Clinical Protocol TCD601B101

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 Recipient

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TCD601 (siplizumab)

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Clinical Trial Phase:	2a
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LIST OF ABBREVIATIONS

Abbreviation	Definition
ABC	antibody biodistribution coefficient
ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
AESI	adverse event of special interest
aGvHD	acute graft-versus-host disease
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMR	antibody-mediated rejection
APC	antigen-presenting cell
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATG	anti-thymocyte globulin
AUC	area under the concentration-time curve
AUC_{inf}	area under the concentration-time curve from time zero to infinity
AxMP	Auxiliary Medicinal Product
BID	twice a day/twice daily
BKV	BK polyomavirus
BMI	body mass index
BMT	bone marrow transplantation
BPAR	biopsy-proven acute rejection
BUN	blood urea nitrogen
CDC	complement-dependent cytotoxicity
CDR	complementarity-determining region
CIT	cold ischemia time
CL/F	total body clearance of drug from the plasma
C_{max}	maximum observed concentration
CMV	cytomegalovirus
CNI	calcineurin inhibitor
CRS	cytokine release syndrome
CS	corticosteroid(s)

Abbreviation	Definition
CsA	cyclosporine
COVID-19	coronavirus disease 2019
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTS	chimeric transition syndrome
CV	coefficient of variation
CV%	percent coefficient of variation
DGF	delayed graft function
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DSA	donor-specific antibody
EBV	Epstein-Barr virus
EC_{50}	half-maximal effective concentration
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOS	End of Study
EU	European Union
FACS	fluorescence-activated cell sorting
FAS	Full Analysis Set
Fc	fragment crystallizable
FcRn	fragment crystallizable neonatal receptor
FcγR	fragment crystallizable gamma receptor
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GvHD	graft-versus-host disease
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus

Abbreviation	Definition
HLA	human leukocyte antigen
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplantation
IAR	infusion-associated reaction
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IL	interleukin
IL-2RA	interleukin-2 receptor antagonist
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IP	investigational product
IV	intravenous
IWRS	interactive web response system
IVIG	intravenous immunoglobulin
KDIGO	Kidney Disease Improving Global Outcomes
K_M	Michaelis constant
LFA	leukocyte function antigen
LGL	large granular lymphocytic
LLOQ	lower limit of quantitation
LOCF	last-observation-carried-forward
LPD	lymphoproliferative disorder
mAb	monoclonal antibody
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MMF	mycophenolate mofetil
MPA	mycophenolic acid
MRI	magnetic resonance imaging
mTOR	mechanistic target of rapamycin
NCI	National Cancer Institute

Abbreviation	Definition
NK	natural killer
PCP	*Pneumocystis jirovecii* (*Pneumocystis carinii*) pneumonia
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PET	positron-emission tomography
PGNF	primary graft non-function
PK	pharmacokinetic(s)
p.o.	orally
PT	Preferred Term
PT	prothrombin time
PTLD	post-transplant lymphoproliferative disorder
PVAN	polyomavirus-associated nephropathy
rATG	rabbit anti-thymocyte globulin
RO	receptor occupancy
REMS	Risk Evaluation and Mitigation Strategy
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
s.c.	subcutaneous
SD	standard deviation
SID	subject identification number
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SoC	standard of care
SOC	System Organ Class
SOP	standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAC	tacrolimus
TB	tuberculosis
tBPAR	treated biopsy-proven acute rejection
TCMR	T-cell mediated rejection
TCR	T-cell receptor

Abbreviation	Definition
TEAE	treatment-emergent adverse event
T_{max}	time to reach maximum observed concentration
TMDD	target-mediated drug disposition
$t_{½}$	half-life
ULOQ	upper limit of quantitation
US	United States
VL	viral load
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

PROTOCOL SYNOPSIS

<table>
<tr><td>Product Name/Number</td><td>TCD601 (siplizumab)</td></tr>
<tr><td>Protocol Number</td><td>TCD601B101</td></tr>
<tr><td>Protocol Title</td><td>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</td></tr>
<tr><td>Investigation Type</td><td>Interventional; Drug (biologic)</td></tr>
<tr><td>Purpose and Rationale</td><td>The purpose of this study is to investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of escalating doses of TCD601 (siplizumab), an anti-cluster of differentiation 2 (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 study will assess the safety, tolerability, PK, and PD activity of siplizumab in the setting of SoC 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.</td></tr>
<tr><td>Objectives and Endpoints</td><td>
<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td colspan="2">Primary</td></tr>
<tr><td>• To assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of siplizumab compared to rabbit anti-thymocyte globulin (rATG), in de novo renal transplant recipients over 12 months post-transplant.</td><td>• Adverse events (AEs)
• Serious adverse events (SAEs)
• Clinically significant changes in clinical chemistry, hematology, vital signs, serology
• Siplizumab PK
• Immunophenotyping
• CD2 receptor occupancy (RO)
• Estimated glomerular filtration rate (eGFR) via Modification of Diet in Renal Disease (MDRD) equation
• Anti-siplizumab antibodies</td></tr>
<tr><td colspan="2">Secondary</td></tr>
<tr><td>• To measure changes in peripheral lymphocyte immunophenotype</td><td>• Immunophenotyping via fluorescence-activated cell sorting (FACS)</td></tr>
</table>
</td></tr>
</table>

Objectives	Endpoints
Secondary, continued	
• To measure the time-course and duration of siplizumab induced lymphocyte depletion and time to recovery	• Lymphocyte counts
• To measure peripheral CD2 RO following siplizumab administration over time	• CD2 RO
• To assess the incidence of treated biopsy-proven acute rejection (tBPAR) over 12 months	• Incidence of tBPAR
• To assess the incidence of treatment-emergent *de novo* donor-specific antibodies (DSA) over 12 months	• *de novo*-DSA/anti-human leukocyte antigen (HLA) antibody measurement
• To assess the incidence of antibody-mediated rejection (AMR) over 12 months	• Incidence of AMR
• To assess renal function via eGFR using MDRD equation at Months 3, 6, and 12 (End of Study [EOS]/Early Termination [ET])	• eGFR
Exploratory	
• [redacted]	[redacted]

Study Design

TCD601B101 is a 12-month, multicenter, randomized, controlled, open-label, dose escalation study to evaluate the safety, tolerability, PK, and PD of siplizumab, an anti-CD2 monoclonal antibody, compared to rATG, as induction therapy in *de novo* renal transplant recipients. All subjects will receive triple regimen 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 40 moderate immunological risk, adult, *de novo* renal transplant candidates will be enrolled in the study.

Cohort Assignment/Randomization/Dosing Regimen

On Study Day 0 (prior to renal transplantation surgery), eligible subjects will be sequentially assigned to 1 of 4 cohorts (A–D) using a time-lagged dose escalation methodology (see Study Schema). Within each cohort, 10 subjects will be randomized in an 8:2 ratio to receive either siplizumab (Arms 1, 2, 3, or 4) or rATG (Control Arm 5), as shown in the table below.

Dosing Cohorts

Cohort	Arm	Subjects (n)	Product	Dosing Regimen
Cohort A	Arm 1	8	Siplizumab	0.2 mg/kg (Days 0 and 4)
	Control Arm 5	2	rATG	1.5 mg/kg (Day 0, 1, and 2)
Cohort B	Arm 2	8	Siplizumab	0.6 mg/kg (Days 0 and 4)
	Control Arm 5	2	rATG	1.5 mg/kg (Day 0, 1, and 2)
Cohort C	Arm 3	8	Siplizumab	1.7 mg/kg (Days 0 and 4)
	Control Arm 5	2	rATG	1.5 mg/kg (Day 0, 1, and 2)
Cohort D	Arm 4	8	Siplizumab	5.0 mg/kg (Days 0 and 4)
	Control Arm 5	2	rATG	1.5 mg/kg (Day 0, 1, and 2)

Investigational Product (IP) Administration (Siplizumab/rATG)

Subjects randomized to receive siplizumab will receive 2 intravenous (IV) doses. The first dose will be administered on Day 0, pre- or intra-operatively, and must be completed prior to revascularization and reperfusion of the allograft. The second dose of siplizumab will be administered on Day 4 post-transplant. Subjects randomized to rATG (Control Arm 5) will receive 1.5 mg/kg IV doses (on Days 0, 1, and 2; for a total of 3 doses), regardless of cohort assignment.

Background Immunosuppressive Therapy

Siplizumab and rATG will be combined with a triple regimen of background immunosuppressive therapy consisting of twice daily (BID) dosing of concentration-controlled TAC (to a whole blood trough concentration of 4–11 ng/mL) and BID dosing of MMF or equivalent (both should be started within 24 hours post-transplant), along with CS per local practice (minimum of 5.0 mg/day prednisone or equivalent) until Month 12.

Post-Transplant Study Visits

Following transplantation, subjects should be treated post-operatively per SoC 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 study site for weekly

	study visits, up to and including Week 10, and then monthly through Month 12 or EOS (all enrolled subjects will be followed for a minimum of 12 months), as indicated in the Schedule of Assessments (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, or are otherwise considered non-evaluable, will be replaced. **Dose Escalation Review** A review of safety/tolerability (e.g., AEs, SAEs, clinical laboratory assessments, vital signs), PD (immunophenotyping), receptor occupancy, and PK (if available) data will be conducted by ITB-MED and an independent Data Monitoring Committee (DMC) at least 28 days following the last IP administration in the 4th siplizumab-treated subject in each cohort prior to dose escalation to the next dose level cohort. This 28-day safety period allows sufficient time for subjects to reach full receptor occupancy, maximum PD activity, and for presentation of acute, drug-related toxicities. Upon completion of the review by the DMC, if there is no evidence of acute, dose-limiting toxicities (DLTs), the DMC may recommend escalation to the next dose level cohort. Alternatively, a decision to terminate the dosing arm could be reached, or the study could be amended to add additional and/or intermediate dose levels or cohorts below the maximum tolerated dose to further evaluate safety, PK, or PD. If escalation to the next dose level cohort is recommended by the DMC and opened for enrollment prior to existing dose level cohorts being filled, the Interactive Web Response System (IWRS) will randomize subjects to either the newly opened dose level cohort or a prior cohort. This will ensure that all cohorts are backfilled to achieve the sample size of 10 subjects (8 siplizumab: 2 placebo). **Data Monitoring Committee (DMC)** In addition to the dose escalation review process described above, the independent Data Monitoring Committee (DMC) will convene as described in the DMC Charter to conduct ongoing review of cumulative PK, PD, and safety data (including DLTs, AEs, SAEs, EBV viral load, post-transplant lymphoproliferative disorder (PTLD) surveillance results, clinical laboratory assessments, and *ad hoc* imaging). **Safety Stopping Rules** If at any time the observed AEs meet or exceed the a priori defined stopping criteria (safety stopping rules), the study will be placed on hold pending further review from the Sponsor and DMC. 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 grade scale, the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

	The following stopping rules based on potential toxicities will serve as the basis for placing enrollment and dose escalation on hold: • 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 (CRS) 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/mm^3 to <500/mm^3 [0.2 to <0.5 × 10^9/L]) considered drug-related as determined by the Investigator. • Two (2) or more subjects presenting with Grade 3 or higher toxicity considered drug-related (including infusion reactions) as determined by the Investigator, 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.
Population	Up to 40 moderate immunological risk, adult, *de novo* renal transplant patients
Planned Study Sites	Up to 10 study sites within Europe (EU)
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-human leukocyte antigen (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.
Exclusion Criteria	Subjects meeting any of the following criteria are not eligible for inclusion in this study: 1. Transplant recipients seronegative 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.

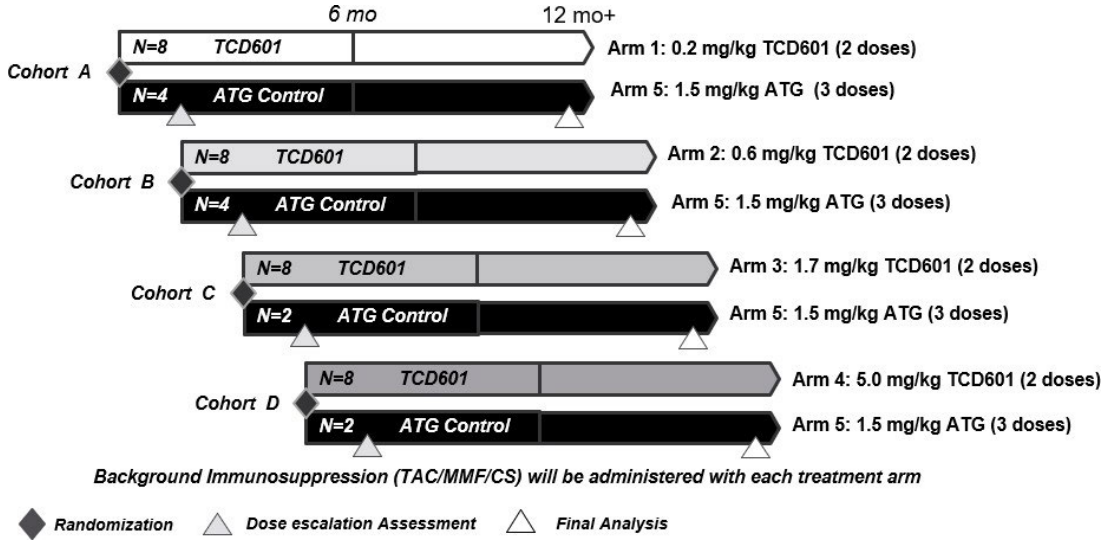
	6. Subjects at high immunological risk for rejection as determined by local practice (e.g., presence of pre-existing donor-specific antibodies [DSA], recipient of high Kidney Donor Profile Index ≥85 kidney [where assessed]). 7. Subjects with anti-HLA donor-specific antibody as measured by complement-dependent cytotoxicity (CDC) assay, 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. For example: >2.5 × upper limit of normal (ULN) values for: - Liver function chemistries (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP]) - Bilirubin - Coagulation studies (International Normalized Ratio [INR]/ prothrombin time [PT], activated partial thromboplastin time [aPTT]). 12. Subjects with any of the following: • Hemoglobin (Hgb) <8 mg/dL • White blood cell (WBC) count ≤2,000/mm^3 • Platelet count ≤75,000/mm^3 13. Seropositive for human immunodeficiency virus (HIV) or hepatitis B surface antigen (HBsAg). Subjects who are seropositive 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/ hepatitis B core antigen (HBcAg) positive, or HCV. 15. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes (e.g., siplizumab, anti-thymocyte globulin [ATG], tacrolimus [TAC], mycophenolate mofetil [MMF], corticosteroids [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 tuberculosis (TB) infection (after anti-TB treatment, patients with history of latent TB may become eligible according to national guidelines). 18. Subjects with severe systemic infections, current or within the 2 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.

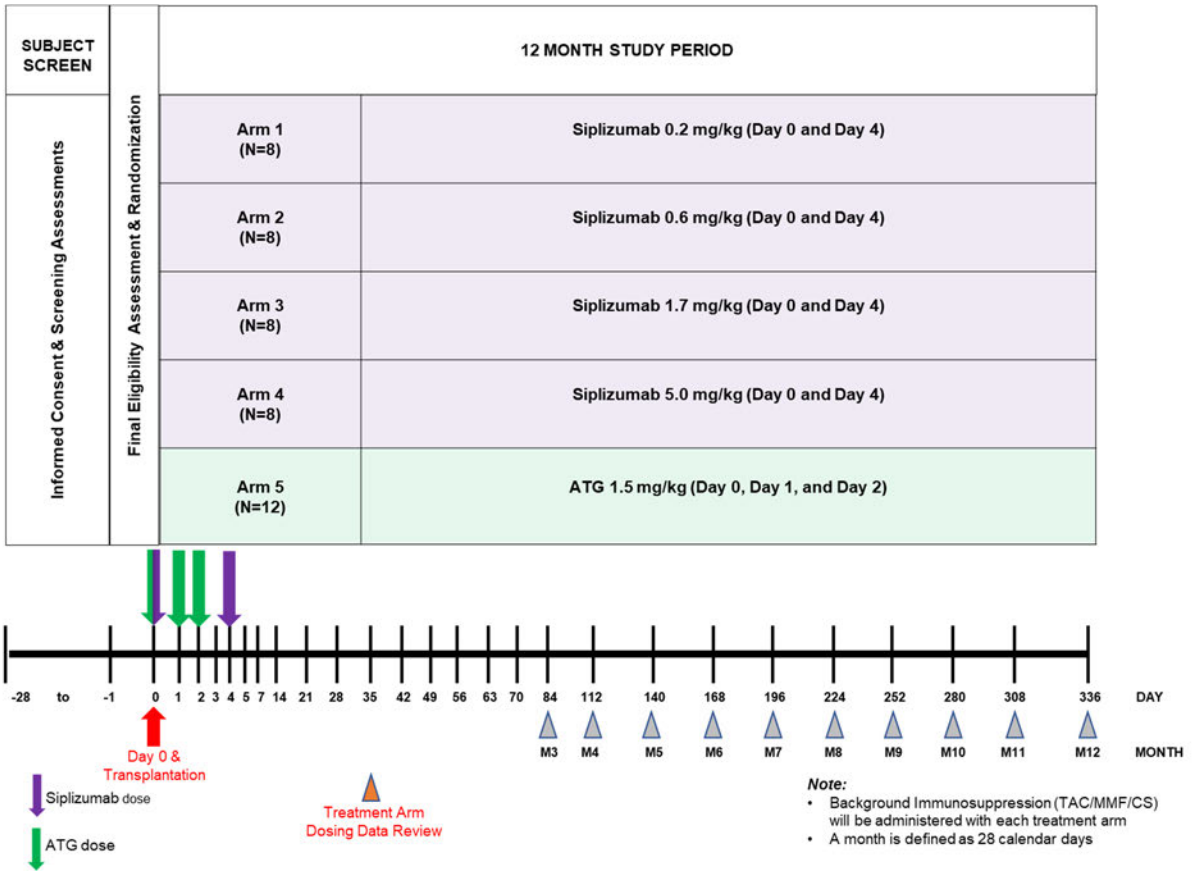
	20. Subjects who, in the opinion of the Investigator, are not capable of giving informed consent for the study or who are unable or unwilling to adhere to the study requirements outlined in the protocol. 21. Use of other investigational products or enrollment in another investigational drug study within 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 childbearing 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 is she considered not of childbearing potential. • 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. Withdrawal and period abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) are not acceptable forms of contraception. 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 is considered not of childbearing potential.

<table>
<tr><td>Investigational Product</td><td>Siplizumab is a humanized IgG1κ class monoclonal antibody supplied in 6 mL vials containing 60 mg at a concentration of 10 mg/mL.</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)
Note: If oral administration is not feasible or practical, IV TAC (containing the equivalent of 5 mg/mL TAC) administration by continuous infusion may be substituted per label)
• 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 1 of 4 cohorts (A–D) and then randomized to 1 of 2 dosing arms in an 8:2 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>Control Arm 5</td><td>2</td><td>rATG</td><td>1.5 mg/kg (Day 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>Control Arm 5</td><td>2</td><td>rATG</td><td>1.5 mg/kg (Day 0, 1, and 2)</td></tr>
<tr><td rowspan="2">Cohort C</td><td>Arm 3</td><td>8</td><td>Siplizumab</td><td>1.7 mg/kg (Days 0 and 4)</td></tr>
<tr><td>Control Arm 5</td><td>2</td><td>rATG</td><td>1.5 mg/kg (Day 0, 1, and 2)</td></tr>
<tr><td rowspan="2">Cohort D</td><td>Arm 4</td><td>8</td><td>Siplizumab</td><td>5.0 mg/kg (Days 0 and 4)</td></tr>
<tr><td>Control Arm 5</td><td>2</td><td>rATG</td><td>1.5 mg/kg (Day 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
All post-dose sample collections are relative to the START time of the infusion.
• Siplizumab (total and free) – Dosing on Day 0 and Day 4:
o Day 0 dosing (pre-dose; and at 1, 3, 6, and 24 hours post-dose) and Day 4 dosing (pre-dose; and at 1, 3, and 6 hours post-dose).
o Post-operative Days 2, 3, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, and 84.
• Anti-siplizumab antibodies: Days 0, 28, 56, 84, 168, and EOS.</td></tr>
</table>

	• 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. • PD: o PD sampling times to be linked with relevant PK time points o Peripheral lymphocyte immunophenotyping (FACS analysis) – CD2, CD3, CD4, CD5, CD8, CD19, CD25, CD27, CD38, CD45RA, CD45RO, CD59, CD127, CD138, CD154, FoxP3, HLA-DR o Peripheral CD2 receptor occupancy
Safety Assessments	• AEs and SAEs • Clinically significant changes in clinical chemistry, hematology, vital signs, and serology • Renal function
Data Analysis	All information obtained on AEs will be displayed by treatment and subject. The number and percentage of subjects with treatment-emergent adverse events (TEAEs) will be tabulated by body system (i.e., System Organ Class [SOC]) and Preferred Term (PT) with a breakdown by treatment arm. A subject with multiple TEAEs within a PT or SOC is only counted once towards the total. No formal statistical analysis will be conducted 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. The magnitude and duration of PD effect of siplizumab will be characterized by measuring the change in peripheral immunophenotype, including all subsets of T-, B-, and natural killer (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 for all PD and biomarker data. The relationship between siplizumab concentration (PK) and PD variables will be explored graphically. 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 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.
Study Duration	All subjects enrolled will be followed for a minimum of 12 months.

STUDY SCHEMA





1. INTRODUCTION

1.1. Background

Since the first successful human kidney transplantation by Murray et al. in 1954 (Murray 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 2015). Immunosuppressive agents are categorized as (1) induction therapy that is administered in the perioperative period and (2) maintenance therapy that transplant recipients require for lifelong use (KDIGO 2009). To maximize efficacy and minimize adverse effects, current immunosuppressive regimens are typically based on combinations of 2 or 3 immunosuppressive drugs with or without induction. Optimal combinations of therapies must be individualized based on the risk and benefit for each individual recipient (Bia 2010).

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

Calcineurin inhibitor-based SoC regimens have resulted in excellent 1-year patient and graft survival rates of 94.7% for deceased donor kidneys and 98.1% for living donor kidneys in the United States (US), with low (7–8%) one-year acute rejection rates (Hart 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 (rATG, Thymoglobulin) and nondepleting monoclonal antibodies such as basiliximab (Simulect) and formerly daclizumab (Zenapax; withdrawn from US in 2009) that inhibit T-cell activation (Hardinger 2013). In the past, the lymphocyte depleting murine anti-human CD3 monoclonal antibody, 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 interleukin-2 receptor antagonists (IL-2RAs; 20.6%) (Hart 2020) whereas almost an inverse use of ATG and IL-2RA is seen in Europe (EU).

1.1.1. Transplant Induction Therapy

Basiliximab is a non-depleting, chimeric murine and human monoclonal antibody (mAb) that specifically targets CD25, or the interleukin (IL)-2 receptor, 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 (CS)-based immunosuppression regimen clinically relevant suppression of IL-2 receptor activity following basiliximab administration is approximately 59 ±17 days (Simulect® Prescribing Information 2020).

Anti-thymocyte globulin (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 et al 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 major histocompatibility complex (MHC) class I (Popow 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-dependent cytotoxicity (CDC) of various immune cells (Andress 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 2004). Mechanistic side effects such as infusion reactions, cytokine release syndrome (CRS), 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 IL-2 receptor antagonists (IL-2RA) and induction-free regimens are primarily utilized in patients with low immunologic risk (e.g., living donor renal transplant) (Hardinger 2013). The current Kidney Disease Improving Global Outcomes (KDIGO) Transplant Work Group guidelines recommend IL-2RA 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 et al assessed the use of induction therapy in living donor renal recipients on

immunosuppression with TAC/MPA ± prednisolone (assessment period 2000–2012). Their conclusions were there was no benefit from use of IL-2RA induction versus no induction in patients maintained on TAC/MPA/ prednisolone with respect to acute rejection or graft survival; and 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 2015).

Overall, antibodies with a high specificity for single T-cell receptors (TCRs) 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 leukocyte function antigen (LFA)-2) is a monomeric transmembrane glycoprotein of 45–50 kDa. CD2 is expressed early during human thymocyte development and is found on about half of thymocytes, thymic B-cells, natural killer (NK) cells and almost all mature peripheral T-cells. CD2 functions as an intercellular adhesion molecule, binding to its ligand LFA-3 (CD58) in humans with high affinity. Human LFA-3 is a surface glycoprotein that contains 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 (Seed 1987, Springer 1987, Davis 1996). The interaction of CD58 with CD2 has been found to be essential for the activation of cellular immunity, such as $CD8^+$ cytotoxic T-lymphocytes and NK cell-mediated cytotoxic reactions (Leitner 2015, Rölle 2016). In addition, CD2 is upregulated on both activated and memory T cells (Tmems) while CD58-ligation to CD2 activates NK and dendritic cells, lowers the threshold for T-cell activation and enhances T-cell responsiveness to pro-inflammatory cytokines such as IL-12 (Lo 2011). Furthermore, CD2-ligation of B-cell specific CD58 induces the upregulation of CD40 expression, suggesting that CD2 may also play a role in the stimulation and/or delivery of T-cell help to B-cells.

1.1.3. Siplizumab (TCD601): Mechanism of Action

Siplizumab (TCD601; previously known as MEDI-507) is a non-agonistic, humanized, anti-CD2 monoclonal antibody of the IgG1κ class. Siplizumab binds to a unique epitope on human CD2, distinct from the CD58 binding site, with high affinity (Kd – 5 nM), inhibiting co-stimulation and T-cell activation. In addition, the fragment crystallizable (Fc) portion of the siplizumab antibody binds to fragment crystallizable gamma receptors (FcγR) on NK cells resulting in ADCC and antibody-dependent cellular phagocytosis (ADCP)-mediated depletion of CD2+ lymphocytes. Siplizumab also demonstrates selective immunomodulatory activity with depletion of Tmems (high CD2 expression) and sparing of regulatory T cells (Treg; low CD2 expression)

in vitro and in vivo 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. Siplizumab Data Summary

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

Siplizumab only cross-reacts with one non-human primate species, the chimpanzee (Damschroder 2004). Toxicology studies with single and multiple doses of siplizumab were conducted in primate (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, 1 single and 3 repeated dose toxicology studies were conducted in chimpanzees. All animals were administered one (0.143 mg/kg) to three, intravenous (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 recur 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.

1.1.4.4. Human Safety and Tolerability Data

The safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (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.

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 Epstein-Barr virus (EBV)-lymphoproliferative disorder (LPD). In renal transplant and psoriasis patients, a total of 59 SAEs were reported in 47 patients. There was 1 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 fragment crystallizable neonatal receptor (FcRn) (a high-capacity receptor responsible for immunoglobulin G [IgG] homeostasis by recycling/salvage), and (ii) through the complementarity-determining regions (CDRs), 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.

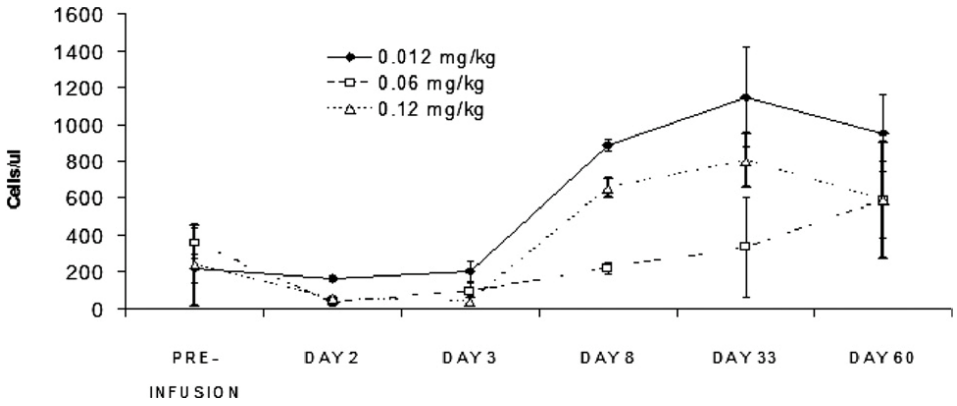
Siplizumab pharmacokinetics in renal transplant patients can be described by a 1-compartment model with 2 parallel mechanisms of clearance, linear and Michaelis-Menten elimination. Siplizumab binds to FcRn receptors in vitro with a half-maximal effective concentration (EC_{50}) of 273.3 nM (0.04 µg/mL). Upon saturation, linear FcRn-mediated recycling and standard IgG clearance dominates as expected. However, at concentrations below ~1.7 µg/mL (Michaelis constant [K_M] EC_{50} 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 ($t_{½}$) 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 $t_{½}$ 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 $t_{½}$ of 14–49 hours and loss of PD activity (rapid lymphocyte recovery) and around Day 8 as illustrated below (Figure 1).

Figure 1: Mean CD3 Lymphocyte Profile Following Siplizumab (MEDI-507) Administration in Study MI-CP027



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

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, 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: Peripheral CD4, CD8, and NK Cell Depletion Following Siplizumab (MEDI-507) Administration in Patients with CD2 Positive T-cell Lymphoma in Study MI-CP099

Regimen and Dose	N	CD4 (%)	CD8 (%)	NK (%)
Multiple Doses Q2 Weeks				
0.6 mg/kg (0.2 mg/kg × 3)	3	88.5	81.3	68.3
1.2 mg/kg (0.4 mg/kg × 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

Abbreviations: CSR = clinical study report; N = subjects; NA = not applicable; NK = natural killer, Q2 = every 2.
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, PK, and PD of escalating doses of siplizumab (TCD601), an anti-CD2 monoclonal antibody, compared to a polyclonal rabbit anti-thymocyte globulin (rATG), as induction therapy in moderate immunologic risk *de novo* renal transplant patients. All subjects will receive the same SoC background immunosuppression.

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 rATG, T-cell depleting induction therapy.

2. OBJECTIVES AND ENDPOINTS

Table 2: Objectives and Related Endpoints

Objectives	Endpoints
Primary	
• To assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of siplizumab compared to rabbit anti-thymocyte globulin (rATG), in *de novo* renal transplant recipients over 12 months post-transplant.	• Adverse events (AEs) • Serious adverse events (SAEs) • Clinically significant changes in clinical chemistry, hematology, vital signs, serology • Siplizumab PK • Immunophenotyping • CD2 receptor occupancy (RO) • Estimated glomerular filtration rate (eGFR) via Modification of Diet in Renal Disease (MDRD) equation • Anti-siplizumab antibodies
Secondary	
• To measure changes in peripheral lymphocyte immunophenotype	• Immunophenotyping via fluorescence-activated cell sorting (FACS)
• To measure the time-course and duration of siplizumab induced lymphocyte depletion and time to recovery	• Lymphocyte counts
• To measure peripheral CD2 RO following siplizumab administration over time	• CD2 RO
• To assess the incidence of treated biopsy-proven acute rejection (tBPAR) over 12 months	• Incidence of tBPAR
• To assess the incidence of treatment-emergent *de novo* donor-specific antibodies (DSA) over 12 months	• *de novo*-DSA/anti-human leukocyte antigen (HLA) antibody measurement
• To assess the incidence of antibody-mediated rejection (AMR) over 12 months	• Incidence of AMR
• To assess renal function via eGFR using MDRD equation at Months 3, 6, and 12 (End of Study [EOS]/ Early Termination [ET])	• eGFR
Exploratory	
• [redacted]	[redacted]
• To assess renal function by treatment [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

3. STUDY DESIGN

3.1. General Overview

This is a 12-month, randomized, controlled, open-label, dose escalation study evaluating safety, tolerability, PK, and PD of siplizumab, an anti-CD2 monoclonal antibody, compared to rabbit polyclonal anti-thymocyte globulin (rATG), as induction therapy in *de novo* renal transplant recipients. All subjects will receive triple regimen 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 40 moderate immunological risk, adult, *de novo* renal transplant candidates will be enrolled in the study.

3.1.1. Screening Period

The screening period is defined as Day -28 to Day -1; Day 0 is defined as the day of transplant/day of first dose of investigational product (IP). If the screening and Day 0 visits occur in close proximity (i.e., within a 24-hour timespan), screening assessments are not required to be repeated.

During the screening period 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 chronic kidney disease [CKD], end stage renal disease [ESRD], and dialysis history) and current medical conditions at screening, a physical examination, vital signs, laboratory assessments, and a pregnancy test (for women of childbearing potential [WOCBP]) 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.

3.1.2. Treatment Period

3.1.2.1. Cohort Assignment/Randomization

Upon confirmation of eligibility for the study, and no later than Day 0, subjects 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 subjects on Day 0, but when logistical considerations prevent this from occurring (e.g., central pharmacy requirements), randomization may occur up to 24 hours pre-transplant.

Eligible subjects will be sequentially assigned to 1 of 4 cohorts (A–D) using a time-lagged dose escalation methodology (see Study Schema). Within each cohort, 10 subjects will be randomized in an 8:2 ratio to receive either siplizumab (Arms 1, 2, 3, or 4) or rATG (Control Arm 5), as shown in Table 3.

Table 3: Dosing Cohorts

Cohort	Arm	Subjects (n)	Product	Dosing Regimen
Cohort A	Arm 1	8	Siplizumab	0.2 mg/kg (Days 0 and 4)
	Control Arm 5	2	rATG	1.5 mg/kg (Day 0, 1, and 2)
Cohort B	Arm 2	8	Siplizumab	0.6 mg/kg (Days 0 and 4)
	Control Arm 5	2	rATG	1.5 mg/kg (Day 0, 1, and 2)
Cohort C	Arm 3	8	Siplizumab	1.7 mg/kg (Days 0 and 4)
	Control Arm 5	2	rATG	1.5 mg/kg (Day 0, 1, and 2)
Cohort D	Arm 4	8	Siplizumab	5.0 mg/kg (Days 0 and 4)
	Control Arm 5	2	rATG	1.5 mg/kg (Day 0, 1, and 2)

3.1.2.2. Investigational Product (IP) Administration (Siplizumab/rATG)

Subjects randomized to receive siplizumab will receive 2 intravenous (IV) doses. The first dose will be administered on Day 0, pre- or intra-operatively, and must be completed prior to revascularization and reperfusion of the allograft. The second dose of siplizumab will be administered on Day 4 post-transplant. Subjects randomized to rATG (Control Arm 5) will receive 1.5 mg/kg IV doses (on Days 0, 1, and 2; for a total of 3 doses), regardless of cohort assignment.

3.1.2.3. Background Immunosuppressive Therapy

Siplizumab and rATG will be combined with concentration-controlled TAC twice daily (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/day prednisone or equivalent until Month 12.

3.1.2.4. Post-Transplant Study Visits

Following transplantation, subjects should be treated post-operatively per SoC 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 study site for weekly study visits, up to and including Week 10, and then monthly through Month 12 or End of Study (EOS; all enrolled subjects will be followed for a minimum of 12 months), as indicated in the Schedule of Assessments (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, or are otherwise considered non-evaluable, will be replaced.

3.2. Dose Escalation Review

A review of all available safety/tolerability (e.g., AEs, SAEs, clinical laboratory assessments, vital signs), PD (immunophenotyping), receptor occupancy, and PK (if available) data will be conducted by ITB-MED and an independent Data Monitoring Committee (DMC) at least 28 days following the last investigational product (IP) administration in the 4th siplizumab-treated subject in each cohort prior to dose escalation to the next dose level cohort. This 28-day

safety period allows sufficient time for subjects to reach full receptor occupancy, maximum PD activity, and for the presentation of acute, drug-related toxicities. See Section 6.2.8 (Dose Escalation Guidelines) for details.

Upon completion of the review by the DMC, if there is no evidence of acute, dose-limiting toxicities (DLTs), the DMC may recommend escalation to the next dose level cohort. Alternatively, a decision to terminate the dosing arm could be reached, or the study could be amended to add additional and/or intermediate dose levels or cohorts below the maximum tolerated dose to further evaluate safety, PK, or PD.

If escalation to the next dose level cohort is recommended by the DMC and opened for enrollment prior to existing dose level cohorts being filled, the IWRS will randomize subjects to either the newly opened dose level cohort or a prior cohort. This will ensure that all cohorts are enrolled to achieve the sample size of 10 subjects (8 siplizumab: 2 placebo).

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

3.3. Safety Stopping Rules

If at any time the observed AEs meet or exceed the a priori defined stopping criteria (safety stopping rules), the study will be placed on hold pending further review from the Sponsor and DMC (Section 9.1.1).

4. STUDY DESIGN RATIONALE

The goal of induction therapy is to prevent acute rejection during the early post-transplant period by providing a high degree of immunosuppression at the time of transplant surgery and 1–2 months thereafter. CD2 represents a unique target for induction considering the broad expression and function in T-cell activation, co-stimulation, and alloantigen recognition. Escalating doses of siplizumab (0.2 mg/kg, 0.6 mg/kg, 1.7 mg/kg, and 5.0 mg/kg) will be administered in place of 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 along with an assessment of safety, tolerability, PK, and PD activity of siplizumab.

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) and is to be completed prior to revascularization and rereperfusion of the allograft to ensure 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 study and the Population PK/PD model may be revised after each dose escalation to predict the concentration-response/exposure-response for the next dose, as appropriate. Overall, the dose 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 an 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 SoC 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 employ an open-label design. This open-label design will not only minimize the risks for subjects during the initial investigation of TCD601 (siplizumab) should the need for rapid intervention arise, such as emergent SAEs, but also avoids the additional difficulties associated with placebo infusions in a 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 of siplizumab, this study will enroll a moderate immunological risk *de novo* patient population who would typically be treated with T-cell depleting induction. This population was selected as 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-IL-2RA therapy (KDIGO 2009), due to the expected overlapping activity with siplizumab, anti-IL-2RA or other T-cell depleting induction (e.g., ATG) will not be allowed in combination with siplizumab. 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 biopsy-proven acute rejection (BPAR) rates of 12.4% and 13.3% for living and deceased donor allografts have been reported, respectively (Tanriover 2015). These rates are similar to those in patients treated with anti-IL-2 induction of 11.7% and 12.4%, respectively, in the same population (Tanriover 2016).

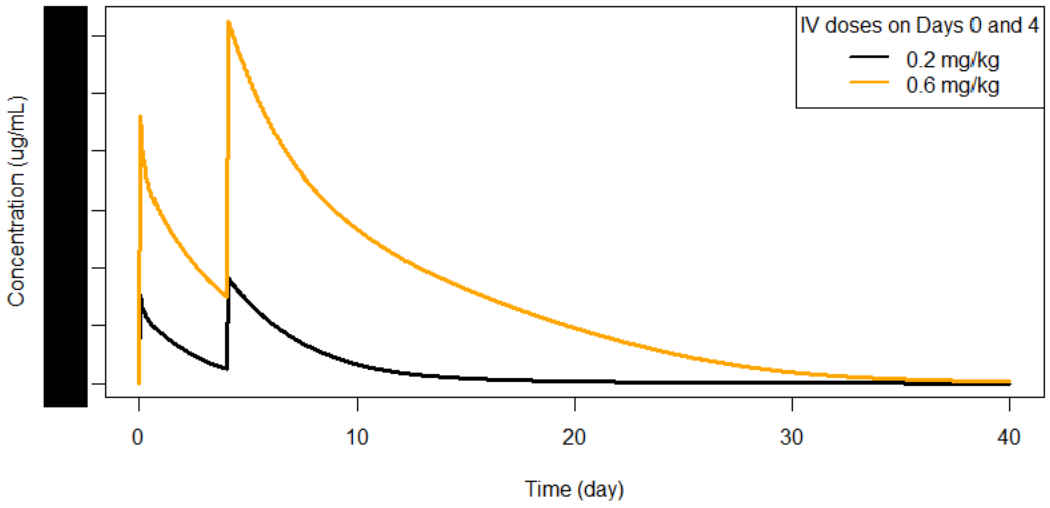
4.1. Dose/Regimen and Treatment Duration Rationale

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) studies in renal transplant, T-cell lymphoma, acute graft-versus-host disease (aGvHD), and patients with psoriasis.

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 elimination.

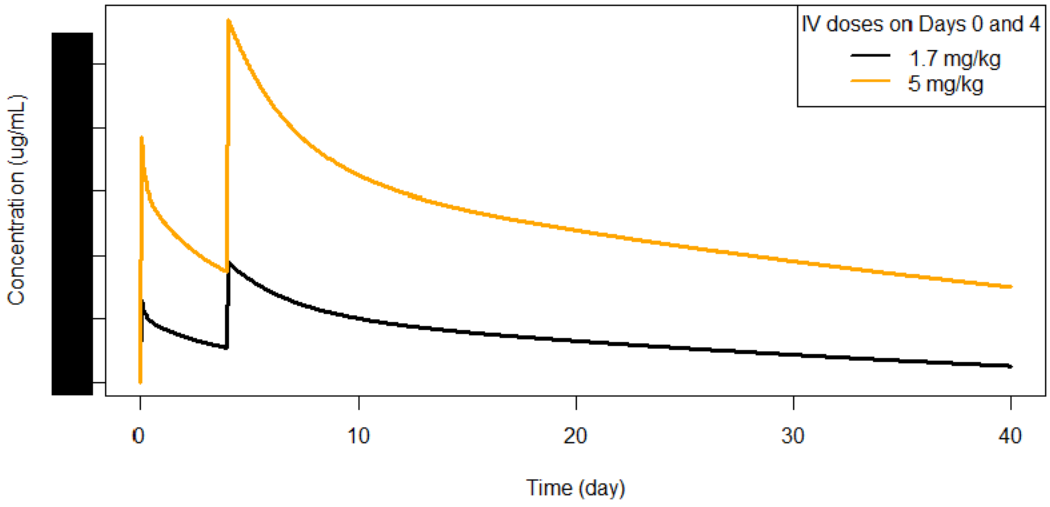
Mean, predicted, time-concentration profiles of the 2-dose regimen planned in renal transplant patients have been simulated and are presented in Figure 2 and Figure 3. Due to the difference in predicted exposure, the 0.2 and 0.6 mg/kg regimens have been plotted separately from the 1.7 and 5.0 mg/kg regimens.

Figure 2: Mean Predicted Serum Concentrations Following Siplizumab Doses of 0.2 and 0.6 mg/kg in Study TCD601B101



Solid curves represent the mean predicted concentration-time profile following 2 simulated siplizumab doses of 0.2 or 0.6 mg/kg on Study Days 0 and 4 in *de novo* renal transplant patients.

Figure 3: Mean Predicted Serum Concentrations Following Siplizumab Doses of 1.7 and 5.0 mg/kg in Study TCD601B101



Solid curves represent the mean predicted concentration-time profile following 2 simulated siplizumab doses of 1.7 or 5.0 mg/kg on Study Days 0 and 4 in *de novo* renal transplant patients.

Siplizumab concentrations are predicted to increase in a dose-proportional manner with mean maximum plasma concentration (C_{max}; peak) concentrations of approximately [redacted] following the second dose of 0.2, 0.6, 1.7 or 5.0 mg/kg on Study Day 4. The apparent PK t½ is predicted to be [redacted] at all doses with concentrations exceeding the TMDD inflection point of [redacted].

Dose escalation in the TCD601B101 study 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 5.0 mg/kg will allow for characterization of the PK/PD profile and investigation of lymphocyte pharmacodynamics. Importantly, all 4 siplizumab doses proposed in this study have been administered to subjects previously with good safety and tolerability, however due to the nature of the renal transplant population, stepwise dose escalation will be employed to ensure subject safety.

The first dose will be administered pre- or intra-operatively and must be completed prior to revascularization and reperfusion of the allograft to ensure both donor and recipient alloreactive T-lymphocytes are rapidly suppressed and depletion is initiated. 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 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 1 µg/mL.

Considering the apparent [redacted] t½ predicted from previous trials with siplizumab (MEDI-507) in renal transplant patients (MI-CP027) and patients with aGvHD (MI-CP046) following bone

marrow transplantation (BMT), 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 2 and Figure 3, it is anticipated that 2 doses of 0.6 mg/kg will result in [redacted] 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 PD 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, it is expected that doses of 1.7 to 5.0 mg/kg will be needed to achieve the PK/PD target. PK/PD modeling planned prior to each dose escalation step will allow for a near real-time exposure-response analysis during the study 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 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 (percent coefficient of variation [CV%] ±3.10) was reported, whereas the ABC for lymph nodes is 8.46 ±11.4% (Shah 2013).

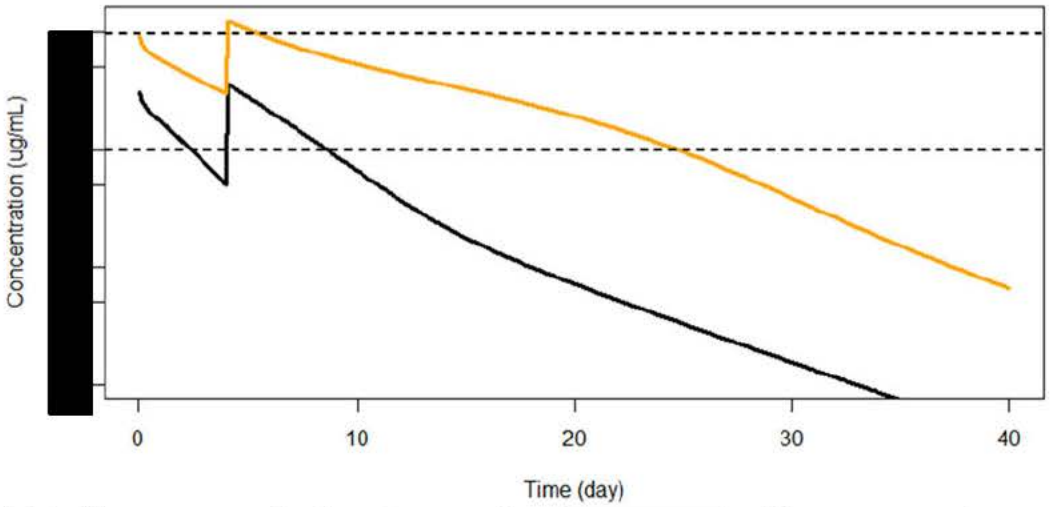
Completed siplizumab (MEDI-507) studies have assessed the effect of anti-CD2 therapy on peripheral lymphocytes and lymphocyte subsets as well as peripheral target saturation and binding. It is expected that administering sufficient siplizumab to achieve adequate exposure in both the peripheral and relevant renal 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] are required for adequate T and NK cell modulation and depletion, target siplizumab trough (C_0) siplizumab concentrations of [redacted] and [redacted] would result in adequate CD2 engagement and lymphocyte suppression in renal tissue and lymph nodes, respectively.

As discussed in Section 1.1.4.5, population pharmacokinetics modeling suggests that concentrations of siplizumab above the K_M of [redacted], which represents the EC_{50} concentration, is necessary to maintain saturation of the TMDD pathway and linear clearance in renal transplant patients. Practically, to maintain full CD2 RO, target engagement and saturation of clearance a target concentration 3–5 fold the K_M ([redacted]) is necessary. This concentration is represented by the inflection point and transition from linear- to non-linear clearance, occurring around the [redacted] concentration range in the simulations. This concentration also represents a key threshold [redacted] for T-cell engagement and depletion, where maintenance of trough concentrations above the threshold in the periphery are expected

for approximately [redacted] following doses of 0.6 to 5.0 mg/kg siplizumab (Figure 4 and Figure 5).

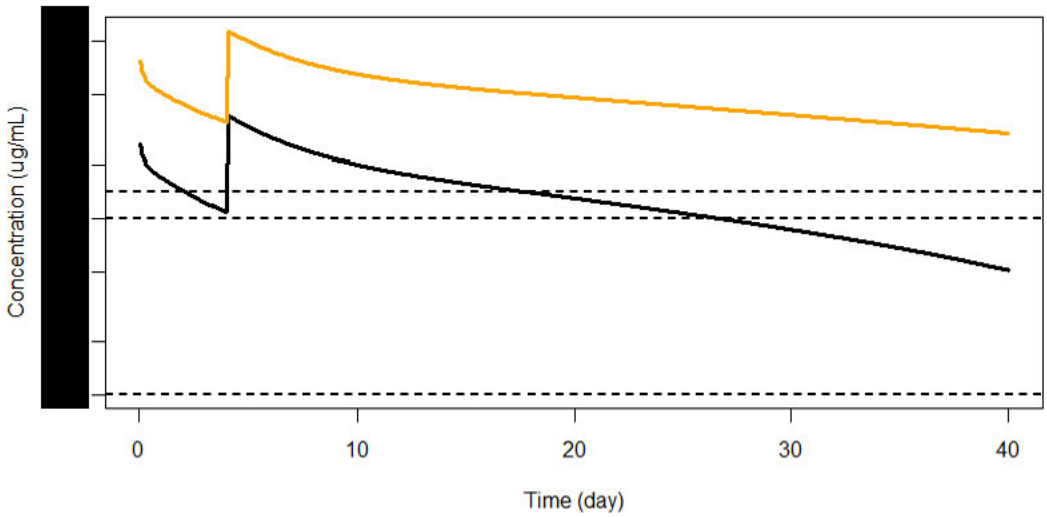
Based on the known variability of siplizumab (MEDI-507) PK, and proposed target tissue concentrations, a mean minimum serum concentration above [redacted] and [redacted] would be required to induce immunomodulatory activity in renal and lymph tissue, respectively. These concentration thresholds are represented as horizontal dashed lines in Figure 4 and Figure 5. It is expected that following the second 0.6 mg/kg dose of siplizumab, only a short duration, measured in hours, above the tissue exposure threshold will be achieved. However, with higher doses, durations of [redacted] could be anticipated.

Figure 4: Mean Predicted, Log-Transformed, Siplizumab Serum Concentrations Following 0.2 and 0.6 mg/kg Siplizumab Administration in Study TCD601B101



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

Figure 5: Mean Predicted, Log-Transformed, Siplizumab Serum Concentrations Following 1.7 or 5.0 mg/kg Siplizumab Administration in Study TCD601B101



Horizontal dashed lines represent predicted trough concentrations at [redacted]. Solid curves represent the mean predicted concentration-time profile of siplizumab (semi-log scale) following 2 simulated 1.7 or 5.0 mg/kg siplizumab doses on Study Days 0 and 4 in *de novo* renal transplant patients.

4.2. Rationale for Active Control

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

ATG is the most frequently used lymphodepleting 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 lymphodepletion, 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 rATG, 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 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 2020), further supporting the restriction to rATG in this clinical study. 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 a 'triple drug regimen' consisting of concentration-controlled TAC, MMF, and CS is the current SoC used in more than 90% of kidney transplants globally. 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. In this study, immediate-release generic or equivalent medications for TAC and MMF are allowed, however, substitution is not permitted for the first 12 months post-transplant. All subjects who start on a brand or a specific generic TAC and MMF should be maintained on the same brand or generic for the duration of this study. TAC will be administered at a dose and frequency that maintains target trough concentrations in a per label range of 4–11 ng/mL. Similarly, MMF will be administered with a target daily dose of 2000 mg, divided BID (see Section 6.4 for further details).

4.4. Risks and Benefits

The risks and benefits of siplizumab in combination with SoC immunosuppression 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. In all subjects, infection risk will be mitigated by following applicable national vaccination guidelines and by use of infection prophylaxis (see Section 6.5). Similarly, the risks of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) will be minimized by following local, national, and international guidelines for immunosuppressed and solid organ transplant patients (see Section 4.4.4). 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.

For further details regarding risks related to siplizumab see Section 7 of the current IB.

It is not expected that treatment with siplizumab will result in any direct benefit to the subject. Subjects randomized to receive siplizumab may incidentally receive the benefit of closer clinical care due to the frequency of study visits and monitoring. Subjects randomized to Control Arm 5 will receive the contemporary SoC with a similar potential benefit of close clinical care during the first year post-transplant. Overall, information gained from this study may help other renal transplant patients in the future.

4.4.1. Risks of 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
- Other hypothetical risks

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

4.4.1.1. Infusion and Inflammatory Reactions and Cytokine Release

Cytokine Release

Cytokine release syndrome (CRS) is an acute clinical syndrome and has been temporally associated with the administration of certain T-cell depleting antibodies, particularly the murine anti-CD3 antibody, muromonab-CD3 (Orthoclone-OKT3). Similar effects are noted with B-cell depleting antibodies such as rituximab (Rituxan). This syndrome has been attributed to the release of cytokines by activated lymphocytes or monocytes.

No severe CRS events have been reported in any subjects receiving siplizumab alone or in combination with other immunosuppressants to date. Siplizumab is a non-activating humanized monoclonal antibody (mAb) that binds to CD2+ immune cells and rapidly eliminates them via ADCC and ADCP. As a result, any CRS events would not be related to direct T cell activation but rather to depletion of CD2-expressing cells. Across all subjects that have received siplizumab, self-limiting infusion reactions have been observed, including fever and chills, which although not meeting the full presentation of CRS could be associated with a milder release of cytokines during ADCC and ADCP.

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 CRS 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.

4.4.1.2. 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 Infection Disease Prophylaxis and Treatment [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 studies with siplizumab there is no clear evidence for a higher rate of infections associated with treatment administration. Infections were common in post-hematopoietic stem cell transplantation (HSCT) patients with Grade 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 patients (MI-CP099), with 5 (26%) patients testing positive for cytomegalovirus (CMV) antigen; 3 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%) 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 4.4.1.3 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 below:

Table 4: Renal Transplantation Pooled Analysis: Opportunistic Infections

Standard or Custom MedDRA Query Preferred Term, n (%)	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)

Abbreviations: CMQ = Custom MedDRA Query; SMQ = Standardized MedDRA Query.

Note: MedDRA Version 22.1.

Source: Table 2.1.5.5 (Listing ADVERSE_EVENTS in CP027 study, Listing AE_LAA in NKD03 study, Listing 16_2_7_1 in ITN036 study.

4.4.1.3. Other Hypothetical Risks

Renal Dysfunction

In 2 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 2 weeks post-transplant and is better described as chimeric transition syndrome (CTS). Patients in these 2 studies 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 with onset around post-transplant Day 10–14 that peaked (range 3.5–15.4 mg/dL) between Days 10–20; resolving by Day 30. Renal biopsies taken during the CTS event were negative for T-cell mediated rejection but showed capillary endothelial injury with cellular infiltrates (CD8+/CD68+ cells) in the peritubular and glomerular capillaries.

Overall, 7/9 (78%) 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 2 remaining patients failed to recover full renal function; this included 1 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 to 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.

Lymphoproliferative Disorders and other Malignancies

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

In patients at a high risk of lymphoproliferative disorders participating in studies with MEDI-507, specifically patients with CD2+ T-cell lymphoma and patients with aGvHD following BMT, EBV-associated 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 (LGL) leukemia (n = 2), cutaneous T-cell lymphoma (n = 1), peripheral T-cell lymphoma (n = 1), and adult T-cell lymphoma (n = 1). One patient with LGL leukemia developed a secondary leukemia (M4 type leukemia) 1 year after completing MEDI-507 therapy. In the GvHD studies EBV-LPD (n = 1), PTLD (n = 1), and EBV-related lymphoma (n = 2) has been reported (4/48 [8.3%] patients). A case of acute myeloid leukemia relapse was also reported. In addition, three cases of LPD have been reported in Investigator-initiated and compassionate use studies of MEDI-507 in patients following BMT.

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).

All of the LPD cases reported with MEDI-507 have been limited to 2 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 2018). In the setting of HSCT, especially in patients who present with multiple risk factors (Curtis 1999, Uhlin 2014), PTLD, rates of 8% up to 40% have been reported (Juvonen 2003). Hence, in the setting of broad T-cell depletion, the reported rates are within the range expected and are not in excess of that anticipated with the use of ATG in the same patient populations.

In the setting of renal transplantation, siplizumab use is not expected to increase the risk of EBV-LPD/PTLD over rATG-based induction in combination with background

immunosuppression. Independent adjudication of all 9 reported 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 as 1.03% (Hart 2020) and as high as high as 2.4% with ATG induction (Thymoglobulin SmPC 2023). The rate of EBV-LPD is known to be higher in patients who are EBV-seronegative with a relative risk up to 33-fold that of EBV+ recipients (Marks 2011). Therefore, all recipients will be screened prior to administration of siplizumab, and EBV-seronegative subjects excluded from participating in the TCD601B101 clinical study. In addition, clinicians who specialize in transplant immunosuppression are aware of the risks for EBV-LPD will be managing patients enrolled in this study. Regular assessments of hematology and EBV-viral load per local practice as well as monitoring of clinical signs and symptoms will be conducted during the 12-month study.

Adjunct Immunosuppression

The combination of escalating doses of siplizumab in the presence of adjunct immuno-suppression 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.

4.4.2. Risks of ATG Induction Therapy

The following summary is taken from the most recent Swedish Medical Products Agency-approved Summary of Product Characteristics (SmPC) and labelling of rATG (Thymoglobulin SmPC 2023). 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 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 (IARs; including Cytokine Release Syndrome [CRS])

Cases consistent with 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 WBC 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 outcomes.

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.

4.4.3. Risks of MMF Concomitant Immunosuppression

The following summary is taken from the most European Medicines Agency (EMA)-approved SmPC and labeling of mycophenolate mofetil (MMF) (CellCept SmPC 2023). For the most recent guidance, refer to the most recently approved local labeling from the appropriate authority.

MMF is a teratogen associated with an increased rate of spontaneous abortion and congenital malformation compared with other immunosuppressants. MMF-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.

WOCBP must be counseled regarding pregnancy prevention and planning. Mycophenolate should not be used in WOCBP unless they are using highly effective contraception. Some local labels for MMF 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 MMF in WOCBP, including use of contraception and wash-out periods following discontinuation of MMF-containing products.

4.4.4. Risks of TAC Concomitant Immunosuppression

The following summary is taken from the most recent Swedish Medical Products Agency-approved SmPC and labeling of TAC (Adoport SmPC 2022). For the most recent guidance, refer to the most recently approved local labeling from the appropriate authority.

Malignant Neoplasms

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

Serious Infections and Reactivation of Pre-Existing Infections

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

Interaction with Other Medication and Herbal Drugs

Inhibitors or inducers of CYP3A4 (e.g., telaprevir, boceprevir, ritonavir, ketoconazole, voriconazole, itraconazole, telithromycin or clarithromycin, rifampicin, rifabutin) should only be co-administered with care. This may result in a change in TAC metabolism and subsequent change in TAC trough level, requiring an adjustment of TAC dose.

Ventricular Hypertrophy and Cardiomyopathies

Ventricular hypertrophy or hypertrophy of the septum, reported as cardiomyopathies, have been observed in patients treated with TAC. Risk factors observed to increase the risk of these clinical conditions included pre-existing heart disease, corticosteroid usage, hypertension, renal or hepatic dysfunction, infections, fluid overload, and edema. Accordingly, high-risk patients receiving substantial immunosuppression should be monitored, using such procedures as echocardiography or electrocardiogram (ECG) pre- and post-transplant (e.g., initially at 3 months and then at 9–12 months).

Use During Pregnancy or Lactation

Use of immunosuppressants, including TAC, is a potential risk to the fetus in utero, and neither pregnancy nor breast-feeding are recommended while receiving TAC.

4.4.5. Risks of SARS-CoV-2 (COVID-19)

The novel coronavirus, SARS-CoV-2, can spread rapidly within healthcare settings and communities and poses a special challenge for organ transplantation. Coronavirus disease 2019 (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 2020). Transmission via droplet spread can occur from both symptomatic and asymptomatic individuals (Arons 2020) and it appears that patients with COVID-19 have the highest viral loads early in the course of their infection. Thus, a reliance on symptom-based screening strategies alone is not sufficient to prevent or diagnose

infection; consideration of symptoms and exposure history, including PCR-based testing per local practice, may be employed.

4.4.6. Risk Mitigation Strategy

With initial administration of any biologic drug, 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 2007). No cytokine release has been detected with IV or s.c. siplizumab (MEDI-507) administration in clinical studies. A mild infusion reaction has been described following the first dose in primates as well as human subjects treated with siplizumab. 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 (paracetamol) and antihistamine (i.e., 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 TCD601B101 study, all subjects will receive premedication prior to each dose of siplizumab to mitigate any infusion reactions.

Safety assessments will include vital signs, physical examinations, clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), AE and SAE monitoring, and PK/PD collections, as outlined in the Schedule of Assessments (Appendix 1).

Infections are a common risk for all transplant recipients. In this study all subjects will be regularly evaluated while hospitalized and following discharge for signs and symptoms which might indicate a severe infection (i.e., fever, nausea, myalgia, headache, arthralgia, chills, diarrhea, stiff neck, and malaise). Appropriate treatment will be administered per local practice. Subjects will be instructed to report any of the aforementioned symptoms to the clinical staff to assure proper assessment and care can be administered in a timely manner. Further, considering the expected immunosuppressive nature of the compound, subjects will be screened for a history of latent infections prior to enrollment. Viral reactivation will be assessed for CMV and BKV according to local practice on a regular basis. Prophylaxis for CMV and *Pneumocystis* pneumonia (PCP) will be administered to all subjects during the study according to local practice. Subjects at-risk for, or with a history of exposure to active/latent tuberculosis (TB) disease, will be assessed per local institutional practice and excluded from participation (exclusion criterion #17) in the study. This assessment will be at the discretion of the Investigator based on subject history and local practice, and in accordance with contemporary local, national, and international guidelines. 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-seronegative subjects will be excluded from participation. EBV viral loads via EBV-PCR will be collected from all subjects throughout the study 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.

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. In addition to vaccination, subjects 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.

Renal function will be assessed frequently post-transplant. Serum creatinine, serum cytokines, and renal injury makers will be measured in the first few weeks post-transplant and thereafter with a focus on renal injury and allograft dysfunction. Changes in renal function will be assessed via serum creatinine and eGFR using Modification of Diet in Renal Disease (MDRD) formula. In the event subjects present with a significant increase in serum creatinine and/or suspected acute rejection, for-cause biopsies are to be performed and collected tissue evaluated according to the standard Banff Classification of Renal Allograft Pathology (Appendix 7). [redacted]

Immunophenotyping via fluorescence-activated cell sorting (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 (Section 11) will review study data and defined stopping criteria (Section 9.1.1) will be employed to protect individual subject safety during the study.

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

5. POPULATION

This multicenter study will be conducted in up to 10 centers in Europe. The study population will consist of approximately 40 male and female *de novo* adult renal transplant patients. The Investigator must ensure that all subjects meet the following eligibility criteria. Subject selection is to be established by checking all inclusion/exclusion criteria at screening and confirming 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-human leukocyte antigen (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.

5.2. Exclusion Criteria

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

1. Transplant recipients seronegative 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 donor-specific antibodies [DSA], recipient of high Kidney Donor Profile Index ≥85 kidney [where assessed]).
7. Subjects with anti-HLA donor-specific antibody as measured by complement-dependent cytotoxicity (CDC) assay, 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.

    For example:

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

    - Liver function chemistries (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP])
    - Bilirubin
    - Coagulation studies (International Normalized Ratio [INR]/prothrombin time [PT], activated partial thromboplastin time [aPTT]).

12. Subjects with any of the following:

    - Hemoglobin (Hgb) <8 mg/dL
    - White blood cell (WBC) count ≤2,000/mm^3
    - Platelet count ≤75,000/mm^3

13. Seropositive for human immunodeficiency virus (HIV) or hepatitis B surface antigen (HBsAg). Subjects who are seropositive 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/hepatitis B core antigen (HBcAg) positive, or HCV.
15. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes (e.g., siplizumab, anti-thymocyte globulin [ATG], tacrolimus [TAC], mycophenolate mofetil [MMF], corticosteroids [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 tuberculosis (TB) infection (after anti-TB treatment, patients with history of latent TB may become eligible according to national guidelines).
18. Subjects with severe systemic infections, current or within the 2 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 childbearing 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 is she considered not of childbearing potential.
    - 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. Withdrawal and period abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) are not acceptable forms of contraception.

    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 is considered not of childbearing potential.

6. TREATMENTS

6.1. Method of Treatment Assignment

Approximately 40 subjects will be sequentially assigned to 1 of 4 cohorts (A–D) using a time-lagged dose escalation methodology (see Study Schema). Within each cohort, 10 subjects will be randomized in an 8:2 ratio to receive either siplizumab (Arms 1, 2, 3, or 4) or rATG (Control Arm 5), as shown in Table 3.

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 Electronic Data Capture (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 for each subject. 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 IP.

6.2. Investigational Product (IP)

6.2.1. Identification of Investigational Product

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

6.2.2. Management of Investigational Product

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

Investigational product must be received at the study site by the Investigator or his/her designee. The Investigator or his/her designee must acknowledge receipt of the IP 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 IP must be stored in an appropriate secure area (e.g., a locked room or a locked refrigerator) and within an adequately monitored 2–8°C refrigerator. Temperature logs must be maintained to document the daily minimum, maximum, and actual temperature to confirm the absence or presence of a temperature excursion. Access to the storage area and/or storage refrigerator must be limited to those persons authorized by the Investigator.

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

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

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

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

  OR

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

6.2.3. Investigational Product Dosing Regimen

The initial siplizumab dose to be investigated will be 0.2 mg/kg (Cohort A/Arm 1) with planned escalation to 0.6, 1.7, and 5.0 mg/kg in subsequent cohorts (see Table 3). Subjects will receive 2 siplizumab IV doses. The first dose will be administered on Day 0, pre- or intra-operatively, and must be completed prior to revascularization and reperfusion of the allograft. The second dose of siplizumab will be administered on Day 4 post-transplant.

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. Subjects may be discontinued from treatment earlier at the discretion of the Investigator or upon request of the subject.

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

6.2.4. Preparation of Siplizumab

As per the treatment assigned upon randomization, the Investigator or his/her designee will obtain the IP to be administered to the subject. The dose of siplizumab must be prepared by and administered either by the Investigator or a 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 (each siplizumab vial contains 60 mg):

$$\textit{Dose (mg)} = \textit{[subject weight (kg)} \times \textit{dose level (mg/kg)]}$$

Example 1:
A subject whose weight is 70 kg in Cohort A (0.2 mg/kg) should receive 14 mg of siplizumab (70 kg × 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 × 0.6 mg/kg = 42 mg) and would require 1 vial of siplizumab.

Example 3:
A subject whose weight is 70 kg in Cohort C (1.7 mg/kg) should receive 119 mg of siplizumab (70 kg × 1.7 mg/kg = 119 mg) and would require 2 vials of siplizumab.

Example 4:
A subject whose weight is 70 kg in Cohort D (5 mg/kg) should receive 350 mg siplizumab (70 kg × 5 mg/kg = 350 mg) and would require 6 vials of siplizumab.

Upon confirmation of subject dose, the product will be prepared from vial(s), using aseptic technique.

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 (using a syringe pump) to the subject by authorized site personnel.

The first dose of siplizumab will be administered on Day 0 over 60 (±5) minutes by IV infusion. The infusion should be administered pre- or intra-operatively and timed so that completion of the infusion is no earlier than 4 hours prior to revascularization and reperfusion 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 dose will be administered by IV infusion over 60 (±5) minutes on Day 4.

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

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 using the same line.

The date, start time, completion time, and volume of siplizumab administration must be recorded in the subject's source documentation and applicable electronic case report form (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 the event 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

The dose levels that may be evaluated during this study are shown in Table 5 below:

Table 5: Provisional Dose Levels

Dose Level	Proposed Daily Dose [a]	Increment From Previous Dose
1	0.2 mg/kg	(starting dose)
2	0.6 mg/kg	½-log
3	1.7 mg/kg	½-log
4	5.0 mg/kg	½-log

Abbreviations: PD = pharmacodynamic(s); PK = pharmacokinetic(s).

a. It is possible for additional and/or intermediate dose levels to be added during the course of the study. Cohorts may be added at any dose level below the maximum tolerated dose 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 (if available) data 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 by ITB-MED and the DMC. This 28-day safety period allows sufficient time for subjects to reach full receptor occupancy, maximum PD 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 IP exposure for dose escalation decisions.

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 DMC.

To ensure 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

- A maximum single dose of 15 mg/kg has been administered in subjects; therefore, this dose will not be exceeded in this study

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 AEs 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
- Administration of an intermediate dose strength between the current and next planned 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 Reactions (SUSARs) and study changes.

6.3. rATG (Standard of Care Control)

6.3.1. rATG 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 3 doses. rATG dose adjustments and/or interruptions for a given subject are not permitted unless warranted (see below). rATG will be administered per applicable local label.

6.3.2. Preparation of rATG

As per the treatment assigned upon randomization, the dose of rATG must be prepared and administered by the Investigator and/or a 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 rATG 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 rATG Infusion

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

Important Note for rATG Administration – Per the Thymoglobulin Data Sheet (Section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction):

- Blood or blood products must not be administered together with Thymoglobulin.

6.3.5. Management of rATG Therapy

Subjects should be monitored for adverse reactions during and after infusion. The total white blood cell (WBC) and platelet counts should be monitored during and after rATG therapy.

The rATG dose should be reduced by one-half if:

- WBC count is between 2,000 and 3,000 cells/mm^3

  OR

- Platelet count is between 50,000 and 75,000 cells/mm^3

rATG treatment may need to be stopped if:

- WBC count falls below 2,000 cells/mm^3

  OR

- Platelet count falls below 50,000 cells/mm^3.

6.4. Background Immunosuppression

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

- Immediate-release TAC as 0.5 mg, 1.0 mg, or 5.0 mg capsules

  Note: If oral administration is not feasible or practical, IV TAC (containing the equivalent of 5 mg/mL TAC) administration by continuous infusion may be substituted per label)

- 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

Not all dosage forms listed are available in each country, dependent on local approval status and regulations. All doses of background immunosuppression medication, along with dose changes during the study, must be recorded with the reason for administration in the

corresponding eCRF, as per the eCRF completion guidelines. At enrollment all subjects must follow the assigned regimen.

The use of immediate-release generic TAC and MMF are permitted in this study. Subjects should remain on the same concomitant immunosuppression medication throughout the duration of the 12-month study (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). 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.

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 6.

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 to keep the subject on study treatment.

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 2000 mg will be administered orally (p.o.) in divided doses (1000 mg per dose) twice a day (BID):

- 2 × 500 mg tablets, or
- 4 × 250 mg capsules, or
- 1000 mg via IV administration (2 × 500 mg vials for IV administration), if oral administration is not feasible. †

† For subjects who remain intubated >24 hours post-transplant and/or are otherwise unable to swallow oral medication, IV MMF may be substituted until oral conversion is possible.

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

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

6.4.2. TAC Administration

TAC will be administered p.o. BID and adjusted to maintain serum trough (C_0) concentrations within the target range of 4–11 ng/mL. If oral administration is not feasible or practical, IV TAC (containing the equivalent of 5 mg/mL TAC) administration by continuous infusion may 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 study, 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 TAC trough concentration falls outside the required target, 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

Corticosteroids should be administered at a minimum of 5.0 mg/day (prednisone or equivalent) from Day 0 until Month 12 per local standard practice in a manner consistent for all subjects enrolled at the site.

6.5. Infectious Disease Prophylaxis and Treatment

Cytomegalovirus (CMV)

CMV prophylaxis, with IV ganciclovir or oral valganciclovir, will be used in subjects (CMV positive and CMV negative) as per local 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 site. 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 permitted and will be administered at the discretion of the Investigator.

BK Polyomavirus

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, or fluconazole) will not be permitted unless subjects are systemically infected since azole antifungal agents may increase blood concentrations of TAC.

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

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 2019).

Vaccination during treatment with siplizumab and prior to clearance of the antibody and PD 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 of any new medications taken after enrollment into the study. All medications, clinically relevant concomitant 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 treatment must be individually assessed against all exclusion criteria/ prohibited medication. If in doubt, the Investigator should contact the ITB-MED Medical Monitor or designee before randomizing a subject or allowing a new medication to be started. If the subject is already enrolled, ITB-MED should be contacted to determine if the subject should continue participation in the study. No other immunosuppressive medications should be administered, other than as permitted per protocol.

† Relevant is defined as: any procedure that is performed due to or to evaluate an AE, to confirm specific medical history, or to provide further information that the Investigator considers relevant, in accordance with his/her own judgement.

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 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 (e.g., sirolimus or everolimus), IVIG, or costimulatory blockade (i.e., belatacept) have not been investigated and may result in overlapping pharmacology. In the event 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 polyomavirus (BKV) screening generally utilizes plasma (or whole blood) viral load (VL) molecular assays. Urine studies (cytology for "decoy cells", BKV DNA, or VP-1 mRNA) are less specific. Decoy cells are shed infected tubular and ureteric epithelial cells with an enlarged nucleus with a large basophilic intranuclear inclusion by urine cytology. Cytology cannot distinguish BKV from adenovirus and false negative tests also occur. A urinary test for BKV (cytology for decoy cells or urine BKV loads over 7-log geq/mL) is adequate for screening; if negative, the risk for polyomavirus-associated nephropathy (PVAN) is low.

Quantitative cutoffs for presumptive diagnosis of BKV nephropathy include plasma DNA VL >10,000 copies/mL (whole blood PCR VL >1500–3500 copies/mL), urine VP1 mRNA load $>6.5 \times 10^5$ copies/ng total RNA, or urine DNA load $>10^7$ copies/mL; higher viral loads are increasingly predictive of PVAN.

World Health Organization (WHO) standards 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 should be managed as per local center practice.

6.7.3. Management of Delayed Graft Function (DGF)

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

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

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

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

DGF treatment will be according to local practice. DGF treatments must maintain sufficient immunological coverage for the graft and may include maintaining, interrupting, or reducing the dose of study treatment and the use of rATG. If a polyclonal antibody or ATG is used prior to Day 4, the IP must be discontinued, and the subject will be placed on SoC per local practice.

6.7.4. Primary Graft Non-Function (PGNF)

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

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

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

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

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

6.8. Prohibited Treatment

Immunosuppressants and induction treatment other than those specified in the protocol are NOT permitted from the signing of informed consent through EOS. 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 TAC levels should be avoided (refer to Appendix 6 and local prescribing information).

6.9. Treatment Exposure and Compliance

Following discharge from the hospital, the Investigator or designee will assure the appropriate amount of concomitant study treatment is dispensed 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 study drugs exactly as prescribed and emphasize that compliance is necessary for the subject's safety and the validity of the study. The subject should be instructed to contact the Investigator if he/she is unable for any reason to take the concomitant study treatment as prescribed.

All drug trough concentrations assessed in this study (siplizumab, TAC) will be measured per the Schedule of Assessments (Appendix 1) 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 IP 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.

7. INFORMED CONSENT PROCEDURES

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), Independent Ethics Committee (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 Council for 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 IEC.

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

8. VISIT ASSESSMENTS

While COVID-19 disease remains a risk, efforts to minimize the time a subject spends indoors at the clinic may be considered. These efforts could include use of virtual or telehealth technology, where appropriate, to remotely capture applicable study data (e.g., overall health status, assessment of medication compliance, review of 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 7 and Study Month 2 is considered to start on Week 5/ Day 28.

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

8.1. Subject Identification

Each subject is identified 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 study. The SID consists of the Site Number (assigned by ITB-MED to the investigative site) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database.

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 eCRF 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 an 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 collected 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 include the examination of the subject's general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen (including spleen and liver), back, lymph nodes, extremities, and vasculature. The examination will also include a thorough neurological evaluation. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

Information for all physical examinations must be included in the source documentation at the study site but are not required to be included in the 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 eCRF that captures medical history. Significant findings discovered after the start of study procedures, which meet the definition, must be recorded as an AE.

8.4.2. Vital Signs

Vital signs include radial pulse rate, blood pressure, and body temperature. Attempts should be made to assess the blood pressure and pulse on the same arm each time of determination and after the subject has rested in the sitting position (may be supine if during hospitalization) for at least 5 minutes. Body temperature should be measured per local practice – the same method should be used consistently for all subjects at each study 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 (Appendix 1). 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.

If a laboratory assessment 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 will be excluded from the study.

The Investigator must document in the source documents the clinical considerations and medical relevance of any values outside 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 AE criteria reported 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/Adverse Event eCRF page as appropriate.

8.4.4.1. Hematology

Hemoglobin, hematocrit, red blood cells (RBCs), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), platelet count, WBCs with differential (percent and absolute).

8.4.4.2. Clinical Chemistry

Albumin, total bilirubin, calcium, creatinine, glucose, phosphorus, magnesium, potassium, ALT, AST, ALP, gamma-glutamyl transferase (GGT), amylase, sodium, uric acid, and urea/blood urea nitrogen (BUN) will be measured.

8.4.4.3. Lipid Panel

Cholesterol, triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (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 WOCBP, at time points designated in the Schedule of Assessments (Appendix 1). A serum or urine pregnancy test must be obtained up to 72 hours prior to the time of transplant and the result must be available and negative prior to administration of IP.

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 WHO EBV international reference standards.

There are currently no consensus guidelines on thresholds for EBV DNAemia or viral load in adult renal transplant recipients, therefore any PCR positive result that is increasing from baseline or a previous assessment 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 6.7.5.

8.4.4.9. Cytomegalovirus (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, 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 BKV per local center practice unless more rigorous testing is required for EBV and CMV monitoring, as noted in Section 8.4.4.8 and Section 8.4.4.9. Results of these assessments are to be recorded in the applicable 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 infections tend 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 WHO 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 2013):

Epstein-Barr virus (EBV) Signs and Symptoms		
Signs:	Pallor Lymphadenopathy Subcutaneous nodules Tonsillar enlargement/inflammation	Hepatosplenomegaly Focal neurologic signs Mass lesions found on imaging obtained for other reasons
Constitutional and systemic symptoms:	Unexplained fever or night sweats Malaise Weight loss and/or anorexia	Sore throat Swollen glands Headache or focal neurological symptoms
Allograft-specific symptoms:	Liver: jaundice, abdominal pain Intestine: abdominal pain, gastrointestinal bleeding, nausea, and vomiting Heart/Lung: shortness of breath, cough, decreased lung function (lung alone) Renal: kidney dysfunction	
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 2013):

Epstein-Barr virus (EBV) Diagnostic Evaluation	
Routine laboratory assessments:	CBC with differential Platelets Serum electrolytes (including BUN/creatinine, calcium) Liver Function Test Uric acid Lactate dehydrogenase Quantitative immunoglobulins EBV serologies (anti-Epstein-Barr nuclear antigen [EBNA], viral capsid antigen [VCA] and early antigen [EA]) EBV viral load from peripheral blood Stool: occult bleeding
Routine procedures:	Chest radiograph (anteroposterior and lateral) CT or PET scan of neck/chest/abdomen/pelvis Core needle or excisional biopsy of lesion(s) with flow cytometry of lymphocytes (when feasible) EBER, CD20 histochemistry studies of pathologic samples
Procedures based on signs and symptoms:	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 (abdomen and allograft)
Laboratory tests:	Serial increase in EBV viral load from peripheral blood

Abbreviations: BUN = blood urea nitrogen; CBC = complete blood count; CT = computed tomography; EBER = Epstein-Barr virus-encoded ribonucleic acid; MRI = magnetic resonance imaging; PET = positron-emission tomography.

Any diagnostic procedures or additional laboratory assessments that result in the diagnosis of EBV-PTLD must be captured in 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. Computed tomography (CT), magnetic resonance imaging (MRI), and/or positron-emission tomography (PET) imaging may be considered for staging and monitoring of biopsy-confirmed PTLD.

8.4.7. Renal Biopsies

Biopsies will be read by the local pathologist according to local practice and scored according to the Banff Classification of Renal Allograft Pathology (Appendix 7). Results of biopsies read by the local pathologist must be recorded in the applicable eCRF.

Preimplantation

Pre-implantation renal biopsies must be collected unless the collection is contraindicated or not possible (e.g., fully robotic-assisted donor nephrectomy). Allograft tissue is to be stored for the purpose of baseline comparison in the event of a for-cause renal biopsy during the course of the study. The immediate processing and histological analysis of pre-implantation renal biopsies is not required.

For-Cause

For all suspected rejection episodes, regardless of initiation of anti-rejection treatment, a renal biopsy must be performed within 48 hours. The results will be used for subject management and assessment of acute rejection (See Section 8.4.8).

Other/Local Practice

Any biopsies performed according to local practice must be recorded in the applicable eCRF.

8.4.8. Treated Biopsy-Proven Acute Rejection (tBPAR)

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 Banff Classification of Renal Allograft Pathology (Appendix 7), including borderline rejections.

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 Adverse Event 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)

Pharmacokinetic samples will be obtained and evaluated in all subjects at all dose levels, as outlined in the Schedule of Assessments (Appendix 1). 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.

The PK parameters listed in Table 6 will be determined using the actual recorded sampling times.

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

8.6. Assessment of Treatment Exposure and Compliance

Pharmacokinetic 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 information 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

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) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

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

- 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 (CRS) 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/mm^3 to <500/mm^3; 0.2 to <0.5 × 10^9/L) considered drug-related as determined by the Investigator.
- Two (2) or more subjects presenting with Grade 3 or higher toxicity considered drug-related (including infusion reactions) as determined by the Investigator, 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 (Section 11). 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., CRS, 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. Subjects should remain in the study, if possible, and receive SoC 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 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 in 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 permitted unless safety findings require communication 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.

For subjects enrolled within the European Union (EU), all biological samples collected at the time of withdrawal but not yet analyzed will not be used unless permitted by applicable law. Sample storage will be according to applicable legal requirements.

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). A subject should not be considered 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 to ensure adequate consideration is given to the protection of the subject's interests. The Investigator will be responsible for informing IECs of the early termination of the study.

9.2. Study Completion

Study completion is defined as when the last subject finishes their final study visit (Month 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 the Month 12/EOS 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

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 version 5.0.

- Relationship to the study treatment

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

- Opportunistic Infections
- Malignancies

10.1.4. SAE Reporting

Every SAE, regardless of causality occurring after the subject has provided informed consent and had at least 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 AESIs, whether serious or not, should also be reported following the same procedure.

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

Information on all SAEs (either initial or follow up) occurring with Investigational Medicinal Products (IMPs) and Auxiliary Medicinal Products (AxMPs) is collected and entered in the eCRF(s). If necessary, relevant safety information on AxMPs may be addressed in the Annual Safety Report (ASR) of the IMP. 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 its 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 (DMC)

This study will include a Data Monitoring Committee (DMC), which will function independently of all other individuals associated with the conduct of this clinical study, including the participating site investigators. The DMC will convene as described in the DMC Charter to conduct ongoing review of cumulative PK, PD, and safety data (including DLTs, AEs, SAEs, EBV viral load, PTLD surveillance results, clinical laboratory assessments, and ad hoc imaging). The DMC will make recommendations to ITB-MED with regard to dose escalation, as well as modification or termination of the study.

Specific details regarding composition, responsibilities, data monitoring, meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter 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 to which they have been assigned during the randomization procedure.

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

The PK Analysis Set will include all subjects who received any study drug with at least 1 available valid PK concentration measurement (i.e., not flagged for exclusion), and experienced no protocol deviations with relevant impact on PK data.

The PD Analysis Set will include all subjects in the FAS with available PD data and no protocol deviations with relevant impact on PD data. Summary statistics will also be provided such as mean, standard deviation (SD), median, minimum, and maximum by treatment and visit/time for all PD and biomarker data.

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

12.2. Baseline

Baseline is defined as the last observation before the first study treatment administration. Baseline for renal function analysis will be based on the nadir post-transplant serum creatinine.

12.3. Subject Demographics and Other Baseline Characteristics

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

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 evaluations, transplant history, donor characteristics (e.g., age, sex, race, type, cold ischemia time [CIT]), and any other relevant information.

Summary statistics will be presented for the subjects in the FAS. Continuous variables will be presented with mean, SD, median, 25th percentile, 75th percentile, minimum, 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).

12.4. Treatments

The duration (days) of IP administration will be summarized. This will be calculated by subtracting the date of the last administration of IP 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 IP 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 IP for any reason.

The number and percentage of subjects who prematurely discontinued IP 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.

12.4.1. Concomitant Immunosuppressants

The average daily dose of administered TAC, MMF, and CS will be summarized by treatment arm. The dose of the induction agent will be summarized for each of the days when it was administered. TAC exposure will be summarized by trough concentration and visit.

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

12.4.2. Other Co-Medications

Concomitant medications, other than immunosuppressants and CS mentioned above, will be summarized by therapeutic class and Preferred Term (PT) and presented by treatment with the number and percentage of subjects using each concomitant medication.

12.5. Analysis of the Primary Endpoint(s)

12.5.1. Definition of Primary Endpoint(s)

All safety data, including AEs, SAEs, clinically significant changes in clinical chemistry, hematology, vital signs, and serology, as well as siplizumab PK, immunophenotyping, CD2 receptor occupancy, eGFR, and anti-siplizumab antibodies are considered primary endpoints.

Pharmacokinetics, anti-siplizumab antibodies, and CD2 receptor occupancy and PD (immunophenotyping) will be summarized by treatment and visit as described in Section 12.5.5, Section 12.5.2.4, and Section 12.6.1, respectively.

12.5.2. Safety Endpoints

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

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

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

12.5.2.1. Adverse Events

All information obtained on AEs will be displayed by treatment and subject.

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

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

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

The number (and proportion) of subjects with adverse events of special interest (AESIs)/related to identified and potential risks (i.e., serious infections, opportunistic infections, CRS, malignancies) will be summarized by treatment.

Multiple Occurrences for Tables

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

Adverse events will be listed by subject, including the verbatim term given by the Investigator, the PT and SOC given by the MedDRA dictionary, start and end date, causality, grade, and relationship to study drug as assessed by the Investigator.

Adverse events which will be counted for the treatment period are those which are treatment-emergent (i.e., TEAEs). 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.

12.5.2.2. 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.

12.5.2.3. Clinical Laboratory Evaluations

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

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

Estimated GFR Using the MDRD Formula

Renal function as assessed by eGFR (MDRD formula) will be evaluated at Months 3, 6, and 12 (EOS/ET) by comparing the mean eGFR values between groups.

12.5.2.4. Immunogenicity

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

12.5.2.5. Other Safety Evaluations

BKV Viremia and Nephropathy

The following variables will be analyzed descriptively:

- Occurrence of BKV viremia any time post-transplantation
- Occurrence of BKV 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, median, minimum, and maximum as well as change from baseline/previous assessment including shift tables will be provided by treatment and visit/time.

12.5.3. Statistical Model, Hypothesis, and Method of Analysis

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

12.5.4. Handling of Missing Values/Censoring/Discontinuations

The analysis will be performed using the FAS. 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 the Schedule of Assessments (Appendix 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.

12.5.5. Pharmacokinetics

Siplizumab concentrations will be determined by a validated enzyme-linked immunosorbent assay (ELISA) method.

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 quantitation (LLOQ). Concentrations below the LLOQ will be reported as “zero” and missing data will be labeled as such in the Bioanalytical Data Report.

Summary statistics will include mean (arithmetic and geometric), SD, coefficient of variation (CV; arithmetic and geometric), median, minimum, and maximum. The anticipated LLOQ is 10 ng/mL and concentrations expressed in mass per volume units. 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.

If data permit, PK parameters in Table 6 will be calculated and listed by treatment and subject. Concentrations below the limit of quantification (BLQ) will not be considered for the calculation of PK parameters. Descriptive summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is time to reach maximum observed concentration (T_{max}), where median, minimum, and maximum will be presented.

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

Table 6: Non-Compartmental Pharmacokinetic Parameters

PK Parameter	Definition
AUC_{last}	Area under the concentration-time curve (AUC) from time zero to the last measurable concentration sampling time (t_{last}) (mass × time × volume^{-1})
AUC_{inf}	AUC from time zero to infinity (mass × time × volume^{-1})
AUC_{tau}	AUC calculated to the end of a dosing interval (tau) at steady-state (amount × time × volume^{-1})
C_{max}	Maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass × volume^{-1})
T_{max}	Time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
Lambda_z (λ_z)	Smallest (slowest) disposition (hybrid) rate constant (time^{-1}) may also be used for terminal elimination rate constant (time^{-1})
$t_{½}$	Elimination half-life associated with the terminal slope (λ_z) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives
CL/F	Total body clearance of drug from the plasma (volume × time^{-1})
V_Z/F	Apparent volume of distribution during terminal phase (associated with λ_z) (volume)

The linear trapezoidal rule will be used for AUC calculation. Regression analysis of the terminal plasma elimination phase for the determination of $t_{½}$ will include at least 3 data points after C_{max}. If the adjusted coefficient of determination (R^2) value of the regression analysis of the terminal phase will be less than 0.75, no values will be reported for $t_{½}$, AUC_{inf}, and CL/F.

12.5.6. 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: population pharmacokinetics will be followed.

12.6. Analysis of Secondary Endpoints

12.6.1. Efficacy and/or Pharmacodynamic Endpoint(s)

Immunophenotyping

The magnitude and duration of PD effect of siplizumab will be characterized by measuring the changes in peripheral lymphocyte immunophenotype, including all subsets of T-, B-, and NK-cells. This data will be summarized by treatment.

Lymphocyte Counts

The time-course and duration of siplizumab-induced lymphocyte depletion and time to recovery will be characterized by measuring the changes in circulating leukocytes and T cells over time. This data will be summarized by treatment.

Biomarkers

All biomarker data (e.g., renal injury markers, cytokine data, CD2 RO) will be listed by treatment, subject, and visit/time. Summary statistics will be provided (mean, SD, median, minimum, maximum) by treatment and visit/time.

In the summary tables, the frequency (n, %) of values below the LLOQ and above the upper limit of quantitation (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.

Treated Biopsy-Proven Acute Rejection

The incidence of tBPAR over 12 months will be summarized by treatment.

Donor-Specific Antibodies

The incidence of antibody-mediated rejection (AMR) over 12 months will be summarized by treatment.

Renal Function

The changes in renal function over time, as measured by eGFR (MDRD formula) will be summarized by treatment.

12.7. Analysis of Exploratory Endpoints

[redacted]

12.8. Interim Analysis

No formal interim analysis is planned, although 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.

12.9. 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 utilizing robust data management standards.

13.2. Investigator Responsibilities

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

Before initiating a study, the Investigator/institution must obtain approval/favorable opinion from the IEC for the study 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 provide access to all relevant data and records to ITB-MED monitors, auditors, ITB-MED Quality Assurance representatives, designated agents of ITB-MED, IECs, and regulatory authorities as required.

If an inspection of the study 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 to 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 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. 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 received training.

The Investigator/designee is responsible for assuring 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, accuracy of data capture/data entry, the adherence to the protocol and GCP, progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits. Continuous remote monitoring of each site's data may be performed by ITB-MED or its designee.

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

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

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

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

In keeping with GCP 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 designee 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, study procedures, and data to be collected on study subjects. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case-by-case basis. Under no circumstances, including incidental collection, is an investigator permitted to collect additional data or conduct additional procedures for any purpose involving the 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 subjects.

Investigators should exercise due diligence to avoid protocol deviations; however, should a deviation occur, the Principal Investigator or 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, the deviation must be considered a protocol amendment, and unless such an amendment is agreed upon by ITB-MED and approved by the 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 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 IEC per the 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 IP 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, and with the ethical principles laid down in the Declaration of Helsinki.

Personal data collection, storage, protection, and record keeping will be conducted according to applicable local regulations (e.g., General Data Protection Regulation).

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 study will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the ITB-MED clinical study results website and all required Health Authority websites (e.g., clinicaltrials.gov, EudraCT, etc.).

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16. APPENDICES

APPENDIX 1. SCHEDULE OF ASSESSMENTS (SOA)

SOA: Screening through Day 4

Period	Screening	Study Treatment Period										
		Day of Transplant										
Visit	V1	V2				V3	V4	V5	V6			
Day	D-28 to -1 [a]	D0				D1	D2	D3	D4			
Hour (PK Collection)		Pre	1	3	6	24			Pre	1	3	6
Permitted Window (±minutes)		---	±10	±30	±30	±60			---	±10	±30	±30
General/Safety Assessments												
Informed consent	✓											
Inclusion/Exclusion	✓	✓†										
Demographics	✓											
Medical history ‡	✓											
Physical examination	SD											
Vital signs [b]	✓			✓[b]		✓	✓				✓[b]	
Height (at screening) and weight [b]	✓	✓[b]				✓[b]	✓[b]		✓[b]			
Prior and ConMeds	✓	←										→
Adverse Events	✓	←										→
Local Laboratory Assessments												
High-Res HLA/ABO typing (D&R) [c]	✓											
Lymphocyte/CDC crossmatch [c]	✓											
Panel reactive antibodies (CDC/Flow) [c]	✓											
HIV, HBsAg, HCV serology (D&R) [d]	✓											
CMV, EBV (D&R), BKV testing [d]	✓											
Chemistry & hematology panels [e]	✓			✓		✓	✓	✓			✓	
Differential leukocyte count	✓											
aPTT, INR/PT	✓											
Lipid panel	✓											
Serum or urine pregnancy testing [f]	✓											
Donor-specific antibodies (DSA) [g]	✓											
TAC trough levels [h]		✓				✓						
Study Treatment Regimen												
Subject randomization		✓										
Kidney transplant procedure				✓								
Siplizumab dosing (Arms 1,2,3,4) [i]				✓							✓	
rATG dosing (Control Arm 5) [i]				✓		✓	✓					
MMF/TAC/Corticosteroid admin. [j]		←										→
TMP/SMX (prophylaxis) [k]		←										→
Disease Monitoring												
Renal biopsy [l]				✓		← as needed (for-cause) →						
Central Laboratory Assessments												
PK assay validation (biobank sample)	✓											
Siplizumab PK sampling [m]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Anti-siplizumab antibodies		✓										
Mechanistic Studies												
Lymphocyte CD2 receptor occupancy [n]		✓	✓	✓	✓	✓			✓	✓	✓	✓
Immunophenotyping (FACS) [o]		✓[o]				✓	✓	✓	✓[o]			
Exploratory Analysis												
Renal injury markers [p]							✓					
Serum cytokine assessments [q]		✓	✓	✓	✓	✓		✓	✓	✓	✓	✓
EBV-PCR surveillance [r]		✓										

SOA: Day 5 through Day 70/Week 10

Period	Study Treatment Period										
Visit	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17
Week			W2	W3	W4	W5	W6	W7	W8	W9	W10
Day	D5	D7	D14	D21	D28	D35	D42	D49	D56	D63	D70
Permitted Window (±days)	---	---	±2 days						±3 days		
General/Safety Assessments											
Physical examination		SD			SD						
Vital signs [b]		✓	✓		✓						
Height (at screening) and weight [b]		✓									
Prior and ConMeds	←	—	—	—	—	—	—	—	—	—	→
Adverse Events	←	—	—	—	—	—	—	—	—	—	→
Local Laboratory Assessments											
CMV, EBV (D&R), BKV testing [d]					✓						
Chemistry & hematology panels [e]	✓	✓	✓		✓		✓		✓		✓
Differential leukocyte count					✓						
Dipstick urinalysis					✓						
Serum or urine pregnancy testing [f]					A/SD				A/SD		
Donor-specific antibodies (DSA) [g]					✓						
TAC trough levels [h]		✓	✓	✓	✓						
Study Treatment Regimen											
MMF/TAC/Corticosteroid admin. [j]	←	—	—	—	—	—	—	—	—	—	→
TMP/SMX (prophylaxis) [k]	←	—	—	—	—	—	—	—	—	—	→
Disease Monitoring											
Renal biopsy [l]	←	—	—	—	—	—	as needed (for-cause)	—	—	—	→
Central Laboratory Assessments											
Siplizumab PK sampling [m]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Anti-siplizumab antibodies					✓				✓		
Mechanistic Studies											
Lymphocyte CD2 receptor occupancy [n]											✓
Immunophenotyping (FACS) [o]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Exploratory Analysis											
Renal injury markers [p]		✓	✓		✓						
Serum cytokine assessments [q]	✓										
EBV-PCR surveillance [r]			✓		✓		✓		✓		✓

SOA: Day 84/Week 12 through Day 336/Week 48

Period	Study Treatment Period									EOS/ET
Visit	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**
Month	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**
Week	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**
Day	**D84**	**D112**	**D140**	**D168**	**D196**	**D224**	**D252**	**D280**	**D308**	**D336**
Permitted Window (±days)	±7 days									
General/Safety Assessments										
Physical examination	**SD**			**SD**						**SD**
Vital signs [b]	✓			✓						✓
Height (at screening) and weight [b]	✓			✓						✓
Prior and ConMeds	◄	—	—	—	—	—	—	—	—	►
Adverse Events	◄	—	—	—	—	—	—	—	—	►
Local Laboratory Assessments										
CMV, EBV (D&R), BKV testing [d]	✓			✓			✓			✓
Chemistry & hematology panels [e]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Differential leukocyte count	✓			✓			✓			✓
aPTT, INR/PT										✓
Lipid panel				✓						✓
Dipstick urinalysis	✓			✓			✓			✓
Serum or urine pregnancy testing [f]	✓	**A/SD**	**A/SD**	✓	**A/SD**	**A/SD**	✓	**A/SD**	**A/SD**	✓
Donor-specific antibodies (DSA) [g]	✓			✓			✓			✓
TAC trough levels [h]	✓			✓						✓
Study Treatment Regimen										
MMF/TAC/Corticosteroid admin. [j]	◄	—	—	—	—	—	—	—	—	►
TMP/SMX (prophylaxis) [k]	◄	—	—	—						
Disease Monitoring										
Renal biopsy [l]	◄	—	—	—	as needed (for-cause)	—	—	—	—	►
Central Laboratory Assessments										
Siplizumab PK sampling [m]	✓									
Anti-siplizumab antibodies	✓			✓						✓
Mechanistic Studies										
Lymphocyte CD2 receptor occupancy [n]	✓	✓	✓	✓	✓	✓	✓			
Immunophenotyping (FACS) [o]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Exploratory Analysis										
Renal injury markers [p]	✓			✓						✓
EBV-PCR surveillance [r]	✓	✓	✓	✓		✓		✓		✓

SOA: Abbreviations and Footnotes

Abbreviations: A = Austria; aPTT = activated partial thromboplastin time; BKV = BK polyomavirus; CDC = complement-dependent cytotoxicity; CMV = cytomegalovirus; ConMeds = concomitant medications; D = day; D&R = donor and recipient; DSA = donor-specific antibodies; EBV = Epstein-Barr virus; EOS = End of Study; ET = early termination; FACS = fluorescence-activated cell sorting; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; INR = International Normalized Ratio; M = month; MMF = mycophenolate mofetil; PCR = polymerase chain reaction; PK = pharmacokinetic(s); Pre = pre-dose; PT = prothrombin time; rATG = rabbit anti-thymocyte globulin; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD = noted in source document; TAC = tacrolimus; TMP/SMX = trimethoprim/sulfamethoxazole; V = visit; W = week.

† Eligibility must also be confirmed on Day 0 prior to randomization and treatment.

‡ Medical history, including disease and procedure background for recipient/donor.

a. All screening procedures may occur on the day of transplant for deceased donors.

b. Vitals collected pre-dose, immediately following the end of infusion, and 6 hours after completion of infusion with siplizumab or rATG. Other time points captured as indicated. Weight is captured pre-dose on Day 0 and Day 4 for siplizumab-treated subjects and on Days 0, 1, and 2 for rATG.

c. Results obtained within the past 6 months acceptable; panel reactive antibodies (PRAs) when available.

d. Results obtained within the past 6 months are acceptable for the initial assessment of EBV (donor and recipient) and CMV; serological testing for BKV is not required at screening (BKV monitoring post-transplant will be performed per local center practice). EBV, CMV, and BKV viral testing via PCR should be conducted thereafter.

e. Daily while in hospital, thereafter as noted above; see protocol for panel analytes.
NOTE: Screening urinalysis not required for anuric recipients.

f. A negative pregnancy test must be available prior to randomization. Assessments designated with A/SD are to be conducted in Austria only and may be documented in source.

g. DSA collected as noted, 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. **Subjects randomized to siplizumab:** First dose administered pre- or intra-operatively, infused over 60 (±5) minutes, and timed so that completion of the infusion is no earlier than 4 hours prior to revascularization and reperfusion of the allograft. The Day 4 dose should be infused over 60 (±5) minutes, between 08:00 and 10:00 to facilitate future sample collections/visits.
Subjects randomized to rATG control: Administration will occur on Day 0, Day 1, and Day 2, per standard of care.
Important Note for rATG Administration – Per the Thymoglobuline Data Sheet (Section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction):
   - Blood or blood products must not be administered together with Thymoglobuline.

j. Must be started within 24 hours post-transplantation.

k. CMV/*Pneumocystis* prophylaxis per local medical practice.

l. Pre-implantation biopsy on Day 0; for-cause and/or protocol biopsies as indicated, per local practice (see Section 8.4.7).

m. Siplizumab PK sampling: All post-dose sample collections are relative to the START time of the infusion.
   - Day 0 dosing (pre-dose; and at 1, 3, 6, and 24 hours post-dose) and Day 4 dosing (pre-dose; and at 1, 3, and 6 hours post-dose).
   - Post-operative Days 2, 3, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, and 84.

n. CD2 receptor occupancy 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. All post-dose sample collections are relative to the START time of the infusion.
   - Day 0 dosing (pre-dose; and at 1, 3, 6, and 24 hours post-dose) and Day 4 dosing (pre-dose; and at 1, 3, and 6 hours post-dose).
   - An additional sample is to be collected on Day 5.

r. Blinded EBV surveillance will be conducted bi-weekly through Month 3; monthly through Month 6; thereafter, bi-monthly though EOS.

APPENDIX 2. AMENDMENT NO. 01 – SUMMARY OF CHANGES

[Appendix removed]

APPENDIX 3. INVESTIGATOR AGREEMENT PAGE

INVESTIGATOR AGREEMENT

Protocol Number: TCD601B101

Version: 3.0

I have read the Investigator's Brochure and protocol TCD601B101, "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

Appendix 4. US-SPECIFIC CELLCEPT® PREGNANCY AND SAFETY INFORMATION

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

- Use of CellCept® during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney.
- Females of reproductive potential must be made aware of the increased risk of first trimester pregnancy loss and congenital malformations with MMF products and must be counseled regarding pregnancy prevention and planning.
- For those females using Cellcept® at any time during pregnancy and those becoming pregnant within 6 weeks of discontinuing therapy, the Investigator or healthcare practitioner should report the pregnancy to the Mycophenolate Pregnancy Registry (1-800-617-8191). The Investigator or healthcare practitioner should strongly encourage the subject to enroll in the pregnancy registry.
- Risks and benefits of CellCept® should be discussed with the subject. When appropriate, consider alternative immunosuppressants with less potential for embryofetal toxicity. In certain situations, the subject and her healthcare practitioner may decide that the maternal benefits outweigh the risks to the fetus. If this drug is used during pregnancy, or if the subject becomes pregnant while taking this drug, the subject should be apprised of the potential hazard to the fetus.
- To prevent unplanned exposure during pregnancy, females of reproductive potential should have a serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL immediately before starting CellCept®. Another pregnancy test with the same sensitivity should be done 8 to 10 days later. Repeat pregnancy tests should be performed during routine follow-up visits. Results of all pregnancy tests should be discussed with the subject.
- Females of reproductive potential taking CellCept® must receive contraceptive counseling and use acceptable contraception. 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 Mycophenolate (MMF) [a]			
Option 1			
Methods to Use Alone Most effective: Less than 1 pregnancy per 100 women in 1 year	Intrauterine device (IUD) Tubal sterilization Patient's partner had a vasectomy		
OR			
Option 2			
Choose 1 Hormonal Method AND 1 Barrier Method 4–7 pregnancies per 100 women in 1 year	**Hormone Methods** choose 1 **Estrogen and Progesterone** Oral contraceptive pill Transdermal patch Vaginal ring **Progesterone-only** Injection Implant	**AND**	**Barrier Methods** choose 1 Diaphragm with spermicide Cervical cap with spermicide Contraceptive sponge Male condom Female condom
OR			
Option 3			
Choose 1 Barrier Method From Each Column (*must choose 2 methods*) Least effective: 13 or more pregnancies per 100 women in 1 year	**Barrier Methods** choose 1 Diaphragm with spermicide Cervical cap with spermicide Contraceptive sponge	**AND**	**Barrier Methods** choose 1 Male condom Female condom

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

APPENDIX 5. GUIDELINES FOR MMF DOSE REDUCTION

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

Dose Reduction or Temporary Interruption May Be Performed for MMF

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

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

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

APPENDIX 6. TACROLIMUS DRUG-DRUG INTERACTIONS

Please refer to the most recent national Prescribing Information for current labeling recommendations.

Drug Interactions

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

Drugs That May Alter Tacrolimus Concentrations

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

Drugs That May Increase Tacrolimus Blood Concentrations [a]

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

a. This table is not all-inclusive.

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

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

Drugs That May Decrease Tacrolimus Blood Concentrations [a]

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

a. This table is not all inclusive.

St. John's Wort (Hypericum perforatum) induces CYP3A4 and P-glycoprotein. Since TAC is a substrate for CYP3A4, there is the potential that the use of St. John's Wort in 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 area under the concentration-time curve (AUC) and a 10% decrease in the mean TAC maximum plasma concentration (C_{max}) relative to TAC administration alone.

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

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

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

Other Drug Interactions

Immunosuppressants may affect vaccination. Therefore, during treatment with TAC, vaccination may be less effective. The use of live vaccines should be avoided; live vaccines may include, but are not limited to measles, mumps, rubella, oral polio, Bacillus Calmette-Guérin (BCG), yellow fever, and TY 21a typhoid (Prograf® Prescribing Information 2023).

APPENDIX 7. BANFF CLASSIFICATION

Category 1: Normal biopsy or nonspecific changes

Category 2: Antibody-mediated changes

Active Antibody-Mediated Rejection (ABMR):

All 3 features must be present for diagnosis. Biopsies showing histological features plus evidence of current/recent antibody interaction with vascular endothelium or donor-specific antibody (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 (glomerulitis [g] >0 in the absence of recurrent or *de novo* glomerulonephritis, and/or peritubular capillaritis [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 immunofluorescence [IF] on frozen sections or C4d >0 by immunohistochemistry [IHC] on paraffin sections)
   - At least moderate microvascular inflammation ([g + ptc] ≥2), although in the presence of acute T-cell mediated rejection (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 (human leukocyte antigen [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 3 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 4 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:**[1]
  Mild to moderate intimal arteritis (v1) with or without interstitial inflammation and tubulitis

- **Grade IIB:**[1]
  Severe intimal arteritis (v2), with or without interstitial inflammation and/or tubulitis

- **Grade III:**[1]
  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:**[1]
  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

Abbreviations: 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 2018, Roufosse 2018).