Establishment of durable chimerism with minimal graft versus host disease in highly mismatched recipients receiving an investigational facilitated allo-HSCT

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Disclosures

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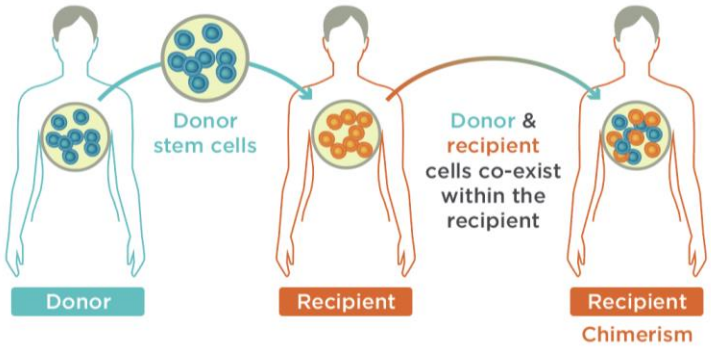
Transplant, allogenic tolerance, and chimerism

- The risk of transplant rejection increases in donor-recipient pairs with greater HLA mismatch[1]
- Facilitated allo-HSC transplantation therapy using FCR001 could prevent organ rejection without the morbidity and mortality that has been associated with the use of lifelong IS

HLA, human leukocyte antigen; HSC, hematopoeitic stem cell; IS, immunosupression.
1. Leeaphorn et al. *Clin J Am Soc Nephrol*. 2018.

Transplant, allogenic tolerance, and chimerism

- FCR001 is an investigational cell therapy derived from donor-mobilized peripheral blood cells, processed to contain an optimized number of HSCs, facilitating cells, and αβTCR+ T-cells that could induce chimerism and immune tolerance in highly HLA-mismatched donor-recipient pairs[2]
  - Facilitating cells promote stem cell engraftment in unmatched recipients, prevent GvHD in mouse models, and induce antigen-specific T_{reg} and B_{reg}
- We previously reported using FCR001 to induce kidney transplant tolerance by establishing durable whole blood and T-cell chimerism that allowed withdrawal of IS in 26 of 37 highly mismatched recipients of combined stem cell and living donor kidney transplant with a low risk of GvHD[2]



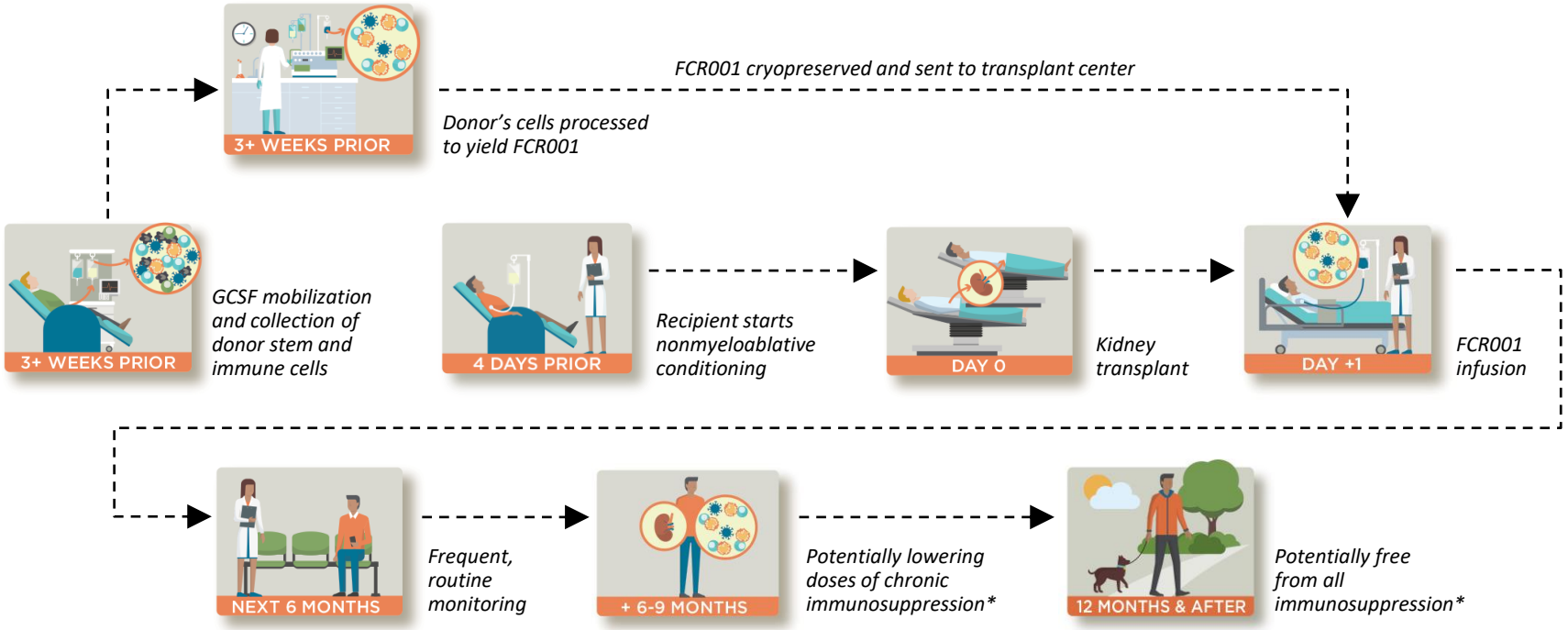
B_{reg}, regulatory B cells; GvHD, graft versus host disease; HLA, human leukocyte antigen; HSC, hematopoeitic stem cell; IS, immunosuppresion; T_{reg}, regulatory T cells.
2. Leventhal et al. *Hum Immunol*. 2018.

Background and objective

- The Phase 2 study protocol included an analysis of HLA matching at HLA-A, -B and DR (limited to 6/6 only)
- The objective of this retrospective analysis was to evaluate the impact of varying degrees of bidirectional donor/recipient mismatching using high-resolution allele typing HLA-A, -B, -C, -DRB1, -DQB1, and -DPB1 on the ability to establish durable chimerism, allowing full IS withdrawal and the induction of transplant tolerance
- HLA typing was performed using sequence specific oligonucleotide probe hybridization or next-generation sequencing for HLA-A, -B, -C, - DRB1, -DRB3/4/5, -DQA1, DQB1, DPA1, and –DPB1. Results were analyzed using Fusion (One Lambda – California, USA) or NGSengine (GenDeX – Utrecht, NL), as appropriate

HLA, human leukocyte antigen; IS, immunosuppression.

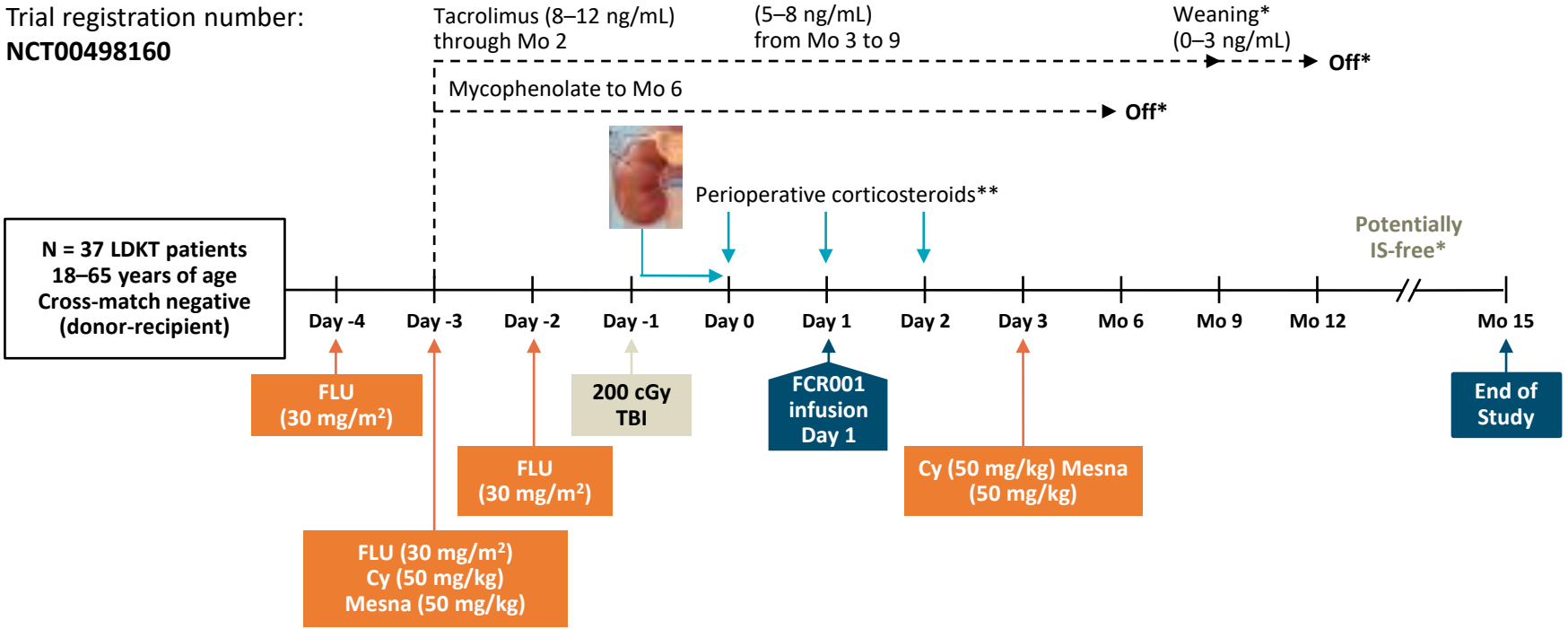
The “Vein to Vein” process



*Assuming no BPAR, stable kidney function, >50% donor T-cell chimerism, no GvHD.
BPAR, biopsy-proven acute rejection; GCSF, granulocyte colony stimulating factor; GvHD, graft versus host disease.

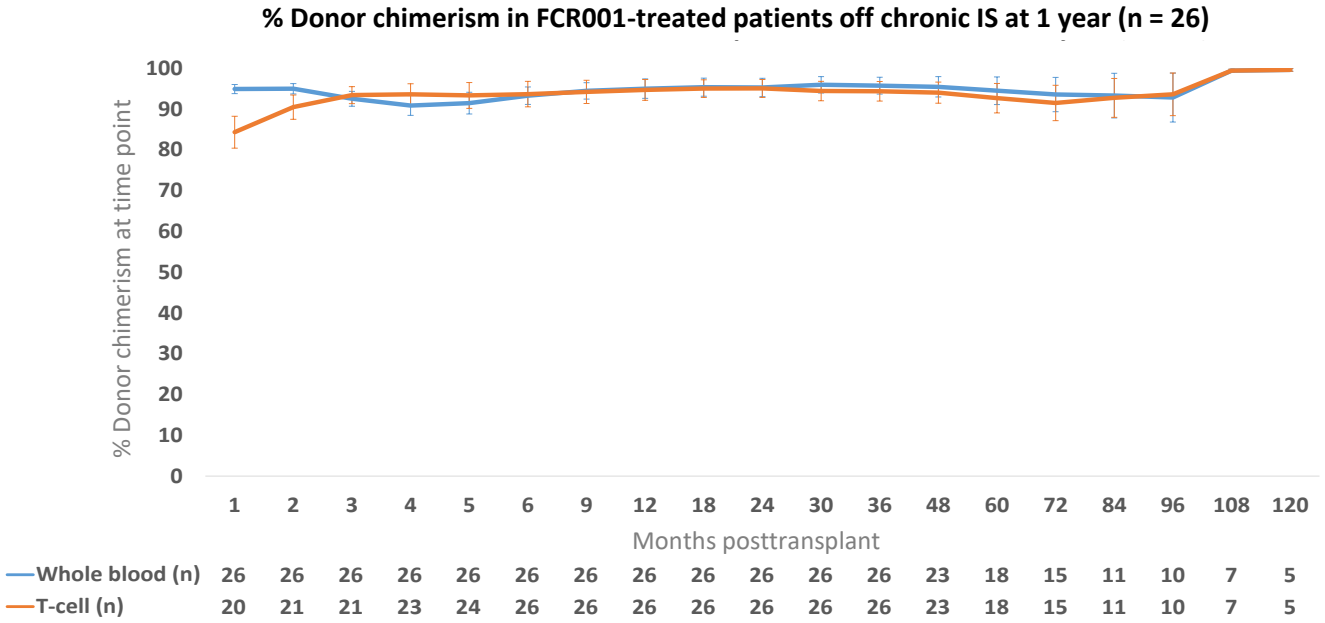
Study design overview

Trial registration number:
NCT00498160



*Assuming no biopsy-proven acute rejection; stable kidney function; >50% donor chimerism; no GvHD.
**Methylprednisolone 500 mg IV on Day 0; 250 mg Day 1 and 125 mg Day 2.
cGy, centigray; Cy, cyclophosphamide; FLU, fludarabine; GvHD, graft versus host disease; IS, chronic immunosuppression; IV, intravenous; LDKT, living donor kidney transplant; Mesna, mercapto-ethyl sulfonate; TBI, total body irradiation.

Whole blood and T-cell chimerism measurements during year 1 and relationship with ability to withdraw from IS at 1-year posttransplant



- **"Chimerism"**
  - % of recipient's T-cells that are donor-derived
  - Simple blood test, measured at multiple time points
- **26/27 patients** (96%) who achieved chimerism at **month 6** were able to be weaned off chronic IS
- **Every patient** weaned off chronic IS by **month 12** has remained off chronic IS for full duration of follow-up
  - Median follow-up >6 years
  - Longest follow-up >11 years

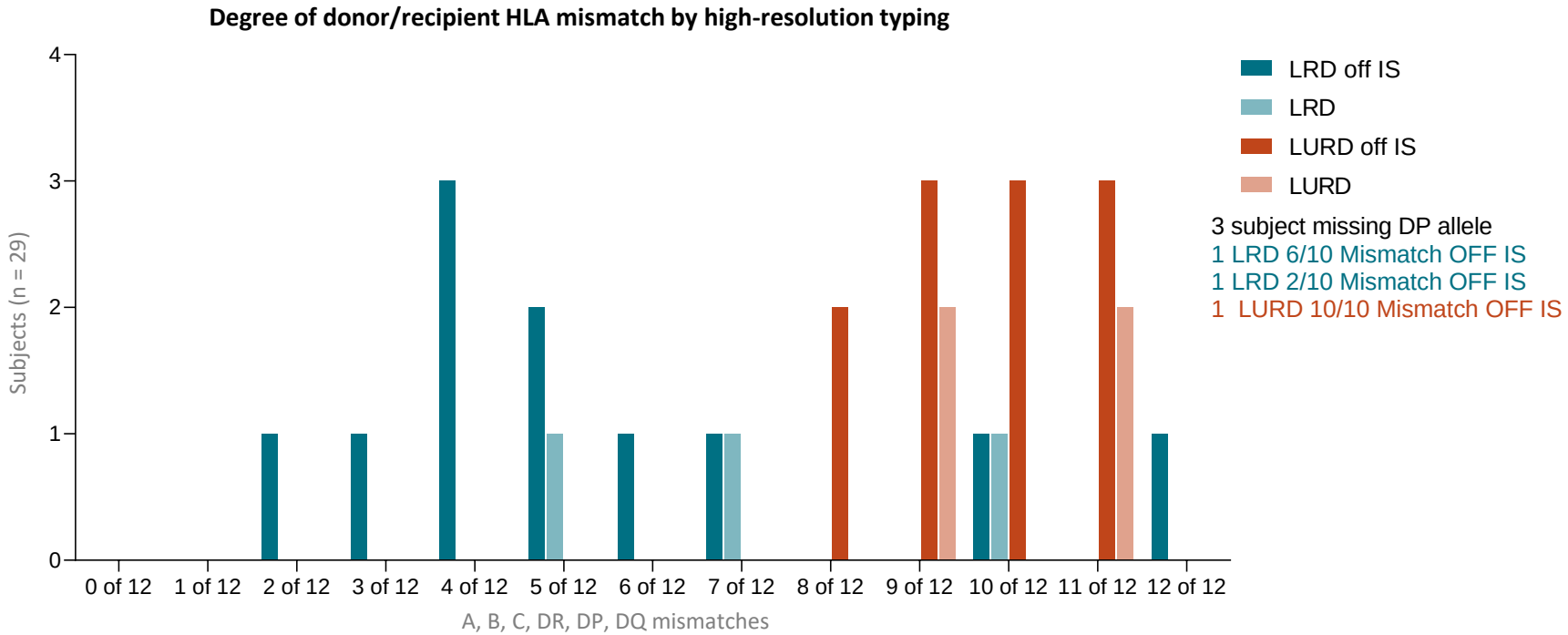
Values are mean +/- standard error. N indicates the number of FCR001 treated patients weaned off IS at approximately 1-year post-transplant for whom % whole blood and T-cell donor chimerism were measured at that time point.
IS, immunosuppression.

Results – Degree of HLA mismatch

- High-resolution allele level typing was performed in 32 of the 37 subject pairs at HLA-A, -B, -C, -DRB1, -DQB1, and -DPB1 (12/12)
  - Three of the 32 subjects did not have sufficient DNA to test for locus DPB1 (10/10)
- All 32 recipients (age range 18–65 years) have reached at least 4.5 years of follow-up (median >6 years, maximum >12 years)
  - Two recipients were re-transplants
  - Of the 29 donor-recipient pairs with data from all 12 alleles:
    - 21 were mismatched between 6–12 alleles (6 related, 15 unrelated)
    - 8 were mismatched between 2 and 5 alleles (all related)

HLA, human leukocyte antigen.

Bidirectional HLA mismatch and immunosuppression status



HLA, human leukocyte antigen; IS, immunosuppression; LRD, living related donor; LURD, living unrelated donor.

Donor chimerism achieved across HLA mismatch

- Despite the high degree of mismatch, 25 of 32 subjects achieved durable chimerism and full IS withdrawal (time off IS 3.5–11 years)
  - 12/25 off IS were from unrelated donor-recipient pairs with ≥8 HLA mismatches; the majority showed >95% donor whole blood/T-cell chimerism
  - Three have exhibited stable mixed chimerism ranging between 40%–60%
  - Durably chimeric patients retained chimerism after removal of IS, remain rejection-free without donor-specific antibodies, and have not resumed IS up to 12 years following transplant
- Of the subjects not off IS, 2 failed to engraft their cells; 4 lost chimerism by 4 months, and 1 developed GvHD
- Transiently chimeric subjects resumed endogenous hematopoiesis and are maintained on low-dose IS with stable renal function

GvHD, graft versus host disease; HLA, human leukocyte antigen; IS, immunosuppression.

Limited incidence of GvHD

- Two cases of GvHD, both in the setting of a female donor to an unrelated male recipient:
  - One Grade 2 lower GI acute GvHD that developed during conversion from tacrolimus to sirolimus and responded to steroids
    - This patient has developed moderate chronic GvHD of the skin. He is off IS with normal renal function
  - The second presented late following development of severe GI symptoms and manifested treatment-resistant lower GI GvHD with associated tissue-invasive cytomegalovirus colitis that proved fatal at 11 months posttransplant
  - An exclusion criterion for this donor-recipient pairing was added to the Phase 2 trial

GI, gastrointestinal; GvHD, graft versus host disease; IS, immunosuppression.

Conclusions

- High levels of durable chimerism and tolerance with a low (5.5%) incidence of GvHD has been achieved in highly mismatched related and unrelated recipients of FCR001 + kidney transplant
- There was no correlation between the degree of HLA mismatch and any of durable chimerism, safety, or GvHD

GvHD, graft versus host disease; HLA, human leukocyte antigen.

Acknowledgments

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