

Background

More than 40,000 people receive a kidney transplant annually in the United States. Twenty-five years ago the calcineurin inhibitor tacrolimus in conjunction with standard polypharmacy regimens was shown to reduce cellular and antibody mediated rejection improving short term outcomes for transplant recipients and making transplant a more viable option for patients in need of an organ transplant. Indeed, kidney transplant survival at 12 months post transplant is greater than 90%. Although tacrolimus has had a dramatic impact on 1 year survival rates for organ transplant, long term survival rates (> 3 years) have not changed since its introduction suggesting that further improvements are needed.

CD40L is a costimulatory type II transmembrane receptor for CD40. Binding of CD40L on T helper cells to CD40 on antigen-presenting cells induces multiple downstream immune and inflammatory responses. These include B and T cell clonal expansion; antibody production, class-switching, and maturation; and pro-inflammatory cytokine and chemokine production. Tegoprubart (AT-1501) is a humanized IgG1, kappa monoclonal antibody that blocks CD40L (CD154, gp39) binding to CD40.

Historical studies over the last 30 years have shown that costimulatory inhibition is an effective strategy for the prevention of transplant rejection in nonhuman primates. These studies suggest the inhibition of CD40L is more effective at preventing transplant rejection than tacrolimus and more effective than the inhibition of other costimulatory signaling pathways.

Tegoprubart has been shown effective in the prevention of cellular and antibody mediated rejection in nonhuman primates and is currently being studied in kidney transplant recipients. Tegoprubart is being evaluated to determine whether it can safely prevent kidney transplant rejection and superior graft function as compared to current standard of care with tacrolimus.

Methods

This is a phase 1B safety study of tegoprubart in the prevention of transplant rejection for adults undergoing a de novo kidney transplant procedure at five transplant centers in Canada, Australia, and the United Kingdom. A minimum of 6 and a maximum of 12 adult participants receiving a kidney transplantation from either a living or deceased donor will be enrolled.

Inclusion/Exclusion

To be eligible, this must be their first transplant, they must be seropositive for EBV, free of donor specific antigens, have low panel reactive antibodies, and the organ cannot be from an extended criteria donor or have a prolonged cold ischemia time.

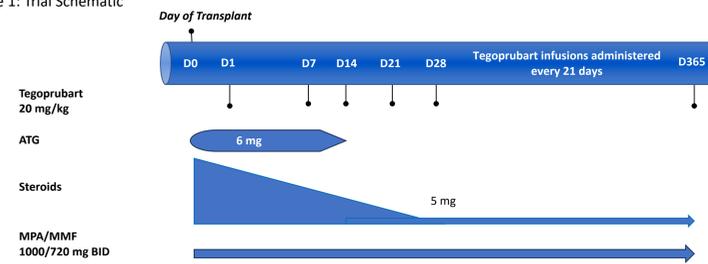
Treatment Schedule (Figure 1)

All participants receive a total dose of 6 mg of rabbit antithymocyte globulin (rATG) starting on day of transplant through the first 10 days after transplant. Participants receive corticosteroids starting on day of transplant tapering to a 5 mg dose by day 28 post transplant. Participants receive 1000 or 720 mg BID mycophenolate mofetil or mycophenolate sodium respectively starting on day of transplant. Participants receive 20 mg/kg of tegoprubart via IV infusion weekly until day 28 followed by infusions every 21 days.

Eleven participants enrolled in the study to date. Participants will remain on study for a year, after which time they will have the option of continuing tegoprubart in an extension study. The primary endpoint is safety. Other endpoints include characterizing the pharmacokinetic profile of tegoprubart, the incidence of biopsy proven rejection (BPAR), changes in estimated glomerular filtration rate (eGFR) and exploratory biomarkers including donor derived cell free DNA.

Results

Figure 1: Trial Schematic



Demographics & Disposition

Participant	Age/Gender	Ethnicity	Donor	Underlying Disease	Days Post TxP (DS: Discontinued Study)	Status
1	60/F	White	Living	Polycystic Kidney Disease	217 (DS)	Discontinued study on day 217 due to alopecia and fatigue
2	77/F	White	Deceased	Diabetes	380	
3	62/M	White	Living	Cystic Disease	54 (DS)	Discontinued study on day 54 due to Polyomavirus viremia
4	68/M	White	Living	Diabetes	217	
5	23/F	Asian	Living	Glomerulonephritis	181	
6	44/M	White	Deceased	Polycystic Kidney Disease	154	
7	65/M	White	Living	Type 1 Diabetes	146	
8	57/F	White	Living	Diabetes	83	
9	35/M	Other	Living	Glomerulonephritis	75	
10	56/F	White	Living	Polycystic Kidney Disease	60	
11	59/M	White	Living	Diabetes	43	

Treatment Emergent Adverse Events*

System Organ Class	Preferred Term	N (%)
Gastrointestinal	Diarrhea	5 (45%)
	Constipation	4 (36%)
	Nausea	3 (27%)
	Vomiting	2 (18%)
Infections	Polyomavirus viremia	4 (36%)
	Urinary tract Infection	2 (18%)
Procedural Complication	Complications of Transplant Surgery	3 (27%)
	Procedural pain	2 (18%)
Blood and Lymphatic System	Leukopenia	2 (18%)
	Neutropenia	2 (18%)
Cardiac	Tachycardia	2 (18%)
General	Oedema peripheral	2 (18%)
	Pyrexia	2 (18%)
Metabolism	Hypoglycemia	2 (18%)
	Hypophosphatemia	2 (18%)
Musculoskeletal and Connective Tissue	Back pain	2 (18%)
Skin and Subcutaneous tissue	Alopecia	2 (18%)
Vascular	Hypertension	2 (18%)
	Hypotension	2 (18%)

* Occurring in 2 or more study subjects as of October 13, 2023. Of all the reported TEAEs, 7 events experienced by 3 subjects are reported as serious. These SAEs include neutropenia, acute kidney injury, T-cell rejection, Polyomavirus viremia, anterior abdominal wall collection, and hyperkalemia

Figure 2: Mean eGFR

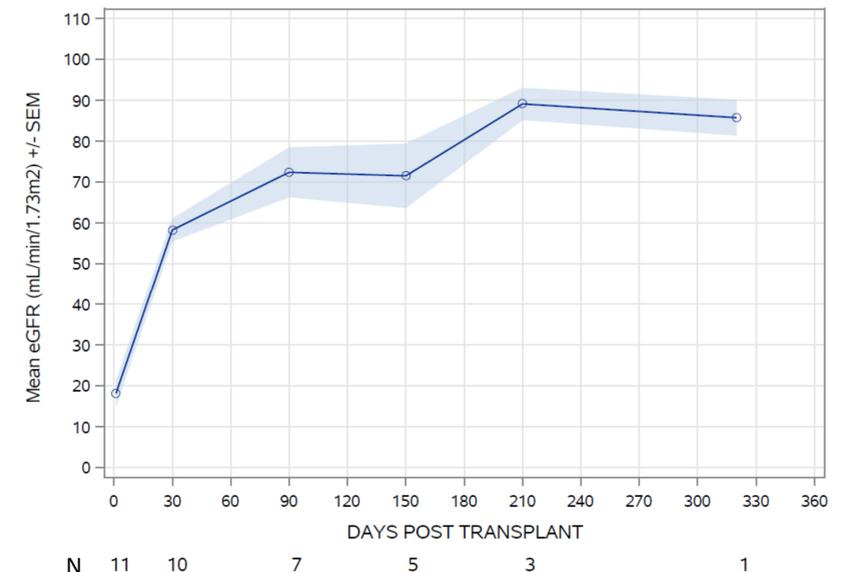


Figure 2: Estimated glomerular filtration rate (eGFR) as of October 19, 2023, calculated using the chronic kidney disease epidemiology collaboration (CKD-EPI) creatinine equation. N is the number of participants at that time contributing data to mean eGFR calculation.

Conclusions

- Preliminary data suggest that tegoprubart is safe and well tolerated in patients undergoing de novo kidney transplantation.
- Aggregate mean eGFR is greater than or equal to 60 mL/min/1.73m² starting thirty days post transplant.
- 1 patient experienced a T cell mediated rejection (Banff score 1a) on day 99 based on local pathology. The patient was treated and remains in the study.
- 1 patient experienced a surgical related acute tubular necrosis on day 0 (prior to administration of study drug) which impacted their kidney function. This patient continues to be in the study.
- There have been no reports of donor specific antibodies (DSA).
- There have been 4 cases of Polyomavirus viremia and viral titers have been well managed with transient reductions in immunosuppressive medications as per standard of care. There have been no cases of BK nephropathy.
- There have been no cases of CMV infection, hyperglycemia, new onset diabetes, or tremor.
- These preliminary data suggest tegoprubart is effective in the prevention of kidney transplant rejection.