TCD601B102 Statistical Analysis Plan (SAP)

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

NCT Number: NCT04311632

Release Date: 11-Jun-2024

STATISTICAL ANALYSIS PLAN FOR TCD601B102

Siplizumab

Clinical Protocol TCD601B102

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

Version Number: 2.0
Clinical Trial Phase: IIA
Release Date: 02-Mar-2022

Sponsor
ITB-MED

US Office: ITB-MED LLC 110 East 59th St FL 28. New York, NY 10022.

SPONSOR APPROVAL

The undersigned have reviewed the format and content of this prospective statistical analysis plan (SAP) and have approved it for use to analyze the TCD601B102 final data.

ITB-Med LLC

Print Name	Signature	Date
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1. DOCUMENT HISTORY

Version	Date	Changes made since previous version
1.0	June 07, 2024	Original

2. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
ATC	anatomical therapeutic chemical
ATG	Anti-thymocyte Globulin
AUC	area under the curve
BID	Twice a day
BMI	Body Mass Index
CD2-RO	CD2-receptor occupancy
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMV	Cytomegalovirus
CRFs	case report forms
CS	corticosteroids
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
DSA	donor specific antibodies
DSA	Donor Specific Antibodies
EBV	Epstein-Barr Virus
EBV	Epstein-Barr Virus
eGFR	Estimated Glomerular Filtration Rate
ELISA	Enzyme-linked Immunosorbent assay
EOS	End of Study
FACS	Fluorescence-activated Cell Sorter
FAS	Full Analysis Set
HLA	Human Leukocyte Antigen
IV	intravenous
LLOQ	the anticipated Lower Limit of Quantification
LOCF	last-observation-carried-forward
MDRD	Modification of Diet in Renal Disease
MMF	mycophenolate mofetil
NCI	Delayed graft function

Abbreviation	Definition
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	standard deviation
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SS	Safety set
TAC	tacrolimus
tBPAR	treated Biopsy Proven Acute Rejection
TCMR	T-cell mediated rejection
TEAE	treatment emergent adverse events
ULOQ	upper limit of quantification
VL	viral load
WHO	World Health Organization

3. INTRODUCTION

This statistical analysis plan (SAP) is based on Protocol TCD601B102, Version 2.0 dated 02-Mar-2022 for Study TCD601B102.

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.

This is the final SAP, and is approved by the Sponsor, and filed within the TMF before the final database is locked. The approved plan will be used to carry out all analyses for the final analysis. Deviations, if any, from the approved plan will be noted in the clinical study report.

4. STUDY DESCRIPTION

4.1. Study Objectives and 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 • Serious adverse events • Clinically significant changes in clinical chemistry, hematology, vital signs, serology • Siplizumab PK • PK-PD relationship
Secondary	
• To measure changes in peripheral lymphocyte immunophenotype	• Immunophenotyping via FACS
• To measure the time-course and duration of Siplizumab induced lymphocyte depletion and time to recovery	• Lymphocyte counts
• To measure peripheral CD2-receptor occupancy following Siplizumab administration over time	• CD2-receptor occupancy (RO)
• To assess the incidence of treated biopsy proven acute rejection (tBPAR) at 12 months	• Incidence of tBPAR
• To assess the incidence of treatment emergent de novo, donor specific antibodies (DSA) at 12 months	• de novo DSA/anti-HLA antibody measurement
• To assess the incidence of antibody meditated rejection at 12 months	• incidence of AMR
• To assess renal function via eGFR using the Modification of Diet in Renal Disease (MDRD) equation at Months 3, 6, 12 or EOS	• eGFR via MDRD

Exploratory
[redacted]

4.2. Study Design

4.2.1. TCD601B102

TCD601B102 is a 12-month, multi-center, randomized, controlled, open-label, dose escalation study to evaluate the safety, tolerability, PK and PD of Siplizumab compared to rATG, as induction therapy, in *de novo* renal transplant recipients. All subjects will receive background immunosuppression with standard exposure tacrolimus (TAC), mycophenolate mofetil (MMF) and corticosteroids (CS).

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

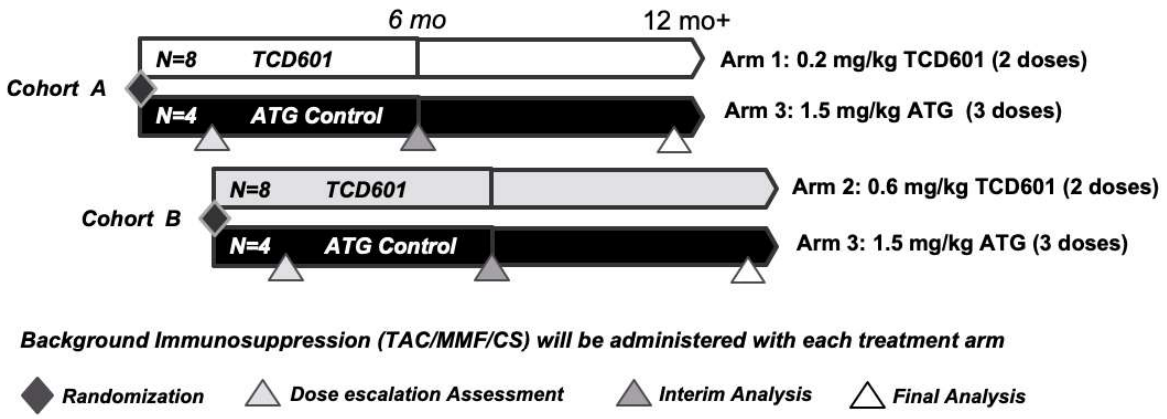
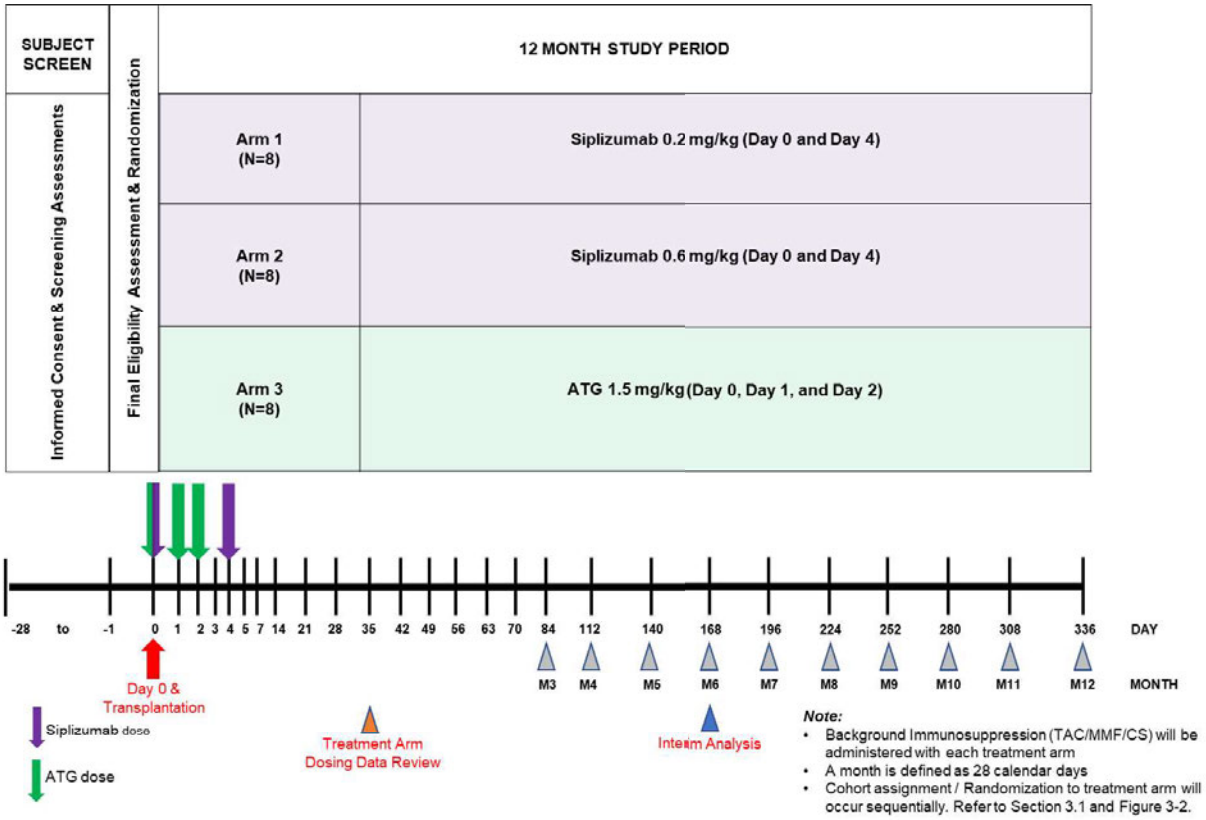


Figure 4-2 TCD601B102 Study Design



Siplizumab Dosing Arms:

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

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

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

4.2.2. Dose Escalation Criteria

TCD601B102

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

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

This escalation data review will occur prior to dose escalation/termination decisions for each Cohort. The review of subject data and dose escalation may occur before all subjects have been randomized to a given Cohort. If the next dose level is opened to subject assignment, Cohorts will be back filled to achieve a final sample size of 10 subjects.

In addition to the review of data for dose decision purposes as noted above, an independent Data Monitoring Committee (DMC) will conduct an ongoing review of cumulative PK, PD and safety, Adverse Events (AEs) and Serious Adverse Event (SAE) data. The Committee will convene on a quarterly basis or as described in the DMC Charter. If at any time the observed AEs meet or exceed the a priori-defined stopping criteria, the study will be placed on hold pending a review.

4.2.3. Safety Stopping Rules

In addition to the formal interim analyses and escalation data reviews for dosing decision purposes, the following Safety Stopping Rules will be in effect at any timepoint in the study. Although the stopping criteria do not incorporate an absolute requirement for causality, the potential relationship between an AE(s) and Siplizumab will be evaluated carefully on a case-by-case basis between ITB-MED and the Investigator. Following a review of the AE(s), a decision to permanently discontinue enrollment or re-initiate dosing will be made by the DMC. Dose-limiting toxicities (DLTs) will be assessed according to the standardized toxicity grading scale, the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (NCI 2017):

- One (1) subject death or graft loss within the first month with the exception of technical failures.
- One (1) subject presents with histologically confirmed EBV-PTLD.

- One (1) subject with Grade 3 or higher cytokine release syndrome within 24 hours of any Siplizumab administration.
- One (1) subject with any Grade 4 toxicity, considered drug related as determined by the Investigator within the first 28 days.
- Two (2) subjects with sustained (>7 days) Grade 3 neutropenia (neutrophil counts 200/mm^3 to <500 to; 0.2 to <0.5 × 10^9/L) considered related to Siplizumab.
- Two (2) or more subjects presenting with Grade 3 or higher toxicity considered related as determined by the Investigator, including infusion reactions, within 24 hours of any Siplizumab administration.
- Three (3) or more subjects per cohort presenting with Grade IIA or higher BPAR (T-cell mediated rejection [TCMR]; central pathology) during the first 6 months post-transplant.

5. INTERIM ANALYSIS

5.1. Interim Analysis Objectives

A formal interim analysis was conducted when 50% of subjects in Cohort 1 and 2 completed their 6-month study assessment according to a separate interim analysis plan (dated 03MAR2023). This formal interim analysis was conducted to assess the safety/tolerability (e.g., AEs, SAEs, clinical laboratory assessments, vital signs, PK data and PK/PD activity [e.g., immunophenotyping and CD2 receptor occupancy]). The analysis also included assessment of biopsy proven acute rejection (BPAR), graft losses deaths, and key safety endpoints. In the event the acute rejection rate exceeds a clinically relevant threshold set forth in the protocol and DMC charter, or the a priori defined stopping rules, enrollment were to be suspended to allow for the early termination of any treatment cohort where the benefit/risk of Siplizumab was deemed unacceptable.

The following treatment arms will be utilized for TCD601B102:

- Arm 1: Siplizumab 0.2 mg/kg (n=8 in Cohort A)
- Arm 2: Siplizumab 0.6 mg/kg (n=8 in Cohort B)
- Arm 3: rATG, a control arm, (n=4 each in Cohort A and B)

Subjects randomized to Siplizumab will receive two intravenous (IV) doses on Day 0 and Day 4 post-transplant and subjects randomized to rATG (Arm 3) will receive three intravenous (IV) doses of 1.5 mg/kg on Days 0, 1, and 2, regardless of Cohort assignment.

6. RANDOMIZATION AND BLINDING

Randomizations will be performed within each cohort:

- A randomization ratio of 2 (active arm):1 (control arm) will be utilized for Study TCD601B102.

7. ANALYSIS POPULATIONS

7.1. Safety Set

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

7.2. Full Analysis Set

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

7.3. PK Analysis Set

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

7.4. PD Analysis Set

The PD Analysis Set will include all subjects in the Full Analysis set with available PD data and no protocol deviations with relevant impact on PD data.

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

8. GENERAL CONVENTIONS

Unless otherwise stated, all analyses will be performed using SAS Version 9.4 or later and all hypothesis tests will be conducted at a two-sided significance level of 0.05. P-values will be presented with 3 decimals and p-values that are less than 0.001 will be presented as <0.001.

Continuous data will be summarized using descriptive statistics: number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Frequencies and percentages will be used to summarize categorical (discrete) data. Presentations of categorical data will generally suppress percentages for items where the count is zero in order to draw attention to the nonzero counts.

Unless otherwise stated, the control arm will include 8 subjects who received (rATG) in study TCD601B102. The active arms will include: 0.2mg/kg (8 subjects) and 0.6mg/kg (8 subjects. Unless otherwise stated, confidence intervals, when presented, will be constructed at the two-sided

95% level. For binomial variables, the 95% confidence intervals will be constructed using the Clopper-Pearson exact method.

Data listings will present all data collected on case report forms (CRFs) by treatment arm, center, and subject number.

8.0. Statistical Model, Hypothesis, and Method of Analysis

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

8.1. 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.

8.2. Definition of Baseline

Unless otherwise stated, the last observed measurement prior to or on the date of first study medication will be considered the baseline measurement.

For eGFR analysis (See Section **Error! Reference source not found.**), the baseline will be based on the Week 4 assessment.

8.3. Software

The PK parameters will be derived using Phoenix WinNonlin® version 8.3 or higher (Certara, L.P.). SAS® 9.4 or higher (SAS institute, Inc., Cary, NC USA) will be used for PK statistical analysis to provide tables, listings, and figures.

8.4. Handling of Missing Values/Censoring/Discontinuations

The following imputation method will be applied for subjects with missing data:

- Subjects who lose their graft will be assigned a value of zero for their missing estimated glomerular filtration (eGFR) value.
- Subjects who 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.

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.

Subjects 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).

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.

9. 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).

9.1. Disposition

Subject disposition summaries will be presented by treatment arm and will include the number of subjects randomized, the number and percentage of randomized subjects in each analysis populations, as well as the number and percentage of subjects who complete the study. The summaries will also include the reasons for early discontinuation from the study.

The table format will be similar to the disposition table presented to the DMC.

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

9.2. Demographic and Baseline Characteristics

Demographic summaries will be provided by treatment arm and will include age, sex, race, ethnicity, height, weight, and BMI. These summaries will be presented for the subjects in the Full Analysis Set (FAS) and Safety set (SS).

Data for demographic variables will be presented in listings by treatment arm and subject.

9.3. Other baseline characteristics

Other baseline disease characteristics include relevant medical history, transplant history, other concomitant procedures, childbearing potential, donor characteristics (e.g., age, sex, race, type, CIT) and any other relevant information.

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

Medical history, current medical conditions, results of laboratory screens, transplant history, donor characteristics will be presented in listings by treatment arm and subject respectively.

9.4. Prior and Concomitant Medications

All medications recorded on the CRFs will be coded using the WHODrug Dictionary (version March 2023 or higher). Prior and concomitant medications will be summarized by treatment arm in the Safety Set by anatomical therapeutic chemical (ATC) Class Level 4 and WHODrug base substance preferred name.

Prior medications are defined as medications with stop dates occurring before the date of first administration of any study treatment. Concomitant medications are defined as medications with start dates occurring on or after the date of first administration of any study treatment and no more than 30 days after the last study visit. Medications with start and stop dates that bracket the date of first administration of a study treatment will be summarized as both prior and concomitant medications.

Medications that were stopped prior to the date of first administration of a study treatment will be included in the prior medications table, and medications that were started on or after the date of first administration of any study treatment component will be included in the concomitant medications table. All other medications will be included in both the prior and concomitant medications tables if the date they were started or stopped is unclear.

Prior and concomitant medications will be summarized for the Safety Set.

Prior and concomitant medications will be presented in listings.

9.4.1. Concomitant Immunosuppressants

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

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

TAC, MMF, and CS administration and average daily dose will be presented in listings.

9.4.2. Other Concomitant Medications

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

Information for other co-medications will be presented in listings.

10. ANALYSIS OF PRIMARY ENDPOINTS

10.1. Safety Analysis

Safety analyses will be performed using the Safety Set. Assessment of safety will be based on the incidence, severity, relatedness, and type of adverse events, as well as on clinically significant changes in the subject's physical examination, and vital signs. Safety variables will be tabulated and presented by study drug received.

Because there is no pre-specified safety outcome defined in terms of AEs or vital signs, any formal comparisons between the treatment arms with respect to specific safety parameters will be *post hoc*.

10.1.1. Extent of Exposure

Summary statistics of exposure to study drug will be tabulated by treatment arm. The exposure will be summarized using duration and average dosing. Duration of exposure is defined as last

dosing date – first dosing date + 40; e.g. 5 PK half-lives. Exposure by average dose is defined as X/Y, where X is the total dose received and Y is planned number of doses to be given.

The duration (days) of study medication administration will be summarized. This will be calculated by subtracting the date of the last administration of study medication from the date of first administration and then adding the dosing interval for Siplizumab, TAC, MMF or CS. In calculating the duration of treatment, days of temporary interruption of study medication for any reason will be included. Further, the frequency of dose changes (including temporary dose interruption) will be presented by reason for the change.

Average daily doses will be presented by treatment. "Zero" will be used for periods of temporary interruption of study medication for any reason.

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

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

Extent of exposure data will be presented in a listing.

10.1.2. Adverse Events

Each AE and SAE term will be recorded as a verbatim term on the case report forms (CRFs). All AEs and SAEs will be coded by primary system organ class (SOC) and mapped to a preferred term using the MedDRA dictionary (version 26.0 or higher). The investigator will assess AE severity and relationship to the study treatment.

All AEs will be listed. However, only treatment emergent adverse events (TEAEs) will be included in the AE summaries. A TEAE is defined as any AE with an onset date on or after the first study treatment dosing date. In addition, any AEs that the investigators deem to be treatment related, regardless of onset date, will also be considered TEAEs and will be included in the AE summaries.

For the purpose of calculating treatment emergence and inclusion in summary tables, incomplete onset dates will be imputed using the method described in Appendix A.

AEs will be summarized by the number and percentage of subjects in each primary SOC and preferred term. Subjects will be counted only once for each primary SOC and each preferred term. Summary tables of AEs by primary SOC, preferred term and severity will be provided. If a subject has more than one AE coded to the same preferred term, the subject will be counted only once for that preferred term by using the event with the highest severity. Similarly, if a subject has more than one AE within a primary SOC category, the subject will be counted only once in that SOC category by using the event with the highest severity. AEs by primary SOC, preferred term and relationship to study drug will be provided as well. If a subject has more than one AE coded to the same preferred term, the subject will be counted only once for that preferred term by using the most related event. Similarly, if a subject has more than one AE within a primary SOC category, the subject will be counted only once in that primary SOC category by using the most related event. In addition, serious adverse events (SAEs) by primary SOC and preferred term will be provided. Deaths and SAEs will be summarized similarly to AEs. All adverse event tables will also include the total number of events, counting multiple events per subject.

In the AE summary, preferred terms within each SOC will appear in alphabetical order.

Frequencies for deaths and hospitalizations will also be summarized by treatment group and overall.

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

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

• AEs by primary System Organ Class (SOC) and Preferred Term

• AEs rated to have relationship to study drug by SOC and Preferred Term

• AEs by primary SOC, Preferred Term, and maximum severity

• SAEs by SOC and Preferred Term

• SAEs rated to have relationship to study drug by SOC and Preferred Term

• Deaths by SOC and Preferred Term

• AEs leading to discontinuation of a study drug by SOC and Preferred Term

• AEs leading to dose adjustment or interruptions of a study drug by SOC and Preferred Term

• Infections by type of infection (viral, bacterial, fungal, and others) and microorganism of infection

• Serious infections by type of infection and micro-organism of infection

• AEs by standardized MedDRA query (SMQ) levels (broad and narrow search)

• AEs by SMQ and Preferred Term (broad and narrow search)

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

All AEs will be presented in individual by-subject data listings. Listings of any subject experiencing TEAEs related to study drug, and an SAE will be provided separately.

10.1.3. Laboratory Assessments

Descriptive statistics (mean, SD, minimum, median and maximum) of quantitative laboratory variables, including change from baseline, will be generated by visit. Summary of change from baseline in liver function tests, renal function tests, and other clinical chemistry and hematology laboratory tests will be provided for the Safety Set. Shift tables describing changes from baseline based on the clinical notable criteria will be presented.

Results of laboratory tests will be presented in listings.

10.1.4. 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 and change from baseline will be provided by treatment and visit/time. Shift tables describing changes from baseline based on the clinically notable criteria will be presented.

10.1.5. Physical Exam

Physical exam data for each subject will be presented in a listing, if it is available.

10.1.6. Graft Loss

Graft Loss data will be summarized by group. If the subject undergoes allograft nephrectomy prior to starting permanent dialysis, then the day of nephrectomy is the day of graft loss.

10.1.7. Death

Primary cause of death will be summarized by treatment arm, and death data will be presented in a listing.

10.2. Pharmacokinetics and Pharmacodynamics

10.2.1. Pharmacokinetics

PK samples will be evaluated for the subjects in PK analysis set at all dose levels.

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

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

The linear trapezoidal rule will be used for (AUC) calculation. Regression analysis of the terminal plasma elimination phase for the determination of $T_{1/2}$ will include at least 3 data points after C_{max}. If the adjusted R^2 value of the regression analysis of the terminal phase will be less than 0.75, no values will be reported for T1/2, AUC_{inf}, and CL.

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

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

Table 9-1 Non-compartmental pharmacokinetic parameters

AUC_{last}	The AUC from time zero to the last measurable concentration sampling time (tl_{ast}) (mass x time x volume-1)
AUC_{inf}	The AUC from time zero to infinity (mass x time x volume-1)
AUC_{tau}	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume-1)

C_{max}	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume-1)
T_{max}	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
Lambda_z	Smallest (slowest) disposition (hybrid) rate constant (time-1) may also be used for terminal elimination rate constant (time-1)
$T_{1/2}$	The 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	The total body clearance of drug from the plasma (volume x time-1)
V_z/F	The apparent volume of distribution during terminal phase (associated with λ_z) (volume)

All calculated PK parameters will be listed by treatment and subject. Concentrations below the limit of quantification will not be considered for the calculation of PK parameters. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is 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 as the initial model used for expected concentration in the protocol. Such analysis may be reported in a separate standalone report.

10.2.2. PK/PD Relationships

The relationship between Siplizumab concentration (PK) and PD variables will be presented graphically.

11. ANALYSIS OF SECONDARY ENDPOINTS

11.1. Immunophenotyping

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

These data will be summarized by treatment and subject for the safety population: CD14+, CD3+, CD3+CD4+, CD3+CD8+, CD3-CD19+, CD3-CD56+/CD16+; Lymphocyte: WBC ratio, WBC dual platform.

11.2. Lymphocyte Count

Lymphocyte count will be summarized by treatment arm and visit.

11.3. CD2 RO

The magnitude and duration of PD effect of Siplizumab will be measured by peripheral blood CD2-receptor occupancy.

11.4. Donor specific antibodies (DSA) results

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

11.5. Efficacy Analysis

Efficacy analysis will be summarized by treatment arm for the FAS.

- **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 2017 Banff criteria, including borderline rejections. Incidence of tBPAR at 12 months will be summarized.

- **AMR**

Incidence of antibody meditated rejection (AMR) at 12 months will be summarized.

11.6. Renal Function

- **Change from baseline in renal function eGFR**

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:

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

- **Change from baseline in CKD-EPI**

The CKD-EPI equation are 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:

$$eGFR = 142 * \min(\text{standardized Scr}/K, 1)^{\alpha} * \max(\text{standardized Scr}/K, 1)^{-1.200} * 0.9938^{Age} * 1.012 \text{ [if female]}$$

Abbreviations / Units:

eGFR (estimated glomerular filtration rate) = mL/min/ 1.73 m^2

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

The above parameters will be summarized by visit. This will also be evaluated at Months 3, 6 and 12 (EOS) by comparing the mean eGFR values between groups.

12. ANALYSIS OF EXPLORATORY ENDPOINTS

[redacted]
(including a category labeled as "missing" when appropriate).

[redacted]

[redacted]

• occurrence of BK[redacted]

• occurr[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Patient's serum creatinine, ser[redacted]

[redacted]

13. IDENTIFICATION AND SUMMARY OF PROTOCOL DEVIATIONS

Major protocol deviations from entry criteria and treatment compliance will be summarized as far as they can be extracted from numeric or coded study data.

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

14. REFERENCES

None

15. APPENDICES

15.1. Appendix A – Imputation Algorithm for Partial and Missing Dates

This section describes missing date imputation methods.

For Adverse Events

If onset date is completely missing, onset date is set to date of randomization.

If (year is present and month and day are missing) or (year and day are present and month is missing):

- If year = year of randomization, then set month and day to month and day of randomization
- If year < year of randomization, then set month and day to December 31.
- If year > year of randomization, then set month and day to January 1.

If month and year are present and day is missing:

- If year = year of randomization and
    - If month = month of randomization then set day to day of first dose
    - If month < month of first dose then set day to last day of month
    - If month > month of first dose then set day to first day of month
- If year < year of randomization then set day to last day of month
- If year > year of randomization then set day to first day of month

For all other cases, set onset date to date of randomization.

For Concomitant Medications

Start Date: If start date is completely missing and end date is not prior to randomization, then the medication will be classified as concomitant. If start date is completely missing and end date is prior to randomization, then the medication will be classified as prior.

If (year is present and month and day are missing) or (year and day are present and month is missing) then set month and day to January 1. If year and month are present and day is missing then set day to first day of month.

End Date: If end date is completely missing then the medication will be classified as concomitant.

If (year is present and month and day are missing) or (year and day are present and month is missing) then set month and day to December 31. If year and month are present and day is missing then set day to last day of the month.

Note: that if both start and end dates are missing then the medication will be classified as concomitant.

15.2. Appendix B – Special Data Handling Instructions

In the case that data has been entered which does not follow a clear handling instruction, the following instructions have been agreed upon and will be followed.

1. For cases in which the site has collected a TAC trough sample, but the patient has not yet received Tacrolimus, the site has been instructed to put in a most recent Tacrolimus dosing time of 00:00.
2. For cases in which the subject has received Tacrolimus before collecting a TAC trough sample, however Time of Previous Tacrolimus Dose is unknown, then the time should be recorded as "00:00".
3. If a PCR viral load is below the lower limit of quantification, then the site will record this data as Negative, with the PCR value as Unknown. If the PCR viral load result is negative or 0 at the site, then it should be recorded as Negative and 0.