DAIT/Rho STATISTICAL ANALYSIS PLAN

FINAL

CTOTC-12: Safety of Donor Alloantigen Reactive Tregs to Facilitate Minimization and/or Discontinuation of Immunosuppression in Adult Liver Transplant Recipients

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DAIT/Rho STATISTICAL ANALYSIS PLAN ACKNOWLEDGMENT AND SIGNATURE SHEET

Safety of Donor Alloantigen Reactive Tregs to Facilitate Minimization and/or Discontinuation of Immunosuppression in Adult Liver Transplant Recipients

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Document History

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0.1		Initial Draft	
0.2			
1.0	04MAR2020	Final Version	Katharine Spain

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1. PROTOCOL SYNOPSIS

Title	Safety of Donor **A**lloantigen **R**eactive **T**r**e**gs (darTregs) to Facilitate **M**inimization and/or Discontinuation of **I**mmuno**s**uppression in Adult Liver Transplant Recipients **(ARTEMIS)**
Short Title	darTregs for CNI Reduction
Protocol Number	CTOTC-12
ClinicalTrials.gov Identifier	NCT02474199
Clinical Phase	Phase I/II
Primary Safety Objective	This study will evaluate the safety and tolerability of a single IV dose of the darTregs product.
Secondary Safety Objective	This study will evaluate the safety of immunosuppression (IS) 1) minimization and 2) discontinuation after one IV dose of darTregs.
Primary Efficacy Objective	The study will evaluate the ability of a single IV dose of darTregs to reduce baseline, standard of care (SOC) calcineurin inhibitor (CNI) dosing by 75% along with discontinuation of either prednisone or mycophenolate mofetil (MMF), as applicable.
Secondary Efficacy Objective	This study will determine whether a single IV dose of darTregs can induce operational tolerance.
Mechanistic Objectives	We will assess the pharmacokinetic profile of darTregs by measuring the level of deuterium-labeled Tregs in circulation. Potential impact of darTregs therapy on immunological profiles will be assessed by comparing leukocyte phenotypes, tissue histology and gene expression in protocol and for-cause biopsies, and alloantibody before and after darTregs infusion.
Study Design	A multi-center, open-label clinical trial in adult liver transplant recipients with two primary interventions: • administration of a single IV dose of darTregs and • reduction of IS dosing with possible complete IS discontinuation. Adult living donor liver recipients two to six years after LT will initiate IS withdrawal. Twelve to 14 weeks later, they will receive a single dose of darTregs and continue IS withdrawal.
Primary Safety Endpoint	The safety and tolerability of a single infusion of darTregs administered to LT recipients will be assessed 24 weeks after darTregs by describing: 1. Occurrence of CTCAE Grade 3 or higher adverse events (AEs) attributable to the darTregs infusion including infusion reaction / cytokine release syndrome 2. Occurrence of study defined Grade 3 or higher infections 3. Occurrence of any malignancy, including PTLD
Secondary Safety Endpoint	The trial will assess the safety of IS withdrawal in the context of darTregs therapy by describing the following secondary safety endpoints: 1. Rate of composite outcome measure including refractory acute rejection, chronic rejection, re- transplantation, and death 2. Incidence of biopsy proven or clinical acute rejection and/or chronic rejection 3. Timing of biopsy proven or clinical acute rejection and/or chronic rejection 4. Severity of biopsy proven acute rejection and/or chronic rejection

Primary Efficacy Endpoint	The efficacy of a single IV dose of darTregs will be assessed by the number and proportion of LT subjects who are able to reduce CNI dosing by 75% and discontinue a 2nd IS drug (if applicable) with stable liver tests for at least 12 weeks. The frequency of successful CNI minimization will be compared to historical cohorts of comparable adult LT recipients undergoing IS withdrawal.
Secondary Efficacy Endpoints	The efficacy of a single IV dose of darTregs infusion will be assessed by determining the number and percentage of subjects who have received darTregs and are identified as operationally tolerant, defined by maintaining stable allograft function (assessed by liver tests) and histology (determined by central pathologist reading in comparison to screening liver biopsy at study entry) in the absence of IS for one year. The frequency of tolerance will be compared to historical cohorts of adult liver transplant recipients undergoing IS withdrawal.
Primary Mechanistic Endpoints	The level and persistence of deuterium-labeled darTregs in the circulation will be determined by serial measurements of deuterium content in DNA from purified peripheral blood Tregs after darTregs infusion using gas chromatography-mass spectrometry (GC-MS) testing.
Secondary Mechanistic Endpoints	The overall increase of darTregs in circulation will be assessed using the alloreactive T cell frequency (ATF) assay
Exploratory Mechanistic Endpoints	The immunologic impact of infused darTregs will be determined by assessing the following: • Leukocyte phenotypes before and after darTregs infusion using multi-parameter flow cytometry (MFC). • Alloantibody responses before and after darTregs infusion during IS withdrawal. • Histology and multiplex immunohistochemistry of protocol and for cause biopsies • The composition of immune infiltrate in liver biopsies post Treg infusion and at the time of for-cause biopsies will be profiled using single-cell RNA+TCRseq
Accrual Objective	Up to 18 participants will be screened and enrolled to target up to 11 participants eligible for both IS withdrawal and darTregs infusion
Study Duration	The maximal length of trial participation for an individual subject is anticipated to be 2 years. The total trial duration will be 3 years. • One year period to accrue nine patients eligible for both IS withdrawal and darTregs infusion that will be given approximately 10-11 weeks after initiating IS withdrawal • Minimum of 52 weeks follow-up after any AR episode or or darTregs infusion • For all subjects able to discontinue IS, 52 weeks of follow-up after the last IS dose to assess for operational tolerance The duration of study participation will vary by subject depending on his/her duration of IS withdrawal. Accounting for a one year enrollment period, the primary endpoint for all participants will be assessed approximately 1.5 years after trial initiation.
Treatment Description	All eligible participants will initiate IS withdrawal. Approximately 10-12 weeks after initiating IS withdrawal, subjects will have autologous Tregs collected for darTregs manufacturing. During the last 2 weeks of IS withdrawal Step 2 (CNI reduced by 25%), **a single total dose of 400 x 10^6 ± 100 deuterium-labeled darTregs** will be infused intravenously. The subject will then, if eligible, resume IS withdrawal within 2 weeks after darTregs infusion (see Section entitled "Resumption of IS Withdrawal after darTregs Infusion" below). Only subjects who receive 300-500 x 10^6 darTregs and who meet the primary endpoint of 75% reduction in CNI from baseline after darTregs will be offered the opportunity to continue IS withdrawal until complete discontinuation of IS (secondary endpoint). Those who receive 100-300 x 10^6 darTregs will only be allowed to proceed to the primary endpoint but will not be eligible for complete IS withdrawal.

Study Enrollment/ IS Withdrawal Inclusion Criteria	Subjects who meet all of the following criteria are eligible for enrollment as study participants: 1. Able to understand and provide informed consent 2. Have received primary, solitary, living donor liver transplant more than 24 months but less than 84 months ago 3. Have a living donor who is willing to consent to one time phlebotomy of 100 mLs to enable manufacture of darTregs 4. Between 18 and 70 years of age at the time of study entry/consent 5. Have ALT consistently <60 U/L and either alkaline phosphatase consistently <150 U/L or GGT consistently <60 U/L 6. Currently receiving a calcineurin inhibitor (CNI) with 12 hour trough levels consistently <6.0ng/mL for tacrolimus; <150ng/mL for cyclosporine 7. Currently receiving CNI monotherapy or CNI and ONE of the following: a. Prednisone: maximum dose of 5mg / day b. Mycophenolate mofetil (MMF): maximum dose of 500mg bid for Cellcept or 360mg bid for Myfortic 8. Female and male subjects with reproductive potential must agree to use effective methods of birth control for the duration of the study 9. If history of HCC, LT recipients who have: a. AFP less than 100 µg/L at the time of transplant AND b. Explanted liver: i. with tumor burden within the Milan criteria and ii. without macro- or micro-vascular invasion and iii. without any lesions with poorly differentiated HCC and iv. without cholangiocarcinoma morphology c. Risk Estimation of Tumor Recurrence After Transplant (RETREAT) Score less than or equal to 3 10. If history of HCC, at the time of enrollment, subjects must also: a. Be 36 months or more post-transplant AND b. Without evidence of recurrent HCC defined as i. AFP within normal limits for performing laboratory ii. Confirmatory chest CT and iii. Confirmatory CT or MRI of the abdomen and pelvis 11. If history of HCV, recipients must be: a. Cured of HCV as defined by achieving SVR and be greater than or equal to six months after the end of treatment b. HCV RNA negative at time of study enrollment

Study Enrollment/ IS Withdrawal Exclusion Criteria	Subjects who meet any of these criteria are not eligible for study enrollment. 1. Transplant for liver disease secondary an autoimmune etiology (e.g. autoimmune hepatitis, primary sclerosing cholangitis, or primary biliary cirrhosis) 2. Matched at both HLA-DR loci to the donor 3. Organ, tissue or cell transplant prior to or after the primary solitary living donor liver transplant 4. For subjects with hepatitis B, detectible HBV DNA 5. History of malignancy within 5 years of enrollment. History of adequately treated in-situ cervical carcinoma and/or skin cancer (basal or squamous cell) will be permitted. 6. Serologic evidence of human immunodeficiency 1 or 2 infection 7. Epstein Barr Virus (EBV) sero-negativity (EBV naïve) if living donor is EBV sero-positive 8. Cytomegalovirus (CMV) sero-negativity (CMV naïve) if living donor is CMV sero-positive 9. Calculated GFR less than 50 mL/min/1.73m^2 at the time of enrollment 10. An episode of AR within one year of enrollment 11. Systemic illness requiring or likely to require recurrent or chronic IS drug use 12. Any chronic condition for which anti-coagulation cannot be safely interrupted for liver biopsy 13. Positive pregnancy test 14. Participation in any other studies that involved investigational drugs or regimens in the preceding year 15. Any other condition, in the investigator's judgment, that increases the risk of darTregs infusion or prevents safe trial participation 16. Unwilling or unable to adhere to study requirements and procedures 17. Screening liver biopsy with any of the following histological criteria, as determined by the reading of a central pathologist (Table 9)
darTregs Infusion Inclusion Criteria	Subjects will initiate IS withdrawal and, at the beginning of the 2nd step of the withdrawal algorithm (week 1-2), undergo a final assessment to ensure eligibility for darTregs infusion. Subjects must meet the following criteria to receive darTregs infusion: 1. Stable liver tests, defined as ALT and either alkaline phosphatase or GGT either within normal limits OR <1.5 X baseline 2. No detectible circulating EBV or CMV DNA prior to darTregs infusion, assessed at the time of PBMC collection for manufacture 3. For subjects with HBV, no detectible circulating HBV DNA prior to darTreg infusion, assessed at the time of PBMC collection for manufacture 4. Able to understand and provide informed consent
darTregs Infusion Exclusion Criteria	Subjects who meet any of these criteria are not eligible for darTregs infusion: 1. Diagnosis of AR after initiation of IS withdrawal 2. Any vaccination given within 28 days prior to Treg collection for Treg production 3. Receipt of a vaccination within 14 days prior to Treg infusion 4. Unacceptable darTregs product 5. Positive pregnancy test 6. Clinical evidence of viral syndrome less than 7 days prior to darTregs infusion

Field Code Changed

Eligibility Criteria to Resume IS Withdrawal after darTregs infusion	Subjects are eligible to resume IS withdrawal after darTregs infusion if all criteria below are met: 1. Subject received at least 100×10^6 darTregs 2. ALT and either alkaline phosphatase or GGT remain within normal limits or ≤ 1.5 x baseline after darTregs infusion 3. For subjects with elevated liver tests as defined above, local pathology reading of liver biopsy 6-10 days after darTregs infusion is without acute rejection according to Banff criteria 4. IS withdrawal resumes no later than 14 days after darTregs infusion 5. Site principal investigator determines it is acceptable for the study subject to resume IS withdrawal
Study Stopping Rules	If one of the following events occurs any time during the study, the study will be paused for DSMB review: • Death or graft loss • Chronic Rejection • Severe AR (histological or steroid refractory rejection) If any of the following events occurs after darTregs Infusion, the study will be paused for DSMB review: • CTCAE Grade 3 or higher AEs attributable to the darTregs infusion including infusion reaction/cytokine release syndrome in 2 subjects • Any infections of Grade 3 or higher as defined in Section 14.3.1 • Any malignancy, including PTLD Failure to manufacture and supply the cellular product for 2 subjects will also require a pause in the trial.

2. INTRODUCTION

This statistical analysis plan includes pre-planned analyses related to the study objectives outlined in the protocol.

3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

The following analyses and reporting conventions will be used:

- Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form "n (%)." Percentages will be rounded to one decimal place.
- Numeric variables will be summarized using n, mean, standard deviation (SD), median, minimum (min), maximum (max). The min/max will be reported at the same level of significance as original data. The mean and median will be reported at one more significant digit than the precision of the data, and SD will be reported at two more significant digits than the precision of the data.
- The median will be reported as the average of the two middle numbers if the dataset contains an even number of observations.
- Test statistics including *t* and *z* test statistics will be reported to two decimal places.
- *P*-values will be reported to three decimal places if greater than or equal to 0.001. If less than 0.001, the value will be reported as "<0.001." A *p*-value can be reported as "1.000" only if it is exactly 1.000 without rounding. A *p*-value can be reported as "0.000" only if it is exactly 0.000 without rounding.

If departures from these general conventions are present in the specific evaluations section of this SAP, then those conventions will take precedence over these general conventions.

4. ANALYSIS SAMPLES

The summary descriptive analyses will be performed on the following subject populations:

1. All subjects who give informed consent and undergo the screening liver biopsy (Safety Sample).
2. The Intent-to-treat I sample (ITT1) will be defined as all subjects who initiate IS withdrawal
3. The Intent-to-treat II sample (ITT2) will be defined as all subjects who receive darTregs.
4. The Per-Protocol sample (PP) will be defined as all subjects who receive at least 300 x 10^6 cells of darTregs.

5. STUDY SUBJECTS

5.1. Disposition of Subjects

The disposition of all enrolled subjects will be summarized in tables and listed.

The numbers and percentages of subjects in each analysis sample, and completing each tapering level, as well as reasons for early termination from the study will be presented. For subjects discontinuing study treatment early, the reasons for discontinuing study treatment early will also be presented.

5.2. Demographic and Other Baseline Characteristics

Summary descriptive statistics for baseline and demographic characteristics will be reported for the ITT1, ITT2, PP samples. Characteristics to be summarized include age, race, ethnicity, sex, body weight at screening, height, time from transplant and primary reason for transplant.

6. STUDY OPERATIONS

6.1. Protocol Deviations

Protocol deviations will be listed by site with information such as type of deviation, severity of the deviation (major or non-major), date of occurrence, and the reason for the deviation. Protocol deviations will be summarized in tabular format by type of deviation.

6.2. Treatment Adherence

A summary of each subject's adherence to the tapering schedule will be presented in graphical form, with indications for pauses at each level and any deviations from the recommended dose at each taper level.

A summary of the number of cells infused will be presented for the darTregs as well as a categorical summary of the number of subjects that received between 100 and 300 x 10^6 cells of darTregs, and the number of subjects that received at least 300 x 10^6 cells of darTregs.

7. ENDPOINT EVALUATION

7.1. Overview of Analysis Methods

7.1.1. Multicenter Studies

Study subjects will be recruited from three study sites. Due to the small number of subjects in the study, study data will be analyzed as a whole, and no formal accommodation for site-to-site variation will be made.

7.1.2. Assessment Time Windows

Allowable visit windows for all scheduled visits are provided in Table 7-1.

Table 7-1 Visit Windows

High Frequency SOE Visit Windows	
Study Visit	**Visit Window**
Study Entry Eligibility Screening Visit (Screen 1)	Eligibility labs and biopsy should be within 8 weeks prior to initiation of IS withdrawal
Remote Visits (Telephone and Local Liver Tests)	± 3 days
Transplant Center Visits	± 14 days
Recipient PBMC Collection for Manufacturing	17 (UCSF) or 18 (Mayo) days before darTreg infusion
Medium Frequency SOE Visit Windows	
Study Visit	**Visit Window**
Entry into Medium Frequency SOE	Within 2 weeks after rejection (Appendix 7) Within 4 weeks after completing high frequency SOE (Appendix 8)
Week 2 (Appendix 7)	± 3 days
Remote Visits (Telephone and Local Liver Tests)	± 5 days
End of Study	± 14 days
darTregs Infusion SOE Visit Windows	
Study Visit	**Visit Window**
darTregs Eligibility Screening Visit	Between day 14-41 of the 2nd withdrawal step (10-13 weeks)
Treg Blood Draw for darTregs manufacturing	Between day 18-45 of the 2nd withdrawal step
Day 0 = darTregs Infusion	During the last 2 weeks of the 2nd withdrawal step
Day 1 after darTregs infusion	± 1 hour
Protocol biopsy visit after darTregs infusion	Between 6-10 days after darTregs infusion
Resumption of IS withdrawal	Between day 1-14 after darTregs infusion; corresponds to between day 36 – day 63 of the 2nd withdrawal step
Day 14 after darTregs infusion	± 2 days

Unscheduled visits may also occur throughout the study. All data will be included in analyses, regardless of time of assessment.

7.2. Primary Efficacy Endpoint

The primary efficacy endpoint is the number and proportion of subjects who reduce CNI by 75% and discontinue a 2nd IS drug, if applicable, with stable liver tests for at least 12 weeks.

7.2.1. Computation of the Primary Efficacy Endpoint

All subjects that successfully complete Step 5 of the tapering algorithm and have stable liver tests (ALT and alkaline phosphatase or GGT either ≤1.5 X upper limit of normal or ≤1.5 X baseline) for at least 12 weeks will be counted as meeting the primary efficacy endpoint

7.2.2. Primary Analysis of the Primary Efficacy Endpoint

The primary efficacy endpoint will be descriptively summarized with an exact binomial proportion and an exact 95% confidence interval using the ITT1 population.

7.2.3. Sensitivity Analyses of the Primary Efficacy Endpoint

A sensitivity analysis using both the ITT2 and PP populations will also be performed.

7.3. Primary Safety Endpoint

The primary safety endpoint is a descriptive analysis of three outcomes assessed 24 weeks after darTregs:

- CTCAE Grade 3 or higher AEs attributable to the darTregs infusion including infusion reaction / cytokine release syndrome
- study defined Grade 3 or higher infections (Protocol section 14.3.1)
- any malignancy, including PTLD

7.3.1. Computation of the Primary Safety Endpoint

All subjects who have any of the listed outcomes above will be counted as meeting the primary safety endpoint.

7.3.2. Primary Analysis of the Primary Safety Endpoint

The primary safety endpoint will be descriptively summarized with an exact binomial proportion and an exact 95% confidence interval using the ITT1 population.

7.3.3. Additional Analyses of the Primary Safety Endpoint

The outcomes in the primary safety endpoint will also be analyzed individually. A sensitivity analysis using the PP population will also be performed.

7.4. Secondary Efficacy Endpoints

All secondary efficacy endpoint analyses will use the ITT2 population, with a sensitivity analysis using the PP population.

7.4.1. Number and proportion of subjects who successfully withdrawal from all IS after darTregs infusion

Variable: Complete withdrawal from all IS

Analysis: Proportion with exact binomial 95% confidence limits

7.4.2. Duration that subjects tolerate complete IS discontinuation

Variable: Time off all IS

Analysis: Kaplan-Meier estimates of time to re-initiation of IS after completion of ISW (or censoring if no re-initiation occurs by the end of study). Duration will be displayed graphically with a Kaplan-Meier curve and the corresponding median and two-sided 95% confidence interval.

7.4.3. Number and proportion of subjects who successfully withdrawal from all IS after darTregs infusion and are operationally tolerant

Variable: Complete withdrawal from all IS and meets definition of operational tolerance (Protocol section 5.4)

Analysis: Proportion with exact binomial 95% confidence limits

7.5. Secondary Safety Endpoints

All secondary safety endpoint analyses will use the ITT1 population, with a sensitivity analysis using the PP population unless otherwise stated.

7.5.1. Rate of composite outcome measure including refractory AR, CR, re-transplantation, and death

Variable: Occurrence of refractory AR, CR, re-transplantation, or death

Analysis: Proportion with exact binomial 95% confidence limits

7.5.2. Incidence of biopsy proven or clinical AR and/or CR

Variable: Biopsy proven or clinical AR or CR

Analysis: Proportion with exact binomial 95% confidence limits; Also number of biopsy proven or clinical AR and/or CR AEs

7.5.3. Timing of biopsy proven or clinical AR and/or CR in ITT2 population

Variable: Time to biopsy proven or clinical AR and/or CR

Analysis: Kaplan-Meier estimates of time to re-initiation of IS after completion of ISW (or censoring if no rejection occurs by the end of study). Duration will be displayed

graphically with a Kaplan-Meier curve and the corresponding median and two-sided 95% confidence interval.

7.5.4. Severity of biopsy proven or clinical AR and/or CR in ITT2 population

Variable: Biopsy proven or clinical AR or CR

Analysis: Proportion of subjects in each observed BANFF severity category

8. SAFETY EVALUATION

8.1. Overview of Safety Analysis Methods

All safety analyses will be carried out using the safety sample defined in Section 4 unless otherwise noted. Missing safety information will not be imputed. These analyses will not be stratified by site.

8.2. Adverse Events

All AEs will be classified by system organ class (SOC) and preferred term, according to a standardized thesaurus (Medical Dictionary for Regulatory Activities [MedDRA] version 18.0). The severity of AEs will be classified using the National Cancer Institute's (NCI's) Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0. Each AE is entered on the electronic case report form (eCRF) once at the highest severity. As such, no additional data manipulation is needed to identify events.

An overall summary table will be developed to report the number of events and the number and percentage of subjects having at least one event in the following categories:

- AEs
- AEs indicated as serious
- AEs of interest (Acute Rejection, Clinical Rejection, Chronic Rejection, Malignancy, Study defined Grade 3 or higher infections, and Grade 3 or higher Infusion Reactions)AEs that lead to study drug discontinuation
- AEs with an outcome of death
- SAEs that were reported as being related to ISW or darTregs
- AEs reported by severity

In addition, AEs classified by MedDRA SOC and preferred term will be summarized for each treatment group and overall for each of the following:

- All AEs
- AEs by maximum severity
- AEs by relationship to ISW or darTregs (site investigator determination)

Summary tables will present the total number of events as well as the number and percentage of subjects experiencing the events. If a subject experiences the same AE on multiple occasions, the event will be counted once for each occurrence when reporting the number of AEs. When reporting the number of subjects experiencing the events, a subject will only be

counted once if they experience an event within the particular SOC or preferred term. Percentages will be based on the number of subjects in the safety population.

8.3. Deaths and Serious Adverse Events

Serious adverse events (SAEs) will be listed and summarized in the same manner described in Section 8.2~~8.3~~. As applicable, separate displays listing and summarizing death, including time to death and cause of death, will also be created.

8.4. Clinical Laboratory Evaluation

Clinical laboratory measurements include serum chemistry, urinalysis, and hematology. Results will be converted to standardized units where possible. For numeric laboratory results, descriptive statistics of laboratory values and the change from baseline of laboratory values will be presented for each analysis sample and overall. For categorical laboratory results, the number and percentage of subjects reporting each result will be presented for each analysis sample and overall.

Liver test data will be plotted to show patterns over time. For each test with a numeric result, data will be plotted as a spaghetti plot where each subject's values will be plotted and connected by line segments, forming one line per subject. For each test with a numeric result, quantile plots with treatment group means (or medians) as well as 25th and 75th percentiles plotted over time will be created. Tests with qualitative results (such as "present" or "positive") will not be plotted. Normal ranges will also be plotted using Harrison's normal range.

8.5. Vital Signs, Physical Findings, and Other Observations Related to Safety

8.5.1. Vital Signs

Vital sign measures will be plotted over time for each subject. If needed to fulfill regulatory reporting obligations, listings of vital sign data over time may also be created.

8.5.2. Physical Examinations

If needed to fulfill regulatory reporting obligations, listings of physical examination data will be produced. These listings may include, but are not limited to hepatic body system results.

9. INTERIM ANALYSES AND DATA MONITORING

The progress of the study will be monitored by the Data and Safety Monitoring Board (DSMB). The NIAID Transplant DSMB will be chartered to review safety data and to make recommendations regarding continuation, termination, or modification of the study. The DSMB will formally review the safety data at least yearly. The discontinuation of study treatment will also be periodically reported to the DSMB.

In addition, safety data will be reviewed by the DSMB when an event occurs that is of sufficient concern to the National Institute of Allergy and Infectious Diseases (NIAID) medical monitor or protocol chair to warrant review, or when an event occurs that could contribute to a predefined stopping rule specified in the protocol.

Findings will be reported to Institutional Review Boards (IRBs) and health authorities.

10. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL