Long-Term Follow-Up of a Phase 2 Clinical Trial to Induce Tolerance in Living Donor Renal Transplant Recipients

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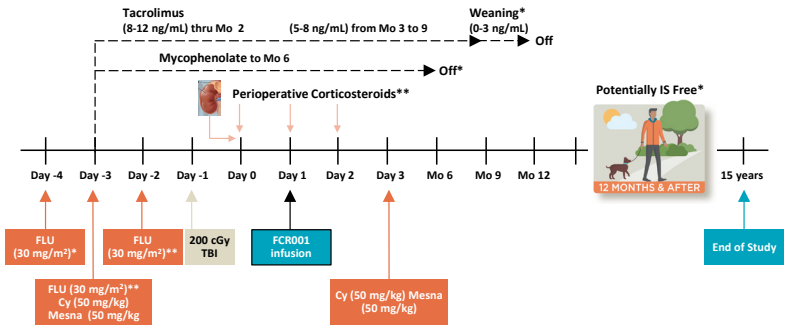
INTRODUCTION

- Long-term outcomes in living donor kidney tranplant (LDKT) patients are suboptimal due to the complications associated with taking lifelong chronic immunosuppression medications
- Talaris Therapeutics is developing FCR001, a single-dose, investigational cell therapy intended to induce durable immune tolerance to transplanted solid organs, without need for chronic immunosuppression
- Facilitated Allo-HSCT Therapy has the potential to reprogram the immune system to recognize transplanted solid organs as "self," avoiding organ rejection without the limitations associated with immunosuppression (IS)
- Purpose: An open-label, single-arm Phase 2 trial was initiated to investigate whether administration of FCR001 along with nonmyeloablative conditioning can induce durable immune tolerance to a donated kidney in adult LDKT recipients

METHODS

- 37 subjects were transplanted in a phase 2 trial based upon tolerogenic CD8+/TCR-facilitating cells (FCR001) to induce tolerance in recipients of living donor renal allografts (KTx)
- Recipients were conditioned with fludarabine (30mg/m2/dose, days -4, -3, -2), cyclophosphamide (50mg/kg/dose, day-3 and+3), 200 cGy TBI (day-1) followed by KTx (day0)
- A G-CSF mobilized product was apheresed from the donor, processed to remove graft-versus-host disease (GVHD)-producing cells yet retain CD34+ cells and FC, and cryopreserved until administration day+1 post-KTx
- Mycophenolate mofetil (MMF) and tacrolimus IS was weaned and discontinued at 1 year if post-Tx chimerism, normal renal function and normal KTx biopsy were noted
- The primary endpoint was to determine whether the administration of FCR001 can induce durable tolerance to the donated kidney and substantially reduce or eliminate the requirement for immunosuppression within 12 months following transplant
  - This trial will continue to monitor the FCR001-dosed patients for up to 15 years from the time of their transplant and thereby provide long-term follow-up safety and durability data

Figure 1. Phase 2 Trial Design



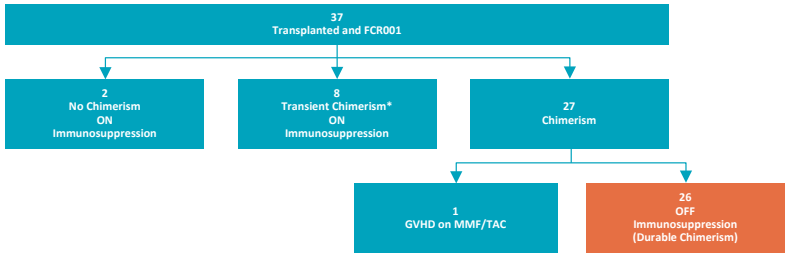
*Assuming no biopsy-proven acute rejection (BPAR); stable kidney function; >50% donor chimerism; no GvHD.
**Methylprednisolone 500 mg IV on Day 0 in OR; 250mg Day 1 and 125 mg Day 2.
cGy, centigray; Cy, Cyclophosphamide; FLU, Fludarabine; IS, chronic immunosuppression; Mesna, mercapto-ethyl sulfonate; TBI, total body irraditation.

Table 1. Phase 2 Trial Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• 18 and 65 years of age	• Clinically active bacterial, fungal, viral, or parasitic infection
• Meet the institution's criteria for living renal and stem cell transplantation	• Clinical or serologic evidence of viral infection
• Cross-match negative (donor-recipient)	• HBV, HCV, HIV positive
• No evidence of donor-specific antibody (DSA) presently or historically	• Pregnancy
• HLA matching not required	• Previous radiation therapy at a dose which would preclude TBI
	• PRA >20%
	• BMI >35 or <18
	• Unrelated female donor to male recipient, to be implemented moving forward

DSA, donor specific antibody; HBV, hepatitis b virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; TBI, total body irradiation; PRA, panel reactive antibodies; BMI, body mass index.

Figure 2. Phase 2 Trial Inclusion of 37 Subjects

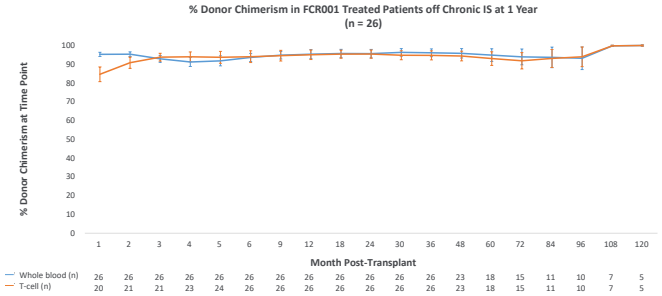


GVHD, graft versus host disease; MMF/TAC, mycophenolate mofetil tacrolimus.

RESULTS

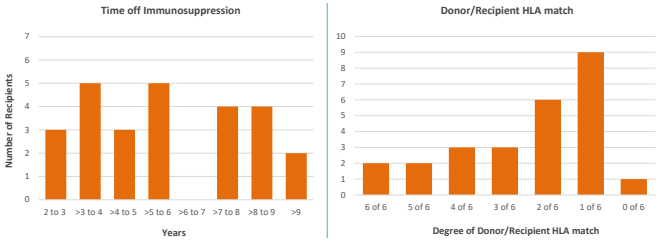
- Patients ranged in age from 18 to 64 years and were 6/6 HLA matched related to 0/6 matched unrelated
- Factors limiting HSC engraftment
  - Suboptimal HSC/FC cell counts
  - Failure to administer a post-transplant dose of cyclophosphamide per protocol
  - The presence of infection at the time of the transplant
  - A lack of adherence to best clinical practices for management of allo-HSCT patients, and a Panel Reactive Antibody (PRA) greater than 20%
- Durable chimerism allowing for full IS withdrawal developed in 26 patients (time off IS 37- 124 months); the majority (23/26) showed full (>95%) donor whole blood/T cell chimerism (**Figure 3**)
  - Every patient weaned off chronic IS by month 12 has remained off chronic IS for full duration of follow up (median >6 years, longest >11 years) (**Figure 4**)

Figure 3. Percentage of Donor Chimerism in FCR001-Treated Patients Who Are Off Chronic Immunosuppression



Values are mean +/- standard error. N indicates the number of FCR001 treated patients weaned off IS at approximately one year post-transplant for whom % whole blood and T-cell donor chimerism were measured at that time point.
IS, immunosuppression.

Figure 4. Distributions of 26 Patients Durably Free of Chronic Immunosuppression



Efficacy Summary

- 26/37 (70%) subjects achieved stable chimerism and weaned off immunosuppression:
  - No patients experienced Biopsy Proven Acute Rejection (BPAR) or Donor Specific Antibody (DSA)
  - All had normal renal histology and preserved renal function, mean eGFR at 5 years was 66.1 ml/min
  - 7/7 subjects with sustained chimerism off IS and with autoimmune kidney disease had no recurrence

	Durable Chimerism		Disease Recurrence	
Condition	Durable Chimerism	Disease Recurrence	Transient or no Chimerism	Disease Recurrence
IGA Nephropathy	4	0	2	1
Focal Segmental Glomerulosclerosis	2	0	0	0
Membranous Glomerulonephritis	1	0	1	1
Total	7	0	3	2

IGA, immunoglobulin A.

- Of the 7 subjects with BPAR, all were transiently chimeric, not off IS (4 were on monotherapy with Tacrolimus or Sirolimus; 2 were maintained on very low levels of tacrolimus / MMF dual therapy due to serious infections)

Safety Summary

- Recipient Safety: approximately 235 patient-years of exposure of FCR001
  - Post-transplant nadir period is brief (< 2-3 weeks), mostly managed as outpatient; limited need for blood product support; 4-day median time for neutrophil and platelet recovery
  - Nonmyeloablative conditioning performed as inpatient; 1 subject developed idiosyncratic reaction to Cyclophosphamide
  - No infusion reactions
  - 3 deaths (month 11 – GVHD see below; year 4 – lung cancer in heavy smoker; year 3.5 – pneumococcal sepsis in a subject traveling back from India, who was not compliant with and did not receive revaccinations per stem cell protocol)
  - 3 kidney graft losses (month 3, 9 and 47; all were transient chimeric subjects and none were taken off IS; their IS was markedly decreased due to concurrent severe infections)
  - 2 cases of GVHD: 1 (Day 135, acute grade 2 after switching to sirolimus) treated with steroids, off IS, later developed chronic GVHD with ocular and musculoskeletal symptoms; 1 (month 1, acute grade 3) requiring 3rd line treatment resulting in death (month 11)
- Donor Safety: No Serious AEs; AEs primarily musculoskeletal pain, fatigue (related to mobilization meds)

CONCLUSIONS

- 26/37 (70%) patients achieved stable chimerism and weaned off IS. Every patient weaned off IS by month 12 has remained off IS for the full duration of follow up (median >6 years, longest >11 years)
- The ability to discontinue chronic immunosuppression was observed across all levels of donor and recipient HLA matching, with 19 out of 26 recipients (73%) who were able to durably discontinue their chronic immunosuppression having an HLA match of three or less to their donor. We did not observe any correlation between the degree of HLA mismatch and any of durable chimerism, safety, or GVHD
- Through January 31, 2021, we have accumulated a total of approximately 235 patient-years of exposure to FCR001 in LDKT, and the safety profile observed in our patients was generally consistent with that expected if a patient were to separately receive both a standard kidney transplant and an allo-HSCT with nonmyeloablative conditioning
- Most adverse events occurred during the first 12 months post-transplant when the patients were on conventional immunosuppression, and no events of infusion toxicity following FCR001 administration were observed

Acknowledgments

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