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

Protocol Number: TCD601A201

STATISTICAL ANALYSIS PLAN

Sponsor:	ITB-MED
Clinical Phase	2a
Statistical Analysis：	TCM Groups, Inc.
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LIST OF ABBREVIATIONS

Abbreviation	Definition
ABO	major human blood group system (Type A, Type B, Type O)
AE	adverse event
AESI	adverse event of special interest
aGvHD	acute graft-versus-host disease
aPTT	activated partial thromboplastin time
BID	twice a day/twice daily
BMCI	bone marrow cell infusion
BMI	body mass index
BPAR	biopsy-proven acute rejection
BUN	blood urea nitrogen
CBC	complete blood count
CDC	complement-dependent cytotoxicity
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMV	cytomegalovirus
COVID-19	coronavirus disease 2019
CP	cyclophosphamide
CRS	chimeric release syndrome
CS	corticosteroids
CsA	cyclosporine
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTS	chimeric transition syndrome
DGF	delayed graft function
DMC	Data Monitoring Committee
DSA	donor-specific antibodies
EBV	Epstein-Barr virus
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOS	End of Study
ESRD	end stage renal disease
FACS	fluorescence-activated cell sorter
FAS	Full Analysis Set
GCP	Good Clinical Practice
GI	gastrointestinal
GvHD	graft-versus-host disease
HLA	human leukocyte antigen
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Abbreviation	Definition
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	Intravenous(ly)
IVIG	intravenous immunoglobulin
LLOQ	lower limit of quantitation
LOCF	last-observation-carried-forward
LPD	lymphoproliferative disorder
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MFI	median fluorescence intensity
MHC	major histocompatibility complex
MMF	mycophenolate mofetil
MPA	mycophenolic acid
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NMA	non-myeloablative
NODAT	new onset diabetes post-transplant
PCP	Pneumocystis jirovecii (Pneumocystis carinii) pneumonia
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PGNF	primary graft non-function
PO	orally
PRA	panel reactive antibodies
PT	Preferred Term
PT	prothrombin time
PTLD	post-transplant lymphoproliferative disorder
PTT	partial prothrombin time
RIC	reduced intensity conditioning
RNA	ribonucleic acid
SAB	single antigen bead
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
sCr	serum creatinine
SD	standard deviation
SID	subject identification number
SMAC	supramolecular activation cluster
SMQ	standardized MedDRA query
SMZ-TMP	sulfamethoxazole and trimethoprim
SoC	standard of care
SOC	System Organ Class

Abbreviation	Definition
SOP	standard operating procedure
TAC	tacrolimus
TB	tuberculosis
TBI	total body irradiation
TCMR	T cell-mediated rejection
TEAE	treatment-emergent adverse event
TMA	thrombotic microangiopathy
TSH	thyroid-stimulating hormone
ULOQ	upper limit of quantitation
US	United States
VL	viral load
VNTR	variable number tandem repeats
WBC	white blood cell(s)
WHO	World Health Organization
WOCBP	women of childbearing potential

1 INTRODUCTION

This statistical analysis plan (SAP) is based on Protocol TCD601A201, Version 3.0 dated 18-Jul-2024.

The purpose of this document is to provide details on the analysis populations and on derivation of the variables, handling of missing data, as well as detailing the statistical methodologies to be used to analyze the safety and efficacy data for the final analysis.

Specifications for tables, figures, and listings are contained in a separate document. Unless otherwise stated with reasoning, the methods discussed in this SAP are the ones outlined in the Protocol. The final clinical study report (CSR) will discuss deviations from the final SAP, if any.

This SAP is written in compliance with the ICH E3 (Structure and Content of Clinical Study Reports) [1] and ICH E9 (Statistical Principles for Clinical Trials) [2] published by the International Coordination of Technical Requirements for the Registration of Human Drugs (ICH).

2 OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

To determine the optimal regimen for renal allograft tolerance (defined as proportion of recipients off immunosuppression with maintenance of good renal function at Month 24 post-transplant) while minimizing chimeric transition syndrome.

2.1.2 Key Secondary Objectives

- To determine the composite incidence of BPAR, death and graft loss (with and without lost to follow-up) at Month 24 post-transplant
- To determine the incidence and mean fluorescence intensity (MFI) of donor-specific antibody (DSA) at Month 24 post-transplant.

2.1.3 Secondary Objectives

The secondary objectives of this study are as follows:

- Incidence, duration, severity of CTS
- Proportion of recipients with transient mixed chimerism without CTS
- Proportion of recipients off immunosuppression for at least 12 Months
- Incidence of BPAR and treated BPAR (with Banff classification)
- Incidence of de novo DSA presentation
- Incidence of death and graft loss
- Incidence of chronic rejection
- Renal function (eGFR) and change of eGFR over time
- Incidence of AEs and SAEs
- Incidence of severe and clinically significant opportunistic infections
- Incidence of BK viremia, infection, and nephropathy

- Incidence of malignancies
- Incidence and severity of graft-versus-host disease (GvHD)
- Incidence of new onset diabetes post-transplant (NODAT)

2.1.4 Exploratory Objectives

The exploratory objectives include:

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
    - [redacted]
    - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

2.2 Study Endpoints

2.2.1 Primary Endpoints

Number and percentage of subjects achieving renal allograft tolerance at Month 24 post-transplant as assessed by:

- Immunosuppression dosing
- Serum creatinine (estimated glomerular filtration rate [eGFR])
- Incidents of Chimeric Transition Syndrome (CTS) and biopsy proven acute rejection (BPAR)
- Renal biopsy

2.2.2 Key Secondary Endpoints

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

2.2.3 Secondary Endpoints

- Number and percentage of subjects experiencing CTS by severity
- Time from onset of CTS to resolution

- Number and percentage of subjects with transient mixed chimerism without CTS
- Number and percentage of subjects off immunosuppression for at least 12 months
- Number and percentage of subjects experiencing BPAR
- Number and percentage of subjects treated for BPAR (with Banff classification)
- Number and percentage of subjects with positive, semi-quantitative, DSA assay results
- Number and percentage of subjects experiencing death and graft loss
- Number and percentage of subjects with chronic rejection
- eGFR and change in eGFR
- Number and percentage of subjects with treatment-emergent AEs/SAEs by system organ class (SOC) and preferred term (PT)
- Number and percentage of subjects with clinically significant opportunistic infections
- Number and percentage of subjects with BK viremia, infection, and nephropathy.
- Number and percentage of subjects with malignancies.
- Number and percentage of subjects with GvHD by severity
- Number and percentage of subjects with NODAT

2.2.4 Exploratory Endpoints

- [redacted]

3 STUDY DESIGN

3.1 Study Design Overview

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

The study will evaluate 2 siplizumab-based treatment regimens in a sequential manner with up to 18 recipients planned. Subjects in both arms will receive the same background conditioning and immunosuppression. Arm 1 subjects will receive 4 doses of siplizumab; Arm 2 subjects will receive 5 doses of siplizumab. In either arm, if CTS occurs, tocilizumab will be administered as treatment (Table 3.1).

Table 3.1 Dosing Regimens

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

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

Subjects will be enrolled using a modified 3+3 study methodology with the regimens investigated sequentially following a 'learning' and 'confirming' design. The first 3 subjects in each study arm will be enrolled one at a time. Acceptable safety and tolerability through Week 4 must be demonstrated before the next subject can be enrolled. After the first 3 subjects have been enrolled and completed assessments at Week 4, the remaining subjects in that arm will be enrolled simultaneously across centers to 'confirm' the initial response. If any subject in Arm 1 presents with severe CTS, the arm will be closed to further recruitment and the study will progress to Arm 2. A severe case of CTS in Arm 2 would constitute a stopping rule for further enrollment to that arm (see Protocol Section 9.1.2).
No formal interim analysis will be conducted. The decision to proceed to Arm 2 will be made in close contact with all Principal Investigators (PIs) and the DMC (see Protocol Section 11) based on reports of AEs, SAEs, and clinical data captured in the clinical study database.

The study periods are shown below in Table 3.2.

Table 3.2 Study Periods

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

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

b. Immunosuppression weaning Month 6 to Month 12.

During the screening period (from Day -37 to Day -10) and after informed consent has been obtained, baseline information will be obtained from the donor and recipient, including date of birth (month and year), age, sex, race, and ethnicity. In addition, relevant medical history, including current medical conditions, cause of end stage renal disease (ESRD), dialysis, and medication history for the recipient will be reviewed.
Pre-transplant screening procedures will include donor/recipient HLA typing (molecular), CDC lymphocyte crossmatch (or virtual crossmatch), qualitative DSA by single antigen bead (SAB) assay, and donor/recipient viral serology. Standard of care procedures performed prior to consent may be considered in the determination of subject eligibility (e.g., HLA/ABO typing, specific laboratory results).
Refer to the Schedule of Assessments (see Protocol Appendix 1) for a comprehensive list of all assessments and procedures performed during screening.
Subjects confirmed to meet all inclusion and none of the exclusion criteria, recipients, and their respective donors, will be enrolled in the study.

The study design overview is presented in Table 3.3 below.

Table 3.3 Study Design Overview

Study Periods	
Day -9	Recipients will initiate pre-transplant conditioning with outpatient administration of rituximab (375 mg/m2).
Day [redacted]	Administration of siplizumab ([redacted] mg/kg).
Day -5	Recipients will be admitted to the hospital and continue as an inpatient until discharge from the hospital post-transplant (discharge will vary based on the clinical status of the donor and recipient and will be determined at the discretion and judgment of the clinical team and Principal Investigator [PI]).
Days -5, -4	Administration of cyclophosphamide (60 mg/kg).
Day -2	Administration of rituximab (375 mg/m2).
Day -1	Thymic irradiation (700 cGy). Administration of siplizumab [redacted] mg/kg).
Day 0	Administration of siplizumab [redacted] mg/kg) perioperatively. Concentration-controlled background immunosuppression will start with administration of tacrolimus (TAC; target trough concentration of 4–11 ng/mL) and mycophenolate mofetil (MMF; 2.0 g/day), perioperatively. Combined renal transplant and donor bone marrow cell infusion (BMCI) will be performed.
Day 0 to ~Day 4	On the day of transplant (Day 0) and post-operatively through approximately Day 4, intravenous (IV) corticosteroids will be administered based on dose and tolerability. Note: During the first week post-transplant, subjects will transition from IV to oral corticosteroids then taper until stopping at Day 20.
Day 1	Administration of siplizumab [redacted] mg/kg).
Day 5	Administration of rituximab (375 mg/m2).
Day [redacted]	Arm 2 only: Administration of siplizumab ([redacted]mg/kg).
Day 12	Administration of rituximab (375 mg/m2).
Week 8	At Week 8 post-transplant, if the weaning criteria in Table 7 continue to be met, MMF will be discontinued.
Month 6	A biopsy will be conducted, and if the a priori defined immunosuppression weaning criteria are met, TAC dose reduction based on guidelines provided in the weaning schedule will begin (Table 9).
Month 12	At Month 12 post-transplant, if the weaning criteria continue to be met (based on assessment of the scheduled Month 12 biopsy and allograft function), TAC will be withdrawn completely.
Month 12 to Month 24	Following the Month 12 visit, subjects will return for study visits on a quarterly basis through Month 24 for overall health and laboratory assessments and for evaluation of adverse events (AEs).
Month 24 to Month 60	Following completion of the Month 24 visit, subjects will enter a long-term follow-up period with study visits every 6 months until the final study visit at Month 60.

4 SAMPLE SIZE DETERMINATION

No formal sample size or power analysis has been performed. A sample size of 18 subjects (Arm 1 = 12; Arm 2 = 6) was chosen to characterize the incidence and severity of CTS in the immediate post-transplant time period while balancing the overall risk-benefit in a regimen finding study.

The study is early terminated by the sponsor. Total of 4 subjects were enrolled in Arm 1 only. All of these 4 subjects are expected to be called for an EOS/PDV visit in accordance with the early termination of the study.

5 ANALYSIS SETS

5.1 Full Analysis Set

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

5.2 Safety Set

The Safety Set (SS) 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).

5.3 PD Analysis Set

The PD Analysis Set (immunophenotyping) will include all subjects in the FAS with available PD data and no protocol deviations with relevant impact on PD data. Subjects will be analyzed according to the study treatment(s) received.

6 Assessments

6.1 Efficacy Assessments

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

6.2 Safety Assessments

6.2.1 Adverse events

AE

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.

TEAE

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

In addition, any AEs that the investigators deem to be treatment related will also be considered TEAEs and will be included in the AE summaries. It should be noted that any ongoing AEs prior to the first dosing date that get worse are required to be entered as new AEs with new starting dates. The new starting dates are the dates when the AEs get worse. An AE with partial or missing onset date will be classified as a TEAE unless the onset date is definitely prior to the first dose of study treatment.

Serious Adverse Events

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

- Results in death
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Is an important medical event

Treatment-related Adverse Events

A treatment-related AE is defined as any adverse event for which the relationship or association of the investigational product is “Possible” or higher. A TEAE with missing causality relationship will be considered as related to the study drug.

Adverse Events of Special Interest (AESIs)

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

- CTS
- Opportunistic Infections
- Malignancies

6.2.2 Laboratory Assessments

Samples for the following local laboratory assessments will be performed at the time points noted in the Schedule of Assessment and as clinically indicated.

Table 6.1 Laboratory Assessments

Laboratory Panel	Analytes	
Complete Blood Count (CBC) with differential	Red blood cells (RBCs) Hemoglobin Hematocrit Mean corpuscular volume (MCV)	Mean corpuscular hemoglobin (MCH) White blood cells (WBCs) with differential (percent and absolute) Platelet count
Coagulation studies	Prothrombin time (PT)/ International	Activated partial thromboplastin

	Normalized Ratio (INR)	time (aPTT)
Comprehensive metabolic panel	Albumin Total protein Sodium Potassium Bicarbonate (CO2) Chloride Total calcium Blood urea nitrogen (BUN) Creatinine	Alanine aminotransferase (ALT)/ serum glutamic-pyruvic transaminase (SGPT) Aspartate aminotransferase (AST)/ serum glutamic-oxaloacetic transaminase (SGOT) Alkaline phosphatase Total bilirubin Glucose
Lipid panel	Total cholesterol Triglycerides	Low-density lipoprotein (LDL) High-density lipoprotein (HDL)
Thyroid panel	T3/ T4/Thyroid-stimulating hormone (TSH)	
Urinalysis	Leukocytes Nitrites Urobilinogen Protein pH Blood	Specific Gravity Ketones Bilirubin Glucose Microscopic, as indicated
Pregnancy testing (urine or serum)	A negative serum pregnancy test for women of childbearing potential (WOCBP) required during screening; negative urine pregnancy test prior to treatment on Day -9 (if anuric, serum test on Day -9).	
Donor-specific antibodies (DSA)	Blood samples (antibodies directed against antigens expressed on donor organs) will be processed and analyzed locally.	
[redacted]	Site dependent: panel to be defined by local laboratories	
[redacted]	Site dependent: panel to be defined by local laboratories	
Chimerism	[redacted]	

6.2.3 Renal Biopsy

Protocol biopsies are required at the time of transplant (Day 0); nominally at Month 6 and Month 12 (to allow the weaning of immunosuppression); and at Month 24 to support the primary analysis. The biopsy is to be read by the local pathologist and results, including component scores and final assessment, recorded in the applicable eCRF. In the event a biopsy result is inconclusive, central pathology and an independent adjudication committee may be convened on an ad hoc basis.

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

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

6.2.4 Treated Biopsy-Proven Acute Rejection

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

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

6.2.5 Graft-versus-Host Disease (GvHD)

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

6.2.6 Graft Loss

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

6.2.7 Death

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

6.2.8 Other

Other safety assessments include physical examination, electrocardiogram (ECG), infection surveillance and EBV-PTLD surveillance.

6.3 Pharmacodynamic (PD) Assessments

6.3.1 Chimerism Assessment

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

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

6.4 Exploratory Assessments

[redacted]

[redacted]

7 GENERAL CONVENTIONS

7.1 General Methods

Software

Statistical analysis will be performed using SAS software Version 9.4.

Statistics and Decimals

Data will be listed and summarized by arm, unless stated otherwise.

Individual subject data obtained from electronic case report forms (eCRFs), external sources, and any derived data will be presented in data listings by subject.

Summary statistics will be presented for values and changes from baseline for Arm 1 and Arm 2. Continuous data will be summarized using descriptive statistics: number of observations (n), mean, standard deviation (SD), median, 25th (Q1) and 75th (Q3) percentiles, minimum, and maximum. Derived data will retain one more decimal place than the raw data, unless otherwise specified.

Frequencies and percentages will be used to summarize categorical (discrete) data. Categories whose counts are zero will be displayed for the sake of completeness. Percentages will be presented to 1 decimal place, with the exception of 0, which will be presented without percent, and 100, which will be presented without decimal places. Values less than 0.1% will be presented as "<0.1%." Values less than 100% but greater than 99.9% will be presented as ">99.9%".

Table 7.1 No. of Decimal Places

Statistics	**No. of decimal places (dp)**
n	Always present to 0 dp
Mean	1 dp more than raw data
GeoMean	1 dp more than raw data
%CV	2 dp

Statistics	No. of decimal places (dp)
SD	2 dp more than raw data
Q1	Same as raw data
Median	1 dp more than raw data
Q3	Same as raw data
Min	Same as raw data
Max	Same as raw data
Percentage (%)	1 dp

Conventions

The precision of original measurements will be maintained in summaries, when possible.

Quantitative safety laboratory tests containing less than (<) and greater than (>) symbols are test results that are below and above quantifiable limits, respectively. To retain these values for analysis purpose, the following will be imputed and stored within the analysis datasets:

- For values with <, the imputed value will be the numeric portion × 0.9.
- For values with >, the imputed value will be the numeric portion × 1.1.

Standard Calculations

Variables requiring calculation will be derived using the following formulae:

- Change from baseline = value at the time point – baseline value.
- Percent change from baseline = [(value at the time point – baseline value) / baseline value] x 100%.
- Study day = date of specific assessments or procedures – date of renal transplant.

7.2 Definition of Baseline

Unless otherwise stated, baseline will be defined as the last observed measurement prior to the first study treatment administration.

For eGFR analysis (See Protocol Section 11.4.1), the baseline will be based on the Week 4 assessment.

7.3 Visit Window

Unless otherwise stated, scheduled visits will be used in analyses. For the analysis of primary endpoint eGFR, unscheduled visits or early treatment termination (ET) assessments will be reassigned to a scheduled visit for analysis purposes. If multiple assessments occur within a single visit window, after reassignment of unscheduled visits and ET assessments, the assessment closest to the target day of the visit window will be used in the analysis. If there is a tie, the later assessment will be used in the analysis.

Table 7.2 Visit Windows for Serum Creatinine (for eGFR calculation)

Target Scheduled Visit	Target Study Day [a]	Analysis Window Study Day [a]	
		Low	High
Baseline	28	27	30
Month 24	730	724	737

[a] Study day will be calculated from renal transplant procedure. The study day of surgical procedures is Day 0.

[b] Every other week from Month 6 through Month 18. The x indicates the number of assessments conducted after Month 6.

7.4 Handling of Missing Values/Censoring/Discontinuations

For primary endpoint, the handling of missing values will be specified in Section 10.3.

Unless otherwise stated, no imputation method will be applied for other endpoints.

8 DESCRIPTION OF THE ANALYSIS POPULATION

Summary statistics will be presented for the subjects in the FAS.

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

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

8.1 Disposition

Subject disposition summaries will be presented by arm and will include the number of subjects screened, the number of subjects with screen success and screen failure, and the reasons for screen failure, the number of subjects enrolled, the number and percentage of subjects in each analysis set, as well as the number and percentage of subjects who complete the study and subjects who discontinued from the study. The summaries will also include the reasons for early termination.

Data for disposition variables will be presented in a listing by arm and subject.

8.2 Demographic and Baseline Characteristics

All data for background and demographic variables will be listed by arm and subject. Summary statistics will be provided by arm. Subject demographics will include age, sex, race, ethnicity, height, weight, and BMI.

8.3 Other Baseline Characteristics

Other baseline disease characteristics include relevant medical history, results of laboratory screens, transplant history (e.g., warm ischemia time [WIC]/cold ischemia time [CIT], clinically significant prolongation of aPTT that required treatment) and donor characteristics (e.g., age, sex, race) and any other relevant information. These characteristics will be summarized by arm and subject.

Baseline laboratory results will be presented alongside post-baseline results, grouped by visit in safety analysis. Detailed summary of medical history is provided in the following section.

8.4 Medical History

Medical history will be coded by MedDRA (Medical Dictionary for Regulatory Activities, version 26.0 or higher). Medical history will be summarized by arm according to System Organ Class (SOC) and Preferred Term (PT).

Medical history will be presented in listings by arm and subject.

8.5 Protocol Deviations

Major protocol deviations from entry criteria and treatment compliance will be listed.

All protocol deviations, both minor and major, will be presented in a data listing.

9 ANALYSIS OF TREATMENT

Summaries and listings of treatment will be presented for the subjects in the SS.

9.1 Study Treatment Exposure

The duration (days) of study medication administration will be summarized by study drug and overall. This will be calculated by subtracting the date of the last administration of study medication from the date of first administration and then adding the dosing interval for siplizumab, rituximab, cyclophosphamide, tocilizumab. TAC, MMF. In calculating the duration of treatment, days of temporary interruption of study medication for any reason will be included.

Table 9.1 Dosing Interval for Treatment Duration Calculation

Study Drug	Frequency	Dosing Interval
Siplizumab	Days -6, -1, 0, and 1; also Day 6 for Arm 2 only	1 day
Rituximab	Days -9, -2, 5, and 12	1 day
Cyclophosphamide	Days -5 and -4	1 day
Tocilizumab	ONLY permissible as treatment for the presentation of CTS	1 day
Mycophenolate Mofetil (MMF)	BID	1 day
Tacrolimus (TAC)	BID or QD	1 day
Overall	N/A	1 day

Further, the following summaries will be presented by arm and study drug:

- Number and percentage of subjects of with at least one treatment error;
- Number and percentage of subjects with at least one dose change;
- Frequency of dose changes (including temporary dose interruptions) by reason for the change;

- Number and percentage of subjects who prematurely discontinued study medication by reason.

Subjects listing of study treatment data will be provided.

9.2 Background Immunosuppressants and Conditioning

The average daily dose of TAC, MMF, and CS will be summarized by arm for subjects on study medication. Where concentrations are measured, trough concentrations will be summarized by subject and treatment arm. The dose of antibodies used for the treatment of acute rejection episodes will be recorded as well. For rituximab and cyclophosphamide, presentation will include the total calculated dose (per kg) and number of doses. Similarly, the dose of thymic irradiation will be given.

The time to complete weaning of immunosuppression and the number of days off immunosuppression will be calculated for each subject and summary statistics prepared.

Time to off immunosuppression (days) = date of event or censoring – start date of transplantation + 1.

Resumption of immunosuppression after complete discontinuation will be recorded as a failure. The status of the subject as "off immunosuppression" will be derived from the dose administration records.

Table 9.2 Calculation for Time to Off Immunosuppression

Situation	Date of Event or Censoring	Event/ Censored
Complete withdrawal of immunosuppression	Date of drug discontinuation of immunosuppression	Event
Did not stop all immunosuppressant medication	Last participation date	Censored
Resumption of immunosuppression after completing discontinuation	Date of last dose of immunosuppression	Censored

9.3 Other Concomitant Treatments

Concomitant medications are defined as medications with start dates occurring on or after the date of first administration of study treatment and no more than 30 days after the last study visit. Concomitant medications, other than immunosuppressants and conditioning agents mentioned above, will be summarized by therapeutic class and Preferred Term (PT) by presenting the number and percentage of subjects using each medication for each treatment arm.

For infectious prophylaxis the medications used will be tabulated separately.

Concomitant medications and procedures will be presented in listings.

10 ANALYSIS OF PRIMARY ENDPOINTS

10.1 Definition of Primary Endpoint(s)

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

This will be assessed by summarizing the number and percentage of subjects achieving renal allograft tolerance based on the FAS. The following summaries will be presented:

- Summary for observed value and change from baseline in serum creatinine and eGFR (Modification of Diet in Renal Disease [MDRD] and Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]) at Month 24;
- Number and percentage of subjects who completed weaning of immunosuppression on or before Month 24;
- Incidence of CTS (assessed by renal biopsy and serum creatinine) up to Month 24;
- Incidence of biopsy proven acute rejection (BPAR) up to Month 24.

10.2 Statistical Model, Hypothesis, and Method of Analysis

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

10.3 Handling of Missing Values/Censoring/Discontinuations

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

- Subjects that lose their graft will be assigned a value of zero for their missing estimated glomerular filtration (eGFR) value.
- Subjects that die or are lost to follow-up with a functioning graft will have an imputed value using the last-observation-carried-forward (LOCF) method.

For subjects that discontinue treatment, the eGFR will be considered missing after applying the windows defined in Section 7.3.

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

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

11 ANALYSIS OF KEY SECONDARY ENDPOINTS

Key secondary endpoints include:

- Composite incidence: number and percentage of subjects experiencing BPAR or death or graft loss (with and without lost to follow-up) up to Month 24 post-transplant.
- Number and percentage of subjects of DSA positivity up to Month 24 post-transplant.

- Mean fluorescence intensity (MFI) of DSA at Month 24 post-transplant.

The analysis will be based on the FAS. Incidence data will be summarized by number and percentage of subjects. Observed value and change from baseline for MFI of DSAs will be summarized. The summary will be presented with mean, median, 25th percentile, 75th percentile, SD, minimum and maximum, and the number of non-missing observations.

12 ANALYSIS OF OTHER SECONDARY ENDPOINTS

Other secondary endpoints include:

- Number and percentage of subjects experiencing CTS by severity
- Duration of CTS defined as time from onset of CTS to resolution
- Number and percentage of subjects with transient mixed chimerism without CTS
- Number and percentage of subjects off immunosuppression for at least 12 months
- Number and percentage of subjects experiencing death and graft loss.
- Number and percentage of subjects experiencing BPAR
- Number and percentage of subjects treated for BPAR (with Banff classification)
- Number and percentage of subjects with positive, semi-quantitative DSA
- eGFR and change in eGFR
- Number and percentage of subjects with treatment-emergent AEs/SAEs by System Organ Class (SOC) and PT
- Number and percentage of subjects with clinically significant opportunistic infections
- Number and percentage of subjects with BK viremia, infection, and nephropathy
- Number and percentage of subjects with malignancies
- Number and percentage of subjects with GvHD by severity
- Number and percentage of subjects with NODAT

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

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

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

12.1 Safety Endpoints

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

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

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

12.1.1 Adverse Events

All information obtained on TEAEs will be displayed by arm. Listings of deaths, SAEs and TEAEs leading to study discontinuation will also be provided.

An overall summary of TEAEs will include the number of events, number and percentage of subjects for:

- TEAEs
- Treatment-related TEAEs
- SAEs along with the reason
- Treatment-related SAEs
- TEAEs leading to dose adjustment or interruption
- TEAEs leading to drug withdrawn
- TEAEs leading to study discontinuation
- TEAEs leading to antiviral therapy given or adjusted
- TEAEs leading to immunosuppression therapy added or Adjusted
- AESIs (CTS, opportunistic infections and malignancies)
- Infections by type of infection (viral, bacterial, fungal, and others)
- Serious infections by type of infection AESIs

The number (and percentage) of subjects with TEAEs will be summarized in the following ways:

- TEAEs by primary SOC and PT
- Treatment-related TEAEs by primary SOC and PT
- SAEs by SOC and PT

Multiple Occurrences for Tables

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

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

12.1.2 Vital Signs

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

12.1.3 Physical Examination

All vital sign data will be listed by arm, subject, and visit/time. Shift tables describing changes from baseline of the abnormalities will be presented.

12.1.4 Clinical Laboratory Evaluations

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

12.1.5 Other Safety Evaluations

BK-polyoma viremia and nephropathy; the following variables will be analyzed descriptively:

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

12.1.5.1 EBV and CMV Surveillance

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

12.2 Estimated GFR (eGFR)

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

12.3 Chimerism Assessments

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

13 ANALYSIS OF EXPLORATORY ENDPOINTS

[redacted]

14 INTERIM ANALYSES

Not applicable.

15 DESCRIPTION OF STATISTICAL ANALYSIS PLAN

This SAP describes the analysis for study TCD601A201. Any post-hoc or unplanned analyses that are performed but not identified in this SAP will be clearly identified in the clinical study report (CSR).

15.1 Changes from the Protocol Specified Statistical Analyses

None.

16 REFERENCE

[1] International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.
[2] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

17 APPENDIX

17.1 Appendix 1 Mock Shell of Tables, Figures and Listings

The information and explanatory notes to be provided in the footnote or bottom of each table, figure and listing will include the following information: date and time of output generation; SAS program name; any other output specific details (for example, definition of abbreviations) that require further elaboration. Some of the TFLs may not have sufficient numbers of subjects or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the table, such as, “No data available for this report”.

The arm and subject number will be included in all data listings. All listings will be sorted by arm, subject number, parameter and date, as applicable. See separate file for mock shell of tables, figures and listings.

17.2 Appendix 2 Estimated GFR

MDRD

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

MDRD 4-variable GFR Equation as below:

*GFR in mL/min per 1.73 m^2 = 175 x $SerumCr^{-1.154}$ * $age^{-0.203}$ * 1.212 (if patient is black) * 0.742 (if female)*

CKD-EPI

The CKD-EPI equation is modeled using least squares linear regression to relate log transformed measured GFR to log-transformed filtration markers, age and sex with two slope splines for creatinine, Expressed as a single equation:

*eGFR =142*min(standardized Scr/K, 1)α *max(standardized Scr/K, 1) -1.200*0.9938Age *1.012 [if female]*

Abbreviations / Units:
eGFR (estimated glomerular filtration rate) = mL/min/ 1.73 m2
Scr (serum creatinine) = mg/dL K = 0.7 (females) or 0.9 (males) α = -0.241 (females) or -0.302 (males) min = indicates the minimum of Scr/K or 1 max = indicates the maximum of Scr/K or 1

18 REVISION RECORD

Version	Version Date	Author	Modify Reason
V1.0	October 9, 2025	Lena Liu	Original Version