Joseph Leventhal, MD, PhD, FACS
Fowler McCormick Professor of Surgery
Feinberg School of Medicine, Northwestern University, Chicago, Illinois, United States

I have financial relationship with:
Talaris Therapeutics:
Grant/ Research Support

My presentation includes discussion of an investigational product, FCR001.

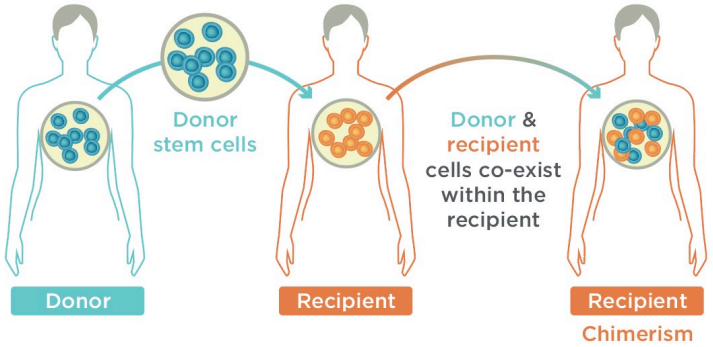
Long-Term Follow-Up of a Phase 2 Clinical Trial to Induce Tolerance in Living-Donor Kidney Transplant Recipients

J Leventhal,[1] J Galvin,[2] J Mathew,[3] L Gallon,[3] D Belshe,[4] M Gibson,[4] K Ravindra,[5] M Horwitz,[6] S Ildstad[7]

[1]Feinberg School of Medicine, Northwestern University, Chicago, IL; [2]University of Illinois Chicago, Chicago, IL; [3]Northwestern University, Chicago, IL; [4]Comprehensive Transplant Center, Northwestern University, Chicago, IL; [5]Department of Surgery, Duke University Medical Center, Durham, NC; [6]Adult Blood and Marrow Transplant Program, Duke University Medical Center, Durham, NC; [7]Talaris Therapeutics, Louisville, KY

Transplant, Allogeneic Tolerance, and Chimerism

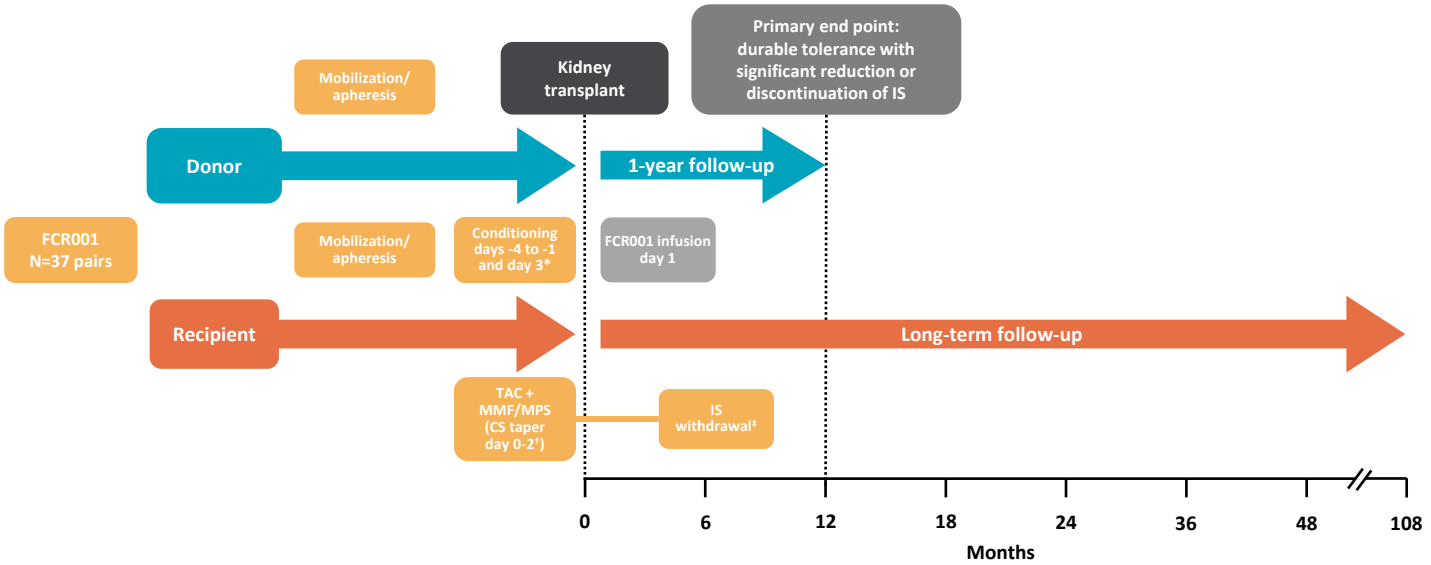
- The risk of transplant rejection increases in donor-recipient pairs with greater HLA mismatch[1]
  - Chronic IS often helps prevent organ rejection, however, contributes to morbidity and mortality
- Facilitated allo-HSCT using **FCR001** may prevent organ rejection while allowing for IS withdrawal
- **FCR001** is an investigational allogeneic stem cell therapy derived from mobilized peripheral blood from the kidney donor and administered to the recipient following NMA conditioning and kidney transplant
- **FCR001** contains an optimized number of HSCs, facilitating cells, and αβTCR+ T-cells that could induce chimerism and immune tolerance across HLA mismatches[2]
  - Facilitating cells promote stem cell engraftment in unmatched recipients, prevent GvHD in mouse models, and induce antigen-specific T_{regs} and B_{regs}



Allo-HSCT, allogeneic hematopoietic stem cell transplant; B_{regs}, regulatory B-cells; HLA, human leukocyte antigen; GvHD, graft-vs-host disease; HSC, hematopoeitic stem cell; IS, immunosuppresion; NMA, nonmyeloablative; T_{regs}, regulatory T-cells.

1. Leeaphorn et al. *Clin J Am Soc Nephrol*. 2018. 2. Leventhal et al. *Hum Immunol*. 2018.

FCR001 Phase 2 Trial Design[1,2]



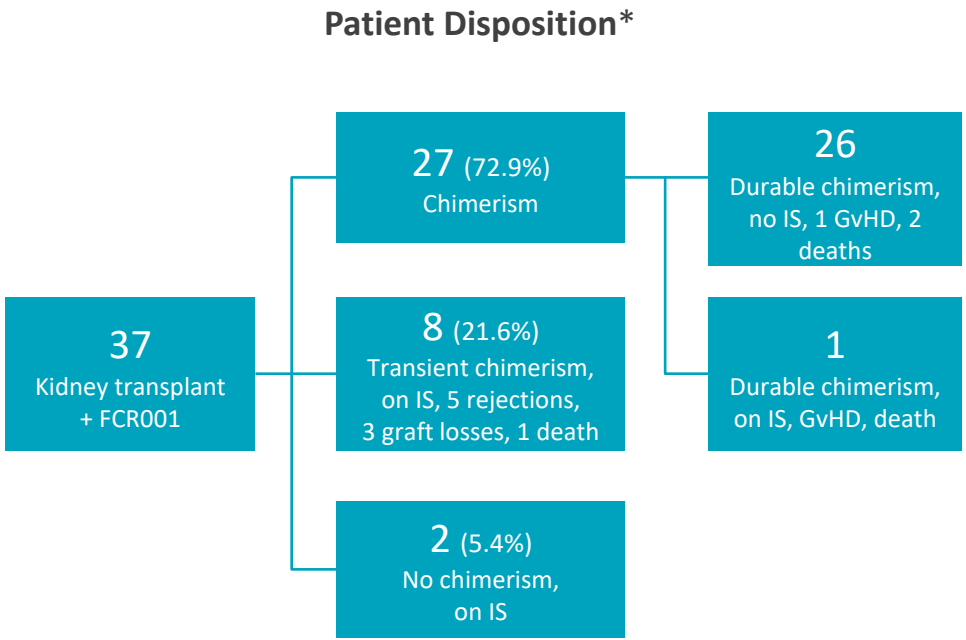
- Donor and recipient pairs were adults between the ages of 18 and 65 years who met eligibility criteria[1]
- All levels of HLA mismatching between donor and recipients were allowed[1]

As of March 01, 2022, 33 recipients had ≥36 months of follow-up and 21 had ≥60 months of follow-up. Exposure to FCR001 was approximately 235 patient-years[1,2]

BPAR, biopsy-proven acute rejection; CS, corticosteroid; GvHD, graft-vs-host disease; HLA, human leukocyte antigen; IS, immunosuppression; MMF, mycophenolate mofetil; MPS, mycophenolate sodium; TAC, tacrolimus.
*The nonmyeloablative conditioning regimen consisted of low total doses of fludarabine (30 mg/m^2 on days -4 to -2) and cyclophosphamide + mesna (50 mg/kg each on day -3) and one-time 200 centigray total body irradiation on day -1. Patients also received cyclophosphamide + mesna (50 mg/kg each) on post-transplant day 3.[1] †Methylprednisolone 500 mg IV on day 0 in the operating room; 250 mg day 1 and 125 mg day 2.[1] ‡In patients demonstrating no BPAR, stable kidney function, >50% donor chimerism, and no GvHD, MMF were withdrawn at the end of month 6 and TAC weaning took place between month 9 and month 12.[1]

1. Leventhal J et al. *Am J Transplant*. 2021;21(suppl 3). Accessed February 9, 2022. https://atcmeetingabstracts.com/abstract/long-term-follow-up-of-a-phase-2-clinical-trial-to-induce-tolerance-in-living-donor-renal-transplant-recipients-3/. 2. SEC. Filed May 31, 2021. Accessed February 9, 2022. https://www.sec.gov/Archives/edgar/data/0001827506/000119312521146474/d51356ds1a.htm.

The Majority of Patients in the Phase 2 Trial of FCR001 Discontinued Immunosuppression



As of March 01, 2022
(median follow-up time >6 years),
70% (n=26/37) of patients had stable chimerism and were off IS (time off IS 48–136 months)
with no BPAR and normal kidney histology/function[1]

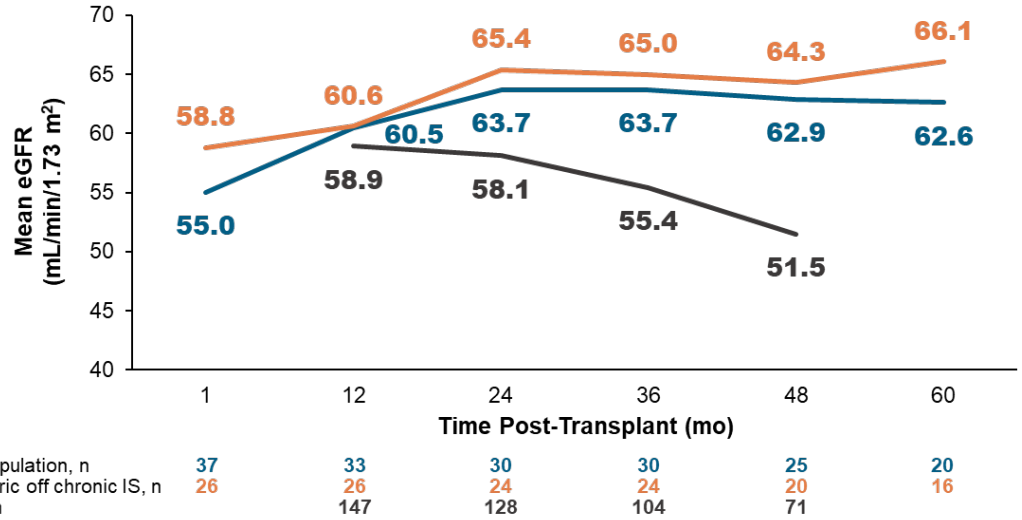
Overall patient survival: 89.2%
Death censored graft survival: 91.9%

BPAR, biopsy-proven acute rejection; GvHD, graft-vs-host disease; IS, immunosuppression.

*Data as of March 01, 2022.

FCR001 Preserved Kidney Function in Patients Off Chronic Immunosuppression

Mean eGFR Post-Transplant[1,2,a,b]



Kidney function was preserved in patients who were chimeric and discontinued immunosuppression: 66.1 mL/min/1.73 m^2 mean eGFR at 5 years

eGFR, estimated glomerular filtration rate; mo, months; ITT, intent to treat; SoC, standard of care.
[a]Retrospective analysis of patients at the same site between 2009 and 2012 who met FCR001 phase 2 study eligibility criteria (n=132) and received SoC immunosuppression. [b]Because of the retrospective nature of the analysis, which is not included in the Talaris Therapeutics database, data from the SoC cohort do not include baseline eGFR data or Year 5 data.

1. Tollerud D et al. *Am J Transplant*. 2021;21(suppl 3). Accessed February 9, 2022. https://atcmeetingabstracts.com/abstract/peripheral-blood-hematopoietic-chimerism-a-robust-biomarker-for-transplantation-tolerance/ 2. SEC. Filed May 31, 2021. Accessed February 9, 2022. https://www.sec.gov/Archives/edgar/data/0001827506/000119312521146474/d51356ds1a.htm.

Graft Loss[1,2,*]

Graft loss occurred in 3 patients in whom IS was markedly decreased or temporarily stopped because of severe infections. Graft losses occurred at[2]:

- Month 3: graft thrombosis during a viral sepsis episode in which the patient was hypotensive, hemodynamically unstable, and required continuous veno-venous hemofiltration[2]
- Month 9: the patient experienced sepsis that was unresponsive to antibiotics, requiring complete interruption of IS[2]
- Month 47: loss of donor chimerism at month 4 secondary to CMV reactivation; switch to belatacept at month 26 because of CNI nephrotoxicity; IS reduction due to recurrent CMV/BK viremia and a *Pseudomonas* infection; subsequently experienced ACR and chronic ABMR and started dialysis following decline in kidney function[2]

ACR, acute cellular rejection; ABMR, antibody mediated rejection; BK, BK virus; CMV, cytomegalovirus; CNI, calcineurin inhibitors; IS, immunosuppression.
*Data as of March 01, 2022.

1. Leventhal J et al. *Am J Transplant*. 2021;21(suppl 3). Accessed February 9, 2022. https://atcmeetingabstracts.com/abstract/long-term-follow-up-of-a-phase-2-clinical-trial-to-induce-tolerance-in-living-donor-renal-transplant-recipients-3/
2. Data on file, Talaris Therapeutics.

GvHD and Deaths

Acute GvHD occurred in two durably chimeric patients, both in the setting of a female donor to an unrelated male recipient[1]:

- Grade 2, treated with steroids; developed chronic GvHD with ocular and musculoskeletal symptoms; now off IS with normal kidney function
- Grade 3, requiring third-line treatment; death occurred at 0.9 years
- An exclusion criterion for this donor-recipient pairing was added to the Phase 2 trial

Three deaths occurred in durably chimeric patients at the following times[1]:

- 0.9 years: Grade 3 GvHD
- 3.5 years: pneumococcal sepsis in a subject who was nonadherent to stem cell revaccination protocol and was traveling abroad
- 4.5 years: lung cancer in a heavy smoker (>100 packs/year)

One death occurred in a transiently chimeric patient[2]:

- 4.5 years: candidiasis, respiratory failure secondary to septic shock and aspiration pneumonia

GvHD, graft-vs-host disease; IS, immunosuppression.
*Data as of March 01, 2022.

1.Leventhal J et al. *Am J Transplant*. 2021;21(suppl 3). Accessed February 9, 2022. https://atcmeetingabstracts.com/abstract/long-term-follow-up-of-a-phase-2-clinical-trial-to-induce-tolerance-in-living-donor-renal-transplant-recipients-3/. 2. Talaris Therapeutics. Safety Data Monitoring Board. V3.0. January 8, 2021.

Conclusions

- High levels of durable chimerism and tolerance with a low incidence of GvHD have been achieved in highly mismatched related and unrelated recipients of FCR001 + kidney transplant
- There are significant long-term medical benefits to establishing tolerance in KTx recipients using the FCR001 approach

GvHD, graft-vs-host disease; HLA, human leukocyte antigen; KTx, Kidney transplant.