

A Two Part, Phase 1/2, Safety, PK and PD Study of TOL101, an Anti-TCR Monoclonal Antibody for Prophylaxis of Acute Organ Rejection in Patients Receiving Renal Transplantation

This study is currently recruiting participants.

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| Principal Investigator: | Stuart Flechner, MD |
| Sponsor: | Tolera Therapeutics, Inc |
| Participating Sites: | Cleveland Clinic, Cleveland, OH University of Colorado, Denver, CO University of Michigan, Ann Arbor, MI St. Barnabus Medical Center, Livingston, NJ Medical University of South Carolina, Charleston, SC Baylor University Medical Center, Dallas, TX University of Utah, Salt Lake City, UT |
| ClinicalTrials.gov Identifier: | NCT01154387 |

Purpose

Induction therapy with antibodies is administered during transplant surgery and for a short period of time following transplant surgery in an effort to render the immune system less able to mount an initial rejection response. In general, induction therapy is associated with better outcomes compared to the absence of induction therapy. However, currently used induction agents, some of which are not labeled or indicated for induction therapy in transplantation, have drawbacks related to long-term immune system suppression increasing susceptibility to opportunistic infections or malignancies, and other immune-mediated side effects.

An unmet medical need exists for a more specific approach to prevent acute organ rejection, without unnecessarily exposing the patient to non-specific or open-ended immune suppression, which may exacerbate the risks of infections and malignancies. TOL101 is a novel antibody that targets a very specific immune cell type that is critical in the acute organ rejection response. In this two-part study, TOL101 will be evaluated for the prophylaxis of acute organ rejection when used as part of an immunosuppressive regimen that includes steroids, MMF, and tacrolimus in first time kidney transplant recipients.

This study will test the hypothesis that a more specific approach (with TOL101) to prevention of acute organ rejection may provide similar or better efficacy than the currently used induction antibodies (such as Anti-Thymocyte Globulin or Thymoglobulin) while carrying fewer risks in terms of opportunistic infections, malignancies and adverse effects.

Objectives

Primary Objective:

To assess the safety and tolerability of ascending doses of TOL101 and the effectiveness of TOL101 to target and downregulate T cells in patients undergoing first renal transplantation

Secondary Objective:

1. The effects of ascending doses of TOL101 on CD3+ T lymphocyte numbers and other immune cell subsets
2. The pharmacokinetic (PK) profile of TOL101 in renal transplant recipients and the exposure-response (PK parameter to CD3+ T lymphocyte numbers) relationship over time
3. Biopsy-proven acute organ rejection
4. Graft survival
5. Patient survival
6. Renal function by measured GFR at 6 months post-transplant
7. Delayed graft function
8. Immunogenicity of TOL101 by measurement of anti-TOL101 antibodies

Study Design

This is an open label, two part, multicenter, first-in-humans study designed to investigate the safety, preliminary efficacy, and immunogenicity of TOL101 administered to first time kidney transplant recipients. It has a modified adaptive design including an initial dose-escalation component followed by a randomized active control component. The first part of the study (Part A) is planned to enroll between 4-14 cohorts (2-3 subjects per cohort) at successively higher dose levels with the goal of identifying two

potentially therapeutic dose levels (PTD-A & PTD-B) to be evaluated further in a larger number of subjects in the second part of the study (Part B), using a randomized, parallel arm design with Thymoglobulin as the standard of care comparator.

Subjects will receive a daily dose of TOL101 for 6-10 doses (or Thymoglobulin for 3-7 doses in Part B) beginning in the operating room on the day of transplant. To minimize the risk of infusion-related reactions, all subjects will be pre-treated with intravenous diphenhydramine and methylprednisone prior to the first and second doses of study drug. Subjects in the first cohort and any cohort testing a new TOL101 dose for the first time will be dosed no closer than 48 hours apart. All subjects will receive an immunosuppressive regimen consisting of steroids, mycophenolate mofetil (MMF), and tacrolimus. They also will receive anti-infective prophylaxis for CMV and PCP according to the protocol.

Part A:

Part A is the dose escalation phase of the study in which all subjects will receive TOL101 daily at one of the following dose levels: 0.28mg, 1.4mg, 7mg, 14mg, 28mg, 42mg, or 56 mg, or until two PTDs are identified. The first cohort of subjects at each dose level will consist only of subjects who are scheduled to receive kidneys from Living Donors (LD). Following successful completion of an LD cohort (3 subjects who meet safety and PD criteria per the Data Monitoring Committee (DMC)), another cohort consisting of only cadaver donor (CAD) recipients will be enrolled at the same dose level. If this CAD cohort also is successful (3 subjects who meet safety and PD criteria per the DMC), that dose level will be considered the PTD-A for testing in Part B.

Part B:

Part B will be a randomized, open-label, three-arm design (with an adaptive capacity to return to Part A as described below) comparing the safety, pharmacodynamics and preliminary efficacy of the two PTDs (PTD-A and PTD-B) identified in Part A with an active control, Thymoglobulin (rATG), a widely used induction therapy in the United States (US). Eligible subjects will include recipients of kidney allografts from LDs or CADs, to be stratified based on donor type. Subjects will be randomized 3:3:2 to PTD-A, PTD-B or to the comparator arm of Thymoglobulin.

Eligibility

Inclusion Criteria:

1. Recipient of a primary renal transplant from a living or standard criteria cadaveric donor
2. Male or female 18-60 years of age
3. Recipient with a PRA < 20%

Exclusion Criteria:

1. Previous solid organ transplant
2. Recipient of HLA-identical kidney allograft transplant
3. Recipient of an ABO incompatible donor kidney
4. Known HIV infection or other major infection
5. History of malignancy within 3 years (excluding treated basal cell or squamous cell carcinoma of the skin) prior to enrollment
6. History of tuberculosis
7. Recipient with cardiovascular disease
8. Treatment with immunosuppressive medications within 1 month prior to enrollment
9. Known or suspected allergy to mice
10. Pregnant or lactating
11. Unable or unwilling to participate in all required study activities for the duration of the study (6 months)

Enrollment Information

Estimated Enrollment: 85

Study Start Date: July 2010

Estimated Completion Date: October 2011

Contacts

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