ITB-MED immediately.

13.5. Study Site Closure

A study site's participation in the study may be terminated at any time by ITB-MED. At the end of the study, all study sites will be closed. This will include the Investigator's final approval and lock of all subject data, return of unused study material and investigational product unless otherwise provided in writing by ITB-MED, and final visits by the monitor.

13.5.1. Records Retention

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. Study documents should not be destroyed without prior written agreement between ITB-MED and the Investigator. If the Investigator wishes to assign the study records to another party or move them to another location, ITB-MED must be notified in writing in advance.

14. ETHICAL CONSIDERATIONS

14.1. Regulatory and Ethical Compliance

This clinical study was designed and shall be implemented, executed, and reported in accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice, with applicable national regulations, and with the ethical principles laid down in the Declaration of Helsinki.

14.2. Publication of Study Protocol and Results

The protocol will be registered in a publicly accessible database where required. In addition, the results of this study will be submitted for publication and posted in a publicly accessible database of clinical study results.

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16. APPENDICES

APPENDIX 1. SCHEDULE OF ASSESSMENTS (SOA)

SOA: Screening through Day 0

Study Period	Screening	Conditioning								CP/IS
Visit	V1	V2		V3	V4	V5	V6	V7	V8	V9
Day	D -37 to -10 [a]	D -9 Pre	D -9	D -6	D -5 IPH	D -4	D -3	D -2	D -1	D0 KTX/BMCI
General/Safety Assessments										
Informed consent	✓									
Inclusion/Exclusion	✓	✓								
Demographics	✓									
Medical history	✓									
Physical examination	✓									
Electrocardiogram (ECG)	SD									
Vital signs; Height and weight [b]	✓	✓	✓	✓				✓	✓	✓
Prior and concomitant medications	✓	←								→
Adverse events (AEs) [c]	✓	←								→
Histocompatibility/IDS (D&R)										
HLA and ABO typing	✓									
Lymphocyte/CDC crossmatch	←	→								
Panel reactive antibody (PRA) [u]	✓									
Donor-specific antibodies (DSAs) [d]	✓									
CMV, EBV, HBV, HCV, TB, HIV [v]	✓									
HTLV and syphilis	✓									
Local Laboratory Assessments										
CBC w/differential and platelets	✓			✓	✓	✓	✓	✓	✓	✓[e]
Comp metabolic (chemistry)	✓			✓	✓	✓	✓	✓	✓	✓[e]
Lipid panel	✓									
Coagulation panel (PT/INR, aPTT)	✓				✓					✓
Thyroid function (T3, T4, TSH)	✓									
Urinalysis	✓[e]									
Serum pregnancy testing [w]	✓	✓								
CMV DNA PCR surveillance	✓									✓[g]
[redacted]		✓								
[redacted]		✓								
Chimerism assessment		✓								
Prophylaxis Treatment										
MESNA for hemorrhagic cystitis [h]					✓	✓				
P. jirovecii pneumonia [i]			✓	✓	✓	✓	✓	✓	✓	Interrupt [i]
Antimicrobial prophylaxis (surgery)										✓
Conditioning Regimen (Treatment Arms 1 & 2)										
Rituximab + premeds [l]			✓					✓		
Siplizumab + premeds [m]				✓					✓	✓[m]
Hemodialysis [n]				✓	✓	✓				
Cyclophosphamide + premed [o]					✓	✓				
Thymic irradiation									✓	
Renal allograft/Donor BMCI										✓
Background Immunosuppression										
Corticosteroids										✓[p]
Tacrolimus (TAC) [q]										✓
MMF [r]										✓
Disease Monitoring										
Renal biopsy [s]										✓
Post-transplant hemodialysis										as needed

SOA: Day 1 to Week 11

Study Period	Conditioning/Immunosuppression							Immunosuppression									
Visit	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
Day/Week/Month	D1	D3	D5	D6	D7	D10	D12	D14 /W2	W3	W4	W5	W6	W7	W8	W9	W10	W11
Permitted Window	---								±2 days								
General/Safety Assessments																	
Physical examination								✓		✓							
Vital signs and weight [b]	✓		✓	✓	✓		✓	✓		✓							
Concomitant medications	◄																►
Adverse events [c]	◄																►
Telehealth wellness (Donors)										✓							
Local Laboratory Assessments																	
CBC w/diff and platelets	Daily while in hospital									✓	✓	✓	✓	✓		✓	
Comp metabolic (chemistry)	Daily while in hospital									✓	✓	✓	✓	✓		✓	
Serum creatinine (sCR) [f]															✓		✓
Coag panel (PT/INR, aPTT)					✓												
Urinalysis										✓							
Urine pregnancy testing										✓				✓			
CMV DNA PCR surveillance	Weekly monitoring while neutropenic [g]																
EBV and BKV surveillance										✓							
Donor-specific antibodies														✓			
[redacted]						✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
[redacted]		✓			✓	✓		✓	✓	✓				✓			
Chimerism assessment					✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prophylaxis Treatment																	
P. jirovecii pneumonia	Interrupt treatment as of Day 0 and until neutrophil count >500/µL [i]																
Fungal yeast prophylaxis [j]	◄																
CMV prophylaxis [k]	◄																►
Herpes prophylaxis	◄																►
Conditioning Regimen																	
Rituximab + premeds [l]																	
Treatment Arms 1 & 2			✓				✓										
Siplizumab + premeds [m]																	
Treatment Arm 1	✓																
Treatment Arm 2	✓	[redacted]															
Tocilizumab																	
Treatment Arms 1 & 2	Initiation of Treatment for CTS (when required)																
Background Immunosuppression																	
Corticosteroids [p]	IV post-op through ~Day 4. Oral to Day 20 [p]																
Tacrolimus (TAC) [q]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
TAC concentrations [q]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
MMF [r]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Disease Monitoring																	
Post-transplant hemodialysis	◄							as needed									►
Rejection	◄							as needed									►
Graft loss	◄							as needed									►
GvHD assessment [t]	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD

SOA: Week 12/Month 3 to Month 12

Study Period	Immunosuppression			Immunosuppression Weaning						
Visit	27	28	29	30	31	32	33	34	35	36
Day/Week/Month	W12 /M3	M4	M5	M6	M7	M8	M9	M10	M11	M12
Permitted Window	±4 days									
General/Safety Assessments										
Physical examination	✓			✓						✓
Vital signs and weight [b]	✓			✓						✓
Concomitant medications	←									→
Adverse events	←									→
Local Laboratory Assessments										
CBC w/differential and platelets	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Comp metabolic (chemistry)	✓	✓	✓	✓		✓		✓		✓
Serum creatinine (sCR) [f]	✓	✓	✓	← every other week sampling [f]						→
Lipid panel				✓						✓
Coagulation panel (PT/INR, aPTT)	✓									
Urinalysis	✓			✓						✓
Urine pregnancy testing	✓			✓			✓			✓
CMV DNA PCR surveillance [g]				✓						✓
EBV and BKV surveillance				✓						✓
Donor-specific antibodies (DSAs)				✓						✓
[redacted]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Chimerism assessment	✓			✓			✓			✓
Prophylaxis Treatment										
P. jirovecii pneumonia	Interrupt until neutrophils >500/µL [i]									
CMV prophylaxis [k]	→									
Herpes prophylaxis	→									
Background Immunosuppression										
Tacrolimus [q]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Tacrolimus concentrations [q]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Disease Monitoring										
Renal biopsy [s]				✓						✓
Post-transplant hemodialysis	← as needed →									
Rejection	← as needed →									
Graft loss	← as needed →									
GvHD assessment [t]	SD			SD						SD

SOA: Month 15 to Month 60/EOS/ET

Study Period	Immunosuppression-Free									
Visit	37	38	39	40	41	42	43	44	45	46
Day/Week/Month	M15	M18	M21	M24	M30	M36	M42	M48	M54	M60 EOS
Permitted Window	±7 days									
General/Safety Assessments										
Physical examination		✓		✓	✓	✓	✓	✓	✓	✓
Electrocardiogram (ECG)				SD						SD
Vital signs and weight [b]		✓		✓	✓	✓	✓	✓	✓	✓
Concomitant medications	←									→
Adverse events	←									→
Local Laboratory Assessments										
CBC w/differential. and platelets	✓	✓		✓	✓	✓	✓	✓	✓	✓
Comp metabolic (chemistry)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Serum creatinine (sCR)	every other wk [f]									
Lipid panel				✓						
Coagulation panel (PT/INR, aPTT)				✓						
Thyroid function (T3, T4, TSH)				✓						
Urinalysis				✓		✓		✓		✓
Serum pregnancy testing				✓						✓
Urine pregnancy testing		✓			✓	✓	✓	✓	✓	
CMV DNA PCR surveillance [g]				✓						
EBV and BKV surveillance				✓						
Donor-specific antibodies (DSAs)		✓		✓	✓	✓	✓	✓	✓	✓
[redacted]	✓	✓	✓	✓						
Chimerism assessment	✓	✓	✓	✓						
Disease Monitoring										
Post-transplant hemodialysis	←			as needed						→
Rejection	←			as needed						→
Graft loss	←			as needed						→
GvHD assessment [t]		SD		SD						

SOA: Abbreviations

Abbreviations: aPTT = activated partial thromboplastin time; BKV = BK polyomavirus; BMCI = bone marrow cell infusion; CBC = complete blood count; CDC = complement-dependent cytotoxicity; CMV = cytomegalovirus; Comp = comprehensive; CP = Conditioning Period; D = day; D&R = donor and recipient; EBV = Epstein-Barr virus; EOS = End of Study; ET = early termination; [redacted] GvHD = graft-versus-host disease; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; HTLV = human T-lymphotropic virus; IDS = infectious disease screening; INR = International Normalized Ratio; IPH = start inpatient hospitalization; IS = Immunosuppression; IV = intravenous(ly); KTX = kidney/renal transplant; M = month; MMF = mycophenolate mofetil; NAAT = nucleic acid amplification test; PCR = polymerase chain reaction; post-op = post-operatively; Pre = pre-dose; premed(s) = premedication(s); PT = prothrombin time; SD = noted in source document; TB = tuberculosis; TSH = thyroid-stimulating hormone; V = visit; W = week; wk = week.

SOA: Footnotes

Note: Subjects who prematurely discontinue the study prior to Month 24, should have all M24 assessments and procedures performed. Subjects terminating after the Month 24 time point should have all assessments and procedures noted under the M60/EOS visit performed.

a. All screening procedures will be completed by the donor (where appropriate) as well as the recipient.

b. Vital signs: Blood pressure, pulse, respiratory rate, temperature. Height collected at the first visit only.
Dosing vital signs (rituximab or siplizumab): Collected pre-dose; post-infusion (within 10 minutes after completion of infusion) and again within 60 to 70 minutes after completion of infusion; and any other time points as clinically indicated.

c. Donor to be followed for AEs post-surgery to Week 4.

d. DSA pre-transplant is an exclusion; therefore this test must be performed during screening (Day -37 to Day -10) and must be negative prior to starting any treatment. DSA pre- and post-transplant will be assessed locally.

e. Daily while in hospital.
NOTE: Screening urinalysis not required for anuric recipients.

f. Serum creatinine (sCR) analyte is included in the chemistry panel, however additional sCR samples are required at the following time points:
- Weekly through Month 3
- Monthly from Month 3 through Month 6
- Every other week from Month 6 through Month 18

Additional sCR notes:
- The approximately 20 additional sCR samples collected every other week between Month 6 and Month 18 do not require a clinic visit unless clinically indicated.
- On visit dates that include a comprehensive metabolic panel (Months 6, 8, 10, 12, 15, and 18), an additional sample will not need to be drawn during the visit, as it is included in the panel.

g. Weekly monitoring while neutropenic (quantitative CMV NAAT); subsequent testing via PCR or pp65 antigenemia assay.

h. Prophylaxis in conjunction with cyclophosphamide dosing (see Section 6.5.3 for details).

i. Prophylaxes (see Section 6.7 and Section 6.7.3):
- Sulfamethoxazole and trimethoprim (SMZ-TMP) should be started on Day -9 and continued for 6 months post-transplant while neutrophil count is >500/µL. Treatment may be interrupted on Day 0 and during periods of neutropenia.
- During periods of neutropenia (ANC <500 cells/µL) levofloxacin 500 mg once a day should be administered for general infection prophylaxis.

j. Systemic fungal prophylaxis (itraconazole or fluconazole) starts on Day 1 and continues for 2 months or until resolution of neutropenia (see Section 6.7.5).

k. CMV prophylaxis for all donor and recipient CMV positive combinations (see Section 6.7.1 for details).

l. See Section 6.5.2 for rituximab premedications. See footnote b for timing of vital signs collection around rituximab dosing.

m. Siplizumab premedication to be administered no less than [redacted] minutes and no more than [redacted] hours prior to start of infusion. Day 0 premedications in consultation with anesthesiologist. Subjects should be observed for 2 hours post-dose (see Section 6.5.1).
- First dose only: Premedication with methylprednisolone/acetaminophen/antihistamine (e.g., diphenhydramine or chlorpheniramine).
- Subsequent doses: Premedication with acetaminophen/antihistamine (e.g. diphenhydramine or chlorpheniramine).
- All siplizumab doses to be administered over [redacted] minutes.

n. Subjects who were not on dialysis prior to transplant will require hemodialysis treatment on Days -6, -5, and -4 as prophylaxis against cyclophosphamide toxicity. See Section 6.5.4 for complete details and duration/ timing. Post-transplant hemodialysis (renal replacement therapy) should be performed as clinically indicated.

o. Administer cyclophosphamide pretreatment prophylaxis for nausea, vomiting, and infusion reaction per local institutional guidelines. Administer MESNA pretreatment prophylaxis for hemorrhagic cystitis (see Section 6.5.3.

p. IV corticosteroids administered Day 0 and post-operatively through approximately Day 4. Switch to oral administration first week post-operatively with rapid taper to discontinue by Day 20. Corticosteroids may also be used to treat chimeric transition syndrome (CTS) and rejection. (see Section 6.6.3 for details).

q. TAC should be started as soon as possible in the peri-transplant period and may follow local practice but must be initiated no later than 24 hours after reperfusion of the allograft. TAC will be administered as capsules or tablets orally (PO) twice a day (BID) and adjusted to maintain serum trough (C_0) concentrations within the target range of 4–11 ng/mL. (see Section 6.6.2).

   Starting at Month 6, once all weaning criteria listed in Table 8 are met, the dose of TAC should be reduced as suggested in Table 9.

   A biopsy will be repeated at Month 12 and if weaning criteria continue to be met and there remains no evidence of rejection, TAC may be stopped completely.

r. The first dose of MMF will be administered at the time of transplant, but no later than 24 hours after reperfusion of the allograft (Section 6.6.1). Dose adjustment/interruption guidance for MMF is provided in Appendix 5. Once the weaning criteria are met, MMF should be discontinued at Week 8 (see Section 6.6.1.1).

s. Wedge or needle biopsy on day of transplant. In addition to the protocol-specified biopsies, all suspected rejection episodes will require a biopsy unless medically contraindicated.

t. For subjects with persistent T-cell chimerism beyond Month 3, additional GvHD assessments should be performed weekly until resolution of chimerism, including (where applicable) laboratory assessments (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, bilirubin), skin rash assessment, and stool volume (see Section 8.4.8 for details).

u. PRA results up to 2 months prior to Day -37 are acceptable.

v. **Recipient and donor** must be negative for latent TB infection, as detected by QuantiFERON Gold Plus interferon-gamma release assay (IGRA; or current standard interferon-gamma release assay for TB), during screening (Day -37 to Day -10), unless treated per US Centers for Disease Control and Prevention (CDC), World Health Organization (WHO), and/or institutional guidelines within 6 months prior to Day -9.

   Donor must be negative for hepatitis B surface antigen (HBsAg), human immunodeficiency virus (HIV), hepatitis C virus (HCV) ribonucleic acid (RNA), and human T lymphotropic virus type 1 (HTLV-1) during screening (Day -37 to Day -10).

   Recipient must be negative for HIV-1, HBsAg, and HCV. Results within 6 months of transplant are acceptable. Recipients who are seropositive for HCV are excluded without proof of sustained viral response (SVR) after anti-HCV treatment.

w. A negative serum pregnancy test for women of childbearing potential (WOCBP) required during screening; negative urine pregnancy test prior to treatment on Day -9 (if anuric, serum test on Day -9).

APPENDIX 2. INVESTIGATOR AGREEMENT PAGE

INVESTIGATOR AGREEMENT

Protocol Number: TCD601A201 (PANORAMA)
Version: 3.0

I have read the Investigator's Brochure and protocol TCD601A201, "An adaptive, regimen finding, safety and tolerability study of TCD601 (siplizumab), a human anti-CD2 antibody, combined with donor bone marrow cell infusion and non-myeloablative conditioning, for tolerance induction in living donor renal transplantation (PANORAMA)" and agree to conduct this clinical study as outlined in the protocol. I will also ensure that all sub-investigators and other study staff members have read and understand all aspects of the protocol.

I agree to cooperate fully with ITB-MED and its designated vendors during the study. I will carry out the study in accordance with FDA, EMA and ICH guidelines and applicable local and government regulations.

I agree to the following:

- To use the Investigational Product (TCD601) only as specified in the protocol and Pharmacy Manual
- Understand that changes cannot be made to the protocol and study procedures without prior written approval from ITB-MED
- Understand that any violation of the protocol may lead to termination of the study
- Agree to comply with ITB-MED and regulatory requirements for the monitoring and auditing of the study

_____

Principal Investigator Name

_____ _____

Principal Investigator Signature Date

APPENDIX 3. DONOR BONE MARROW PROCUREMENT

This procedure outlines the process for the collection of Donor Bone Marrow in the Operating Room, transportation to the cell processing laboratory and preparation for infusion using sterile technique. The cell processing laboratory should be accredited by FACT-JACIE or equivalent body for the handling of bone marrow cells intended for infusion into human subjects and should follow established standards and guidelines (e.g., https://www.factglobal.org/standards/hct-standards/). In particular, sample labelling and tracking procedures and adherence to sterile technique are of paramount importance.

Institutions should follow their established standard operating procedures within the applicable bone marrow guidelines and use the following as an outline of the process for this study.

- Prior to procurement, recipient weight will be used to calculate a target number of cells based on 2 $\times 10^8$ TNC/kg for the donor collection. A midpoint collection evaluation of the number of TNCs collected should be considered to assess the progress of collection
- Marrow will be taken from each posterior iliac crest using needle/trocar sets and aspirating marrow into heparinized syringes with a maximum of 5–10 mL of marrow per aspiration. Repeated aspirations are then performed by reinserting the needle through the same skin puncture site into different bone sites until approximately 20–33% of the intended volume is collected. Skin puncture sites are then changed, and the aspirations are repeated. With this method, 3 to 5 skin puncture sites overlying each iliac crest are utilized
- Prior to completion of bone marrow procurement a TNC count should be performed; if additional cells are required, they should be obtained, provided institutional guidelines for bone marrow volume are not exceeded.
- Once sufficient cells are obtained the bone marrow will be filtered to remove fat, bone and clots.
- Anticoagulant should be added to the bone marrow extract to prevent clotting (e.g., heparin or anticoagulant citrate-dextrose or according to local practice). In order to minimize the effect of the anticoagulant at the time of infusion (given the risk of intra- and post-operative bleeding), the marrow will be plasma depleted and partially resuspended in saline.
- The plasma will be removed by transferring the marrow product into standard blood transfer pack containers, centrifuging, and expressing the supernatant plasma with a plasma extractor into another transfer pack container.
- Intravenous 0.9% sodium chloride in a volume equivalent to approximately one-half of the volume of the expressed plasma is then added to the bone marrow cells. This will also lower the volume of the infusion.
- The bone marrow cell collection will be characterized as to the total volume, total nucleated cell content, total CD3+ T-cell content, and total CD34+ cell content.
- The final bone marrow cell collection should be stored in a cooler or as appropriate for transport back to the operating room and infusion into the renal transplant recipient.

APPENDIX 4. TACROLIMUS DRUG-DRUG INTERACTIONS

Please refer to most recent national prescribing information for current labeling recommendations.

Drug Interactions

Due to the potential for additive or synergistic impairment of renal function, care should be taken when administering tacrolimus (TAC) with drugs that may be associated with renal dysfunction. These include, but are not limited to, aminoglycosides, amphotericin B, and cisplatin. Initial clinical experience with the co-administration of TAC and cyclosporine (CsA) resulted in additive/synergistic nephrotoxicity.

Drugs That May Alter Tacrolimus Concentrations

Since TAC is metabolized mainly by the CYP3A enzyme systems, substances known to inhibit these enzymes may decrease the metabolism or increase bioavailability of TAC as indicated by increased whole blood or plasma concentrations. Drugs known to induce these enzyme systems may result in an increased metabolism of TAC or decreased bioavailability as indicated by decreased whole blood or plasma concentrations. Monitoring of blood concentrations and appropriate dosage adjustments are essential when such drugs are used concomitantly.

Drugs That May Increase Tacrolimus Blood Concentrations [a]

Calcium Channel Blockers	Antifungal Agents	Macrolide Antibiotics	Gastrointestinal Prokinetic Agents	Other Drugs
diltiazem	clotrimazole	clarithromycin	cisapride	bromocriptine
nicardipine	fluconazole	erythromycin	metoclopramide	chloramphenicol
nifedipine	itraconazole	troleandomycin		cimetidine
verapamil	ketoconazole [b]			cyclosporine
	voriconazole			danazol
				ethinyl estradiol
				methylprednisolone
				lansoprazole [c]
				omeprazole
				protease inhibitors
				nefazodone
				magnesium-aluminum hydroxide

a. This table is not all-inclusive.

b. In a study of 6 normal volunteers, a significant increase in TAC oral bioavailability (14 ±5% vs 30 ±8%) was observed with concomitant ketoconazole administration (200 mg). The apparent oral clearance of TAC during ketoconazole administration was significantly decreased compared to TAC alone (0.430 ±0.129 L/hr/kg vs 0.148 ±0.043 L/hr/kg). Overall, intravenous (IV) clearance of TAC was not significantly changed by ketoconazole co-administration, although it was highly variable between patients.

c. Lansoprazole (CYP2C19, CYP3A4 substrate) may potentially inhibit CYP3A4-mediated metabolism of TAC and thereby substantially increase TAC whole blood concentrations, especially in transplant patients who are intermediate or poor CYP2C19 metabolizers, as compared to those patients who are efficient CYP2C19 metabolizers.

Drugs That May Decrease Tacrolimus Blood Concentrations [a]

Anticonvulsants	Antimicrobials	Herbal Preparations	Other Drugs
carbamazepine	rifabutin	St. John's Wort	sirolimus
phenobarbital	caspofungin		
phenytoin	rifampin		

a. This table is not all inclusive.

St. John's Wort (Hypericum perforatum) induces CYP3A4 and P-glycoprotein. Since TAC is a substrate for CYP3A4, there is the potential that the use of St. John's Wort in subjects receiving TAC could result in reduced TAC levels.

In a single-dose crossover study in healthy volunteers, co-administration of TAC and magnesium-aluminum hydroxide resulted in a 21% increase in the mean TAC area under the concentration-time curve (AUC) and a 10% decrease in the mean TAC maximum plasma concentration (C_{max}) relative to TAC administration alone.

In a study of 6 normal volunteers, a significant decrease in TAC oral bioavailability (14 ±6% vs 7 ±3%) was observed with concomitant rifampin administration (600 mg). In addition, there was a significant increase in TAC clearance (0.036 ±0.008 L/hr/kg vs 0.053 ±0.010 L/hr/kg) with concomitant rifampin administration.

Interaction studies with drugs used in human immunodeficiency virus (HIV) therapy have not been conducted. However, care should be exercised when drugs that are nephrotoxic (e.g., ganciclovir) or that are metabolized by CYP3A (e.g., nelfinavir, ritonavir) are administered concomitantly with TAC. Similarly, care should be exercised when hepatitis C virus (HCV) protease inhibitors (e.g., boceprevir and telaprevir), also metabolized by CYP3A, are administered concomitantly with TAC.

TAC may affect the pharmacokinetics of other drugs (e.g., phenytoin) and increase their concentration. Grapefruit juice affects CYP3A-mediated metabolism and should be avoided.

Other Drug Interactions

Immunosuppressants may affect vaccination. Therefore, during treatment with TAC, vaccination may be less effective. The use of live vaccines should be avoided; live vaccines may include, but are not limited to measles, mumps, rubella, oral polio, BCG, yellow fever, and oral TY 21a typhoid (Prograf® USPI).

APPENDIX 5. GUIDELINES FOR MMF DOSE REDUCTION

An Investigator may interrupt temporarily or reduce the dosage of MMF if in his/her opinion this is clinically warranted, in response to any causally associated AE (e.g., neutropenia, thrombocytopenia, leukopenia, hyperlipidemia, hypertriglyceridemia, or gastrointestinal intolerance). The following guidelines should be followed:

Dose Reduction or Temporary Interruption May Be Performed for MMF

Implementation of MMF dose reduction will be based on thrombocytopenia, leukopenia, neutropenia, or other AEs which are suspected to be related to this medication, and in the opinion of the Investigator, are clinically warranted. The following guidelines should be used for both dose reduction and, once the event has resolved, restarting or increasing the dose of MMF back to original levels.

Mycophenolate Mofetil (MMF) Dose Reduction Guidelines	
Platelets	
Platelet count <100,000 mm³	Dose **may** be reduced at the discretion of the Investigator
Platelet count <75,000/mm³	A second dose reduction should be **considered**
Platelet count <50,000/mm³	**MANDATORY** interruption of medication
White Bloods Cells (WBCs)	
WBC <3500/mm³	Dose **may** be reduced at the discretion of the Investigator
WBC <2500/mm³	A second dose reduction should be **considered**
WBC <2000/mm³	Interruption of medication should be **considered**

Note: All MMF dose changes must be recorded in the MMF Dosage Administration Record eCRF.

APPENDIX 6. US-SPECIFIC CELLCEPT® PREGNANCY AND SAFETY INFORMATION

The US mycophenolate REMS can be accessed at www.mycophenolaterems.com.

- Use of CellCept® during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney.
- Females of reproductive potential must be made aware of the increased risk of first trimester pregnancy loss and congenital malformations with MMF products and must be counseled regarding pregnancy prevention and planning.
- For those females using Cellcept® at any time during pregnancy and those becoming pregnant within 6 weeks of discontinuing therapy, the Investigator or healthcare practitioner should report the pregnancy to the Mycophenolate Pregnancy Registry (1-800-617-8191). The Investigator or healthcare practitioner should strongly encourage the subject to enroll in the pregnancy registry.
- Risks and benefits of CellCept® should be discussed with the subject. When appropriate, consider alternative immunosuppressants with less potential for embryofetal toxicity. In certain situations, the subject and her healthcare practitioner may decide that the maternal benefits outweigh the risks to the fetus. If this drug is used during pregnancy, or if the subject becomes pregnant while taking this drug, the subject should be apprised of the potential hazard to the fetus.
- To prevent unplanned exposure during pregnancy, females of reproductive potential should have a serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL immediately before starting CellCept®. Another pregnancy test with the same sensitivity should be done 8 to 10 days later. Repeat pregnancy tests should be performed during routine follow-up visits. Results of all pregnancy tests should be discussed with the subject.
- Females of reproductive potential taking CellCept® must receive contraceptive counseling and use acceptable contraception. Subjects must use acceptable birth control during entire CellCept® therapy, and for 6 weeks after stopping CellCept®, unless the subject chooses abstinence (she chooses to avoid heterosexual intercourse completely).
- Subjects should be aware that CellCept® reduces blood levels of the hormones in the oral contraceptive pill and could theoretically reduce its effectiveness.

Table 12: Acceptable Contraception Methods for Females of Reproductive Potential Using Mycophenolate (MMF)

Acceptable Contraception Methods for Females of Reproductive Potential Using Mycophenolate (MMF) [a]			
Option 1			
Methods to Use Alone Most effective: Less than 1 pregnancy per 100 women in 1 year	Intrauterine device (IUD) Tubal sterilization Subject's partner had a vasectomy		
OR			
Option 2			
Choose 1 Hormonal Method AND 1 Barrier Method 4–7 pregnancies per 100 women in 1 year	**Hormone Methods** choose 1 **Estrogen and Progesterone** Oral contraceptive pill Transdermal patch Vaginal ring **Progesterone-only** Injection Implant	**AND**	**Barrier Methods** choose 1 Diaphragm with spermicide Cervical cap with spermicide Contraceptive sponge Male condom Female condom
OR			
Option 3			
Choose 1 Barrier Method From Each Column (*must choose 2 methods*) Least effective: 13 or more pregnancies per 100 women in 1 year	**Barrier Methods** choose 1 Diaphragm with spermicide Cervical cap with spermicide Contraceptive sponge	**AND**	**Barrier Methods** choose 1 Male condom Female condom

a. Females of reproductive potential include girls who have entered puberty and all women who have a uterus and have not passed through menopause.

APPENDIX 7. UPDATED 2019 BANFF CLASSIFICATION

Category 1: Normal Biopsy or Nonspecific Changes

Category 2: Antibody-Mediated Changes

Active ABMR; all 3 criteria must be met for diagnosis

1. Histologic evidence of acute tissue injury, including 1 or more of the following:
   - Microvascular inflammation (g >0 and/or ptc >0), in the absence of recurrent or *de novo* glomerulonephritis although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥1 alone is not sufficient and g must be ≥1
   - Intimal or transmural arteritis (v >0) [a]
   - Acute thrombotic microangiopathy, in the absence of any other cause
   - Acute tubular injury, in the absence of any other apparent cause
2. Evidence of current/recent antibody interaction with vascular endothelium, including 1 or more of the following:
   - Linear C4d staining in peritubular capillaries or medullary vasa recta (C4d2 or C4d3 by IF on frozen sections, or C4d >0 by IHC on paraffin sections)
   - At least moderate microvascular inflammation ([g + ptc] ≥2), in the absence of recurrent or *de novo* glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥2 alone is not sufficient, and g must be ≥1
   - Increased expression of gene transcripts/classifiers in the biopsy tissue strongly associated with ABMR, if thoroughly validated
3. Serologic evidence of donor-specific antibodies (DSA to HLA or other antigens). C4d staining or expression of validated transcripts/classifiers as noted above in criterion 2 may substitute for DSA; however thorough DSA testing, including testing for non-HLA antibodies if HLA antibody testing is negative, is strongly advised whenever criteria 1 and 2 are met.

Chronic active ABMR; all 3 criteria must be met for diagnosis

1. Morphologic evidence of chronic tissue injury, including 1 or more of the following:
   - Transplant glomerulopathy (cg >0), if no evidence of chronic TMA or chronic recurrent/*de novo* glomerulonephritis; includes changes evident by electron microscopy (EM) alone (cg1a)
   - Severe peritubular capillary basement membrane multilayering (ptcml1; requires EM)
   - Arterial intimal fibrosis of new onset, excluding other causes; leukocytes within the sclerotic intima favor chronic ABMR if there is no prior history of TCMR, but are not required

2. Identical to criterion 2 for active ABMR, above
3. Identical to criterion 3 for active ABMR, above, including strong recommendation for DSA testing whenever criteria 1 and 2 are met. Biopsies meeting criterion 1 but not criterion 2 with current or prior evidence of DSA (posttransplant) may be stated as showing chronic ABMR, however remote DSA should not be considered for diagnosis of chronic active or active ABMR

Chronic (inactive) ABMR

1. cg >0 and/or severe ptcml (ptcml1)
2. Absence of criterion 2 of current/recent antibody interaction with the endothelium
3. Prior documented diagnosis of active or chronic active ABMR and/or documented prior evidence of DSA

C4d staining without evidence of rejection; all 4 features must be present for diagnosis [b]

1. Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d >0 by IHC on paraffin sections)
2. Criterion 1 for active or chronic, active ABMR not met
3. No molecular evidence for ABMR as in criterion 2 for active and chronic active ABMR
4. No acute or chronic active TCMR, or borderline changes

Category 3: Borderline (Suspicious) for Acute TCMR:

- Foci of tubulitis (t1, t2, or t3) with mild interstitial inflammation (i1), or mild (t1) tubulitis with moderate-severe interstitial inflammation (i2 or i3)
- No intimal or transmural arteritis (v = 0)

Category 4: TCMR

Acute TCMR

Grade IA: Interstitial inflammation involving >25% of non-sclerotic cortical parenchyma (i2 or i3) with moderate tubulitis (t2) involving 1 or more tubules, not including tubules that are severely atrophic [c]

Grade IB: Interstitial inflammation involving >25% of non-sclerotic cortical parenchyma (i2 or i3) with severe tubulitis (t3) involving 1 or more tubules, not including tubules that are severely atrophic [c]

Grade IIA: Mild to moderate intimal arteritis (v1) with or without interstitial inflammation and/or tubulitis

Grade IIB: Severe intimal arteritis (v2), with or without interstitial inflammation and/or tubulitis

Grade III: Transmural arteritis and/or arterial fibrinoid necrosis involving medial smooth muscle with accompanying mononuclear cell intimal arteritis (v3), with or without interstitial inflammation and/or tubulitis

Chronic Active TCMR [d]

Grade IA: Interstitial inflammation involving >25% of sclerotic cortical parenchyma (i-IFTA2 or i-IFTA3) AND >25% of total cortical parenchyma (ti2 or ti3) with moderate tubulitis (t2 or t-IFTA2) involving 1 or more tubules, not including severely atrophic tubules [c]; other known causes of i-IFTA should be ruled out

Grade IB: Interstitial inflammation involving >25% of sclerotic cortical parenchyma (i-IFTA2 or i-IFTA3) AND >25% of total cortical parenchyma (ti2 or ti3) with severe tubulitis (t3 or t-IFTA3) involving 1 or more tubules, not including severely atrophic tubules [c]; other known causes of i-IFTA should be ruled out

Grade II: Chronic allograft arteriopathy (arterial intimal fibrosis with mononuclear cell inflammation in fibrosis and formation of neointima). This may also be a manifestation of chronic active or chronic ABMR or mixed ABMR/TCMR

Category 5: Polyomavirus Nephropathy [e]

PVN Class 1
pvl 1 and ci 0-1

PVN Class 2
pvl 1 and ci 2-3 OR
pvl 2 and ci 0-3 OR
pvl 3 and ci 0-1

PVN Class 3
pvl 3 and ci 2-3

Abbreviations: ABMR = antibody-mediated rejection; cg = glomerular double contours; DSA = donor-specific antibody; EM = electron microscopy; g = glomerulitis; HLA = human leukocyte antigen; i = inflammation; IF = immunofluorescence; IHC = immunohistochemistry; ptc = peritubular capillaritis; t = tubulitis; TCMR = T-cell mediated rejection; TMA = thrombotic microangiopathy; v = intimal arteritis.

a. It should be noted that these arterial lesions may be indicative of ABMR, TCMR, or mixed ABMR/TCMR. "v" lesions and chronic allograft arteriopathy are only scored in arteries having a continuous media with ≥2 smooth muscle layers.

b. The clinical significance of these findings may be quite different in grafts exposed to anti–blood group antibodies (ABO-incompatible allografts), where they do not appear to be injurious to the graft and may represent accommodation. However, with anti-HLA antibodies, such lesions may progress to chronic ABMR, and more outcome data are needed.

c. Severely atrophic tubules are defined as having each of 3 features: diameter <25% of unaffected or minimally affected tubules in the same biopsy, an undifferentiated-appearing, cuboidal or flattened epithelium, and pronounced wrinkling and/or thickening of the tubular basement membrane.

d. It was felt by the majority of Banff 2019 meeting attendees that reporting of chronic active TCMR should be accompanied by a second diagnosis of borderline acute TCMR or acute TCMR (with appropriate grade) when criteria for both diagnoses are met.

e. pvl scores are defined in Table 5 and in detail in ref. 4. An adequate sample for such scoring should include 2 biopsies cores and contain medulla. PVN can coexist with ABMR or with TCMR grades 2 or 3.

Source: Loupy 2020.

APPENDIX 8. ACUTE GVHD ASSESSMENT

Organ Staging of Acute Graft-versus-Host Disease

Stage	Skin	Liver (bilirubin)	Upper GI	Lower GI Gut
0	No active (erythematous) GvHD rash	<2 mg/dL[b]	No or intermittent nausea, vomiting, or anorexia	<500 mL/day or <3 episodes/day
1	Maculopapular rash, <25% BSA[a]	2–3 mg/dL[b]	Persistent nausea, vomiting or anorexia	500–999 mL diarrhea/day [c]
2	Maculopapular rash, 25–50% BSA[a]	3.1–6 mg/dL[b]		1000–1500 mL diarrhea/day [c]
3	Maculopapular rash, >50% BSA[a]	6.1–15 mg/dL[b]		>1500 mL diarrhea/day [c]
4	Generalized erythroderma (>50% BSA) plus bullous formation and desquamation >5% BSA	>15 mg/dL[b]		Severe abdominal pain with or without ileus

Abbreviation: BSA = body surface area

a. Use "Rule of Nines" to determine extent of rash.

b. Range given as total bilirubin. Downgrade one stage if an additional cause of elevated bilirubin has been documented.

c. Downgrade one stage if an additional cause of elevated stool output has been documented.

Source: Harris 2016.

Overall Clinical Grading of Acute GVHD

Grade	Degree of Organ Involvement
0	No stage 1–4 of any organ
I	Stage 1–2 rash and no liver, lower GI or upper GI involvement
II	Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI.
III	Stage 2–3 liver and/or stage 2–3 lower GI, with stage 0–3 skin and/or stage 0–1 upper GI.
IV	Stage 4 skin, liver, or lower GI involvement, with stage 0–1 upper GI.