Clinical Protocol TCD601B102

A 12-Month, Randomized, Controlled, Open-Label, Dose Escalation Study evaluating Safety, Tolerability, Pharmacokinetics (PK) and Pharmacodynamics (PD) of an anti-CD2 monoclonal antibody, TCD601(siplizumab) compared to anti-thymocyte globulin (rATG), as induction therapy in de novo Renal Transplant Recipients

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TCD601(siplizumab)

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List of Abbreviations

ABC	Antibody Biodistribution Coefficient
ADCC	Antibody-Dependent Cell-mediated Cytotoxicity
ADCP	Antibody-Dependent Cellular Phagocytosis
AE	Adverse Event
AKI	Acute Kidney Injury
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
APC	Antigen Presenting Cell
aPTT	Activated Partial Thromboplastin time
AST	Aspartate Aminotransferase
ATG	Anti-thymocyte Globulin
ATL	Adult T-cell Leukemia
AUC	Area Under the Curve
BID	Twice a day
BMI	Body Mass Index
BMT	Bone Marrow Transplantation
BPAR	Biopsy Proven Acute Rejection
BUN	Blood Urea Nitrogen
CDC	Complement-dependent cytotoxicity
CDR	Complementarity-determining regions
CIT	Cold Ischemia time
CMV	Cytomegalovirus
CNI	Calcineurin Inhibitor
CS	Corticosteroids
CsA	Cyclosporine
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTS	Chimeric Transition Syndrome
CV	Coefficient of Variation
DGF	Delayed Graft Function
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DSA	Donor Specific Antibodies
EBV	Epstein-Barr Virus
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
ELISA	Enzyme-linked Immunosorbent assay
EOS	End of Study
eTMF	Electronic Trial Master File
EU	European Union
FACS	Fluorescence-activated Cell Sorter
FAS	Full Analysis Set
FDA	Food and Drug Administration

FRP	Females of reproductive potential
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
GvHD	Graft-versus-host disease
HbsAg	Hepatitis B Surface Antigen
Hbg	Hemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HLA	Human Leukocyte Antigen
HIV	Human Immunodeficiency Virus
IMPDH	Inosine Monophosphate Dehydrogenase
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive Web Response System
IVIG	Intravenous Immunoglobulin
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
LGL	Large Granular Lymphocytic Leukemia
LLOQ	Lower Limit of Quantification
LOCF	Last-Observation-Carried-Forward
LPD	Lymphoproliferative Disorder
MDRD	Modification of Diet in Renal Disease
MLR	Mixed lymphocyte reaction
M-M	Michaelis-Menten
MMF	Mycophenolate Mofetil
MoA	Mechanism of Action
MPA	Mycophenolic acid
NCI	National Cancer Institute
NSAID	Nonsteroidal anti-inflammatory drug
PCP	Pneumocystis Pneumonia
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic(s)
PGNF	Primary Graft Non-Function
pMHC	Peptide-major histocompatibility complex
PK	Pharmacokinetic(s)
PPK	Population Pharmacokinetic(s)
PRA	Panel Reactive Antibodies
PRED	Prednisolone
PT	Prothrombin Time
PTT	Partial Prothrombin Time

PTLD	post-transplant lymphoproliferative disorder
PVAN	Polyoma Virus Associated Nephropathy
QMS	Quality Management System
QNAT	Quantitative Nucleic Acid Testing
rATG	rabbit anti-thymocyte globulin
RBC	Red Blood Cell(s)
RO	Receptor occupancy
REMS	Risk Evaluation and Mitigation Strategy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
s.c.	Subcutaneous
SCr	Serum Creatinine
SD	Standard deviation
SID	Subject Identification Number
SMQ	Standardized MedDRA Query
SoC	Standard of Care
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Sustained Viral Response
TAC	Tacrolimus
TB	Tuberculosis
tBPAR	treated Biopsy Proven Acute Rejection
TCD601 or siplizumab	Investigational Product
TCMR	T-cell Mediated Rejection
TCR	T-cell Receptor
TDM	Therapeutic Drug Monitoring
TMDD	Target-Mediated Drug Disposition
ULN	upper limit of normal
ULOQ	upper limit of quantification
US	United States
VL	Viral Load
WBC	White Blood Cell(s)
WHO	World Health Organization

Protocol History

Amendment 01:

This document (TCD601B102 Protocol Version 2.0) incorporates changes and editorial updates to harmonize the US clinical study protocol with TCD601B101 Protocol Version 2.0, which is active in the EU. Key revisions include the addition of an inclusion criterion, which requires study subjects to have a negative SARS-CoV-2 test at screening, an outline of the Risks associated with COVID-19 disease (See Section 4.5.3), and Risk Mitigation Strategies to minimize exposure to SARS-CoV-2 (See Section 4.5.4). These revisions and additions are in consideration of the ongoing global SARS-CoV-2 pandemic and harmonize with FDA and EU guidance documents and updated global protocol template.

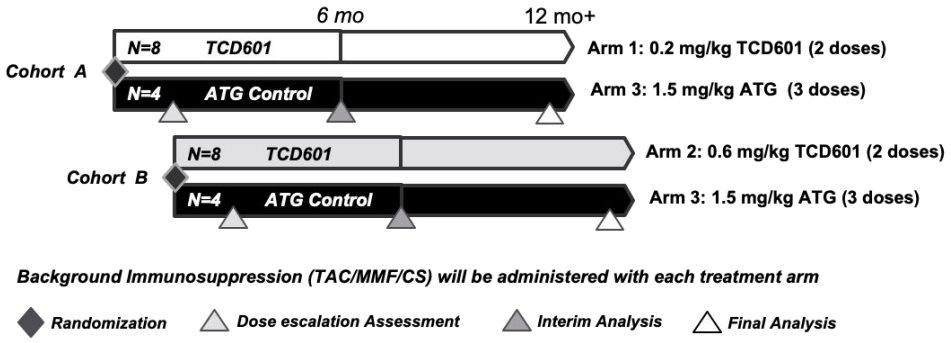
A tabulation of all changes can be reviewed in Appendix 2 of this protocol.

Protocol Synopsis

Product Name/Number	TCD601 (siplizumab)
Protocol Number	TCD601B102
Protocol Title	A 12-month, randomized, controlled, open-label, dose escalation study evaluating safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of an anti-CD2 monoclonal antibody, TCD601 (siplizumab), compared to anti-thymocyte globulin (rATG), as induction therapy in *de novo* renal transplant recipients
Investigation Type	Interventional; Drug (biologic)
Purpose and Rationale	The purpose of this study is to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of escalating doses of TCD601 (siplizumab), an anti-CD2 monoclonal antibody, compared to a rabbit polyclonal anti-thymocyte globulin (rATG), as induction therapy in *de novo* renal transplant patients. All subjects will receive the same standard of care (SoC) background immunosuppression. This trial will focus on profiling the safety, tolerability, PK and PD activity of siplizumab in the setting of standard-of-care immunosuppression in a moderate immunologic risk renal transplant population. Overall, results of this study will be used to inform the siplizumab dose and regimen selection for investigation in later phases of clinical development and serve as proof-of-principal study in the replacement of SoC, polyclonal, T-cell depleting induction therapy.
Primary Objective	To assess the safety, tolerability, PK and PD of siplizumab compared to rATG, in *de novo* renal transplant recipients at 12 months post-transplant.
Secondary Objectives	• To measure changes in peripheral lymphocyte immunophenotype • To measure the time-course and duration of siplizumab induced lymphocyte depletion and recovery • To measure peripheral CD2-receptor occupancy following siplizumab administration over time • To assess the incidence of treated biopsy proven acute rejection (tBPAR) at 12 months • To assess the incidence of treatment emergent *de novo*, donor specific antibodies (DSA) at 12 months • To assess the incidence of antibody meditated rejection at 12 months • To assess renal function via eGFR using the Modification of Diet in Renal Disease (MDRD) equation at Months 3, 6, 12 or EOS
Exploratory Objectives	• [redacted]
Study Design	TCD601B102 is a 12-month, multi-center, randomized, controlled, open-label, dose escalation study to evaluate the safety, tolerability, PK and PD of siplizumab compared to rATG, as induction therapy, in *de novo* renal transplant recipients. All subjects will receive

background immunosuppression with standard exposure tacrolimus (TAC), mycophenolate mofetil (MMF) and corticosteroids (CS).

Following a screening period of up to 4-weeks to confirm study eligibility, up to 24 moderate immunological risk, *de novo* renal transplant candidates will be enrolled into the study. Eligible subjects will be sequentially assigned to one of two Cohorts (A or B) using a time-lagged dose escalation methodology. Within each Cohort, it is planned that 12 subjects will be randomized to siplizumab or rATG, in an 8:4 ratio prior to renal transplantation on Study Day 0, as outlined below:



Subjects randomized to siplizumab will receive two intravenous (IV) doses on Day 0 and Day 4 post-transplant as follows:

Siplizumab Dosing Arms:

- Arm 1: 0.2 mg/kg (n=8)
- Arm 2: 0.6 mg/kg (n=8)

Subjects randomized to rATG (Arm 3), will receive three intravenous (IV) doses of 1.5 mg/kg on Days 0, 1 and 2, regardless of Cohort assignment.

Siplizumab and rATG will be combined with concentration-controlled TAC (BID) dosing to a whole blood trough concentration 4-11 ng/mL, and MMF or equivalent (BID), and should be started within 24 hours post-transplant. Subjects will also receive CS per local practice with a minimum of 5.0 mg/d prednisone or equivalent until Month 12.

Dose Escalation Criteria:

28 days following the last investigational product administration in the 4th siplizumab treated subject in each treatment Cohort and prior to dose escalation to the subsequent Cohort, a review of all available safety, tolerability and PD data will be conducted by ITB-MED in collaboration with the Investigators. This 28-day safety period allows sufficient time for subjects to reach full-receptor occupancy, maximum pharmacodynamic activity, and for the presentation of acute, drug related toxicities.

In the event there is no evidence of acute, dose limiting toxicity (DLT), randomization to the next dose level may be initiated. Alternatively, a decision to terminate the dosing arm could be reached. It is also possible additional and/or intermediate dose level(s) could be added during the course of the study per amendment. Cohorts may be added at any dose level below the maximum tolerated dose in order to better understand safety, PK or PD.

This escalation data review will be repeated prior to dose escalation/termination decisions for each Cohort. The review of subject data and dose escalation may occur before all subjects have been randomized to a given Cohort. If the next dose level is opened to subject assignment, Cohorts will be back filled to achieve a final sample size of 12 subjects.

In addition to the review of data for dose decision purposes as noted above, an independent Data Monitoring Committee (DMC) will conduct an ongoing review of cumulative PK, PD, safety, Adverse Events (AEs) and Serious Adverse Event (SAE) data as well as EBV-viral load and PTLD surveillance results, including clinically relevant changes on physical exam and clinical laboratory assessments and ad hoc imaging. The Committee will convene on a quarterly basis or as described in the DMC Charter. If at any time the observed AEs meet or

	exceed the a priori defined stopping criteria, the study will be placed on hold pending a review. **Interim Analysis:** A formal interim analysis will occur once 50% of subjects in Cohort 1 and 2 complete their 6-month study assessment. This formal interim analysis will be conducted to assess the safety/tolerability (e.g., AEs, SAEs, clinical laboratory assessments, vital signs, PK data and PK/PD activity (e.g., immunophenotyping and CD2 receptor occupancy). The analysis will also include assessment of biopsy proven acute rejection (BPAR), graft losses deaths, and key safety endpoints. In the event the acute rejection rate exceeds a clinically relevant threshold set forth in the protocol and DMC charter, or the *a priori* defined stopping rules, enrollment will be suspended to allow for the early termination of any treatment cohort where the benefit/risk of siplizumab is deemed unacceptable. **Safety stopping rules:** In addition to the formal interim analyses and escalation data reviews for dosing decision purposes, the following Safety Stopping Rules will be in effect at any timepoint in the study. 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. Dose limiting toxicities (DLTs) will be assessed according to the standardized toxicity grading scale, the National Cancer Institute (NCI) CTCAE version 5.0 (NCI 2017): ▪ 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, considered drug related as determined by the Investigator within the first 28 days. ▪ Two (2) subjects with sustained (>7 days) Grade 3 neutropenia (neutrophil counts 200/mm3 to < 500 to; 0.2 to <0.5 x 10e9/L) considered related to siplizumab. ▪ Two (2) or more subjects presenting with Grade 3 or higher toxicity considered related as determined by the Investigator, including infusion reactions, within 24 hours of any siplizumab administration. ▪ Three (3) or more subjects per cohort presenting with Grade IIA or higher BPAR (T-cell mediated rejection (TCMR); central pathology) during the first 6 months post-transplant. Following discharge from the hospital, subjects will have study assessments conducted weekly through Week 10 and then monthly from Month 3 through Month 12 or end of study (EOS). All subjects enrolled will be followed for a minimum of 12 months.
Population	Up to 24 moderate immunological risk, adult, *de novo* renal transplant patients
Planned Study Sites	Up to 5 study sites within the United States (US)
Key Inclusion Criteria	Subjects eligible for inclusion in this study have to fulfill all of the following criteria: • Able to understand the study requirements and provide written informed consent before any study assessment is performed. • Male or female patients ≥ 18 to 70 years of age. • Recipients of a *de novo* renal allograft from a heart-beating deceased, living unrelated or non-Human Leukocyte Antigen (HLA) identical living related donor.

	• Recipients of a kidney with a cold ischemia time (CIT) < 30 hours; hypothermic machine perfusion within the same timeframe is acceptable. • Subjects who test negative for SARS-CoV-2 via molecular testing (PCR)
Key Exclusion Criteria	Subjects meeting any of the following criteria are not eligible for inclusion in this study: • Transplant recipients sero-negative for Epstein-Barr virus (EBV). • Multi-organ transplant recipients. • Subjects who have received a kidney allograft previously, e.g., re-transplant. • Recipient of a kidney from an HLA identical living related donor. • Recipient of a kidney from a donor after cardiac death. • Subjects at high immunological risk for rejection as determined by local practice [(e.g., presence of pre-existing DSA, recipient of high Kidney Donor Profile Index ≥ 85 kidney (where assessed)]. • Subjects with donor specific anti-HLA antibody as measured by complement-dependent cytotoxicity assay (CDC), enzyme-linked immunosorbent assay (ELISA), or flow cytometry within 90 days prior to transplant or as performed per the center's local practice. • Complement-dependent cytotoxicity (CDC) crossmatch positive transplant (isolated positive B cell crossmatches are not an exclusion criterion). • ABO incompatible recipient. • History of malignancy of any organ system, except for localized excised non-melanomatous skin lesions or carcinoma *in situ* of the cervix. • Subjects with clinically significant laboratory abnormality that would preclude participation in the study (e.g., >2.5 x Upper Limit of Normal (ULN) values for (a) liver function chemistries (ALT, AST, alkaline phosphatase (ALP)), (b) bilirubin, (c) coagulation studies (INR/PT, aPTT). • Patient with any of the following: hemoglobin (Hbg) < 8 mg/dL, WBC count ≤ 2,000/mm3 or platelet count ≤ 75,000/mm^3. • Sero-positive for Human Immunodeficiency Virus (HIV) or Hepatitis B Surface Antigen (HBsAg). Subjects who are sero-positive for Hepatitis C virus (HCV) are excluded without proof of sustained viral response (SVR) after anti-HCV treatment. • Recipient of a kidney from a donor who tests positive for HIV, HBsAg/HBc positive or HCV. • History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes (e.g., siplizumab, ATG, TAC, MMF, CS). • Any additional contraindication to the use of TAC or MMF according to the national labeling information of these products (refer to the local product label). • Evidence of TB infection (after anti-TB treatment, patients with history of latent TB may become eligible according to national guidelines). • Patient with severe systemic infections, current or within the two weeks prior to randomization. • Subjects with any other clinically significant medical condition, active infection or laboratory abnormality that would, in the judgment of the investigator, interfere with the subject's ability to participate in the study. • 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. • Use of other investigational products or enrollment in another investigational drug study within 30 days of screening or 5 half-lives of the medication, whichever is longer. • 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. • Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 24 weeks after the study medications have been stopped.

<table>
<tr><td>Investigational Product</td><td>Siplizumab</td></tr>
<tr><td>Reference Product (Active Control)</td><td>rabbit anti-thymocyte globulin (rATG; Thymoglobulin; Genzyme)</td></tr>
<tr><td>Background Therapy</td><td>• Immediate release tacrolimus (TAC)
• Mycophenolate mofetil (MMF) or equivalent
• Corticosteroids (CS)</td></tr>
<tr><td>Treatment Regimen</td><td>Prior to surgery, on Day 0, eligible subjects will be sequentially assigned to one of 2 Cohorts (A or B) and then randomized to one of two dosing arms in an 8:4 ratio (siplizumab: rATG) as follows:

<table>
<tr><th>Cohort</th><th>Arm</th><th>Subjects (n)</th><th>Product</th><th>Dosing Regimen</th></tr>
<tr><td rowspan="2">Cohort A</td><td>Arm 1</td><td>8</td><td>Siplizumab</td><td>0.2 mg/kg (Days 0 and 4)</td></tr>
<tr><td>Arm 3</td><td>4</td><td>rATG</td><td>1.5 mg/kg (Days 0, 1 and 2)</td></tr>
<tr><td rowspan="2">Cohort B</td><td>Arm 2</td><td>8</td><td>Siplizumab</td><td>0.6 mg/kg (Days 0 and 4)</td></tr>
<tr><td>Arm 3</td><td>4</td><td>rATG</td><td>1.5 mg/kg (Days 0, 1 and 2)</td></tr>
</table>
Background Treatment:
Subjects across all treatment arms will receive triple regimen background immunosuppressive therapy (TAC/MMF/CS).
Concomitant Treatments:
• Premedication (prior to siplizumab and rATG infusions): diphenhydramine, paracetamol or acetaminophen
• Cytomegalovirus (CMV), pneumocystis pneumonia (PCP) prophylaxis, per local practice
• Oral Candida treatment, per local practice</td></tr>
<tr><td>PK/PD Assessments</td><td>PK: Siplizumab and TAC
• Siplizumab (total and free) - Dosing on Days 0 and Day 4:
▪ Sampling pre-dose (0h), 1h, 3h, 6h, and 24h after the first dose on Day 0;
▪ Sampling pre-dose (0h), 1h, 3h, and 6h on Day 4;
▪ Additional collection on Days 2 ,3, 7, 14, 21, 28, 35, 42, 49, 56, 63*, 70*, 84*, 112*, 140*, 168*, 196*, 224*, and 252* (*Note: collections designated with an asterisk may be truncated based on half-life of siplizumab and serum concentrations below limit of quantification)
• anti-siplizumab antibodies: Days 0, 28, 56, 84, 168, and EOS
• TAC: Days 0, 1, 7, 14, 21, 28, month 3, 6, 12 post-transplant and as needed following a change in dose based on local standard of care (SoC)
• PD:
▪ PD sampling times to be linked with relevant PK timepoints
▪ Peripheral lymphocyte immunophenotyping (FACS analysis) – CD2, CD3, CD4, CD5, CD8, CD19, CD25, CD27, CD38, CD45RA, CD45RO, CD59, CD127, CD138, CD154, FoxP3, HLA-DR
▪ Peripheral CD2 receptor occupancy</td></tr>
<tr><td>Safety Assessments</td><td>• AEs and SAEs
• Clinically significant changes in clinical chemistry, hematology, vital signs, and serology
• EBV-viral load measurement via PCR
• Renal function
• Comprehensive Physical Examination</td></tr>
</table>

Data Analysis	All information obtained on AEs will be displayed by treatment and subject. The number and percentage of subjects with AEs will be tabulated by body system and preferred term with a breakdown by treatment arm. A subject with multiple AEs within a body system is only counted once towards the total of this body system. No formal statistical analysis will be done for the safety and tolerability evaluation. Siplizumab serum concentration data will be listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the lower limit of quantification (LLOQ), which will be reported as zero. Summary statistics will include mean (arithmetic and geometric), standard deviation (SD), coefficient of variation (CV) (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ will be treated as zero in summary statistics. A geometric mean will not be reported if the dataset includes zero values. The magnitude and duration of pharmacodynamic effect of siplizumab will be characterized by measuring the change in peripheral immunophenotype, including all subsets of T-, B- and NK-cells. Similarly, biomarkers, such as inflammatory cytokines and CD2 RO will be summarized by cohort, treatment and subject. Summary statistics will also be provided such as mean, median, SD, minimum and maximum, by treatment and by visit/time for all PD and biomarker data. The relationship between siplizumab concentration PK and PD (immunophenotype) will be explored. Modeling of PK/PD data using a population approach will be performed as appropriate.
Sample Size Determination	No formal sample size and power analysis has been performed. A sample size of 8 subjects for each arm was chosen based on practical considerations, including the need to adequately characterize siplizumab PK and PD activity in renal transplant patients in the immediate post-transplant time period while balancing the overall exposure in a mechanistic profiling study.
Study Duration	All subjects enrolled will be followed for a minimum of 12 months.

1 Introduction

1.1 Background

Since the first successful human kidney transplantation by Murray et al. in 1954 (Murray et al 1958), 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 et al 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 two or three immunosuppressive drugs with or without induction. Optimal combinations of therapies must be individualized based on the risk and benefit for each individual recipient (Bia et al 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 a CNIs include antiproliferative agents such as mycophenolic acid (MPA) based drugs (Mycophenolate Mofetil (MMF), CellCept or Myfortic) which block inosine monophosphate dehydrogenase (IMPDH) or 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 are usually started in the peri-transplant period and continued post-transplant in a triple therapy standard of care regimen.

CNI based standard of care regimens have resulted in excellent one-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%) one-year acute rejection rates (Hart et al 2020). However, use of currently available immunosuppressive drugs is still limited by mechanism-based side effects and poor long-term graft and patient survival. Side effects such as hypertension, dyslipidemia and diabetes as well as gastro-, hematologic-, neuro- and nephrotoxicity are common and result in poor long-term patient survival.

Induction therapy use varies based on recipient risk and regional preference. There are two broad categories of induction therapies, lymphocyte-depleting antibodies, such as polyclonal rabbit anti-thymocyte globulin (ATG, Thymoglobulin) and nondepleting monoclonal antibodies such as basiliximab (Simulect) and formerly daclizumab (Zenapax; withdrawn from US in 2009) that inhibit T-cell activation (Hardinger et al 2013). In the past, the lymphocyte depleting murine anti-human CD3 mAb, muromonab-CD3 (Orthoclone; OKT3, withdrawn 2010) and humanized anti-CD52 antibody alemtuzumab (Campath / Lemtrada) have sometimes been used (off-label) in high-risk transplant patients. Currently, in the US, lymphocyte-depleting antibodies are increasingly favored for induction (73.6% of adult renal transplants) over IL-2 receptor antagonists (IL2-RAs; 20.6%) (Hart et al 2020) whereas almost an inverse use of ATG and IL2-RA is seen in Europe (EU).

1.1.1 Transplant Induction Therapy

Basiliximab is a non-depleting, chimeric murine and human monoclonal antibody that specifically targets CD25, or the IL-2 receptor (IL2-RA), on the surface of T-lymphocytes. Administration of basiliximab in the peri-transplant time period inhibits IL-2 mediated lymphocyte activation, a critical signaling pathway involved in allograft rejection. Basiliximab is generally well tolerated with minimal toxicities or infusion reactions and does not result in lymphocyte depletion. When combined with a CsA, MMF, and corticosteroid-based (CS) immunosuppression regimen clinically relevant suppression of IL2 receptor activity following basiliximab administration is approximately 59 ±17 days (Simulect PI 2018).

ATG is a polyclonal mixture of chimeric (rabbit / human) immunoglobulins derived from the serum of rabbits inoculated with human thymocytes. The precise mechanisms underlying the therapeutic efficacy of ATG are not entirely known, although T-cell depletion plays a critical role. Quantitative analysis by Popow and colleagues demonstrated that ATG is largely comprised of T-cell specific antibodies to CD2 (7.5%), CD4 (1.2%) and CD8 (14.3%). In addition, a high proportion of antibodies to cell surface markers like CD11a/CD18 and CD45 that are broadly expressed on all leukocytes as well as antigens expressed on endothelial cells and cells of non-hematopoietic origin like CD98, CD99, CD147 and MHC class I (Popow et al 2013). This broad expression of pleiotropic antibodies has been linked to the exaggerated pharmacology and off-target toxicities expected with ATG administration. In addition, both *in vitro* and *in vivo* studies have suggested a number of other possible ATG mechanisms, including lymphocyte surface antigen modulation and transcription factor activation. ATG may disrupt immune cell processes, such as cytokine production, chemotaxis, endocytosis, stimulation and proliferation, as well as leukocyte-endothelial cell adhesion. Finally, ATG may also promote cell death via the induction of apoptosis, antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-mediated cytolysis (CDC) of various immune cells (Andress et al 2014) Considering the profound immunologic consequences of complete, long-term, lymphocyte depletion, polyclonal induction with ATG is not a benign therapy. The benefits of reduced acute rejection rates can come with the risks associated with over-immunosuppression and mechanism-based side effects. A course of ATG induction results in profound lymphocyte depletion for >12 months with slow recovery and inversion of CD4/CD8 populations that can take an additional 2-3 years to reach pre-transplant levels (Hardinger et al 2004). Mechanistic side effects such as infusion reactions, cytokine release syndrome, increased risk of infections and post-transplant lymphoproliferative disorder (PTLD) have also been reported with ATG administration.

Lymphocyte-depleting agents are primarily used in patients with immunologic risk factors for acute rejection. Whereas IL2 receptor antagonists (IL2-RA) and induction-free regimens are primarily utilized in patients with low immunologic risk (e.g., living donor renal transplant) (Hardinger et al 2013). The current Kidney Disease Improving Global Outcomes (KDIGO) Transplant Work Group guidelines recommend IL2-RA as a first-line induction agent in all types of donor-recipient profiles to reduce risk of acute rejection and allograft loss. These recommendations are primarily based on a meta-analysis that predominantly used cyclosporine-based maintenance immunosuppression (KDIGO 2009). A recent retrospective analysis by Tanriover and colleagues assessed the use of induction therapy in living donor renal recipients on immunosuppression with TAC/MPA ± prednisolone (PRED) (assessment period

2000–2012). Their conclusions were (i) There was no benefit from use of IL-2RA induction versus no induction in patients maintained on TAC/MPA/PRED with respect to acute rejection or graft survival (ii) ATG use was associated with 22% (combined with steroids) and 27% (in the setting of steroid withdrawal) reduction in the risk of acute rejection compared with IL-2RA in this population. (Tanriover et al 2015).

Overall, antibodies with a high specificity for single T-cell receptors (TCR) and low immunogenicity, such as siplizumab, may present an opportunity to develop very specific and substantial immunomodulation in the immediate post-transplant time period. Considering the efficacy of ATG and safety profile of basiliximab, developing a therapy that targets and modulates the various T-cell clones without the indiscriminate lymphocyte activation and depletion, could be useful in bridging the gap between these two therapies.

1.1.2 CD2 Biology

Human CD2 (also known as LFA-2, for leukocyte function-associated antigen-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, 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 two extracellular 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 induced a conformation change. The formation of the conjugate gives the T-cell receptor (TCR) a longer interval to scan various peptide-major histocompatibility complex (pMHC) combinations presented by the APCs, determine if a match has been made, and, if so, complete the intracellular signaling and co-stimulation necessary for T-cell activation (Springer et al 1987; Davis and van der Merwe 1996; Seed and Aruffo 1987). 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 (Rölle et al 2016, Leitner et al 2015). In addition, CD2 is up-regulated on both activated and memory T-cells 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 IL-12 (Lo et al 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.

1.1.3 TCD601 (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 Fc portion of the siplizumab antibody binds to FcγR receptors on NK cells resulting in ADCC and antibody-dependent cellular phagocytosis (ADCP) mediated depletion of CD2+ lymphocytes. Siplizumab also demonstrates selective immunomodulatory activity with depletion of memory T-cells (Tmem; high CD2 expression) and sparing of regulatory T-cells (Treg; low CD2 expression) *in vitro* and *in vivo* based on the differential expression of

CD2 on lymphocytes. Considering this activity, siplizumab is expected to modulate T-cell memory and immune reactivity in the setting of transplantation. For complete information on the mechanism of action (MoA) please refer to the latest edition of the siplizumab Investigator's Brochure (IB).

1.1.4 Relevant Data Summary

Data regarding the pharmacology, toxicology, pharmacokinetics (PK), and pharmacodynamics (PD) activity of siplizumab have been obtained from *in vitro* experiments, non-clinical studies and clinical trials in 779 patients. Siplizumab only cross-reacts with one non-human primate species, the chimpanzee (Damschroder et al 2004). Key results relevant to this trial are highlighted in this section. For complete information on these studies please refer to the latest edition of the siplizumab Investigator's Brochure (IB).

1.1.4.1 In Vitro Pharmacology

Tissue cross-reactivity of siplizumab was assessed in human tissues. Siplizumab binds to CD2 bearing cells including human lymphoid tissue and T-cell rich regions of thymus, lymph node, spleen, tonsil, stomach as well as small and large intestine and lung tissue. Siplizumab did not bind to other tissues, including reproductive organs and neural tissues, that do not present the CD2 target.

In pharmacology studies, siplizumab induced lymphocyte hypo-responsiveness and T- and NK cell depletion in a mixed lymphocyte reaction (MLR) assay at concentrations of 50 ng/mL and greater (Branco 1999). Maximal depletion (via ADCC) of CD2+ lymphocytes was measured with siplizumab concentrations between 10 and 100 ng/mL. In vivo activity was further investigated in a human-xenomouse model where weekly MEDI-507 administration for 6 months increased survival of mice bearing a CD2+ human adult T-cell leukemia (ATL) cell line.

1.1.4.2 Toxicology Data

Toxicology studies with single and multiple doses of siplizumab were conducted in primates (chimpanzees) and rodent models. Studies in rodents were conducted to assess off-target pharmacologic toxicity. In rats, after daily administration of MEDI-507 at 35 mg/kg or 70 mg/kg for 10 days, no gross or microscopic changes were observed. The lack of cross-reactivity between rat and human CD2 means this model cannot detect the on-target pharmacologic activity expected to exhibit in humans.

To further explore the safety and pharmacologic activity of siplizumab, one single and three repeated dose toxicology studies were conducted in chimpanzees. All animals were administered one (0.143 mg/kg) to three, IV doses of 0.143, 0.43, 0.60, 1.43 or 5 mg/kg MEDI-507. Following doses up to 1.43 mg/kg MEDI-507, 4/7 animals presented with a transient, acute, toxic event (e.g., brief apnea, respiratory symptoms or seizure activity) around the time of the first infusion. All animals recovered within 24 hours and symptoms did not reoccur upon re-challenge. With the highest dose, 5 mg/kg MEDI-507, animals (n=2) presented with symptoms of mild/moderate hypotension and diarrhea following the first dose. Symptoms in both animals resolved within a few hours and did not recur on subsequent administrations, resembling an infusion reaction.

A mild, transient decrease in platelet count around the time of first infusion was noted and attributed to activation of the reticuloendothelial system by large numbers of antibody-coated lymphocytes. In addition, a mild, transient increase in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) was noted at Day 7 that subsequently normalized by the next assessment on Day 42. Across all MEDI-507 treated animals, a rapid, dose-dependent depression in absolute lymphocyte counts and CD2-bearing lymphocyte subsets was noted by day 2; after the second dose. Recovery to pre-administration values occurred between 4-8 weeks after MEDI-507 administration. One animal that received MEDI-507 developed pneumonia of the right lung and died on study Day 29. On autopsy, it was noted that lymphoid tissues were atrophic, consistent with a treatment-related effect, however a causal relationship between the infection and MEDI-507 administration was not certain as pneumonia can occur in this animal group. For additional details, please refer to the siplizumab IB.

1.1.4.3 Teratogenicity and Reproductive Toxicology Data

The reproductive/developmental toxicity profile of siplizumab has not been fully characterized. In consideration of the patient population and overall risk benefit profile, women of childbearing potential must utilize highly effective contraception methods to avoid becoming pregnant while receiving siplizumab and for 24 weeks after the last dose.

Women who are nursing may not participate in this trial. The washout period of 24 weeks after the last dose is justified based on predicted PK profiles at 5 mg/kg, where siplizumab is predicted to be fully cleared from plasma and tissues by 12 weeks. The additional 12 weeks is a safety margin to assure complete clearance of siplizumab and recovery of lymphocyte activity.

Concomitant medications may present a separate reproductive risk and are to be used according to local guidelines and label. Please refer to original package leaflets for complete information and guidance and the risks and potential toxicities of each concomitant medication.

In addition, specific guidance on MPA can be located below.

Mycophenolate (MMF; mycophenolate mofetil or MPA; mycophenolic acid) is a confirmed teratogen associated with an increased rate of spontaneous abortion and congenital malformation compared with other immunosuppressants. MPA containing products carry a warning for female patients in the US and EU who may become pregnant and must not be used during pregnancy unless there is no suitable alternative to prevent transplant rejection. Use during pregnancy is associated with increased risks of first trimester pregnancy loss and pregnancy should be ruled out by use of a sensitive serum or urine test before starting mycophenolate; confirmation immediately before starting the medicine is also recommended.

Females of reproductive potential (FRP) must be counseled regarding pregnancy prevention and planning. Mycophenolate should not be used in women of childbearing potential unless they are using highly effective contraception. Some local labels for MPA recommend male contraception (condom). Due to the risks related to the drug's use during pregnancy, a Risk Evaluation and Mitigation Strategy (REMS) program has been established in the US for products containing mycophenolate and details pertaining to this program are provided in Appendix 4.

Please refer to local labeling and guidelines for the use of MPA in women of childbearing potential, including use of contraception and wash-out periods following discontinuation of MPA containing products.

1.1.4.4 Human Safety and Tolerability Data

In subjects, the safety, tolerability, PK and PD activity of siplizumab has been investigated in clinical trials across 4 distinct patient populations with hematologic T-cell malignancies, acute graft-versus-host disease (GvHD), psoriasis or following *de novo* renal transplantation.

In clinical trials, single-and multiple doses of MEDI-507 from 0.0004 mg/kg to 15 mg/kg IV and 0.1 to 10 mg subcutaneous (s.c.) have been administered to over 779 patients including 23 *de novo* renal transplant patients who have received multiple doses of 0.012 to 0.6 mg/kg. Across all patient populations, the most common adverse events (AEs) reported following MEDI-507 administration included lymphopenia (Grade 1-3) as well as a first dose effect manifesting as an infusion related reaction (Grade 1-2; pyrexia, chills, nausea and fatigue).

The decrease in lymphocytes is dose-dependent and expected based on the known pharmacology of siplizumab. For subjects who present with infusion reactions, the events were generally mild, transient and resolved spontaneously or were managed with nonsteroidal anti-inflammatory drugs (NSAIDs) and antihistamines. Serious adverse events (SAEs) were reported more frequently in patients with lymphoma and GvHD; including 36 deaths related to complications of GvHD and 9 cases of EBV-LPD. In renal transplant and psoriasis patients, a total of 59 SAEs were reported in 47 patients. There was one death in a renal transplant patient reported as a complication of a post-transplant cardiac procedure not related to MEDI-507 administration.

1.1.4.5 Human Pharmacokinetic Data

Siplizumab pharmacokinetics have been characterized with doses from 0.06 to 4.8 mg/kg in patients with T-cell lymphoma, psoriasis as well as patients following *de novo* renal transplantation. The disposition of siplizumab was mainly the consequence of its interaction (i) through the Fc region and FcRn receptor (a high-capacity receptor responsible for IgG homeostasis by recycling/salvage), and (ii) through the Complementarity – determining regions (CDR), to CD2 expressed on T-cells, leading to receptor mediated clearance. As with all IgG monoclonal antibodies, the primary route of elimination of siplizumab is via proteolytic catabolism, occurring at sites that are in rapid equilibrium with plasma. Siplizumab also binds to Fc receptors on NK cells resulting in T- and NK-cell depletion via ADCC or ADCP mechanisms and subsequent clearance of drug via target-mediated drug disposition (TMDD). In addition to depletion of CD2-bearing lymphocytes and proteolysis, binding and internalization of siplizumab-CD2 complexes all results in rapid and saturable routes of clearance.

Siplizumab pharmacokinetics in renal transplant patients can be described by a 1-compartment model with 2 parallel mechanisms of clearance, linear and Michaelis-Menten (MM) elimination. Siplizumab binds to FcRn receptors *in vitro* with an EC50 of 273.3 nM (0.04 μg/mL). Upon saturation, linear FcRn mediated recycling and standard IgG clearance dominates as expected. However, at concentrations below ~1.7 μg/mL (MM K_M EC50 0.34 μg/mL), TMDD elimination

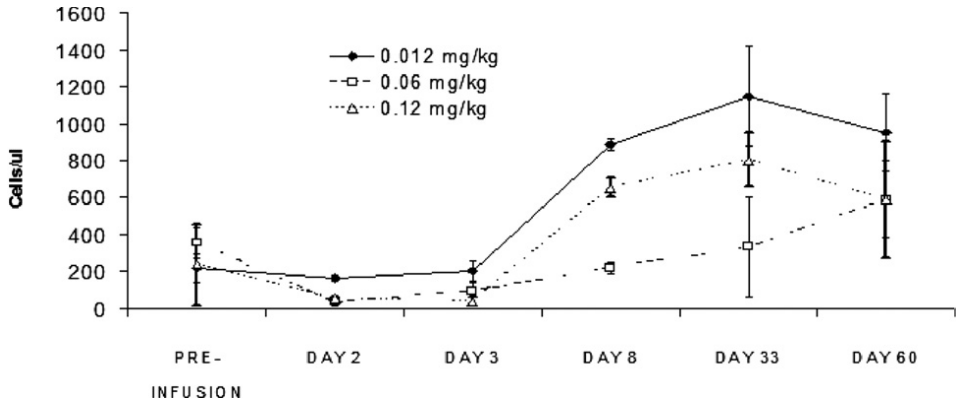
is the dominate clearance pathway and results in an inflection point and transition to very rapid clearance.

Preliminary modeling of the limited PK/PD data available in renal transplant patients and T-cell lymphoma patients suggests a strong population effect on the pharmacokinetics of siplizumab (MEDI-507). In renal transplant patients, the apparent PK half-life ($T_{1/2}$) is 8.5 days. In lymphoma patients, where there is an abundance of CD2+ lymphocytes and CD2 target to which siplizumab can bind, a higher clearance and shorter $T_{1/2}$ has been estimated of approximately 4.75 days. The primary difference is inflection point concentration at which linear clearance transitions to a more rapid clearance. In T-cell lymphoma patients, this transition occurs at a concentration ~40-fold higher (15 μg/mL) than renal transplant patients (0.35 μg/mL).

1.1.4.6 Human Pharmacodynamic Data

The primary PD markers measured across study populations are related to peripheral T-cell counts and CD2 receptor occupancy. In study MI-CP027, which enrolled *de novo* renal transplant patients, the 0.06 and 0.12 mg/kg doses were pharmacologically active with a short half-life of 14-49 hours and loss of PD activity (rapid lymphocyte recovery) and around Day 8 as illustrated below (Figure 1-1).

Figure 1-1 **Mean CD3 lymphocyte profile following siplizumab (MEDI-507) administration in study MI-CP027**



SOURCE: MI-CP027; Mean (+/- standard error) CD3 lymphocyte phenotypes by dose level at day 1 pre-infusion and at days 2 (P= 0.027), 3 (P= 0.016), 8 (P= 0.17), 33 (P = 0.21), and 60 (P = 0.20).
Note: N = 4 (0.012 and 0.06 mg/kg); N = 5 (0.12)

In Study MI-CP099, conducted in T-cell lymphoma patients, doses from 0.4–4.8 mg/kg of siplizumab were administered as 1–3 consecutive daily doses every 14 days for 1–8 cycles. As presented in Table 1-1, depletion of CD4, CD8 and NK cells is near complete with a 4.8 mg/kg administered every 2 weeks achieving ~97% suppression of circulating peripheral T-cells and 90% suppression NK cells.

Table 1-1 Peripheral CD4, CD8, and NK cell depletion following siplizumab (MEDI-507) administration in patients with CD2 Positive T-cell lymphoma in Study MI-CP099

Dose and regimen	N	CD4(%)	CD8 (%)	NK (%)
Multiple Doses Q2 weeks				
0.6 mg/kg (0.2 mg/kg X 3)	3	88.5	81.3	68.3
1.2 mg/kg (0.4 mg/kg X 3)	4	64.3	76.3	81.3
2.4 mg/kg (0.4, 0.8, 1.2 mg/kg)	3	87.1	84.9	92.2
3.4 mg/kg (0.4, 1.2, 1.8 mg/kg)	3	96.2	75.1	92.2
4.8 mg/kg (0.4, 1.8, 2.6 mg/kg)	3	97.1	96.4	89.7
Single Dose Weekly				
3.4 mg/kg	3	98.9	94.2	73.4
4.8 mg/kg	1	NA	NA	NA

N= subjects

SOURCE: MI-CP099 CSR; Reported percentages are the amount of depletion i.e., 90% would represent 10% of baseline lymphocytes remain in the peripheral circulation. Mean due to variability; Multiple dose arms, total dose of 0.6-4.8 mg/kg administered over 3 days in divided doses as indicated.

1.2 Study Purpose

The purpose of this study is to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of escalating doses of TCD601 (siplizumab), an anti-CD2 monoclonal antibody, compared to a rabbit polyclonal anti-thymocyte globulin (rATG), as induction therapy in *de novo* renal transplant patients. All subjects will receive the same standard of care (SoC) background immunosuppression. This trial will focus on profiling the safety, tolerability, PK and PD activity of siplizumab in the setting of standard-of-care immunosuppression in a moderate immunologic risk renal transplant population.

Overall, results of this study will be used to inform the siplizumab dose and regimen selection for investigation in later phases of clinical development and serve as proof-of-principal study in the replacement of SoC, polyclonal, T-cell depleting induction therapy.

2 Objectives and Endpoints

Table 2-1 Objectives and Related Endpoints

Objective(s)	Endpoint(s)
Primary Objective	**Endpoints for primary objective**
To assess the safety, tolerability, PK and PD of siplizumab compared to rATG, in *de novo* renal transplant recipients at 12 months post-transplant.	• Adverse events • Serious adverse events • Clinically significant changes in clinical chemistry, hematology, vital signs, serology • siplizumab PK • Immunophenotyping • CD2 RO • eGFR via MDRD
Secondary Objectives	**Endpoints for secondary objectives**
• To measure changes in peripheral lymphocyte immunophenotype • To measure the time-course and duration of siplizumab induced lymphocyte depletion and time to recovery • To measure peripheral CD2-receptor occupancy following siplizumab administration over time • To assess the incidence of treated biopsy proven acute rejection (tBPAR) at 12 months • To assess the incidence of treatment emergent *de novo*, donor specific antibodies (DSA) at 12 months • To assess the incidence of antibody meditated rejection at 12 months • To assess renal function via eGFR using MDRD equation at Months 3, 6, 12 or EOS	• Immunophenotyping via FACS • Lymphocyte counts • CD2 RO • Anti-siplizumab Ab • Incidence of BPAR • *de novo*-DSA / anti-HLA antibody measurement • incidence of AMR
Exploratory Objectives	**Endpoints for exploratory objectives**
• [redacted]	[redacted]

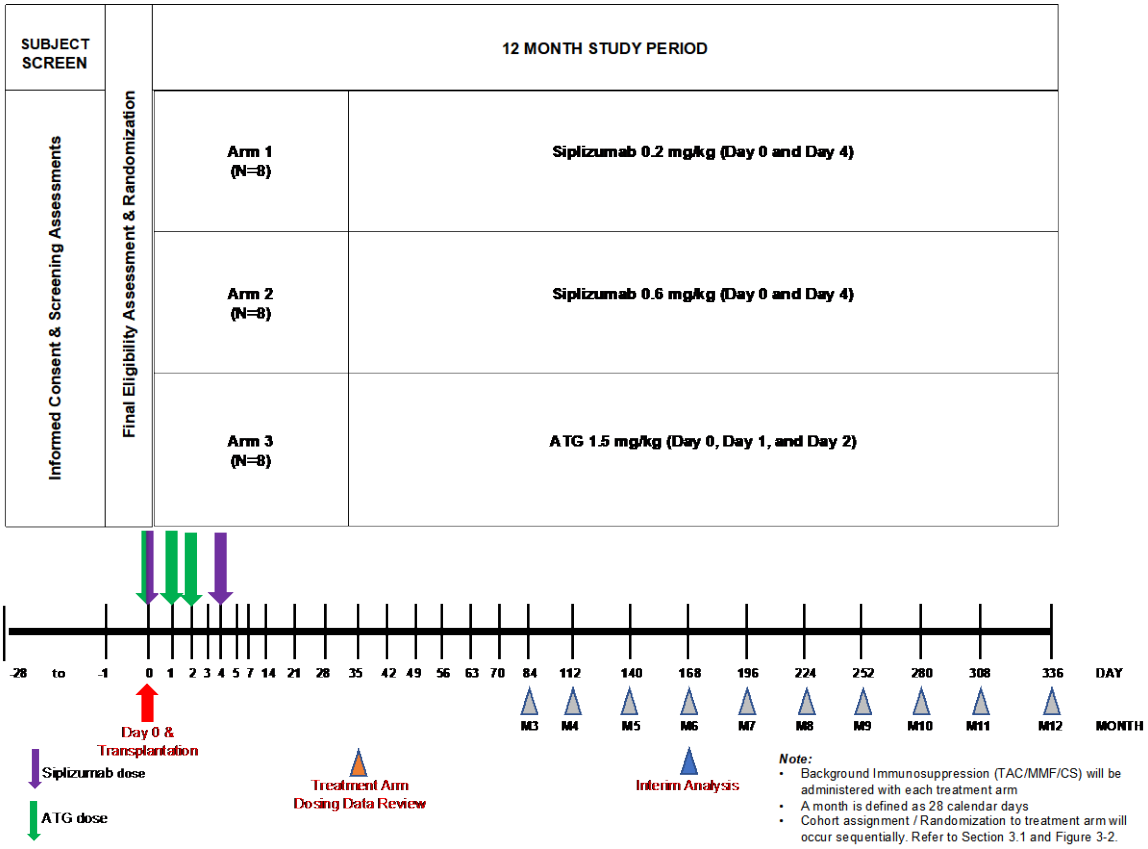
3 Study Design

3.1 General Overview

The TCD601B102 study is a 12-month, randomized, controlled, open-label, dose escalation study to evaluating safety, tolerability, pharmacokinetics and pharmacodynamics of an anti-CD2 monoclonal antibody, siplizumab, compared to anti-thymocyte globulin (rATG), as induction therapy in *de novo* renal transplant recipients. All subjects will receive background immunosuppression with standard exposure tacrolimus (TAC), mycophenolate mofetil (MMF) and corticosteroids (CS).

Up to 24 moderate immunological risk, *de novo* renal candidates will be enrolled into the study.

Figure 3-1 TCD601B102 Study Design



During the screening period (Day -28 to -1) and after informed consent has been signed, baseline subject information will be obtained in accordance with local regulations, including date of birth (month and year), age, sex (with childbearing status for females), race and ethnicity. In addition, relevant medical history (including CKD, ESRD and dialysis history) and current medical conditions at screening, a physical examination, vital signs, laboratory assessments, and a pregnancy test for female subjects of child-bearing potential will also be obtained.

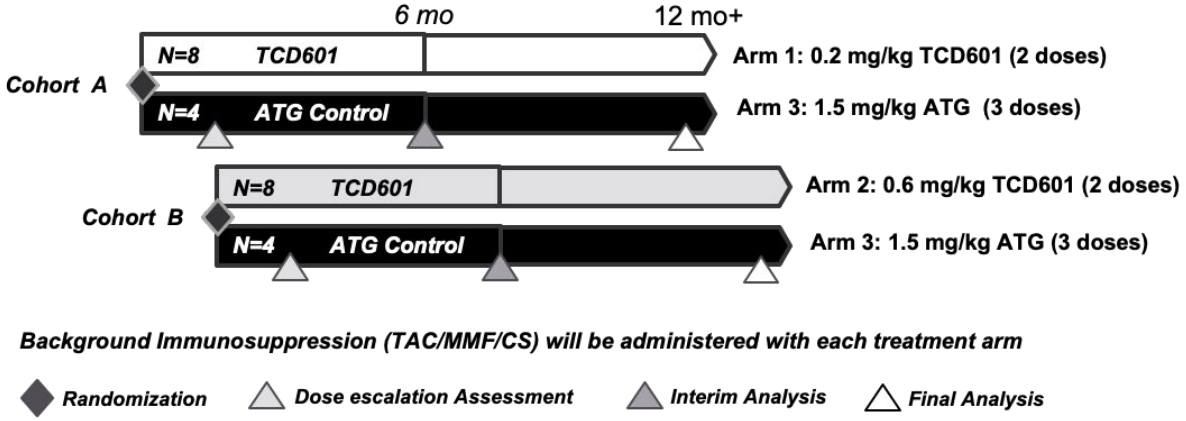
Transplant procedures will also include information on the renal transplant procedure, recipient and donor transplant background, recipient and donor viral serology and recipient/donor HLA testing results.

Procedures performed prior to consent as part of medical standard of care may be considered in the determination of subject eligibility (e.g., HLA/ABO typing, laboratory results). Additionally, if the screening and study Day 0 visits occur in close proximity (i.e., within a 24-hour timespan), screening assessments are not required to be repeated.

Day 0 is defined as the day of transplant/day of first dose of study product. Upon confirmation of eligibility for the study, and no later than Day 0 (Day of Transplant), the subject will be randomized and assigned a treatment number within the electronic data capture (EDC) System/Interactive Web Response System (IWRS). Every effort should be made to randomize the subject on Day 0, but when logistical considerations prevent this from occurring (e.g., central pharmacy requirements), the subject may be randomized up to 24 hours pre-transplant.

Eligible subjects will be sequentially assigned to one of two Cohorts (A or B) using a time-lagged dose escalation methodology as illustrated in Figure 3-2 below.

Figure 3-2 TCD601B102 Treatment Regimen



Within each Cohort, it is planned that 12 subjects will be randomized between siplizumab (at two dose levels, increasing per Cohort as above) or rATG control, in an 8:4 ratio prior to renal transplantation on Study Day 0, as outlined in Table 3-1.

Table 3-1 Dosing Regimen

Cohort	Arm	Subjects (n)	Product	Dosing Regimen
Cohort A	Arm 1	8	Siplizumab	0.2 mg/kg (Days 0 and 4)
	Arm 3	4	rATG	1.5 mg/kg (Day 0, 1 and 2)
Cohort B	Arm 2	8	Siplizumab	0.6 mg/kg (Days 0 and 4)
	Arm 3	4	rATG	1.5 mg/kg (Day 0, 1 and 2)

Subjects randomized to receive siplizumab will receive two intravenous (IV) doses on Days 0 and Day 4 post-transplant. The first dose will be administered intravenously, peri-operatively and must be completed prior to revascularization and perfusion of the allograft. The second and final dose of siplizumab will be administered intravenously on Day 4 post-transplant (Study Day 4). Subjects

randomized to the rATG control arm (Arm 3) will receive three intravenous (IV) doses of 1.5 mg/kg on Days 0, 1 and 2, regardless of Cohort assignment.

Siplizumab and rATG will be combined with concentration-controlled TAC (BID) dosing to a whole blood trough concentration 4-11 ng/mL, and MMF or equivalent (BID), and should be started within 24 hours post-transplant. Subjects will also receive CS per local practice with a minimum of 5.0 mg/d prednisone or equivalent until Month 12.

Dose escalation from one Cohort to the next will be determined 28 days following the last investigational product administration in the 4th siplizumab treated subject in each treatment Cohort and prior to dose escalation to the subsequent Cohort, a review of all available safety, tolerability and PD data will be conducted by ITB-MED in collaboration with the Investigators. This 28-day safety period allows sufficient time for subjects to reach full-receptor occupancy, maximum pharmacodynamic activity, and for the presentation of acute, drug related toxicities.

In the event there is no evidence of acute, dose limiting toxicity (DLT), randomization to the next dose level may be initiated. Alternatively, a decision to terminate the dosing arm could be reached. It is also possible for additional and/or intermediate dose level to be added during the course of the study per amendment (See Section 13.4.4). Cohorts may be added at any dose level below the maximum tolerated dose in order to better understand safety, PK or PD.

This escalation data review will be repeated prior to dose escalation/termination decisions for each Cohort. The review of subject data and dose escalation may occur before all subjects have been randomized to a given Cohort. If the next dose level is opened to subject assignment, Cohorts will be back filled to achieve a final sample size of 12 subjects.

Dose escalation will be based on *a priori* defined criteria outlined in Section 6.2.8.

In addition to the review of data for dose decision purposes as noted above, an independent Data Monitoring Committee (DMC) will conduct an ongoing review of cumulative PK, PD, safety, Adverse Events (AEs) and Serious Adverse Event (SAE) data as well as EBV-viral load and PTLD surveillance results, including clinically relevant changes on physical exam and clinical laboratory assessments and ad hoc imaging. The Committee will convene on a quarterly basis or as described in the DMC Charter. If at any time the observed AEs meet or exceed the *a priori*-defined stopping criteria, the study will be placed on hold pending a review as outlined in Section 9.1.1.

Additionally, a formal interim analysis will occur once 50% of subjects assigned to the treatment Cohorts complete their 6-month study assessment.

This formal interim analysis will be conducted to assess the safety/tolerability (e.g., AEs, SAEs, clinical laboratory assessments, vital signs, PK data and PK/PD activity (e.g., immunophenotyping and CD2 receptor occupancy). The analysis will also include assessment of biopsy proven acute rejection (BPAR), graft losses deaths, and key safety endpoints. In the event the acute rejection rate exceeds a clinically relevant threshold set forth in the protocol and DMC charter, or the *a priori* defined stopping rules, enrollment will be suspended to allow for the early termination of any treatment cohort where the benefit/risk of siplizumab is deemed unacceptable.

Following transplantation, subjects should be treated post-operatively per standard-of-care clinic practice and per the assessments outlined in the protocol. Following discharge from the hospital

and unless more frequent clinic visits are required for laboratory specimen collection, subjects will present to the clinical site for study visits weekly up to and including Week 10 and then monthly through Month 12 or EOS, and as outlined per the Schedule of Assessments outlined in Appendix 1.

All randomized subjects are expected to continue in the study up to Month 12 regardless of being on or off assigned treatment. Subjects who are randomized but not transplanted or administered their first dose of siplizumab will be replaced.

4 Study Design Rationale

The goal of induction therapy is to prevent acute rejection during the early post-transplant time period by providing a high degree of immunosuppression at the time of transplant surgery and 1-2 months thereafter. Escalating doses of siplizumab will be administered in place of SoC (e.g., rATG) induction therapy in combination with a TAC/MMF/CS based treatment regimen. The time course, depth and duration of lymphocyte depletion and immunomodulation will be profiled in combination with the assessment of safety, tolerability, PK and PD activity. CD2 represents a unique target for induction considering the broad expression and function in T-cell activation, co-stimulation and alloantigen recognition. This trial will characterize the safety, tolerability, PK and PD activity of 0.2 mg/kg and 0.6 mg/kg siplizumab in comparison to rATG induction, in the setting of *de novo* renal transplantation.

Siplizumab will be administered in two separate IV infusions over a ~5-day time period. The first infusion will be administered on study day 0 at the time of transplant (pre- or intra-operatively). The infusion is to be completed prior to revascularization and reperfusion of the allograft to assure both donor and alloreactive T-lymphocytes are suppressed and depletion is initiated in the hours and days post-transplant. The second dose will be administered on post-operative Day 4.

PK and PD data will be analyzed during the trial and the Population PK/PD model will be revised after each dose escalation to predict the concentration- exposure-response for the next dose as appropriate. Overall, the escalation scheme is designed to collect data and measure siplizumab concentrations that demonstrate a positive benefit/risk profile while providing approximately 45 days of T-cell and NK-cell suppression and immunomodulation.

The randomized, controlled, open-label, dose escalation design selected for this multicenter study will allow for a cautious assessment and evaluation of the multiple dose siplizumab safety, tolerability, PK and PD when added to TAC/MMF/CS based treatment regimen in comparison to standard of care induction with rATG.

Although the ideal study would employ a double-blind, double-dummy methodology to minimize bias, in consideration of the inherent complexity of this study (multiple arms, frequent visits, siplizumab PD activity, interim assessment after each dose, the different dosing schedules of siplizumab and ATG and extensive investigations), it has been decided to utilize an open-label design. This open-label design will not only minimize the risks for subjects during the initial investigation of siplizumab should the need for rapid intervention arise, such as emergent SAEs, but also avoids the additional difficulties associated with placebo infusions in the control group. It is recognized that Investigator bias can affect the management of subjects receiving investigational

treatment; especially in an open-label study setting. In general, such scrutiny biases the study in favor of the control arm. As such, efforts to minimize bias for or against the siplizumab treatment arms will be managed through the use of a limited number of high-quality transplant centers with similar SoC and subject management.

Due to the unknown tolerability and PD activity, this study will enroll a moderate immunological risk *de novo* patient population who would typically be treated with ATG induction. This population was selected since they typically present a lower risk of post-transplant complications, including delayed graft function (DGF) and provide a fair assessment of clinical activity while not requiring the highest level of immunosuppression. While it is recommended per current KDIGO guidelines, that ALL renal transplant patients receive induction with anti-IL2R therapy (KDIGO 2009), due to the expected overlapping activity with siplizumab, inhibition of T-cell activation, anti-IL2R or other T-cell depleting induction (e.g., ATG) will not be allowed in combination with siplizumab in this trial. In the setting of acute rejection prophylaxis with induction or no induction in the planned study population, the risk of 'omitting' SoC induction is manageable. Without induction and SoC therapy (TAC, MMF and CS) 12-month BPAR rates of 12.4% and 13.3% for living and deceased donor allografts have been reported, respectively (Tanriover 2015). These rates (BPAR) are similar to those in patients treated with anti-IL2 induction of 11.7% and 12.4%, respectively in the same population (Tanriover 2016).

Overall, safety risks will be reviewed on a regular basis by ITB-MED and an external independent DMC, with particular attention given to acute rejections, infusion reactions, serious infections, EBV-reactivation and malignancies associated to those (e.g., PTLD).

4.1 Dose/Regimen and Treatment Duration Rationale

While siplizumab (MEDI-507) has been administered to 779 subjects, the characterization of PK and PD activity following IV administration remains incomplete. An initial population PK/PD model has been developed based on data collected in previous siplizumab (MEDI-507) trials in renal transplant, T-cell lymphoma, aGvHD and patients with psoriasis.

The following section supports the rationale for the investigation of two siplizumab doses via a two-dose regimen.

As described in Section 1.1.4.5, siplizumab pharmacokinetics in renal transplant patients can be described by a 1-compartment model with 2 parallel mechanisms of clearance, linear and Michaelis-Menten (MM) elimination.

Mean, predicted, time-concentration profiles of the two-dose regimen planned in renal transplant patients have been simulated and are presented in Figure 4-1.

Figure 4-1 **Mean predicted siplizumab serum concentrations in study TCD601B102: 0.2 and 0.6 mg/kg**

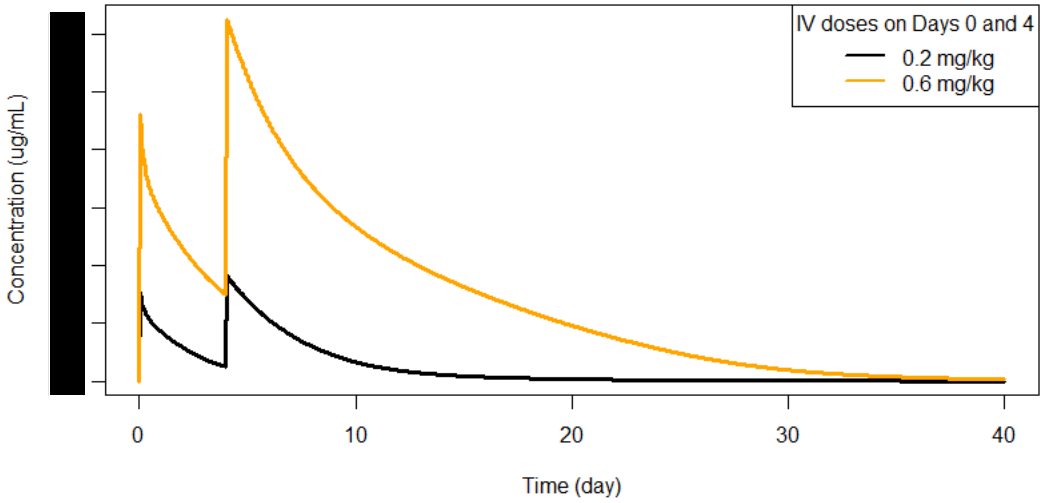


Figure 4-1: Solid curves represent the mean predicted time-concentration profile of siplizumab following two simulated 0.2 or 0.6 mg/kg siplizumab doses on Study Day 0 and 4 in *de novo* renal transplant patients.

Siplizumab concentrations are predicted to increase in a dose proportional manner with mean Cmax (peak) concentrations of approximately [redacted] µg/mL following the second dose of 0.2 or 0.6 mg/kg on Study Day 4. The apparent PK half-life is predicted to be ~[redacted] days at both doses with peak concentrations exceeding the TMDD inflection point of ~[redacted] µg/mL.

Dose escalation in the TCD601B102 trial will start with 0.2 mg/kg, which is 3-fold less than the highest dose investigated in the setting of previous renal transplantation studies (0.6 mg/kg; Studies NKD03 and ITN036) and ~1.7-fold higher than the 0.12 mg/kg dose investigated in the MI-CP027 renal transplant induction study. A semi-log dose escalation up to 0.6 mg/kg will allow for adequate characterization of the PK/PD profile and investigation of lymphocyte pharmacodynamics. Importantly, all of the siplizumab doses proposed in this trial have been administered to subjects previously with good safety and tolerability, however due to the nature of the renal transplant population, cautious dose escalation will be conducted to ensure subject safety is managed closely during this trial.

It is planned to administer the first dose prior to revascularization of the allograft to ensure both donor and recipient alloreactive T-lymphocytes are rapidly suppressed and depletion is initiated within hours of allograft perfusion. It is expected that initial distribution within the periphery and various tissue compartments as well as ADCC mediated depletion of lymphocytes will result in enhanced siplizumab clearance following the first dose. Therefore, a second dose of siplizumab will be administered on Day 4 with the intent of replenishing the free-siplizumab (TCD601) to account for redistribution of CD2 bearing lymphocytes as well as maintain saturation of the TMDD clearance pathways; maintaining prolonged serum concentrations above the tissue and peripheral concentration threshold of [redacted] µg/mL.

Considering the apparent [redacted]-day half-life predicted from previous trials in renal transplant patients (MI-CP027) and acute GvHD (MI-CP046) following bone marrow transplantation with siplizumab (MEDI-507) high serum concentrations will be required to prolong the peripheral immune modulation and T-cell suppression during the first month post-transplant; a time when patients are at the highest risk of acute rejection. Based on current modeling presented in Figure 4-1 it is anticipated that two doses of 0.6 mg/kg will result in ~30 days above the [redacted] µg/mL target. While the 0.2 mg/kg dose is not expected to provide the same duration of PK coverage, accounting for the post-depletion lymphocyte dynamics and redistribution from lymphoid tissues, the pharmacodynamic activity induced by selective T-cell depletion is expected to persist following siplizumab clearance.

While the duration of activity in renal transplant recipients is yet to be determined, PK/PD modeling planned prior to the dose escalation step will allow for a near real-time exposure-response analysis during the trial and modification of the escalation scheme or dosing regimen per amendment.

4.1.1 Siplizumab Tissue Distribution / Effect Compartment

Recent characterization of monoclonal antibody distribution by Shah and Betts allows for the rational targeting of various tissue compartments based on the expected distribution of therapeutic antibodies as a percentage of the free plasma concentration (Shah & Betts 2013). In the setting of solid organ transplantation, the peripheral (vascular) compartment is not the only location of alloreactivity. Acute cellular rejection occurs within the parenchyma and vasculature of the allograft. Similarly, allorecognition occurs, to a large extent, in lymph nodes and secondary lymphoid tissues; therefore, these tissues represent an equally important compartment outside of the peripheral vasculature to target. For renal tissue, an antibody biodistribution coefficient (ABC) of 13.7% of plasma concentration (CV% (± 3.10) was reported whereas the ABC for lymph nodes is 8.46 ±11.4% (Shah & Betts 2013).

Completed siplizumab (MEDI-507) studies have assessed the effect of anti-CD2 therapy on peripheral lymphocytes and lymphocyte subsets as well as peripheral target saturation and binding. It is expected that administering sufficient siplizumab to achieve adequate exposure in both the peripheral and relevant tissue compartments will lead to more complete immune regulation. Based on the expected PD activity outlined in Section 1.1.4.6, where siplizumab concentrations of [redacted] µg/mL are required for adequate T and NK cell modulation and depletion, peripheral siplizumab trough (C0) concentrations of [redacted] µg/mL and [redacted] µg/mL would result in adequate target engagement and lymphocyte suppression in renal tissue and lymph nodes, respectively.

As discussed in Section 1.1.4.5, population pharmacokinetics (PPK) modeling suggests that concentrations of siplizumab above the MM K_M of [redacted] µg/mL, which represents the EC50 concentration, is necessary to maintain saturation of the TMDD pathway and linear clearance in renal transplant patients. To maintain full CD2 RO, target engagement and saturate clearance mechanisms, the relevant concentration is 3-5-fold greater than the K_M; a concentration of [redacted] µg/mL. This concentration is represented by the inflection point and transition from linear- to non-linear clearance, occurring around the [redacted] mg/mL concentration range in the simulations. This concentration also represents a key threshold ([redacted] µg/mL) for T-cell engagement and depletion,

where maintenance of trough concentrations above the threshold in the periphery are expected for approximately [redacted] following 0.6 mg/kg siplizumab (Figure 4-2).

Figure 4-2 **Mean predicted, log-transformed, siplizumab serum concentrations in study TCD601B102 following 0.2 and 0.6 mg/kg siplizumab administration**

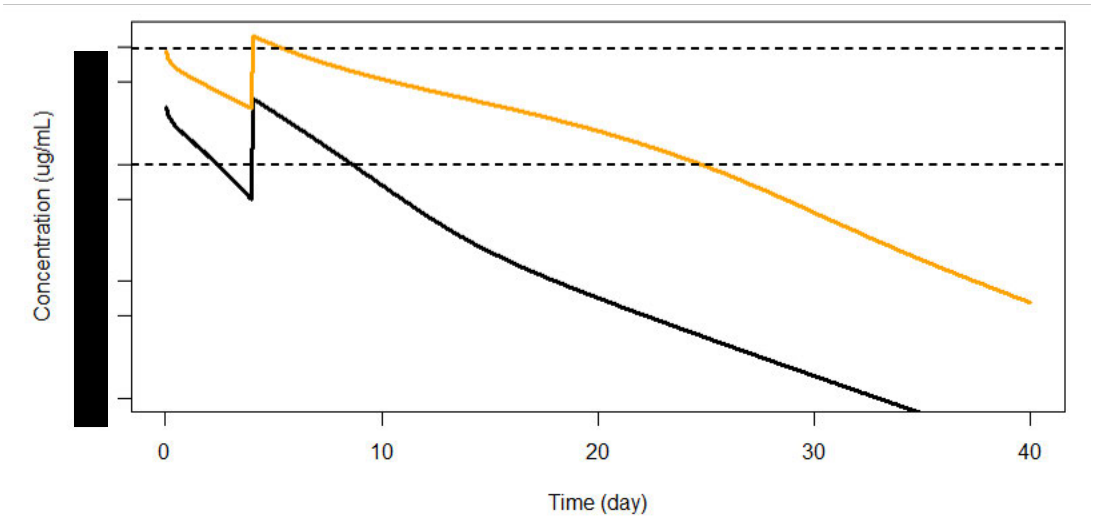


Figure 4-2: Horizontal dashed lines represent predicted trough concentrations at [redacted] ug/mL. Solid curves represent the mean predicted time-concentration profile of siplizumab (semi-log scale) following two simulated 0.2 or 0.6 mg/kg siplizumab doses on Study Day 0 and 4 in *de novo* renal transplant patients.

Based on the known variability of siplizumab (MEDI-507) PK, and proposed target tissue concentrations, a mean minimum serum concentration above [redacted] µg/mL would be required to maintain tissue concentrations above the [redacted] µg/mL threshold to induce immunomodulatory activity in renal and lymph tissue, respectively. These concentration thresholds are represented as horizontal dashed lines in Figure 4-2. It is expected that following the second 0.6 mg/kg dose of siplizumab a short duration, above the tissue exposure threshold will be achieved.

4.2 Rationale for Active Control

In the completed renal transplant siplizumab clinical trials, no controlled studies have been performed, therefore the comparative safety and efficacy data will allow for a better estimation of effect size and AE rates for future clinical trials in this population. The use of an active control arm was selected to allow for enrollment and randomization of a relevant moderate immunologic risk patient population who would be generally treated with ATG induction therapy. In addition, the comparative safety, biomarker and pharmacodynamic data within the control population will facilitate a more comprehensive assessment of siplizumab safety and tolerability in comparison to SoC.

ATG is the most frequently used depleting agent for induction therapy in solid organ transplantation. The use of rATG (Thymoglobulin; Genzyme) is more common in North America compared to Europe. In Europe ATG-F (ATG-Fresenius; Grafalon, Fresenius Biotech GmbH, Munich, Germany) is used for those deceased donor transplant recipients that are considered at

risk for DGF and may be effective in reducing ischemia reperfusion injury in this setting (Guirado 2018).

The mechanism of action of both ATG products is lymphodepleting, therefore there are mechanistic similarities as well as differences between rATG, ATG-F and siplizumab. The ATG products are both generated by immunization of rabbits but use different immunogens, namely fresh human thymocytes for ATG and a Jurkat T-cell line for ATG-F. Furthermore, the proportion of antibodies directed at CD2 in ATG has been estimated as 7.5% (Popow et al 2013). However, ATG-F targets CD28, CD29, CD45, CD49, CD98, and CD147 but rarely targets CD3, CD4, CD44, and HLA-DR, thus rATG and ATG-F may have different immunosuppressive activities (Song et al 2020), further supporting the restriction to rATG in this clinical trial. For these reasons rATG is considered an appropriate control for this induction study.

4.3 Rationale for Background Immunosuppression

In adult *de novo* kidney transplant recipients, the use of TAC, MMF and CS is an approved regimen for renal transplantation across the world and is the current SoC used in more than 90% of kidney transplants. Over the past decade, the clinical use of CNIs, including TAC, has focused on minimization of the CNI to mitigate many of the associated adverse effects. Current clinical use of TAC with an MMF-based regimen and CS results in excellent graft and patient survival as well as low rates of acute rejection. When TAC is combined with an MMF-based regimen and induction using an IL-2 antagonist, the labeled trough concentration range for TAC is 4-11 ng/mL (e.g., Prograf® PI 2019); this range will be employed in this clinical study.

Similarly, MMF or equivalent, at a dose of 1.0 g BID will be utilized per label (e.g., CellCept PI 2019).

For CS, all subjects should receive a minimum of 5.0 mg/d (prednisone or equivalent) from Day 0 until Month 12 with administration according to local practice.

The use of immediate-release generic or equivalent medications for TAC and MMF are allowed in the TCD601B102 study, however, substitution is not allowed for the first 12 months post-transplant. All subjects who start on brand or a specific generic TAC and MMF are to be maintained on the same brand or generic for the duration of this trial.

For subjects who are inadvertently switched, or in the event of a drug shortage need to change to another manufacturer, ITB-MED is to be informed and the site should consider more intense therapeutic drug monitoring (TDM) to ensure the subject achieves similar TAC concentrations.

4.4 Purpose and Timing of Interim Analyses/Design Adaptations

During the conduct of this study, ITB-MED and the DMC will review safety, PK and PD results of the trial on an ongoing basis. A regular review of cumulative safety data, including as well as EBV-viral load and PTLD surveillance results, including clinically relevant changes on physical exam and clinical laboratory assessments and ad hoc imaging, biopsy proven acute rejection (BPAR), graft losses deaths, and key safety endpoints, will be conducted by ITB-MED. In the event safety endpoints or the acute rejection rate exceeds a clinically relevant threshold set forth in the protocol and DMC charter, *or* the *a priori* defined Stopping Rules as outlined in

Section 9.1.1 are met, enrollment will be suspended to allow for the early termination of any treatment cohort where the benefit/risk of siplizumab is deemed unacceptable.

Formal analyses to assess PK, PD as well as safety will be performed as follows:

- **Escalation analysis:** After the first 4 siplizumab treated subjects who have been enrolled in each cohort reach 28 days after the last siplizumab infusion.
- **Interim analysis:** Once 50% of subjects assigned to the two treatment Cohorts complete their 6-month study assessment.

The purpose of the Day 28 escalation analysis is to confirm progression to the next cohort while the 6-month interim analysis is to support PK/PD modeling activities and clinical trial and dose escalation planning.

4.5 Risks and Benefits

The risks and benefits are expected to be broadly similar to that of ATG in combination with SoC immunosuppression. In particular, the risk of increased infections and first dose effect, will be minimized by adherence to the inclusion/exclusion criteria, premedication, close clinical monitoring and minimization of protracted siplizumab exposure during treatment period. Infection risk will be mitigated by following applicable national vaccination guidelines and by use of prophylaxis (See Section 6.5). Similarly, the risks of SARS-CoV-2 will be minimized by following local, national and international guidelines for immunosuppressed and solid organ transplant patients (See Section 4.5.3).

The risks of insufficient efficacy (higher rate of acute rejection-tBPAR than SoC) will be minimized by enrolling a moderate immunologic risk patient population, frequent monitoring of clinical labs and signs and symptoms suggesting BPAR and the early discontinuation of any treatment arm that is unsafe or ineffective according to the Stopping Rules detailed in Section 9.1.1.

The below sections list the possible risks related to siplizumab treatment. For further details please refer to Section 7 of the current IB.

Information and guidance for the SoC treatment used in this study is provided in the local labelling information and should be strictly followed.

4.5.1 Siplizumab

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. A serious infusion reaction that results in anaphylaxis is a rare event in monoclonal antibody therapy. Siplizumab is a fully humanized monoclonal antibody of the IgG1 class. This class of antibody is normally abundant in humans. Therefore, the antibody itself is expected to be less immunogenic in humans compared to chimeric or other humanized antibodies.

Assays to detect a putative antibody response to siplizumab are included in the study design.

In consideration of the clinical and non-clinical toxicology study results for siplizumab (MEDI-507) as well as clinical studies with antibodies that target CD2, the potential risks of siplizumab in humans may include:

- Infusion reactions, inflammatory reactions and cytokine release
- Immunosuppression and infections
- EBV-associated lymphoproliferative disorders
- Other hypothetical risks

These risks and an overall risk mitigation strategy are discussed below.

4.5.1.1 Infusion and Inflammatory Reactions and Cytokine Release

Cytokine Release

Siplizumab is a non-activating humanized mAb that binds to CD2+ immune cells and rapidly eliminates them via ADCC therefore cytokine release syndrome may be observed after administration. Cytokine release syndrome 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. The clinical manifestations have ranged from a more frequently reported mild, self-limited, "flu-like" illness to a less frequently reported severe, life-threatening, shock-like reaction, which may include serious cardiovascular, pulmonary and central nervous system manifestations. The syndrome typically begins approximately 30 to 60 minutes after administration (but may occur later) and may persist for several hours. The frequency and severity of this symptom complex is usually greatest with the first dose. With each successive dose, both the incidence and severity of the syndrome tend to diminish. Increasing the amount of a dose or resuming treatment after an interruption may result in a reappearance of the syndrome.

A cytokine release event has not been reported in any subjects receiving siplizumab alone and in combination with other immunosuppressants to date. However due to the target cell population, CRS remains a hypothetical risk.

Infusion Reactions

Infusion-related reactions, such a chills, pyrexia, and fatigue, have been commonly seen in siplizumab (MEDI-507) treated patients with cancer, GvHD, psoriasis and following organ transplantation. These 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. In the cancer studies, as prophylaxis for infusion type reactions, patients have been premedicated with acetaminophen and diphenhydramine before each siplizumab infusion. Demerol has been administered for treatment of patients with rigors. Chills without rigors have been managed with warm blankets.

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. Patients 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.

Serious allergic events including anaphylactic or anaphylactoid reactions have been reported in patients re-exposed to antibodies derived from foreign protein such as OKT3 or ATG. Since it can be very difficult to distinguish between cytokine release syndrome and anaphylaxis, extra caution must be taken. Reactions occurring within 10 minutes of the start of an infusion are usually anaphylaxis and should preclude re-administration of the antibody. Vasculitides may occur, most commonly leukocytoclastic vasculitis or palpable purpura.

4.5.1.2 Immunosuppression and Infections

Siplizumab is being developed for its expected immunomodulatory and T-cell depleting activity. CD2 ligation is linked to the functional activity of T-cell activation and co-stimulation. T-cell depleting antibodies may be immunosuppressive and prolonged immunosuppression may increase the risk of infection, including opportunistic infections. Administration of escalating doses of siplizumab is expected to result in general immunosuppression due to T- and NK-cell depletion when full receptor occupancy has been achieved. Siplizumab induction will be combined with background, CNI-based triple-therapy immunosuppression in renal transplant patients. Subjects treated with siplizumab may present with an increase in the overall degree of immunosuppression from days to weeks depending on the dose and regimen as intended in induction treatment with SoC T-cell depleting antibodies. During this time of immunosuppression subjects may be at a higher risk for infection.

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) (see Section 6.5) 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.

In completed clinical trials with siplizumab there is no clear evidence for a higher rate of infections associated with treatment administration. Infections were common in Post-HSCT patients with Garde II-IV aGvHD where an increased risk of immunosuppression related opportunistic infections, including viral reactivation, is common. In study MI-CP046 (adult GvHD), infections were common in both MEDI-507 (19 [90%]) and placebo control arms (12 [92%]). When the investigator's assessment of relatedness is considered, all of the infection events are consigned to background. In oncology studies, infections occurred in 3/19 (16%) T-cell lymphoma patents

(MI-CP099), with 5 patients (26%) testing positive for CMV antigen; three of whom discontinued treatment per protocol. In Study MI-CP107, 4 infection-associated SAEs (infection, respiratory syncytial virus, sepsis, and staphylococcal bacteremia) were reported in 4/22 (18.2%) of patients. One event (infection) was judged by the Investigator as being related to MEDI-507. In the CD2+ T-cell lymphoma patient pool, there was no dose related increase in infection rates between arms, although there was an increase in EBV-related events; EBV-associated lymphoproliferative disease was reported in 9 patients treated across the T-cell lymphoma and aGvHD populations; see ***Lymphoproliferative Disorders and other Malignancies*** in Section 4.5.1.3 for details.

Assessing the rates of treatment emergent infections in a relatively healthy population, psoriasis, the placebo group was higher as compared to the siplizumab treated group.

While the sample size in the renal transplant pool is limited, the reported infections were as expected, and none were suspected by the investigator to be due to siplizumab administration as presented in Table 4-1 below.

Table 4-1 Renal transplantation pooled analysis: Opportunistic infections

Standard or Custom MedDRA Query Preferred Term	IV: ≤ 0.12 mg/kg (n=13)	IV: > 0.12 mg/kg (n=10)	Total (N=23)
Opportunistic Infection (CMQ)	2 (15.4%)	4 (40.0%)	6 (26.1%)
Clostridium difficile colitis	0	2 (20.0%)	2 (8.7%)
Gastritis	1 (7.7%)	1 (10.0%)	2 (8.7%)
Gastroenteritis	0	1 (10.0%)	1 (4.3%)
Herpes esophagitis	1 (7.7%)	0	1 (4.3%)
Urinary tract infection	0	1 (10.0%)	1 (4.3%)
Viral infection	0	1 (10.0%)	1 (4.3%)

Source: Table 2.1.5.5 (Listing ADVERSE_EVENTS in CP027 study, ListingAE_LAA in NKD03 study, listing16_2_7_1 in ITN036 study.; Abbreviations: CMQ = Custom MedDRA Query; SMQ = Standardized MedDRA Query; Note: MedDRA Version 22.1.

4.5.1.3 Lymphoproliferative Disorders

In patients at a high risk of lymphoproliferative disorders participating in studies with MEDI-507, specifically patients with CD2+ T-cell lymphoma and patients with ongoing acute GvHD following a bone marrow transplant, EBV-associated lymphoproliferative disorder (LPD), PTLD, and lymphoma have been reported. In the T-cell lymphoma trials (MI-CP099 and MI-CP107), EBV-LPD was reported in 5/51 (9.8%) patients including large granular lymphocytic leukemia (LGL; n=2), cutaneous T-cell lymphoma (n=1), peripheral T-cell lymphoma (n=1), and adult T-cell lymphoma (ATL; n=1). In the aGvHD studies EBV-LPD (n=1), PTLD (n=1) and EBV-related lymphoma (n=2) was reported in 4/48 (8.3%) patients. In addition, three cases of LPD have been reported in Investigator-initiated and compassionate use studies of MEDI-507 in patients following bone marrow transplantation.

All of the LPD cases reported with MEDI-507 have been limited to two unique patient populations, both of whom had a history of malignancies and increased risk factors for EBV-LPD, notwithstanding their primary T-cell lymphoma and aGvHD following BMT. While rare, EBV-associated secondary hematological malignancies are not unexpected in the setting of profound immunosuppression associated with T-cell lymphoma where B-cell lymphoma rates vary

from 2-15% based on patient age, ethnicity and immune status (Dojcinov et al 2018). In the setting of HSCT, especially in patients who present with multiple risk factors (Curtis et al 1999; Uhlin et al 2014), PTLD, rates of 8% up to 40% have been reported (Juvonen et al 2003).

In the setting of renal transplantation, siplizumab use is not expected to increase the risk of EBV-LPD/PTLD over ATG-based induction in combination with background immunosuppression. Independent adjudication of all 9 EBV-LPD cases was conducted to assess the overall risk of EBV-LPD in the setting of renal transplantation. While a notable risk of EBV-LPD in the setting of T-cell lymphoma was assessed by the committee it was stated that experience to date does not demonstrate that this risk exceeds that associated with ATG.

This rate in the US has been reported to be 1.03% (Hart et al 2020) and as high as high as 2.4% with ATG induction (Thymoglobulin PI 2020). 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 et al 2011). Therefore, all recipients will be screened prior to administration of siplizumab, and EBV-seronegative subjects excluded from participating in the TCD601B102 clinical trial. In addition, clinicians who specialize in transplant immunosuppression, and are aware of the risks for EBV-LPD, will be managing patients enrolled in this study. Regular assessments of hematology, EBV-viral load as well as PTLD surveillance including full physical exams at each visit as well as monitoring of clinical signs and symptoms will be conducted during the 12-month study.

4.5.1.4 Other Hypothetical Risks

Renal Dysfunction

In two renal transplant tolerance studies, NKD03/ITN010ST (n=5) and ITN036ST (n=5), a transient, acute kidney injury (AKI)-like syndrome was reported in a majority (9/10) of patients early in the post-transplant course. The syndrome was associated with recovery of host hematopoietic cells and rapid loss of donor chimerism at approximately two weeks post-transplant and is better described as Chimeric Transition Syndrome (CTS). Patients in these two trials received siplizumab (0.6 mg/kg MEDI-507 on Days -1, 0 and 1) in combination with a non-myeloablative, cyclophosphamide-based, conditioning regimen, thymic irradiation and rituximab pre- and post-transplant. Patients also received a combined haploidentical bone marrow cell infusion to induce transient chimerism and a renal allograft from the same donor on Day 0.

Patients with CTS presented with a significant increase in serum creatinine (SCr) with onset around post-transplant day 10-14 that peaked (SCr range 3.5 to 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 but showed capillary endothelial injury with cellular infiltrates (CD8+ / CD68+ cells) in the peritubular and glomerular capillaries.

Overall, 78% (7/9) of patients recovered normal renal function following the CTS event; 3 patients recovered with minimal intervention (corticosteroid pulse) while 4 patients required treatment (Intravenous Immunoglobulin (IVIG), ATG and/or plasma exchange). The two remaining patients failed to recover full renal function; this included one patient who lost their graft at day 10 due to severe antibody mediated rejection as well as a patient who presented with subsequent CNI toxicity and later progressed graft loss associated with thrombotic microangiopathy at Month 7.

Renal dysfunction, including significant changes in serum creatinine or eGFR has not been reported in other patient populations receiving siplizumab alone or in combination with SoC immunosuppression, including 13 patients enrolled in study MI-CP027 following renal transplantation. Patient's serum creatinine, serum cytokines and renal injury makers will be measured frequently in the first few weeks post-transplant with a focus on renal injury and dysfunction. In addition, urinary injury biomarkers will be collected for future analysis and biopsies will be evaluated for CTS in the event patients present with BPAR.

Malignancies

Prolonged and sustained immunosuppression may result in an increased risk of developing certain types of cancer.

In the T-cell lymphoma trials one patient with LGL developed a secondary leukemia (M4 type leukemia) one year after completing MEDI-507 therapy was reported. In the GvHD studies a case of acute myeloid leukemia relapse was reported.

In the study 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 the psoriasis studies had secondary malignancies (squamous cell carcinoma of the skin and myelodysplastic syndrome) following treatment with MEDI-507. Both patients had a prior history of these respective conditions and were entered into a MEDI-507 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).

Adjunct Immunosuppression

The combination of escalating doses of siplizumab in the presence of adjunct immunosuppression with TAC, MMF, and CS is not known. Please refer to the local labeling for the other agents for full disclosure of the expected risks associated with use in the setting of *de novo* renal transplantation for the investigational arms.

4.5.2 Risks of ATG Induction Therapy

The following summary is taken from the most recent US FDA-approved labelling of ATG (Thymoglobulin, Genzyme, 2020). For the most recent guidance refer to the most recently approved local labeling from the appropriate authority.

Immune-Mediated reactions

Serious immune-mediated reactions, including anaphylaxis or severe cytokine release syndrome (CRS), have been reported with the use of ATG. Fatal anaphylaxis has been reported. If an anaphylactic reaction occurs, terminate the infusion immediately and provide emergency treatment as indicated per local practice and clinical expertise.

Infusion-Associated Reactions (IAR) (including Cytokine Release Syndrome)

Cases consistent with cytokine release syndrome (CRS) have been reported with rapid infusion rates. CRS is attributed to the release of cytokines by activated monocytes and lymphocytes. Severe acute CRS can cause serious cardiorespiratory events and/or death. Close compliance with the recommended dosage and infusion time may reduce the incidence and severity of infusion-associated reactions (IARs). Slowing the infusion rate may minimize many of these IARs.

Local reactions at the infusion site may include pain, swelling, and redness of the skin.

Hematologic Effects

Low platelet and white blood cell (WBC) counts, including low counts of lymphocytes and neutrophils, have been identified and are reversible following dose adjustments. Total white blood cell and platelet counts should be monitored.

Infections

ATG is routinely used in combination with other immunosuppressive agents. Infections (bacterial, fungal, viral and protozoal), reactivation of infection (particularly cytomegalovirus) and sepsis have been reported after ATG administration in combination with multiple immunosuppressive agents. These infections can be fatal.

Malignancy

Use of immunosuppressive agents, including ATG, may increase the incidence of malignancies, including lymphoma or lymphoproliferative disorders. These events have been associated with fatal outcome.

Immunizations

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

Laboratory Tests

ATG may interfere with rabbit antibody-based immunoassays and with crossmatch or panel-reactive antibody cytotoxicity assays. ATG has not been shown to interfere with any routine clinical laboratory tests that do not use immunoglobulins.

4.5.3 Risks of SARS-CoV-2 (COVID-19)

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. Ongoing community transmission has been noted on all continents except Antarctica. Person-to-person transmission of SARS-CoV-2 occurs during close exposure

(< 2 meters) to an infected person, primarily via respiratory droplets produced when the infected person coughs or sneezes. COVID-19 disease 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 et al 2020). Transmission via droplet spread can occur from both symptomatic and asymptomatic individuals (Arons et al 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, along with PCR-based testing is imperative.

COVID-19 Disease:

Case series on COVID-19 disease in transplant recipients have been published, however data remains very limited. Imaging demonstrates pneumonia in the majority of patients that are hospitalized (75-100%). Patients with less severe infections may have lower rates of clinical abnormalities. Mild infections are common, however preliminary experience suggests that infection, once acquired by immunosuppressed transplant recipients, may be of greater severity than in normal hosts after the initial incubation period. Experience with other viruses including prior outbreaks of coronaviruses, also suggests that severe infections will occur in some transplant recipients.

At this time, the risk factors for severe disease have been characterized by observational studies. An initial report by (Pereira et al 2020) showed that advanced age was associated with severe disease in their transplant cohort, which is not different from the disease profile in the immunocompetent population (Kates et al 2020) reported age >65, chronic lung disease, congestive heart failure, and obesity were independently associated with poor outcomes of COVID-19 in solid organ transplantation. It is anticipated that transplant recipients may have a greater viral burden and shedding resulting in greater infectivity and potential spread to other individuals.

Limited data are available on optimal treatment protocols, and none have been clearly demonstrated to optimize outcomes. When considering potential therapies, clinicians should consider the need for immunosuppression reduction and presence of potential drug-drug interactions that may result in toxicity or therapeutic failure, e.g., beta interferon or CYP3A inducers/inhibitors.

The risk of a COVID-19 infection from an infected organ donor is unknown at this time. To date, there has been one documented case (Kaul et al 2021) of donor-derived disease transmission in a bilateral lung transplant recipient. Transmission from blood banks has not been documented at this time.

Guidelines on the risks and management of SARS-CoV-2 in the setting of clinical trials as well as that of renal transplant patients have been published by the European Medicines Agency (EMA), US National Institutes of Health (NIH), Transplantation Society (TTS) and American Society of Transplantation (AST). Treatment guidelines on the use in immunocompromised and transplant recipients are updated periodically as knowledge of COVID-19 disease management evolves.

Cumulative cases and incidence rates are tracked and published by the World Health Organization (WHO) and other public and private entities and should be used to guide local management of patients.

With active circulation of SARS-CoV-2 in the community, it is appropriate to counsel all candidates about the risk for acquisition from the community and hospital environment. Candidates should be educated about preventive strategies such as social distancing, masking when in proximity to non-household contacts, frequent hand washing, and avoidance of travel to high-risk areas.

A compendium of global guidance documents is maintained by the NOTIFY library and can be found at the following URL:

https://www.notifylibrary.org/background-documents#SARSCoV-2.

4.5.4 Risk Mitigation Strategy

Safety and tolerability data for doses up to 15 mg/kg IV have been collected in patients with T-cell lymphoma with good tolerability. With initial administration of a biologic, the first 4 hours of exposure are most critical with most infusion reactions (including hypersensitivity, cytokine release, anaphylaxis) occurring within the first 2 hours of exposure (Tabrizi and Roskos 2007). No cytokine release has been detected with IV or s.c. siplizumab (MEDI-507) administration in the completed patient studies. Cytokine release or anaphylaxis have not been reported with similar compounds specifically targeting the CD2 receptor. A mild infusion reaction has been described in primates as well as clinical studies with siplizumab following the first dose. This first-dose-effect presents as mild and transient pyrexia with chills, nausea and fatigue. These infusion reactions are self-limiting and respond well to premedication with acetaminophen and diphenhydramine. Subjects will receive their first dose of siplizumab in the pre- to inter-operative time period, at a time when patients are 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. In the TCD601B102 study all subjects will receive premedication prior to each dose of siplizumab to mitigate any infusion reactions.

Infections are a common risk for all transplant recipients. Subjects will be regularly evaluated while hospitalized and upon return to the clinic for signs and symptoms which might indicate a severe infection, i.e., fever, nausea, myalgia, headache, arthralgia, chills, diarrhea, stiff neck, and 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.

Considering the expected immunosuppressive nature of the compound, subjects will be screened for a history of latent infections. Viral reactivation will be assessed for CMV and BK virus according to local practice on a regular basis. Prophylaxis for CMV and pneumocystis pneumonia (PCP) will be administered to all subjects during the trial according to local practice. A negative test result for TB performed within 6 months of randomization will be required prior to enrollment. If there is suspicion of TB, a chest x-ray may be performed in accordance with local guidelines; subjects with a positive test will be excluded from participation.

EBV serology will serve as a key inclusion criterion, where EBV-sero*negative* subjects will be excluded from participation. EBV viral loads via EBV-PCR will be collected from all subjects throughout the trial and will be analyzed centrally to minimize inter-laboratory variation. Positive results that demonstrate an increase over time will be communicated to the investigator for additional follow-up and per-protocol PTLD surveillance as described in Section 8.4.5.

The ongoing SARS-Cov-2 pandemic represents a challenge for all renal transplant candidates and recipients. Due to the dynamic nature of COVID-19 infection rates, centers should continue to follow local and national guidelines and set policies based on the local incidence and prevalence of infections as well as hospital and staffing resources. This includes decisions to conduct or defer solid organ transplant procedures as well as the ongoing management of donors and recipients.

Subjects eligible for the TCD601B102 study will be randomized from the pool of active candidates who are currently undergoing transplantation and will be receiving T-cell depleting induction and standard of care immunosuppression. All eligible subjects will be informed of the risks of SARS-COV-2 during the consent process. To decrease the risk to study subjects, all candidates will be screened for SARs-CoV-2 prior to enrollment and excluded if positive.

Ongoing surveillance per standard of care will occur thereafter based on local conditions and signs and symptoms. In renal transplant patients who experienced COVID-19 disease, common presenting symptoms were fever, dry cough, and diarrhea, with most patients exhibiting lymphopenia and elevated C-reactive protein (CRP) (Fung and Babik 2020). Subjects will be counseled to report any of these physical symptoms to the clinical staff. Clinicians should also consider the common laboratory changes when assessing the potential for COVID-19 disease.

Subjects who may be exposed to SARS-CoV-2 or contract active disease will be managed per local practice and international guidelines including recommendations for seeking treatment or self-quarantine. As with all infection events, SARS-CoV-2 positivity and COVID-19 disease will be captured in the safety database and will be evaluated by the DMC during their periodic dose escalation and ongoing safety review. Within the clinical trial setting, subjects may be required to attend in-person study visits in excess of those based on standard of care for clinical laboratory assessments as well as PK/PD sample collection; this may increase their risk of SARS-CoV-2 exposure. To minimize the time patients, spend indoors and within the clinic for these assessments, phone contact or virtual / telehealth technology will be utilized where appropriate by the site staff. In addition, patients will be counseled on the importance of following proper hygiene, masking and social distancing practices to minimize community and hospital exposure during their standard of care and study specific visits.

SARS-CoV-2 vaccines (i.e., mRNA, adenoviral vector) are under development or have been authorized for clinical use globally. The effectiveness of these vaccines in immunocompetent adults is between 76-95%, however the effectiveness in solid organ transplant recipients is unknown (See Section 6.5). Based on current vaccination guidelines, it is recommended that all transplant candidates and their household members receive SARS-CoV-2 vaccination when it becomes available. Ideally, transplant candidates should be targeted for vaccination while they are awaiting transplant or 3-6 months post-transplant in this trial, based on T-cell recovery.

Subjects will be hospitalized for several days post-transplant. Following discharge from the hospital, subjects will return to the clinic for routine assessments frequently during the first

3-6 months per standard of care. During these visits, safety and PK/PD assessments will be collected. Standard safety assessments will include vital signs, physical examinations, clinical laboratory evaluations (hematology, blood chemistry and urinalysis), AE and SAE monitoring as outlined in the Schedule of Assessments. In addition to standard clinical laboratory assessments, subjects will be monitored regularly for signs and symptoms of infectious, inflammatory, hematologic or renal toxicity / rejection.

Subject's serum creatinine will be assessed frequently in the first few weeks post-transplant and thereafter with a focus on renal injury and dysfunction. Changes in renal function will be assessed via serum creatinine and estimated glomerular filtration rates (eGFR) using Modification of Diet in Renal Disease (MDRD) formula. In the event subjects present with a significant increase in SCr and/or BPAR for-cause biopsies are to be collected for evaluation according to the standard Banff histology system. [redacted]

Immunophenotyping via fluorescence-activated cell sorter (FACS) analysis will be conducted frequently during the study to assess the potential for an increased risk of infection, changes in leukocyte subsets and recovery following depletion anticipated with all siplizumab dosing arms.

Coagulopathy will be assessed using standard hematology (platelets) and coagulation studies, including international normalized ratio (INR)/prothrombin time (PT) and activated partial thromboplastin time (aPTT) according to local practice.

Finally, considering the open-label study design, ITB-MED and an independent DMC will review study data, including safety events and AEs of special interest, regularly and on an *ad hoc* basis. Furthermore, *a priori* defined stopping criteria, infection surveillance and pharmacovigilance by ITB-MED as well as ongoing clinical assessments by Investigator and site staff will be employed to protect individual subject safety during the trial.

Overall, the non-clinical and clinical safety results with siplizumab in human, as well as the comprehensive monitoring plan, *a priori* defined study stopping criteria and ongoing review by an independent DMC support the continued development of this immunomodulatory compound and conduct of further investigational studies. Moreover, in consideration of the ongoing SARS-CoV-2 pandemic, each center will manage their ongoing transplant program and enrollment of patients in this trial based on the Investigator's clinical judgement and individual patient risk assessment in consideration of both local and per protocol risk mitigation plans.

The overall benefit-risk assessment including the aforementioned mitigation strategies and monitorable and manageable risks of administering siplizumab in this patient population is positive and support the conduct of this clinical trial.

5 Population

This multicenter study will be conducted in up to 8 centers worldwide. The study population will consist of approximately 24 male and female *de novo* adult renal transplant patients. 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 through all inclusion/exclusion criteria at screening and confirmed prior to randomization. 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 eligible for inclusion in this study have to fulfill all of the following criteria:

1. Able to understand the study requirements and provide written informed consent before any study assessment is performed.
2. Male or female patients ≥ 18 to 70 years of age.
3. Recipients of a *de novo* renal allograft from a heart-beating deceased, living unrelated or non-HLA identical living related donor.
4. Recipients of a kidney with a cold ischemia time (CIT) < 30 hours; hypothermic machine perfusion within the same timeframe is acceptable.
5. Subjects who test negative for SARS-CoV-2 test via molecular testing (PCR)

5.2 Exclusion Criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study.

1. Transplant recipients sero-negative for Epstein-Barr virus (EBV).
2. Multi-organ transplant recipients.
3. Subjects who have received a kidney allograft previously e.g., re-transplant.
4. Recipient of a kidney from an HLA identical living related donor.
5. Recipient of a kidney from a donor after cardiac death.
6. Subjects at high immunological risk for rejection as determined by local practice [(e.g., presence of pre-existing DSA, recipient of high Kidney Donor Profile Index ≥ 85 kidney (where assessed)].
7. Subjects with donor specific anti-HLA antibody as measured by complement-dependent cytotoxicity assay (CDC), enzyme-linked immunosorbent assay (ELISA), or flow cytometry within 90 days prior to transplant or as performed per the center's local practice.
8. Complement-dependent cytotoxicity (CDC) crossmatch positive transplant (isolated positive B cell crossmatches are not an exclusion criterion).
9. ABO incompatible recipient
10. History of malignancy of any organ system, except for localized excised non-melanomatous skin lesions or carcinoma in situ of the cervix.

11. Subjects with clinically significant laboratory abnormality that would preclude participation in the study (e.g., >2.5 x Upper Limit of Normal (ULN) values for (a) liver function chemistries (ALT, AST, ALP), (b) bilirubin, (c) coagulation studies (INR/PT, aPTT).
12. Patient with any of the following:
    - hemoglobin (Hgb) < 8 mg/dL
    - WBC count ≤ 2,000/mm^3
    - platelet count ≤ 75,000/mm^3.
13. Sero-positive for Human Immunodeficiency Virus (HIV) or Hepatitis B Surface Antigen (HBsAg). Subjects who are sero-positive for Hepatitis C virus (HCV) are excluded without proof of sustained viral response (SVR) after anti-HCV treatment.
14. Recipient of a kidney from a donor who tests positive for HIV, HBsAg/HBc positive or HCV.
15. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes (e.g., siplizumab, ATG, TAC, MMF, CS).
16. Any additional contraindication to the use of TAC or MMF according to the national labeling information of these products (refer to the local product label).
17. Evidence of TB infection (after anti-TB treatment, patients with history of latent TB may become eligible according to national guidelines).
18. Patient with severe systemic infections, current or within the two weeks prior to randomization.
19. Subjects with any other clinically significant medical condition, active infection or laboratory abnormality that would, in the judgment of the investigator, interfere with the subject's ability to participate in the study.
20. 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.
21. Use of other investigational products or enrollment in another investigational drug study within 30 days of screening or 5 half-lives of the medication, whichever is longer.
22. 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.
23. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 24 weeks after the study medications have been stopped. Highly effective contraception methods include:
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

- 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:
  a. 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.
  b. 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.

Additionally, total abstinence, when in line with the preferred and usual lifestyle of the subject may be an acceptable form of contraception. Period abstinence is not an acceptable form of contraception (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal).

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 six weeks prior. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment if she considered not of childbearing potential.

6 Treatments

6.1 Method of Treatment Assignment

Approximately 24 subjects will be randomly assigned to 1 of 2 treatment Cohorts and then, within each Cohort, randomized to one of two treatment arms; siplizumab or rATG active control arm in an 8:4 ratio as noted in the table below.

Table 6-1 Treatment Assignment

Cohort	Arm	Subjects (n)	Product	Dosing Regimen
Cohort A	Arm 1	8	Siplizumab	0.2 mg/kg (Days 0 and 4)
	Arm 3	4	rATG	1.5 mg/kg (Day 0, 1 and 2)
Cohort B	Arm 2	8	Siplizumab	0.6 mg/kg (Days 0 and 4)
	Arm 3	4	rATG	1.5 mg/kg (Day 0, 1 and 2)

The randomization schedule will be generated and verified by independent statisticians.

Prior to surgery, on Day 0 (Day of Transplant), the Investigator or his/her designee will confirm that the subject meets eligibility for randomization within the EDC system. The randomization mechanism for the study will be deployed by an internet-based Interactive Web Response System (IWRS) and accessible 24 hours a day to authorized users. Designated study personnel will access the IWRS to execute each randomization after a subject has met all prerequisites for randomization

and has completed all necessary screening procedures and eligibility for the study has been confirmed.

The EDC/IWRS will provide a notice and assign a unique randomization number to the subject being assigned to Cohort A or B and randomized to receive either siplizumab or rATG (in one of 3 treatment arms)

The randomization number will be linked to the subject's assigned treatment Cohort and Arm. After a subject is assigned a randomization number, the number will not be reused even if the subject withdraws before receiving any investigational product.

6.2 Investigational Product

6.2.1 Identification of Investigational Product

Siplizumab is a humanized IgG1κ class monoclonal antibody, supplied as [redacted] for solution. Siplizumab will be supplied in 6 mL vials containing 60 mg and supplied at a concentration of 10 mg/mL.

6.2.2 Management of Investigational Product

Investigational product will be provided as open-label, bulk medication. Product packaging and labeling will be performed by Klifo, Glostrup, Denmark. Medication labels will be in the local language and comply with the legal requirements of each country.

Investigational product must be received at the study site by the Investigator or his/her designee. The Investigator or his/her designee must acknowledge receipt of the investigational product within the EDC/IWRS. Confirmation of product receipt and condition will be logged into the system and any documentation of receipt maintained in the site's study file.

Following confirmation of receipt, all investigational product 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 Pharmacy Manual should be referenced for additional handling and storage details as well as expectations for reporting temperature excursions to ITB-MED.

The Investigator must maintain an accurate record of the dispensing of all study product 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, Investigational Product accountability will be noted by the Monitor during site visits and/or at the completion of the trial.

All investigational product 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 investigational product supply.

Only after receiving a written authorization by ITB-MED, the Investigator/designee will: (i. 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 ii.) have the unused and partly used drug supplies as well as the empty containers destroyed by the site's pharmacist or designee, providing a drug destruction certificate.

Detailed instructions for the receipt, storage, accountability, and return or destruction will be described in the ITB-MED provided Pharmacy Manual.

6.2.3 Investigational Product Dosing Regimen

The starting dose for siplizumab will be 0.2 mg/kg with escalation to 0.6 mg/kg.

The planned duration of investigational treatment is 5 days. Subjects will receive a total of two doses of siplizumab: pre- or intra-operatively on Day 0 and on Day 4. Subjects may be discontinued from treatment earlier at the discretion of the investigator or upon request of the subject.

Siplizumab dose adjustments and/or interruptions for a given subject are not permitted. The siplizumab infusion rate may be changed in the event of an infusion reaction.

6.2.4 Preparation of Siplizumab

As per the treatment assigned to the subject upon randomization, the Investigator or his/her designee will obtain the investigational product to be administered to the subject. The dose of siplizumab must be prepared by and administered by the Investigator or his/her designee who is properly trained in the handling and aseptic preparation of IV infusions. The subject will be weighed within 24 hours of each infusion administration and this weight will serve as the basis for final dose calculations and compounding.

The dose will be calculated by the following formula: Dose (mg) = [subject weight (kg) x dose level (mg/kg)]. ***60 mg siplizumab/ vial***

Example 1: A subject whose weight is 70 kg in Cohort A (0.2 mg/kg) should receive 14 mg of siplizumab (70 kg x 0.2 mg/kg = 14 mg) and would require 1 vial of siplizumab.

Example 2: A subject whose weight is 70 kg in Cohort B (0.6 mg/kg) should receive 42 mg of siplizumab (70 kg x 0.6 mg/kg = 42 mg) and would require 1 vial of siplizumab.

Upon confirmation of subject dose, the product will be prepared from vial(s), using aseptic technique and administration to the subject via IV infusion using a syringe or infusion pump.

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

6.2.5 Premedication for Siplizumab Infusion

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) to minimize signs and symptoms of an infusion reaction. Premedication administration should occur at least 1 hour and no more than 5 hours prior to the start of the infusion.

6.2.6 Siplizumab Administration

Siplizumab will be administered by IV infusion to the subject by authorized site personnel on Day 0 and Day 4.

The first dose of siplizumab will be administered over an hour (±5 min) by IV infusion. The infusion should be administered pre- or intra-operatively and timed so that the completion of the infusion is no earlier than 4 hours prior to revascularization and perfusion of the allograft. When administered intra-operatively, the infusion must be completed prior to revascularization. This ensures both donor and alloreactive T-lymphocytes are suppressed and depletion is initiated in the hours and days post-transplant. The second and final dose will be administered by IV infusion over an hour on Day 4.

The compatibility of siplizumab with other IV medications is not known and must not be combined with other infusions or medications.

The infusion may be given directly into a peripheral vein or a separate lumen in an indwelling, multi-lumen, central catheter and not administered concurrently with any other medications.

The date, start time, completion time and volume of siplizumab administration must be recorded in the subject's source documentation and applicable eCRF.

For all subjects, regardless of the timing of the Day 0 infusion, the ***Day 4 infusion*** will be administered between 0800 and 1000 to facilitate future sample collection and study visits.

No dose adjustments beyond changes based on the subject's actual weight are permitted to the siplizumab dose during the study.

In case of notable AEs and/or SAEs, including loss of efficacy and/or associated PK/PD data collected during the study, changes to the next planned dose level across the study may be considered and implemented via a protocol amendment.

6.2.7 Provisional Dose Levels

Table 6-2 describes the starting dose and the dose levels that may be evaluated during this trial.

Table 6-2 Provisional dose levels

Dose level	Proposed daily dose*	Increment from previous dose
1	0.2mg/kg	(starting dose)
2	0.6 mg/kg	½-log

*It is possible for an intermediate dose level(s) to be added during the course of the study. Cohorts may be added at any dose level below the maximum tolerated dose in order to better understand safety, PK or PD.

6.2.8 Dose Escalation Guidelines

Before escalating to the next dose level, an interim review of all available safety/tolerability (e.g., AEs, SAEs, clinical laboratory assessments, vital signs), PD (immunophenotyping), receptor occupancy and PK data (if available) up to a minimum of approximately 28 days post dose for at least 4 siplizumab treated subjects in the lower dose arm will be performed.

This 28-day safety period allows sufficient time for subjects to reach full-receptor occupancy, maximum pharmacodynamic activity and for the presentation of acute, drug related, toxicities.

For treatment cohorts where receptor occupancy at the 28-day assessment cut-off is >99% in at least 2 subjects, dose escalation decisions will be deferred by a minimum of approximately 14 days until results of the next PD assessment have been analyzed and reviewed. If the CD2 receptor occupancy remains at >99% in at least 2 subjects at the second assessment time point, reevaluation of receptor occupancy on an approximately 14-day schedule may continue until a decision to escalate has occurred or stopping criteria have been satisfied.

Where siplizumab concentrations are not quantifiable, i.e., with low doses, rapid clearance or assay limits, receptor occupancy or lymphocyte recovery will serve as the only measure of investigational treatment exposure for dose escalation decisions.

In order to escalate to the next dose level, the data at the aforementioned review must be assessed as satisfactory or not clinically significant. The decision to escalate to the subsequent dose cohort will be made jointly between ITB-MED and the Investigator(s) following a review of all relevant safety and PK/PD data.

To assure subjects are not exposed to a prolonged duration of T-cell depletion and/or sustained receptor occupancy and consequent immunomodulation / immunodepletion, the selection of the next highest dose will be guided by the following criteria:

- Escalation will not proceed if the dose is not considered safe, regardless of the duration of target suppression or PD activity

Siplizumab dose escalation will be stopped when:

1. An average of ≥ 24 weeks (168 days) duration of T-cell depletion has been measured (defined as <10% of baseline (i.e., 90% depletion) in ≥2 subjects or
2. An average of ≥ 24 weeks (168 days) duration of >99% peripheral CD2 receptor occupancy has been measured in ≥2 subjects or
3. An average of >36 weeks (252 days) duration of >99% CD2 receptor occupancy and T-cell depletion is accurately predicted using PK/PD modeling for the next dose escalation.

Additionally, based upon the outcome of safety and PK/PD data review during and prior to dose escalation, or in the case of notable adverse events or safety concerns, the following changes to the next planned dose level may be considered:

- Administration of a dose level below the starting dose
- Administration of an intermediate dose strength between the current and preceding dose
- Repeated administration of the current dose strength
- Termination of any further dose escalation

Any change in dosing or clinical conduct of the study will be implemented via an amendment and approved by the ethics committee responsible for initial approval of this study. The local heath authority will also be informed of any Suspected Unexpected Serious Adverse Events (SUSARS) and study changes.

6.3 ATG: Standard of Care Control

6.3.1 ATG Dose and Duration

rATG will be given at a dose of 1.5 mg/kg on Days 0, 1 and 2 for a total of three doses. rATG dose adjustments and/or interruptions for a given subject are not permitted unless warranted (see below).

6.3.2 Preparation of ATG

As per the treatment assigned to the subject upon randomization, the Investigator or his/her designee will prepare the investigational product to be administered to the subject. The dose of rATG must be prepared by and administered by the Investigator or his/her designee who is properly trained in the handling and aseptic preparation of IV infusions. The subject will be weighed within 24 hours of each infusion administration and this weight will serve as the basis for final dose calculations and compounding.

6.3.3 Premedication for ATG Infusion

Prior to each infusion of rATG, subjects should receive premedication with corticosteroids, acetaminophen/paracetamol and/or an H_1-antagonist (antihistamine) to minimize signs and symptoms of an infusion reaction. Premedication administration should occur 1 hour prior to the start of the infusion.

6.3.4 Administration of ATG Infusion

rATG will be administered on Day 0, Day 1, and Day 2 per local label or as outlined in the pharmacy manual.

6.3.5 Management of ATG Therapy

Patients should be monitored for adverse reactions during and after infusion. The total white blood cell and platelet counts should be monitored during and after rATG therapy. The rATG dose should be reduced by one-half if the white blood cell (WBC) count is between 2,000 and 3,000 cells/mm3 or if the platelet count is between 50,000 and 75,000 cells/mm3. rATG treatment may need to be stopped if the WBC count falls below 2,000 cells/mm3 or if the platelet count falls below 50,000 cells/mm3.

6.4 Concomitant Immunosuppression

The following medications will be used in this study and will be administered in accordance with this protocol, SoC practices at the institution, and where applicable, current local labeling. Not all dosage forms listed are available in each country, dependent on local approval status and regulations.

The use of immediate release generic TAC and MMF are allowed in this study. Subjects should remain on the same concomitant immunosuppression medication throughout the duration of the study (12 months), i.e. If the subject starts with brand Prograf® or CellCept®, the subject should

remain on brand and not switch to a generic at any point throughout the 12-month study period; if the subject starts with generic, the subject should remain on the same generic throughout the study.

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, as outlined in Appendix 5.

All doses of TAC, MMF, and CS along with dose changes during the study must be recorded, with reason for administration, on the corresponding eCRF.

In general, symptomatic treatment should be considered first to treat subjects who have difficulties tolerating their immunosuppressive regimen. 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 in order to keep the subject on study treatment.

Concomitant medications will be supplied locally and used according to the local label and will include:

- Immediate release TAC as 0.5 mg, 1.0 mg, or 5.0 mg capsules
- MMF 250 mg or 500 mg film-coated tablets, or 250 mg capsules, or 500 mg vial for IV
- CS for oral and IV administration

Pre-transplant immunosuppression may be administered according to center practice, but such practice must be applied consistently to all subjects at a given center. At randomization/enrollment, all subjects must follow the assigned regimen.

6.4.1 MMF Administration

MMF will be administered p.o. twice per day (BID) as 2 - 500 mg tablets, 4 - 250 mg capsules, or where oral administration is not feasible, as 1000 mg via IV administration (2 – 500 mg vial for IV administration). For subjects who remain intubated >24 hours post-transplant and/or are otherwise unable to swallow oral medication, IV MMF may be substituted 1:1 until oral conversion is possible.

The first dose of MMF will be administered no later than 24 hours after graft reperfusion of the allograft.

Dose adjustment/interruption guidance for MMF is provided in Appendix 5. All MMF doses and changes must be recorded on the applicable electronic case report form (eCRF).

6.4.2 TAC Administration

TAC will be administered as capsules or tablets p.o. BID and adjusted to maintain serum trough (C0) concentrations within the target range of 4-11 ng/mL. If oral administration is not feasible or practical IV TAC containing the equivalent of 5 mg/mL tacrolimus administration by continuous intravenous infusion can be substituted per label.

TAC should be initiated 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 BID or IV equivalent. If TAC is discontinued for more than 14 consecutive days, and the study regimen cannot be maintained, the subject may remain in the trial, however the new immunosuppressive regimen must be documented in the concomitant medications eCRF, including doses 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 recorded on the applicable eCRF at each visit. In the event of TAC intolerance (e.g., nephrotoxicity, neurotoxicity) dose reduction of TAC may be necessary. If it occurs that the TAC trough concentration is outside the required target, then the Investigator will be asked to confirm the intended TAC trough and to record the start date and reason for dose reduction on the applicable eCRF.

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 6) should be avoided if possible. If these drugs are required, the Investigator should carefully monitor TAC trough concentrations and adjust them accordingly during and after the use of the interacting treatment.

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.

6.4.3 Corticosteroid Administration

CS should be administered at a minimum of 5.0 mg/day (prednisone or equivalent) from Day 0 until Month 12 and per local standard practice in a way that is consistent in all subjects enrolled at the site. Dosing of CS should be recorded in the Concomitant Medications eCRF.

6.5 Infectious Prophylaxis Treatment

All medications administered after the subject was enrolled into the study must be recorded on the appropriate eCRF. ITB-MED will provide eCRF completion guidelines with additional detail for recording concomitant medications.

CMV

CMV prophylaxis, with IV ganciclovir or oral valganciclovir, will be used in subjects (CMV positive and CMV negative) as per local medical practice.

Pneumocystis jirovecii (Pneumocystis carinii) pneumonia (PCP)

All subjects will be started on sulfamethoxazole-trimethoprim, starting when oral medication can be tolerated and continued per standard institutional/local practice. The same regimen should be administered to all subjects at a given study center. For subjects unable to tolerate sulfamethoxazole-trimethoprim, atovaquone plus levofloxacin (or equivalent fluoroquinolone), aerosolized pentamidine or dapsone may be administered.

Hepatitis B Virus (HBV)

Prophylaxis for HBV reactivation during the course of this study is allowed and will be administered at the discretion of the Investigator.

BK Virus

Subjects with BK viremia or viruria should be treated according to local practice. If treatment is given or dose adjustments are made, e.g., MMF dose reduction, they should be recorded on the Concomitant Medications eCRF.

Oral Candida

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 unless subjects are systemically infected since azole antifungal agents may increase blood concentrations of TAC.

Systemic therapy will be based on center practice and at the Investigator's discretion. Treatment should be recorded on the Concomitant Medications eCRF.

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, such as following T- or B-cell depletion 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 et al 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.

6.6 Other Concomitant Treatments

The Investigator should instruct the subject to notify the study site about any new medications taken after enrollment into the study. All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded on the appropriate eCRF. ITB-MED will provide eCRF completion guidelines with additional detail for recording concomitant medications.

Each concomitant drug 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, contact ITB-MED to determine if the subject should continue participation in the study.

No other immunosuppressive medications should be administered, other than as per protocol.

6.7 Treatment of Adverse Events

Following are recommended guidelines for the management of AEs. Medications used to treat AEs must be recorded on the appropriate eCRF.

6.7.1 Treatment of Acute Rejection Episodes

In 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 6Appendix 6Appendix 6Appendix 6Appendix 6Appendix 7) may be treated with other anti-rejection therapies (i.e., antibody therapy).

It is important to note that the combination of siplizumab and other T-cell depleting antibodies, e.g., ATG, alemtuzumab, mTOR inhibitors (sirolimus or everolimus), IVIG or costimulatory blockade (belatacept) have not been investigated 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.

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

6.7.2 Management of BK Viremia

BK Polyoma virus (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 polyoma virus associated nephropathy (PVAN) is low.

Quantitative cutoffs for presumptive diagnosis of BKV nephropathy include plasma DNA VL >10,000 copies/mL (whole blood polymerase chain reaction (PCR) VL >1500–3500 copies/mL), urine VP1 mRNA load >6.5 X 10e5 copies/ng total RNA, or urine DNA load >10e7 copies/mL; higher viral loads are increasingly predictive of PVAN.

World Health Organization (WHO) standards will 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 BK Viremia or PVAN, the event should be recorded in the appropriate eCRF as an AE or SAE, and they should be managed as per local center practice.

6.7.3 Management of Delayed Graft Function (DGF)

DGF for this trial is defined as the need for dialysis performed within 7 days of transplant. However, in the event that a subject experiences DGF and does not undergo dialysis, DGF must still be reported as an AE in these subjects.

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

In case DGF is reported as an AE and dialysis is also reported, the end of DGF is considered the day the last dialysis session ends. For all other subjects it is when the renal dysfunction is considered resolved by the investigator.

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

In case of 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 the use of rATG. If a polyclonal antibody or rATG is used prior to Day 4, the investigational product must be discontinued, and the subject will be placed on SoC per local practice.

6.7.4 Primary Graft Non-Function (PGNF)

PGNF is defined as dialysis starting after transplantation with a continuous record of post-transplant dialysis until either transplantectomy, re-transplantation 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.

6.7.5 Management of EBV-PTLD

EBV-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 patients diagnosed with EBV-PLTD, therapy must be individualized. rATG and siplizumab doses planned for this trial are expected to result in T- and NK-cell depletion and minimal to no modulation of the B-cell compartment, respectively. Clinicians should refer to the siplizumab IB or local labelling for rATG 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 (Allen and Preiksaitis 2013 and Parker et al 2010).

6.8 Treatment Exposure and Compliance

Following discharge from the hospital, the Investigator or designee will dispense the appropriate amount of concomitant study treatment per SoC. Drug accountability will be performed to assess compliance at each study visit. The Investigator should promote compliance by instructing the subject to take their study drugs exactly as prescribed and by stating 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 the study drugs as prescribed.

All drug trough concentrations assessed in this study (siplizumab, TAC) will be measured per the Schedule of Assessments and the Laboratory Manual. For all samples sent for central analysis, 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 on the central laboratory request form (refer to the separate Laboratory Manual). Siplizumab will be measured in serum and 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.

6.9 Prohibited Treatment

Immunosuppressants and induction treatment other than those specified in the protocol are NOT allowed after informed consent up to the end of study. If the use of any of these medications or other non-protocol immunosuppressants is discovered prior to randomization/enrollment, the subject must not be randomized and will be recorded as a screen failure. If discovered after randomization/enrollment, no further doses are to be given, and the subject should continue on the randomized/assigned treatment regimen, noting the protocol deviation.

The exception is for the treatment of acute rejection not responding to corticosteroids.

The use of concomitant medications that may influence tacrolimus levels should be avoided, please refer to Appendix 6 and local prescribing information.

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/Independent Ethics Committee (IRB/IEC) 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 Conference on Harmonization 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/IEC.

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

8 Visit Assessments

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

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 adverse events). The intent is to allow centers to minimize in-person onsite clinic visit activities to those assessments that require the subject to be physically present (e.g., laboratory collections or physical assessments). In the event virtual or telehealth technology is utilized to facilitate data collection, it should be done 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 8 and Study Month 2 is considered to start on Day 29 (Start of Week 5).

Following is a description of study assessments/procedures. For the full Schedule and when to collect for each subject, refer to Appendix 1.

8.1 Subject Identification

Each subject is identified in the study by a subject identification number (SID) that is automatically assigned by the EDC system once the subject has signed informed consent, has at least one study assessment or procedure completed, and the relevant data has been entered into the eCRF/EDC by the designated site staff. The SID is retained as the primary identifier for the subject throughout his/her entire participation in the trial. 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.

8.2 Screen Failure Assessments

Subjects who sign an ICF and are subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate eCRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a SAE during the screening phase.

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

8.3 Efficacy / Pharmacodynamic Assessments

All blood samples will be taken by either direct venipuncture or an indwelling cannula. Please refer to the Laboratory Manual for a detailed description of central laboratory sample processing, handling, storage, shipment and analytical measures.

Immunophenotyping

The effect of siplizumab on circulating leukocytes and T-cells will be determined using flow cytometry FACS. Cell subpopulations that will be analyzed may include but are not limited to those bearing one or more of the following cell surface or intracellular markers: CD2, CD3, CD4, CD5, CD8, CD19, CD25, CD27, CD38, CD45RA, CD45RO, CD59, CD127, CD138, CD154, FoxP3 and HLA-DR.

Lymphocyte CD2 Receptor Occupancy

Peripheral CD2 receptor occupancy by siplizumab will be determined by flow cytometry analysis, measuring free or total CD2 receptors on T-cells.

8.4 Safety Assessments

8.4.1 Physical Examination

A comprehensive physical examination will be conducted at screening, on Day 7 and then at each study visit thereafter. The examination 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.

Physical examination findings will be entered in the applicable Physical Examination eCRF. Clinically relevant findings that are present before the subject has had at least one invasive study procedure completed and/or performed must be recorded on the appropriate Medical History eCRF. Significant findings discovered after the start of study procedures, which meet the definition, must be recorded as an adverse event.

8.4.2 Vital Signs

Vital signs (radial pulse rate, blood pressure, respiratory rate, and body temperature) will be recorded as indicated in the Schedule of Assessments. 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 five minutes. Body temperature should be measured as per local practice – the same method to be used consistently for all subjects at each site.

8.4.3 Height and Weight

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 = Body weight (kg) / [Height (m)]^2

8.4.4 Laboratory Evaluations

Samples for the laboratory tests noted below will be collected at the time points specified in Schedule of Assessments. Refer to the Laboratory Manual for detailed instructions regarding the timing of central laboratory specimen collection along with the handling, processing, storage, and shipping of samples.

In the case where a laboratory assessment that is listed in the inclusion/exclusion criteria is outside of a protocol-specified range at screening and/or at the initial baseline, the assessment may be repeated once prior to randomization. If the repeat value remains outside of protocol-specified ranges, the subject is excluded from the study.

The Investigator must document in the source documents, 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 should also 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.

Clinically significant abnormalities should be recorded on the relevant section of the Medical History/Current Medical Conditions/AE eCRF page as appropriate.

8.4.4.1 Hematology

Hemoglobin, hematocrit, red blood cell (RBC), MCV, MCH, Platelet Count, white blood cell (WBC) and differential count (% and abs).

8.4.4.2 Clinical Chemistry

Albumin, total bilirubin, calcium, creatinine, glucose, phosphorus, magnesium, potassium, ALT, AST, ALP, GGT, amylase, sodium, uric acid, and urea/ Blood Urea Nitrogen (BUN) will be measured.

8.4.4.3 Lipid Panel

Cholesterol, triglycerides, LDL, HDL will be measured.

8.4.4.4 Urine Dipstick

At a minimum, the following parameters will be measured: pH, protein, blood, glucose, nitrites, and leukocytes.

In the event of positive findings, follow-up urinalysis should be performed per local standards.

8.4.4.5 Pregnancy

Serum or urine pregnancy testing will be required for females of child-bearing potential, at timepoints as designated in the Schedule of Assessments. A serum or urine pregnancy test must be obtained up to 72 hours prior to time of transplant and the result must be available and negative prior to administration of investigational product.

8.4.4.6 Renal Function

Renal function will be assessed by eGFR, using an automated calculation factoring serum creatinine, demographics and the MDRD4 formula.

8.4.4.7 Coagulation Studies

Coagulation studies will be performed, including international normalized ratio (INR)/prothrombin time (PT) and activated partial thromboplastin time (aPTT).

8.4.4.8 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 centrally by a laboratory utilizing World Health Organization 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 will 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.

8.4.4.9 CMV DNA PCR

All subjects will have quantitative CMV viral load measured by a PCR-based method, preferably calibrated in IU/mL. The CMV titer in blood should be recorded on the applicable eCRF. No specific viral load cutoffs are available to initiate antiviral therapy. However, persistent low-level viremia (<2500 IU) suggests excess immunosuppression or stimulation by other infections or processes (e.g., rejection). If PCR positive, then treatment should be initiated per local practice.

8.4.4.10 Donor Specific Antibodies (DSA)

Blood samples for DSAs (antibodies directed against antigens expressed on donor organs) will be collected and evaluated locally.

8.4.4.11 Immunogenicity

The presence of anti-siplizumab antibodies will be determined using a bridging ELISA-based assay.

8.4.4.12 Viral Testing and Surveillance

All subjects will be screened/monitored for HBV, HCV, HIV, EBV, CMV, and BK virus per local center practice unless more rigorous testing is required for EBV and CMV monitoring, as noted in Section 8.4.4.8 and 8.4.5. Results of these assessments are to be transcribed into the appropriate eCRF pages.

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 (Green and Michaels 2013):

Signs

- Pallor
- Lymphadenopathy
- Subcutaneous nodules

- Tonsillar enlargement or 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 neurologic 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

Laboratory tests:

- Serial increase in EBV viral load from peripheral blood

The following assessments may be considered as part of the diagnostic work-up for suspected EBV-PTLD (Green and Michaels 2013):

Routine:

- CBC, differential, platelets
- Serum electrolytes, calcium, BUN and creatinine
- Liver function tests
- Uric acid
- Lactate dehydrogenase
- Quantitative immunoglobulins
- EBV serologies (anti- Epstein–Barr nuclear antigens (EBNA), viral capsid antigen (VCA) and early antigen (EA)
- EBV viral load from peripheral blood
- Stool: occult bleeding

- 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 possible)
    - EBER, CD20 histochemistry studies of pathologic samples

In select patients, based on signs, symptoms and routine assessments, the following procedures may be considered:

- Bone marrow biopsy
- Bone scan
- Brain CT/MRI
- Gastrointestinal endoscopy
- Lumbar puncture
- Ultrasound assessment of abdomen and allograft

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

8.4.6 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. CT, MRI and/or PET imaging may be considered for staging and monitoring of biopsy confirmed PTLD.

8.4.7 Renal Biopsy

Any biopsies performed according to local practice must be recorded. Biopsies will be read by the local pathologist according to local practice and the 2017 Banff criteria (Appendix 7). The results of the biopsy read by the local pathologist will be listed on the applicable eCRF.

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

Please refer to the Laboratory Manual for details on biopsy handling and histology assessments.

8.4.8 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 2017 Banff criteria, including borderline rejections, as outlined in Appendix 7.

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 on 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 Pharmacokinetic Assessments

Pharmacokinetics (siplizumab / anti-siplizumab antibodies)

PK samples will be obtained and evaluated in all subjects at all dose levels, as outlined in the Schedule of Assessments. The timing of the PK sample collection may be altered based on emergent data, but the total number of samples and total blood volume collected will not exceed those stated in the Laboratory Manual.

Siplizumab concentrations will be determined by a validated ELISA method; the anticipated Lower Limit of Quantification (LLOQ) is 10 ng/mL and concentrations will be expressed in mass per volume units. Concentrations below the LLOQ will be reported as "zero" and missing data will be labeled as such in the Bioanalytical Data Report.

The following PK parameters will be determined using the actual recorded sampling times and non-compartmental method(s): C_{max}, T_{max}, area under the curve (AUC) last, AUC_{inf}, $T_{1/2}$, Vz/F and CL/F from the serum concentration-time data.

The linear trapezoidal rule will be used for (AUC) calculation. Regression analysis of the terminal plasma elimination phase for the determination of $T_{1/2}$ will include at least 3 data points after C_{max}. If the adjusted R^2 value of the regression analysis of the terminal phase will be less than 0.75, no values will be reported for $T_{1/2}$, AUC_{inf} and CL.

Follow instructions outlined in the Laboratory Manual regarding sample collection, numbering, processing and shipment.

8.6 Assessment of Treatment Exposure and Compliance

PK parameters (measures of treatment exposure) will be determined in all subjects treated with study treatment. TAC trough concentrations will be determined locally and recorded on the relevant trough level eCRF. The local trough values will be used to adjust the TAC dosing as needed.

Compliance with the subject's treatment regimen will be assessed by the Investigator and/or designated site personnel at each study visit and info captured in the source and relevant eCRF.

8.7 Exploratory Biomarker Assessments

[redacted]

9 Study Discontinuation and Completion

9.1 Discontinuation

9.1.1 Safety Stopping Rules

The following stopping rules based on potential toxicities will serve as the basis for placing enrollment and dose escalation on hold.

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. Dose limiting toxicities (DLTs) will be assessed according to the standardized toxicity grading scale, the National Cancer Institute (NCI) CTCAE version 5.0 (NCI 2017).

- 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, considered drug related as determined by the Investigator within the first 28 days.

- Two (2) subjects with sustained (>7 days) Grade 3 neutropenia (neutrophil counts 200/mm3 to < 500 to; 0.2 to <0.5 x 10e9/L) considered related to siplizumab.
- Two (2) or more subjects presenting with Grade 3 or higher toxicity considered drug related as determined by the Investigator, including infusion reactions, within 24 hours of any siplizumab administration.
- Three (3) or more subjects per cohort presenting with Grade IIA or higher BPAR (T-cell mediated rejection (TCMR); central pathology) during the first 6 months post-transplant.

*NOTE: in the case of suspected PTLD lesions where a biopsy is not possible (e.g., CNS symptoms), radiographic and imaging (MRI) studies may be used to stage and assess the disease.

In addition, safety data will be regularly reviewed by ITB-MED and an independent DMC. This regular review of cumulative data includes near real-time assessment of acute rejection (BPAR), graft losses deaths, and key safety endpoints. In the event the acute rejection rate exceeds a clinically relevant threshold set forth in the protocol and DMC charter, or the *a priori* defined stopping rules, enrollment will be suspended to allow for the early termination of any treatment cohort where the benefit/risk of siplizumab is deemed unacceptable.

9.1.2 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.

Possible reasons for study treatment discontinuation are:

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

The Investigator should discontinue a subject from their randomized treatment regimen if he/she believes that continuation in the study would be detrimental to the subject's well-being.

Subjects who discontinue their study treatment should NOT be considered withdrawn from the study UNLESS they withdraw their consent to participating in all the elements of the study. Such subjects should remain in the study, if possible, and receive standard of care immunosuppression, according to local practice, and return for follow-up visits through Month 12.

All randomized subjects are expected to continue in the study up to Month 12. If they refuse to return for these 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. 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.

9.1.3 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 of the ICF.

9.1.4 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, etc. A subject should not be considered as lost to follow-up until due diligence has been completed or until the EOS.

9.1.5 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 that adequate consideration is given to the protection of the subject's interests. The Investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

9.2 Study Completion

Study completion is defined as when the last subject finishes their final study visit (Month 12) 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 decision.

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 are prematurely withdrawn from the study should be treated according to local SoC per the Investigator's judgment. The study will complete when the last subject completes their Study Completion Visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator.

9.3 Subject Replacement

Replacement during Dose Escalation

Subjects will not be replaced on study. However, if a subject is considered as non-evaluable, enrollment of a new subject to the current cohort will be considered if there is less than the required number of evaluable subjects. Enrollment of new subjects may be considered until at least the minimum number (4) or at most the maximum number (8) of evaluable subjects is achieved within the cohort.

Minimum and maximum numbers of evaluable subjects per cohort are defined in the guidelines for dose escalation and determination section.

10 Safety Monitoring and Reporting

10.1 Definition of Adverse Events and Reporting Requirements

10.1.1 Adverse Events

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).

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 CTCAE criteria (version 5.0 or higher)

- 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 symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject

- 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

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

AE 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 investigational product.

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent (e.g., continuing at the EOS), and 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 it, and the outcome.

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

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

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

- Serious Infections
- Opportunistic Infections, including EBV, CMV, BK virus
- Malignancies, including LPD/PTLD

10.1.4 SAE Reporting

Every SAE, regardless of causality occurring after the subject has provided informed consent and had at least one 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 AESI 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 in the eCRF(s). Information may also be submitted in writing to [redacted] 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 Package Insert (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 Series Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the Month 12 (EOS) visit should only be reported to ITB-MED Safety if the investigator suspects a causal relationship to study treatment. For subjects who terminate from the study prematurely, SAEs should only be reported if they occur within 6 months following the last administration of study treatment and 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.

10.1.6 Early Phase Safety Monitoring

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 it's designee and the Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

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

10.1.7 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 on the appropriate eCRF irrespective of 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.

11 Data Monitoring Committee

This study will include a DMC which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will assess at defined intervals the progress of the clinical trial, safety data, and

critical efficacy variables and recommend to ITB-MED whether to continue, modify or terminate a trial.

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

This section describes the statistical methods to be used to analyze safety and efficacy. These methods may be revised and updated due to reasons such regulatory requirements or need for further clarifications.

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 SAP, if any.

Any data analysis carried out independently by the investigator must 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 by randomization. According to the intent to treat principle, subjects will be analyzed according to the treatment they have been assigned to during the randomization procedure.

The Safety Set includes all subjects who received at least one 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 one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received.

The PK Analysis Set will include all subjects with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received any study drug and experienced no protocol deviations with relevant impact on PK data.

The PD Analysis Set will include all subjects in the Full Analysis set 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 treatment group and subject. Summary statistics will be provided by treatment group.

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, 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 interruption) will be presented by reason for the change.

Average daily doses will be presented by treatment. "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. AEs as a result of study treatment error will also be summarized.

12.3.1 Concomitant Immunosuppressants

The average daily dose of administered TAC, MMF, and CS will be summarized by treatment arm for subjects on study medication. The dose of the induction agent will be summarized for each of days when it was administered.

The dose of antibodies used for the treatment of acute rejection episodes will be recorded as well.

12.3.2 Other Co-Medications

Concomitant medications, other than immunosuppressants and CS mentioned above, will be summarized by therapeutic class and preferred term by presenting the number and percentage of subjects using each medication for each treatment group.

12.4 Analysis of the Primary Endpoint(s)

12.4.1 Definition of Primary Endpoint(s)

All safety data, including laboratory assessments, vital signs and AEs are considered primary endpoints.

All information obtained on AEs will be displayed by treatment and subject. The number and percentage of subjects with AEs will be tabulated by body system and preferred term with a

breakdown by treatment arm. A subject with multiple AEs within a body system is only counted once towards the total of this body system. No formal statistical analysis will be done for the safety and tolerability evaluation.

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.

The use of the concurrent control group and supplementation with a historical control group to better assess the incidence of AEs and SAEs reported with a TAC/MMF/CS based SoC treatment regimen will be investigated. Details on the methodology for data selection and analysis will be presented in the SAP.

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:

- Patients that lose their graft will be assigned a value of zero for their missing estimated glomerular filtration (eGFR) value.
- Patients 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 randomized treatment, the eGFR will be considered missing after applying the windows defined in Section 12.1.

Graft loss subjects do not have a functioning graft; hence the lowest possible GFR value (zero) will be assigned to such subjects. In contrast, subjects that die with a functioning graft, die for different reasons (e.g., suicide, car accident, cancer) will have an imputed value assigned as described above.

Patients who are lost to follow-up have renal function, but missing values for various reasons (e.g., moving from the area or not being able to make the site visit during the Month 6 or Month 12 visit window). Patients 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 Secondary Endpoints

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Immunophenotyping

These data will be summarized by treatment and subject.

CD2 Receptor Occupancy

The magnitude and duration of PD effect of siplizumab will be as measured by peripheral blood CD2-receptor occupancy. These data will be summarized by treatment and subject. Descriptive

statistics will also be provided such as mean, median, SD, minimum and maximum, by time point and treatment.

12.5.2 Safety Endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

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 AEs).

The on-treatment period lasts from the date of first administration of study treatment through the month 12 or EOS visit.

Adverse Events

All information obtained on AEs will be displayed by treatment group.

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

- AEs by primary System Organ Class (SOC) and Preferred Term
- AEs rated to have relationship to study drug by SOC and Preferred Term
- AEs by primary SOC, Preferred Term, and maximum severity
- SAEs by SOC and Preferred Term
- SAEs rated to have relationship to study drug by SOC and Preferred Term
- Deaths by SOC and Preferred Term
- AEs leading to discontinuation of a study drug by SOC and Preferred Term
- AEs leading to dose adjustment or interruptions of a study drug by SOC and Preferred Term
- 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
- AEs by standardized MedDRA query (SMQ) levels (broad and narrow search)
- AEs by SMQ and Preferred Term (broad and narrow search)

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

The number (and proportion) of subjects with AEs of special interest/related to identified and potential risks (e.g., serious infections, opportunistic infections, cytokine release syndrome, malignancies) will be summarized by treatment.

Multiple Occurrences for Tables:

In all tables about incidence rates of AEs / Infections, if a subject has multiple occurrences of an AE, this subject will be counted only once in the corresponding AE category. If a subject has multiple AEs within a system organ class, s/he will be counted only once for that class. If a subject has multiple severity ratings for an AE while on treatment, s/he is only counted under the maximum rating.

Information pertaining to AEs noted during the study will be listed by subject, including the verbatim term given by the Investigator, the Preferred Term and SOC given by the MedDRA dictionary, start and end date, causality, Grade and relationship to study drug as assessed by the Investigator.

AEs 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.

Vital Signs

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

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 randomization/enrollment based on the clinical notable criteria will be presented.

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

Other Safety evaluations

BK-polyoma viremia and nephropathy

The 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

EBV and CMV Surveillance

All quantitative and qualitative EBV and CMV surveillance data (serology and DNA-PCR) will be listed by treatment, subject, and visit/time and if normal ranges are available, abnormalities will be flagged. Summary statistics including mean, SD, minimum, median and maximum as well as change from baseline / previous assessment including shift tables will be provided by subject and treatment by visit/time.

Immunogenicity

Anti-siplizumab antibodies will be determined at specified time points. Immunogenicity data consisting of anti-siplizumab antibodies information will be listed by subject and visit.

12.5.3 Pharmacokinetics

Siplizumab serum concentration data will be listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations. A geometric mean will not be reported if the dataset includes zero values.

Table 12-1 Non-compartmental pharmacokinetic parameters

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1)
AUCinf	The AUC from time zero to infinity (mass x time x volume-1)
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume-1)
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume-1)
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
Lambda_z	Smallest (slowest) disposition (hybrid) rate constant (time-1) may also be used for terminal elimination rate constant (time-1)
T1/2	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives
CL/F	The total body clearance of drug from the plasma (volume x time-1)
Vz/F	The apparent volume of distribution during terminal phase (associated with λz) (volume)

If data permit, PK parameters will be calculated as described in Section 8.5 and Table 12-1 and will be listed by treatment and subject. Concentrations below the limit of quantification will not be considered for the calculation of PK parameters. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented.

A dose-independent, model-based analysis of the dose / concentration-exposure relationship should be derived using same the approach. Such analysis may be reported in a separate standalone report

12.5.4 Biomarkers

All biomarker data (e.g., renal injury markers, cytokine data) will be listed by treatment, subject, and visit/time. Summary statistics will be provided (mean, median, SD, minimum and maximum) by treatment and visit/time.

In the summary tables, the frequency (n, %) of values below the LLOQ and above the upper limit of quantification (ULOQ), respectively, will be included.

In case of censored values (values below the LLOQ and/or values above the ULOQ), the summary statistics (arithmetic mean, SD, geometric mean and 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 being normally or log-normally distributed.

12.5.5 PK/PD Relationships

The relationship between siplizumab concentration (PK) and PD variables will be explored graphically. Modeling of PK/PD data using a population approach may be performed as appropriate and may be reported in a separate standalone report. The broad principles outlined in the Food and Drug Administration (FDA) Guidance for Industry: PPK will be followed.

12.6 Analysis of Exploratory Endpoints

[redacted]

12.7 Interim Analyses

A formal interim analysis (IA) will occur once 50% of subjects assigned to the treatment Cohorts complete their 6-month study assessment. In consideration of the open-label nature of the study design and plan for descriptive statistical analysis, additional *ad hoc* IA may be performed. Results of the IA will inform decision making on safety, dose escalation and inclusion of additional doses to assure adequate profiling of the siplizumab PK and PD activity.

Details of the IA process and specific analysis will be presented in the SAP.

In addition to the formal planned Interim Analysis, the AE and SAE rates will be monitored on a continuous basis to support the early discontinuation of any treatment arm that is unsafe and/or ineffective according to the Stopping Rules as outlined in Section 9.1.1.

12.8 Dosing Decision Data Review

Prior to dose escalation to the next Cohort all available safety, tolerability, PK and PD data from the previous cohort(s) will be reviewed with the Investigators and a joint decision to escalate or terminate the arm will be made.

Dose escalation from one Cohort to the next will be determined at least 28 days following the last investigational product administration in the 4th siplizumab treated subject in each treatment cohort.

The purpose of the Day 28 data review is to confirm progression to the next cohort while the 6-month IA is to support more PK/PD modeling activities necessary to profile longitudinal siplizumab activity for more formal trial design and development decision making.

Results of the Dosing Decision data review will be communicated to the DMC for information, consulting and/or decision purposes as well as to participating investigators for information as deemed appropriate. A separate, cumulative, data package will be provided to the independent DMC as outlined in the DMC charter.

12.9 Sample Size Calculation

No formal sample size or power analysis has been performed. A sample size of 8 subjects for each treatment arm was chosen based on practical considerations, including the need to adequately characterize siplizumab PK and PD activity in renal transplant patients in the immediate post-transplant time period while balancing the overall exposure in a mechanistic profiling 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, by reviewing protocol procedures with the Investigator and relevant study personnel prior to study initiation, by 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 trial, the investigator/institution must obtain approval/favorable opinion from the IRB/IEC for the trial protocol, written ICF, consent form updates, subject recruitment procedures (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/IECs, 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. Authorization to start the study will not occur until:

- The study site has received the appropriate IRB/IEC approval for the study
- A Clinical Trial Agreement has been executed
- All pertinent study site personnel have received the appropriate protocol and study training
- All regulatory/GCP documents have been submitted and approved by ITB-MED

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 investigational product 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, but no later than 5 working days after a subject study visit. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the 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.

After final database lock, the investigator will receive copies of the subject 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 codes and data about all study treatment (s) dispensed to the subject and all dosage changes will be tracked using an IWRS. 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 Conference on Harmonization 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 trial necessary for the reconstruction and evaluation of the trial. 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.

In keeping with good clinical practice and guidance from the EMA, the principal investigator must clearly define the intended location of all source data by completing the Source Data Location Form prior to subject recruitment. This form should be prepared by the site and should be signed and dated by the principal investigator or by a person whom the principal investigator has assigned this task. The completed form should be filed in the Site Master File.

13.4.4 Protocol Adherence and Amendments

This protocol defines the study objectives, the study procedures, and the data to be collected on study participants. 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. 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 participants.

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

If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by ITB-MED and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

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/IEC 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/IEC per the IRB/IEC's protocol deviation reporting requirements.

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 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 Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), 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 such as clinicaltrials.gov and as required in EudraCT. In addition, after finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the ITB-MED clinical trial results website and all required Health Authority websites (e.g., Clinicaltrials.gov, EudraCT, etc.).

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16 Appendices

16.1 Appendix 1: Schedule of Assessments

STUDY PERIOD	SCR	STUDY TREATMENT PERIOD																																EOS/ET
	D -28 to -1[a]	Randomization (pre-dose) / Day of Transplant (Day 0)																																
VISIT	V1	V2				V3	V4	V5	V6				V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25	V26	V27
MONTH																								M3	M4	M5	M6	M7	M8	M9	M10	M11	M12
WEEK															W2	W3	W4	W5	W6	W7	W8	W9	W10	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48
DAY	D-28 to -1[a]	D0				D1	D2	D3	D4				D5	D7	D14	D21	D28	D35	D42	D49	D56	D63	D70	D84	D112	D140	D168	D196	D224	D252	D280	D308	D336
HOUR (PK Collection)		Pre-Dose	1	3	6	24			Pre-Dose	1	3	6																						
PERMITTED WINDOWS			± 10 min	± 30 min	± 30 min	± 60 min				± 10 min	± 30 min	± 30 min			± 2 days						± 3 days			±7 days										
General / Safety Assessments																																		
Informed Consent	X																																	
Inclusion/Exclusion	▱																																	
Demographics	X																																	
Medical History (including disease & procedure background for recipient/donor)	X																																	
Comprehensive Physical Examination	X													X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[b]	X		X[b]			X[b]	X[b]			X[b]				X	X		X							X			X							X
Height (at screening) and Weight[b]	X	X[b]				X[b]	X[b]		X[b]					X										X			X							X
Prior & Concomitant Medications																	X																	
Adverse Events																	X																	
Imaging (Refer to Protocol Section 8.4.6)																					X													
Local Laboratory Sample Collection																																		
High-resolution HLA/ABO typing (donor & recipient)[c]	X																																	
Lymphocyte/CDC crossmatch[c]	X																																	
Panel reactive antibody (PRA; CDC/Flow)[c]	X																																	
HIV, HbsAg, HCV serology (D and R)[d]	X																																	
CMV, EBV (D and R), BKV serology and surveillance[d]	X																X							X			X			X			X
SARS-CoV-2 Molecular testing at screening	SD																																	
Chemistry & Hematology panels[e]	X						X							X	X		X		X		X		X	X	X	X	X	X	X	X	X	X	X
Differential Leukocyte Count	X																X							X			X			X			X
aPTT and INR/PT	X																																	X
Lipid Panel	X																										X							X
Urine Dipstick																	X							X			X			X			X
Serum or Urine Pregnancy testing[f]	X																							X			X			X			X
DSA[g]	X																X							X			X			X			X
Tacrolimus trough levels[h]		X				X								X	X	X	X							X			X							X
Study Treatment Regimen																																		
Kidney Transplant procedure			X																															
Siplizumab Dosing: (Arms 1 or 2)[i]			X							X																								
rATG Dosing: (Arm 3)[i]			X			X	X																											
MMF/Tacrolimus/Corticosteroid administration[j]																		X																
CMV & Pneumocystis Prophylaxis (TMP/SMX)[k]																	X																	
Disease Monitoring																																		
Renal Biopsy[L]			x																		X													
Central Laboratory Assessments																																		
PK assay validation (biobank sample)	X																																	
TCD601 PK sampling[m]		X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]				
Anti-TCD601 antibodies		X															X				X			X			X							X
Mechanistic Studies																																		
Lymphocyte CD2 receptor occupancy[n]		X[n]	X[n]	X[n]	X[n]	X[n]			X[n]	X[n]	X[n]	X[n]											X	X	X	X	X	X	X	X				
Immunophenotyping (FACS)[o]		X[o]				X	X	X	X[o]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Exploratory Analysis																																		
Renal Injury Markers[p]							X							X	X		X							X			X							X
Serum Cytokine assessments[q]		X[q]	X[q]	X[q]	X[q]	X[q]		X	X[q]	X[q]	X[q]	X[q]	X																					
EBV-PCR Surveillance[r]		X[r]													X[r]		X[r]		X[r]		X[r]		X[r]	X[r]	X[r]	X[r]	X[r]		X[r]		X[r]		X[r]

Schedule of Assessments **Footnotes**
SCR = screening min = minute EOS/ET = end of study or early termination SD = noted in source document EOW = every other week Month = 28 days
▱ = Eligibility must also be confirmed on Day 0 prior to randomization
(a) all screening procedures may occur on the day of transplant for deceased donors
(b) vitals collected pre-dose, immediately following the end of the infusion, and 6 hours after completion of infusion with siplizumab or rATG. Other timepoints captured as indicated. Weight is captured pre-dose on Days 0 and 4 for siplizumab treated subjects and pre-dose on Days 0, 1 and 2 for rATG treated subjects.
(c) results obtained within the past 6 months acceptable; PRA when available
(d) results obtained within the past 12 months are acceptable for the initial assessment of EBV (donor and recipient) and CMV. Serological testing for BKV is not required at Screening. EBV, CMV and BKV viral testing via PCR should be conducted thereafter
(e) daily while in hospital and then as noted above; see protocol for panel analytes
(f) a negative pregnancy test must be available prior to randomization (for females of child bearing potential)
(g) DSA collected as noted above and additional collection with each kidney biopsy
(h) tacrolimus trough concentrations on days 0, 1, 7, 14, 21, 28; on months 3, 6, 12, and as clinically indicated. Sample Collection should be taken before the next dose is administered
(i) Randomization: Subjects randomized to siplizumab: first dose administered pre-or intra-operatively and timed so that completion of the infusion is no earlier than 4 hours prior to revascularization and perfusion of the allograft. The Day 4 dose should be administered between 0800 and 1000 to faciliate future sample collection/visits. Subjects randomized to rATG (Control): administration will occur on Day 0, Day 1 and Day 2 per SoC.
(j) must be started within 24 hours post-transplantion
(k) prophylaxis per local medical practice
(L) pre-implantation biopsy on Day 0; for-cause and/or protocol biopsies as indicated per local practice
(m) TCD601 PK Sampling on Day 0 dosing (pre-dose, hrs 1, 3, 6 and 24) and Day 4 dosing (pre-dose, hrs 1, 3 and 6). Post-dose collection time is based on the START time of infusion. Additional samples include collection on post-operative Days 2, 3, 7, 14, 21, 28, 35, 42, 49, 56, 63*, 70*, 84*, 112*, *140, 168*, 196*, 224*, and 252* (* Note: latter collections may be truncated based on half-life of TCD601 and serum concentrations below limit of quantification)
(n) CD2RO collection times to coincide with PK collection
(o) collect pre-dose when sample collection falls on Dosing Day 0 or Day 4
(p) renal injury markers; clean catch morning void urine collection
(q) sampling to coincide with PK collections for Day 0 dosing (pre-dose, hrs 1, 3, 6 and 24) and Day 4 dosing (pre-dose, hrs 1, 3 and 6). An additional sample to be collected on Day 5
(r) blinded EBV surveillance will be conducted bi-weekly through Month 3, monthly through M6 and then bi-monthly through EOS.

16.2 Appendix 2: Amendment No.1 – Summary of Changes

Section/Title/Page	Original Text	Revision	Reason for Change
Synopsis Exploratory Objectives	To explore changes in serum cytokines over time	To explore changes in serum and plasma cytokines over time	To clarify that both serum and plasma cytokines changes will be explored in the study.
Synopsis Key Inclusion Criteria	Not applicable	Addition of the following inclusion criterion: Subjects who test negative for SARS-CoV-2 via molecular testing (PCR)	To ensure that study participants are tested for COVID-19 prior to study entry and only those who have a negative test are eligible for randomization
Synopsis Planned Study Sites	Up to 5 study sites within the United States (US) and Europe (EU)	Up to 5 study sites within the United States (US)	Europe Sites will participate in the TCD601B101, and the United States are participating in the TCD601B102 study
Synopsis, Data Analysis **Section 6.8** Treatment Exposure and Compliance, 2nd paragraph, last sentence **Section 8.5** Pharmacokinetic Assessments, 3rd paragraph **Section 12.5.3** Pharmacokinetics **1st Paragraph**	Siplizumab plasma concentration data will be listed by treatment, subject, and visit/sampling time point. Siplizumab will be measured in plasma and TAC will be measured in whole blood. The following PK parameters will be determined using the actual recorded sampling times and non-compartmental method(s): Cmax, Tmax, area under the curve (AUC) last, AUCinf, T1/2, Vz/F and CL/F from the plasma concentration-time data. Siplizumab plasma concentration data will be listed by treatment, subject, and visit/sampling time point.	Siplizumab serum concentration data will be listed by treatment, subject, and visit/sampling time point. Siplizumab will be measured in serum and TAC will be measured in whole blood. The following PK parameters will be determined using the actual recorded sampling times and non-compartmental method(s): Cmax, Tmax, area under the curve (AUC) last, AUCinf, T1/2, Vz/F and CL/F from the serum concentration-time data. Siplizumab serum concentration data will be listed by treatment, subject, and visit/sampling time point.	To clarify that siplizumab concentration data will be measured in serum and not plasma.
Section 2	To the time-course and duration of siplizumab induced lymphocyte depletion and time to recovery	To measure the time-course and duration of siplizumab induced lymphocyte depletion and time to recovery	To include how the endpoint would be

Section/Title/Page	Original Text	Revision	Reason for Change
Objectives and Endpoints, Table 2-1			assessed, which was inadvertently omitted in the original protocol
Section 3.1 General overview, 6th paragraph **Section 6.2.4 Preparation of Siplizumab** **Section 6.3.2 Preparation of ATG**	Every effort should be made to randomize the subject on Day 0, but when logistical considerations prevent this from occurring (e.g., central pharmacy requirements), the subject may be randomized up to 12 hours pre-transplant. The subject will be weighed within 12 hours of each infusion administration and this weight will serve as the basis for final dose calculations and compounding. The subject will be weighed within 12 hours of each infusion administration and this weight will serve as the basis for final dose calculations and compounding.	Every effort should be made to randomize the subject on Day 0, but when logistical considerations prevent this from occurring (e.g., central pharmacy requirements), the subject may be randomized up to 24 hours pre-transplant. The subject will be weighed within 24 hours of each infusion administration and this weight will serve as the basis for final dose calculations and compounding. The subject will be weighed within 24 hours of each infusion administration and this weight will serve as the basis for final dose calculations and compounding.	The change from 12 to 24-hours was included to provide additional flexibility to sites when subjects may be scheduled for their transplant in the early hours of the morning.
Section 4.5 Risk and Benefits 1st paragraph	Not applicable	**New Text:** Infection risk will be mitigated by following applicable national vaccination guidelines and by use of prophylaxis (See Section 6.5). Similarly, the risks of SARS-CoV-2 will be minimized by following local, national and international guidelines for immunosuppressed and solid organ transplant patients (See Section 4.5.3).	The existing Risk and Benefits section of the protocol was expanded to include consideration of the current risk of SARS-CoV-2.
Section 4.5.1.3 Lymphoproliferative Disorders 3rd Paragraph	Independent adjudication of all 9 EBV-LPD cases was conducted to assess the overall risk of EBV-LPD in the setting of renal transplantation. While a notable risk of EBV-LPD in the setting of T-cell lymphoma was assessed by the committee it was stated that experience to date does not demonstrate that this risk exceeds that associated with ATG. In the setting of renal transplantation, siplizumab use is not expected to increase the risk of EBV-LPD/PTLD over ATG-based induction in combination with background immunosuppression.	Revision In the setting of renal transplantation, siplizumab use is not expected to increase the risk of EBV-LPD/PTLD over ATG-based induction in combination with background immunosuppression. Independent adjudication of all 9 EBV-LPD cases was conducted to assess the overall risk of EBV-LPD in the setting of renal transplantation. While a notable risk of EBV-LPD in the setting of T-cell lymphoma was assessed by the committee it was stated that experience to date does not demonstrate that this risk exceeds that associated with ATG.	Additional information added to harmonize the section on EBV-LPD risk with that of the global siplizumab development program. Update includes overall conclusion from an independent committee who conducted a case adjudication and risk assessment of siplizumab in comparison to ATG.

Section/Title/Page	Original Text	Revision	Reason for Change
	This rate in the US has been reported to be 1.03% (Hart et al 2020) and as high as high as 2.4% with ATG induction (Thymoglobulin PI 2020). 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 et al 2011). Therefore, all recipients will be screened prior to administration of siplizumab, and EBV-seronegative subjects excluded from participating in the TCD601B102 clinical trial. In addition, clinicians who specialize in transplant immunosuppression, and are aware of the risks for EBV-LPD, will be managing patients enrolled in this study. Regular assessments of hematology, EBV-viral load as well as PTLD surveillance including full physical exams at each visit as well as monitoring of clinical signs and symptoms will be conducted during the 12-month study.	This rate in the US has been reported to be 1.03% (Hart et al 2020) and as high as high as 2.4% with ATG induction (Thymoglobulin PI 2020). 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 et al 2011). Therefore, all recipients will be screened prior to administration of siplizumab, and EBV-seronegative subjects excluded from participating in the TCD601B102 clinical trial. In addition, clinicians who specialize in transplant immunosuppression, and are aware of the risks for EBV-LPD, will be managing patients enrolled in this study. Regular assessments of hematology, EBV-viral load as well as PTLD surveillance including full physical exams at each visit as well as monitoring of clinical signs and symptoms will be conducted during the 12-month study.	There is no change in risk based on this update.
Section 4.5.3 Risks of SARS-CoV-2 (COVID-19)	Not applicable	**New Text:** 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. Ongoing community transmission has been noted on all continents except Antarctica. Person-to-person transmission of SARS-CoV-2 occurs during close exposure (< 2 meters) to an infected person, primarily via respiratory droplets produced when the infected person coughs or sneezes. COVID-19 disease 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 et al 2020). Transmission via droplet spread can occur from both symptomatic and asymptomatic individuals (Arons et al 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	Inclusion of additional text to address the current pandemic including SARS-CoV-2 and COVID-19 disease.

Section/Title/Page	Original Text	Revision	Reason for Change
		symptoms and exposure history, along with PCR-based testing is imperative. **COVID-19 Disease:** Case series on COVID-19 disease in transplant recipients have been published, however data remains very limited. Imaging demonstrates pneumonia in the majority of patients that are hospitalized (75-100%). Patients with less severe infections may have lower rates of clinical abnormalities. Mild infections are common, however preliminary experience suggests that infection, once acquired by immunosuppressed transplant recipients, may be of greater severity than in normal hosts after the initial incubation period. Experience with other viruses including prior outbreaks of coronaviruses, also suggests that severe infections will occur in some transplant recipients. At this time, the risk factors for severe disease have been characterized by observational studies. An initial report by (Pereira et al 2020) showed that advanced age was associated with severe disease in their transplant cohort, which is not different from the disease profile in the immunocompetent population (Kates et al 2020) reported age >65, chronic lung disease, congestive heart failure, and obesity were independently associated with poor outcomes of COVID-19 in solid organ transplantation. It is anticipated that transplant recipients may have a greater viral burden and shedding resulting in greater infectivity and potential spread to other individuals. Limited data are available on optimal treatment protocols, and none have been clearly demonstrated to optimize outcomes. When considering potential therapies, clinicians should consider the need for immunosuppression reduction and presence of potential drug-drug interactions that may result in toxicity or therapeutic failure, e.g., beta interferon or CYP3A inducers/inhibitors. The risk of a COVID-19 infection from an infected organ donor is unknown at this time. To date, there has been one documented case (Kaul et al 2021) of donor-derived disease	

Section/Title/Page	Original Text	Revision	Reason for Change
		transmission in a bilateral lung transplant recipient. Transmission from blood banks has not been documented at this time. Guidelines on the risks and management of SARS-CoV-2 in the setting of clinical trials as well as that of renal transplant patients have been published by the European Medicines Agency (EMA), US National Institutes of Health (NIH), Transplantation Society (TTS) and American Society of Transplantation (AST). Treatment guidelines on the use in immunocompromised and transplant recipients are updated periodically as knowledge of COVID-19 disease management evolves. Cumulative cases and incidence rates are tracked and published by the World Health Organization (WHO) and other public and private entities and should be used to guide local management of patients. With active circulation of SARS-CoV-2 in the community, it is appropriate to counsel all candidates about the risk for acquisition from the community and hospital environment. Candidates should be educated about preventive strategies such as social distancing, masking when in proximity to non-household contacts, frequent hand washing, and avoidance of travel to high-risk areas. A compendium of global guidance documents is maintained by the NOTIFY library and can be found at the following URL: https://www.notifylibrary.org/background-documents#SARSCoV-2.	
Section 4.5.4 Risk Mitigation Strategy, 2 – 9 Paragraph consolidated and moved 14-16 Paragraph (new text)	Safety and tolerability data for doses up to 15 mg/kg IV have been collected in patients with T-cell lymphoma with good tolerability. With initial administration of a biologic, the first 4 hours of exposure are most critical with most infusion reactions (including hypersensitivity, cytokine release, anaphylaxis) occurring within the first 2 hours of exposure (Tabrizi and Roskos 2007). No cytokine release has been detected with IV or s.c. siplizumab (MEDI-507) administration in the	Infections are a common risk for all transplant recipients. Subjects will be regularly evaluated while hospitalized and upon return to the clinic for signs and symptoms which might indicate a severe infection, i.e., fever, nausea, myalgia, headache, arthralgia, chills, diarrhea, stiff neck, and 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.	Text consolidated and moved to improve flow of Risk mitigation section. Inclusion of text around SARS-CoV-2

Section/Title/Page	Original Text	Revision	Reason for Change
	completed patient studies. Cytokine release or anaphylaxis have not been reported with similar compounds specifically targeting the CD2 receptor. A mild infusion reaction has been described in primates as well as clinical studies with siplizumab following the first dose. This first-dose-effect presents as mild and transient pyrexia with chills, nausea and fatigue. These infusion reactions are self-limiting and respond well to premedication with acetaminophen and diphenhydramine. Subjects will receive their first dose of siplizumab in the pre- to inter-operative time period, at a time when patients are 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. In the TCD601B102 study all subjects will receive premedication prior to each dose of siplizumab to mitigate any infusion reactions. Considering the expected immunosuppressive nature of the compound, subjects will be screened for a history of latent infections. Viral reactivation will be assessed for CMV and BK virus according to local practice on a regular basis. Prophylaxis for CMV and pneumocystis pneumonia (PCP) will be administered to all subjects during the trial according to local practice. A negative test result for TB performed within 6 months of randomization will be required prior to enrollment. If there is suspicion of TB, a chest x-ray may be performed in accordance with local guidelines; subjects with a positive test will be excluded from participation. EBV serology will serve as a key inclusion criterion, where EBV-sero*negative* subjects will be excluded from participation. EBV viral loads via EBV-PCR will be collected from all subjects throughout the trial and will be analyzed centrally to minimize inter-laboratory variation. Positive	Considering the expected immunosuppressive nature of the compound, subjects will be screened for a history of latent infections. Viral reactivation will be assessed for CMV and BK virus according to local practice on a regular basis. Prophylaxis for CMV and pneumocystis pneumonia (PCP) will be administered to all subjects during the trial according to local practice. A negative test result for TB performed within 6 months of randomization will be required prior to enrollment. If there is suspicion of TB, a chest x-ray may be performed in accordance with local guidelines; subjects with a positive test will be excluded from participation. EBV serology will serve as a key inclusion criterion, where EBV-sero*negative* subjects will be excluded from participation. EBV viral loads via EBV-PCR will be collected from all subjects throughout the trial and will be analyzed centrally to minimize inter-laboratory variation. Positive results that demonstrate an increase over time will be communicated to the investigator for additional follow-up and per-protocol PTLD surveillance as described in Section 8.4.5. The ongoing SARS-Cov-2 pandemic represents a challenge for all renal transplant candidates and recipients. Due to the dynamic nature of COVID-19 infection rates, centers should continue to follow local and national guidelines and set policies based on the local incidence and prevalence of infections as well as hospital and staffing resources. This includes decisions to conduct or defer solid organ transplant procedures as well as the ongoing management of donors and recipients. Subjects eligible for the TCD601B102 study will be randomized from the pool of active candidates who are currently undergoing transplantation and will be receiving T-cell depleting induction and standard of care immunosuppression. All eligible subjects will be informed of the risks of SARS-COV-2 during the consent process. To decrease the risk to study subjects, all candidates will be screened for SARs-CoV-2 prior to enrollment and excluded if positive. Ongoing surveillance per standard of care will occur thereafter based on local conditions and signs and symptoms. In renal transplant patients who experienced COVID-19 disease, common presenting symptoms were fever, dry cough, and	

Section/Title/Page	Original Text	Revision	Reason for Change
	results that demonstrate an increase over time will be communicated to the investigator for additional follow-up and per-protocol PTLD surveillance as described in Section 8.4.5. Subjects will be regularly evaluated while hospitalized and upon return to the clinic for signs and symptoms which might indicate a severe infection, i.e., fever, nausea, myalgia, headache, arthralgia, chills, diarrhea, stiff neck, and 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. Subjects will be hospitalized for several days post-transplant. Following discharge from the hospital, subjects will return to the clinic for routine assessments. During these visits, safety and PK/PD assessments will be collected. Standard safety assessments will include vital signs, physical examinations, clinical laboratory evaluations (hematology, blood chemistry and urinalysis), AE and SAE monitoring as outlined in the Schedule of Assessments. In addition to standard clinical laboratory assessments, subjects will be monitored regularly for signs and symptoms of infectious, inflammatory, hematologic or renal toxicity / rejection as outlined below. Subject's serum creatinine will be measured frequently in the first few weeks post-transplant and thereafter with a focus on renal injury and dysfunction. Changes in renal function will be assessed via serum creatinine and estimated glomerular filtration rates (eGFR) using Modification of Diet in Renal Disease (MDRD) formula. In the event subjects present with a	diarrhea, with most patients exhibiting lymphopenia and elevated C-reactive protein (CRP) (Fung and Babik 2020). Subjects will be counseled to report any of these physical symptoms to the clinical staff. Clinicians should also consider the common laboratory changes when assessing the potential for COVID-19 disease. Subjects who may be exposed to SARS-CoV-2 or contract active disease will be managed per local practice and international guidelines including recommendations for seeking treatment or self-quarantine. As with all infection events, SARS-CoV-2 positivity and COVID-19 disease will be captured in the safety database and will be evaluated by the DMC during their periodic dose escalation and ongoing safety review. Within the clinical trial setting, subjects may be required to attend in-person study visits in excess of those based on standard of care for clinical laboratory assessments as well as PK/PD sample collection; this may increase their risk of SARS-CoV-2 exposure. To minimize the time patients, spend indoors and within the clinic for these assessments, phone contact or virtual / telehealth technology will be utilized where appropriate by the site staff. In addition, patients will be counseled on the importance of following proper hygiene, masking and social distancing practices to minimize community and hospital exposure during their standard of care and study specific visits. SARS-CoV-2 vaccines (i.e., mRNA, adenoviral vector) are under development or have been authorized for clinical use globally. The effectiveness of these vaccines in immunocompetent adults is between 76-95%, however the effectiveness in solid organ transplant recipients is unknown (See Section 6.5). Based on current vaccination guidelines, it is recommended that all transplant candidates and their household members receive SARS-CoV-2 vaccination when it becomes available. Ideally, transplant candidates should be targeted for vaccination while they are awaiting transplant or 3-6 months post-transplant in this trial, based on T-cell recovery.	

Section/Title/Page	Original Text	Revision	Reason for Change
	significant increase in SCr and/or BPAR for-cause biopsies are to be collected for evaluation according to the standard Banff histology system. In addition, urinary injury biomarkers will be collected for future analysis. This exploratory biomarker assessment will allow for an additional dataset which may help to better assess the type and gross location of renal injury, i.e., glomerular or tubular, should a signal for such emerge during the trial. Immunophenotyping via fluorescence-activated cell sorter (FACS) analysis will be conducted periodically during the study to assess the potential for an increased risk of infection, changes in leukocyte subsets and recovery following depletion anticipated with all siplizumab dosing arms. Coagulopathy will be assessed using standard hematology (platelets) and coagulation studies, including international normalized ratio (INR)/prothrombin time (PT) and activated partial thromboplastin time (aPTT) according to local practice. Finally, considering the open-label study design, ITB-MED and an independent DMC will review study data regularly and on an *ad hoc* basis. In addition to the clinical opinion of the Investigator and biopsy results, *a priori* defined stopping criteria and guidelines will be used to protect individual subject safety during the trial. Overall, the non-clinical results, together with completed single- and multiple-dose studies with siplizumab in humans to date, as well as the comprehensive monitoring plan, *a priori* defined study stopping criteria and monitoring by an independent DMC in the TCD601B102 study support the continued development of this	Subjects will be hospitalized for several days post-transplant. Following discharge from the hospital, subjects will return to the clinic for routine assessments frequently during the first 3-6 months per standard of care. During these visits, safety and PK/PD assessments will be collected. Standard safety assessments will include vital signs, physical examinations, clinical laboratory evaluations (hematology, blood chemistry and urinalysis), AE and SAE monitoring as outlined in the Schedule of Assessments. In addition to standard clinical laboratory assessments, subjects will be monitored regularly for signs and symptoms of infectious, inflammatory, hematologic or renal toxicity / rejection. Subject's serum creatinine will be assessed frequently in the first few weeks post-transplant and thereafter with a focus on renal injury and dysfunction. Changes in renal function will be assessed via serum creatinine and estimated glomerular filtration rates (eGFR) using Modification of Diet in Renal Disease (MDRD) formula. In the event subjects present with a significant increase in SCr and/or BPAR for-cause biopsies are to be collected for evaluation according to the standard Banff histology system. In addition, urinary injury biomarkers will be collected for future analysis. This exploratory biomarker assessment will allow for an additional dataset which may help to better assess the type and gross location of renal injury, i.e., glomerular or tubular, should a signal for such emerge during the trial. Immunophenotyping via fluorescence-activated cell sorter (FACS) analysis will be conducted frequently during the study to assess the potential for an increased risk of infection, changes in leukocyte subsets and recovery following depletion anticipated with all siplizumab dosing arms. Coagulopathy will be assessed using standard hematology (platelets) and coagulation studies, including international normalized ratio (INR)/prothrombin time (PT) and activated partial thromboplastin time (aPTT) according to local practice. Finally, considering the open-label study design, ITB-MED and an independent DMC will review study data, including	

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	immunomodulatory compound in further investigational studies. Based on the information outlined above, the risks of administering siplizumab in combination with TAC, MMF, and CS are monitorable, manageable and the benefit-risk assessment in the intended patient population remains positive.	safety events and AEs of special interest, regularly and on an *ad hoc* basis. Furthermore, *a priori* defined stopping criteria, infection surveillance and pharmacovigilance by ITB-MED as well as ongoing clinical assessments by Investigator and site staff will be employed to protect individual subject safety during the trial. Overall, the non-clinical and clinical safety results with siplizumab in human, as well as the comprehensive monitoring plan, *a priori* defined study stopping criteria and ongoing review by an independent DMC support the continued development of this immunomodulatory compound and conduct of further investigational studies. Moreover, in consideration of the ongoing SARS-CoV-2 pandemic, each center will manage their ongoing transplant program and enrollment of patients in this trial based on the Investigator's clinical judgement and individual patient risk assessment in consideration of both local and per protocol risk mitigation plans. The overall benefit-risk assessment including the aforementioned mitigation strategies and monitorable and manageable risks of administering siplizumab in this patient population is positive and support the conduct of this clinical trial.	
Section 5.1 Inclusion Criteria		**New Text:** Subjects who test negative for SAR-CoV-2 test via molecular testing (PCR)	Addition of SARS-CoV-2 as an exclusion criterion
Section 5.2 Exclusion Criteria	hemoglobin (Hbg) < 8 mg/dL	hemoglobin (Hgb) < 8 mg/dL	Correction to units of measure
Section 6.2.1. Identification of Investigational Product	Siplizumab is a humanized IgG1[kappa] class monoclonal antibody, supplied as a clear to slightly opalescent, colorless to slightly brownish, preservative-free solution for infusion.	Siplizumab is a humanized IgG1[kappa] class monoclonal antibody, supplied as a clear to slightly opalescent, colorless to slightly brownish, preservative-free, concentrate for solution.	Clarification that siplizumab is supplied as a concentrate for solution
Section 6.2.2 Management of Investigational Product	Please refer to the Pharmacy Manual for detailed instructions on the receipt, storage, accountability, and return or destruction will be described in the ITB-MED provided Pharmacy Manual.	Detailed instructions for the receipt, storage, accountability, and return or destruction will be described in the ITB-MED provided Pharmacy Manual.	Clarification to refer to the siplizumab Pharmacy Manual for specifics on the preparation and management of siplizumab infusions

Section/Title/Page	Original Text	Revision	Reason for Change
Section 6.5 Infectious Prophylaxis Treatment (Immunization)		**New Text:** 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, such as following T- or B-cell depletion 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 et al 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.	Information on immunization of transplant recipients and candidates consolidated and expanded under a new section for clarity.
Section 8 Visit Assessments		**New Text:** 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 adverse events). The intent is to allow centers to minimize in-person onsite clinic visit activities to those assessments that require the subject to be physically present (e.g., laboratory collections or physical assessments). In the event virtual or telehealth technology is utilized to facilitate data collection, it should be done per institutional practice and local regulations. Detailed documentation of all contact and information collected virtually is to be recorded in the study records.	Clarification on flexible visit scheduling during the ongoing SARS-CoV-2 pandemic to minimize the amount of time and in-person contact necessary for per protocol study visits.
Section 8 Visit Assessments 3rd Paragraph	This protocol defines 7 days to a week and 4 weeks (or 28 days) to a Study Month. For example, Week	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	Clarification of protocol definitions

Section/Title/Page	Original Text	Revision	Reason for Change
	2 is considered to start on Day 7 and Study Month 2 is considered to start on Week 5/Day 2.	on Day 8 and Study Month 2 is considered to start on Day 29 (Start of Week 5).	
Section 8.4.2 Vital Signs	Vital signs (radial pulse rate, blood pressure and body temperature) will be recorded as indicated in the Schedule of Assessments.	Vital signs (radial pulse rate, blood pressure, respiratory rate, and body temperature) will be recorded as indicated in the Schedule of Assessments.	Clarification that respiratory rate is assessed
Section 8.4.4.5 Pregnancy	Serum or urine pregnancy testing will be required for all females regardless of child-bearing potential, at timepoints as designated in the Schedule of Assessments.	Serum or urine pregnancy testing will be required for females of child-bearing potential, at timepoints as designated in the Schedule of Assessments.	Clarification to only conduct pregnancy testing in WOCBP
Appendix 1 Schedule of Assessments	Not applicable	The following assessments were added: • SARS-CoV-2 Molecular Testing at screen • EBV-PCR (added visit 13 and visit 17)	The Schedule of Assessments was updated to reflect the addition of study assessments and procedures.
Appendix 1 Schedule of Assessments	• Footnote (b) vitals collected pre-dose, immediately following the end of the infusion, and 6 hours after completion of infusion with siplizumab or ATG. Other time points captured as indicated. • Footnote (d) results obtained within the past 6 months are acceptable for the initial assessment; serology samples and donor EBV only at screening • HIV, HbsAg, HCV serology (D and R)[d] • Footnote (f) a negative pregnancy test must be available prior to randomization • Footnote (i) Subjects randomized to ATG (Control) • Footnote (m) TCD601 PK Sampling on Day 0 dosing (pre-dose, hrs 1, 3, 6 and 24) and Day 4 dosing (pre-dose, hrs 1, 3 and 6). Additional samples include collection on post-operative Days 2, 3, 7, 14, 21, 28, 35, 42, 49, 56, 63*,	• Footnote (b) vitals collected pre-dose, immediately following the end of the infusion, and 6 hours after completion of infusion with siplizumab or rATG. Other time points captured as indicated. Weight is captured pre-dose on Days 0 and 4 for siplizumab treated subjects and pre-dose on Days 0,1 and 2 for rATG treated subjects • Footnote (d) results obtained within the past 12 months are acceptable for the initial assessment of EBV (donor and recipient) and CMV. Serological testing for BKV is not required at Screening. EBV, CMV and BKV viral testing via PCR should be conducted thereafter • HIV, HbsAg, HCV serology (D and R) • Footnote (f) a negative pregnancy test must be available prior to randomization (for females of childbearing potential) • Footnote (i) Subjects randomized to rATG (Control) • Footnote (m) New Text: Post-dose collection time is based on the START time of infusion.	Updates to footnotes b, d, f, and i in the Schedule of Assessments.

Section/Title/Page	Original Text	Revision	Reason for Change
	70*, 84*, 112*, *140, 168*, 196*, 224*, and 252* (* Note: latter collections may be truncated based on half-life of TCD601 and serum concentrations below limit of quantification)		
Appendix 7: Update 2018 Banff Classification	Not applicable	New Text: Category 5: IFTA • Grade I (Mild): Banff Lesion Score *ci1* OR Banff Lesion Score *ct1* • Grade II (Moderate) Banff Lesion Score *ci2* OR Banff Lesion Score *ct2* • Grade III (Severe) Banff Lesion Score *ci3* OR Banff Lesion Score *ct3* Category 6: Other changes not considered to be caused by acute or chronic rejection • BK-Virus Nephropathy • Posttransplant Lymphoproliferative Disorder • Calcineurin Inhibitor Toxicity • Acute Tubular Injury • Recurrent Disease • De Novo Glomerulopathy (Other Than TG) • Pyelonephritis • Drug-Induced Interstitial Nephritis	Appendix updated to reflect the 2018 update of the Banff classification standards
Various	Not defined	Correction of minor typos and clarifications throughout the protocol	Typos and minor updates to the text to provide clarification were included throughout the document and are visible within the redlined version of the protocol.

16.3 Appendix 3: Investigator Agreement Page

INVESTIGATOR AGREEMENT

Protocol Number: TCD601B102

Version: 2.0, Incorporating Amendment No.: 1.0

I have read the Investigator's Brochure and protocol TCD601B102, "A 12-Month, Randomized, Controlled, Open-Label, Dose Escalation Study evaluating Safety, Tolerability, Pharmacokinetics (PK) and Pharmacodynamics (PD) of an anti-CD2 monoclonal antibody, TCD601 (siplizumab) compared to anti-thymocyte globulin (rATG), as induction therapy in *de novo* Renal Transplant Recipients" 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 (siplizumab) only as specified in the protocol and Pharmacy Manual
- Agree to reference the Laboratory Manual provided by ITB-MED for detailed instructions on sample collection, processing and analysis (where applicable)
- 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

16.4 Appendix 4: US-Specific CellCept® Pregnancy and Safety Information

- 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 MPA 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 (1800-617-8191). 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. Patients 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).
- Patients should be aware that CellCept® reduces blood levels of the hormones in the oral contraceptive pill and could theoretically reduce its effectiveness.

Acceptable Contraception Methods for Females of Reproductive Potential using MMF*

<table>
<tr><td><u>Option 1</u>
Methods to Use Alone</td><td colspan="3">• Intrauterine device (IUD)
• Tubal sterilization
• Patient’s partner had a vasectomy</td></tr>
<tr><td colspan="4">OR</td></tr>
<tr><td><u>Option 2</u>
Choose One Hormonal Method AND One Barrier Method</td><td>Hormone Methods
choose 1</td><td></td><td>Barrier Methods
choose 1</td></tr>
<tr><td></td><td>Estrogen and Progesterone
• Oral contraceptive pill
• Transdermal patch
• Vaginal ring
Progesterone-only
• Injection
• Implant</td><td>AND</td><td>• Diaphragm with spermicide
• Cervical cap with spermicide
• Contraceptive sponge
• Male condom
• Female condom</td></tr>
<tr><td colspan="4">OR</td></tr>
<tr><td>Option 3
Choose One Barrier Method from Each Column (must choose two methods)</td><td>Barrier Methods
choose 1</td><td></td><td>Barrier Methods
choose 1</td></tr>
<tr><td></td><td>• Diaphragm with spermicide
• Cervical cap with spermicide
• Contraceptive sponge</td><td>AND</td><td>• Male condom
• Female condom</td></tr>
</table>

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

16.5 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, leucopenia, 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.

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

WBC

- 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**

All these changes must be recorded on the MMF Dosage Administration Record eCRF.

16.6 Appendix 6: 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 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 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

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**			cyclosporine
	voriconazole			danazol
				ethinyl estradiol
				methylprednisolone
				lansoprazole***
				omeprazole
				protease inhibitors
				nefazodone
				magnesium-aluminum hydroxide

**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, IV clearance of Tac was not significantly changed by ketoconazole co-administration, although it was highly variable between patients.

*** 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

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

* 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 patients 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 AUC and a 10% decrease in the mean Tac Cmax 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 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 HCV protease inhibitors (e.g., boceprevir and telaprevir), also metabolized by CYP3A, are administered concomitantly with Tac.

Tac may affect the PK 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 TY 21a typhoid (Prograf® PI 2019).

16.7 Appendix 7: Updated 2018 Banff Classification

Category 1: Normal biopsy or nonspecific changes

Category 2: Antibody-mediated changes

- **Active ABMR:** all three features must be present for diagnosis. Biopsies showing histological features plus evidence of current/recent antibody interaction with vascular endothelium or DSA, but not both, may be designated as suspicious for acute/active ABMR. Lesions may be clinically acute or smoldering or may be subclinical; it should be noted if the lesion is C4d-positive or C4d-negative, based on the following criteria:

    1. Histologic evidence of acute tissue injury, including one or more of the following:
        - Microvascular inflammation (g >0 in the absence of recurrent or *de novo* glomerulonephritis, and/or ptc >0)
        - Intimal or transmural arteritis (v >0)[1]
        - 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 at least one of the following:
        - Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections or C4d >0 by IHC on paraffin sections)
        - At least moderate microvascular inflammation ([g + ptc] ≥2), 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 in the biopsy tissue strongly associated with ABMR, *if thoroughly validated*
    3. Serologic evidence of DSAs (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[2]:** all three features must be present for diagnosis. As with active ABMR, biopsies showing histological features plus evidence of current/recent antibody interaction with vascular endothelium or DSA, but not both, may be designated as suspicious, and it should be noted if the lesion is C4d-positive or C4d-negative, based on the criteria listed:

1. Morphologic evidence of chronic tissue injury, including one or more of the following:
    - TG (cg >0), if no evidence of chronic thrombotic microangiopathy or chronic recurrent/*de novo* glomerulonephritis; includes changes evident by electron microscopy (EM) alone (cg1a)
    - Severe peritubular capillary basement membrane multilayering (requires EM)[3]
    - Arterial intimal fibrosis of new onset, excluding other causes; leukocytes within the sclerotic intima favor chronic ABMR if there is no prior history of biopsy-proven TCMR with arterial involvement but are not required
2. Identical to criterion 3 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

- **C4d staining without evidence of rejection**

All three features must be present for diagnosis[4]

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 changes

- **Suspicious for acute TCMR**
    - Foci of tubulitis (t>0) with minor interstitial inflammation (i0 or i1) or interstitial inflammation (i2, i3) with mild (t1) tubulitis; retaining the i1 threshold for borderline with t >0 is permitted although this must be made transparent in reports and publications
    - No intimal or transmural arteritis (v = 0)

Category 4: TCMR

- **Acute TCMR**
    - **Grade IA.** Interstitial inflammation (>25% of nonsclerotic cortical parenchyma, i2 or i3) and foci of moderate tubulitis (t2) involving 1 or more tubules, not including tubules that are severely atrophic[5]
    - **Grade IB.** Interstitial inflammation involving >25% of nonsclerotic cortical parenchyma (i2 or i3) with severe tubulitis (t3) involving 1 or more tubules, not including tubules that are severely atrophic[5]

- **Grade IIA.** Mild to moderate intimal arteritis (v1) with or without interstitial inflammation and tubulitis
- **Grade IIB.** Severe intimal arteritis (v2), with or without interstitial inflammation and/or tubulitis
- **Grade III.** Transmural arteritis and/or arterial fibrinoid necrosis of medial smooth muscle cells with accompanying mononuclear cell intimal arteritis (v3), with or without interstitial inflammation and/or tubulitis

- **Chronic active TCMR**
  - **Grade IA:** Interstitial inflammation involving >25% of the total cortex (ti score 2 or 3) and >25% of the sclerotic cortical parenchyma (i-IFTA score 2 or 3) with moderate tubulitis (t2) involving 1 or more tubules, not including severely atrophic tubules[5]; other known causes of i-IFTA should be ruled out
  - **Grade IB:** Interstitial inflammation involving >25% of the total cortex (ti score 2 or 3) and >25% of the sclerotic cortical parenchyma (i-IFTA score 2 or 3) with severe tubulitis (t3) involving 1 or more tubules, not including severely atrophic tubules[5]; 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)

Category 5: IFTA

- Grade I (Mild): Banff Lesion Score *ci1* OR Banff Lesion Score *ct1*
- Grade Il (Moderate) Banff Lesion Score *ci2* OR Banff Lesion Score *ct2*
- Grade III (Severe) Banff Lesion Score *ci3* OR Banff Lesion Score *ct3*

Category 6: Other changes not considered to be caused by acute or chronic rejection

- BK-Virus Nephropathy
- Posttransplant Lymphoproliferative Disorder
- Calcineurin Inhibitor Toxicity
- Acute Tubular Injury
- Recurrent Disease
- De Novo Glomerulopathy (Other Than TG)
- Pyelonephritis
- Drug-Induced Interstitial Nephritis

Legend:

ABMR, antibody-mediated rejection; cg, glomerular double contours; DSA, donor-specific antibody; EM, electron microscopy; g, glomerulitis; i, inflammation; IF, immunofluorescence; IHC, immunohistochemistry; ptc, peritubular capillaritis; t, tubulitis; TCMR, T-cell mediated rejection; TG, transplant glomerulopathy; TMA, thrombotic microangiopathy; v, intimal arteritis.

[1] It should be noted that these arterial lesions may be indicative of ABMR, TCMR, or mixed ABMR/TCMR. The v lesions are only scored in arteries having a continuous media with two or more smooth muscle layers.

[2] Lesions of chronic, active ABMR can range from primarily active lesions with early TG evident only by EM (cg1a) to those with advanced TG and other chronic changes in addition to active microvascular inflammation. In the absence of evidence of current/recent antibody interaction with the endothelium, the term “active” should be omitted; in such cases, DSAs may be present at the time of biopsy or at any previous time after transplantation.

[3] Seven or more layers in one cortical peritubular capillary and five or more in two additional capillaries, avoiding portions cut tangentially.

[4] The clinical significance of these findings may be quite different in grafts exposed to anti–blood group antibodies (ABO-incompatible allografts), in which 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.

[5] A severely atrophic tubule is defined as one with each of the following 3 features: a diameter <25% of that of unaffected or minimally affected tubules on the biopsy, an undifferentiated-appearing, cuboidal or flattened epithelium, and pronounced wrinkling and/or thickening of the tubular basement membrane (Source: Haas et al 2017, Roufosse 2018).