STATISTICAL ANALYSIS PLAN
31 August 2017

Bone Marrow Transplantation and High Dose Post-Transplant Cyclophosphamide for Chimerism Induction and Renal Allograft Tolerance

PROTOCOL NUMBER ITN054ST
IND # 118,975

SPONSOR

This clinical study is supported and conducted by the Immune Tolerance Network, which is sponsored by the National Institute of Allergy and Infectious Diseases.

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1. ANALYSIS PLAN SYNOPSIS

Accrual Objective	The accrual goal for this study was six renal transplant recipient-donor pairs who meet the per- protocol (PP) analysis sample definition. The protocol was stopped after accruing one transplanted subject due to a re-assessment of the risks related to the study.
Study Design	This trial was designed to be a phase II, single arm, open-label, single center pilot study to assess a reduced-intensity conditioning regimen, bone marrow transplantation and high dose PT/Cy in six recipients of renal allografts from Human Leukocyte Antigen-haploidentical (HLA-haploidentical) living related donors
Primary Endpoint	The primary endpoint was designed to be the proportion of participants who achieved operational tolerance, defined as remaining off all immunosuppression 52 weeks after completion of immunosuppression withdrawal with: a) no evidence of biopsy-proven allograft rejection and b) acceptable renal function, defined as a serum creatinine that has increased no more than 25% above baseline (see protocol section 6.5.1 for baseline thresholds) at the primary endpoint visit. All participants who successfully complete immunosuppression withdrawal were to undergo a protocol biopsy at this time point to assess the primary endpoint.
Secondary Endpoints	**Safety** 1. The incidence, severity and duration of graft versus host disease (GVHD) in transplanted participants. 2. The incidence, severity and duration of engraftment syndrome in transplanted participants. 3. The proportion of transplanted participants who died. 4. The proportion of transplanted participants with acute renal allograft rejection demonstrated by a biopsy or clinically if a biopsy could not be performed. If participant had allograft dysfunction as defined in protocol section 6.5 and could not undergo biopsy he or she would be presumed to have rejection without biopsy confirmation. 5. The histological severity of biopsies demonstrating acute rejection as measured by Banff Grade per Banff 2007 Classification Renal Allograft Pathology[1]. 6. The proportion of transplanted participants with chronic T cell-mediated or antibody-mediated rejection. This assessment also included progressive interstitial fibrosis/tubular atrophy (IF/TA), transplant glomerulopathy or chronic obliterative arteriopathy without an alternative, non-rejection-related cause. See Banff 2007 Classification Renal Allograft Pathology for definition of terms[1]. 7. Time from transplant to the first episode of acute rejection requiring treatment. 8. The incidence, severity and duration of adverse events including infection, wound complications, post-transplant diabetes, hemorrhagic cystitis and malignancy. 9. The proportion of transplanted participants who developed donor specific antibody: a. after initiation of immunosuppression withdrawal b. at any time during trial participation 10. The time to absolute neutrophil recovery. This was defined as the interval from the neutrophil nadir to the first day of three consecutive daily neutrophil counts $\geq$ 500 per μL. The neutrophil nadir was defined as the first day post-transplant on which the absolute neutrophil count (ANC) was

	below 500 per μL. 11. The time to platelet count recovery. This is defined as the interval from transplant to the first day of a platelet count of 20,000 per μL without a prior platelet transfusion in the preceding seven days. **Efficacy** 1. The proportion of transplanted participants who remained off immunosuppression for at least 52 weeks including those in whom the 52 week biopsy was not performed. 2. The proportion of participants who remained free from return to immunosuppression for the duration of the study. **Mechanistic** 1. The correlation of operational tolerance with the extent and durability of donor hematopoietic and T cell chimerism as measured by serial short tandem repeat analysis of recipients' peripheral blood mononuclear cells (PBMCs) and T cells. 2. The correlation of operational tolerance with other biomarkers such as cell subsets or gene expression. **The following secondary endpoints pertaining to safety and efficacy were to be assessed only in participants who completed tacrolimus withdrawal:** 1. Immunosuppression-free duration, defined as time from completion of tacrolimus to end of trial participation or to time of restarting immunosuppression. 2. Time from completion of tacrolimus withdrawal to first episode of acute rejection or presumed acute rejection, defined per Banff 2007 Classification Renal Allograft Pathology[1]. 3. Time from completion of tacrolimus withdrawal to first diagnosis of chronic T cell mediated or antibody-mediated rejection. This assessment also included IF/TA, transplant glomerulopathy or chronic obliterative arteriopathy without an alternative, non-rejection related cause. See Banff 2007 Classification Renal Allograft Pathology[1].
Analysis Methods for Primary and Secondary Endpoints	Due to the early study closure after one transplanted subject none of the endpoints will be analyzed.
Safety Analysis	All adverse events will be listed and classified by body system and preferred term according to MedDRA dictionary. All medication use will be listed.

2. REFERENCES

1. Solez K, Colvin RB, Racusen LC, et al. Banff 07 classification of renal allograft pathology: updates and future directions. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons.* 2008;8(4):753-760.