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STEADFAST Study Update: A Phase I/II Clinical Trial of Regulatory T Cells Expressing a Chimeric Antigen Receptor Directed Towards HLA-A2 in Renal Transplantation

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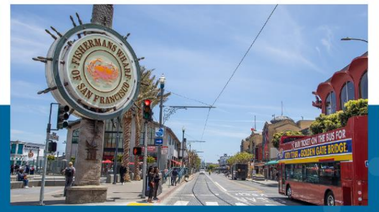
I am the coordinating investigator for the STEADFAST study and a member of the Safety Monitoring Committee. I received a fee for these activities.

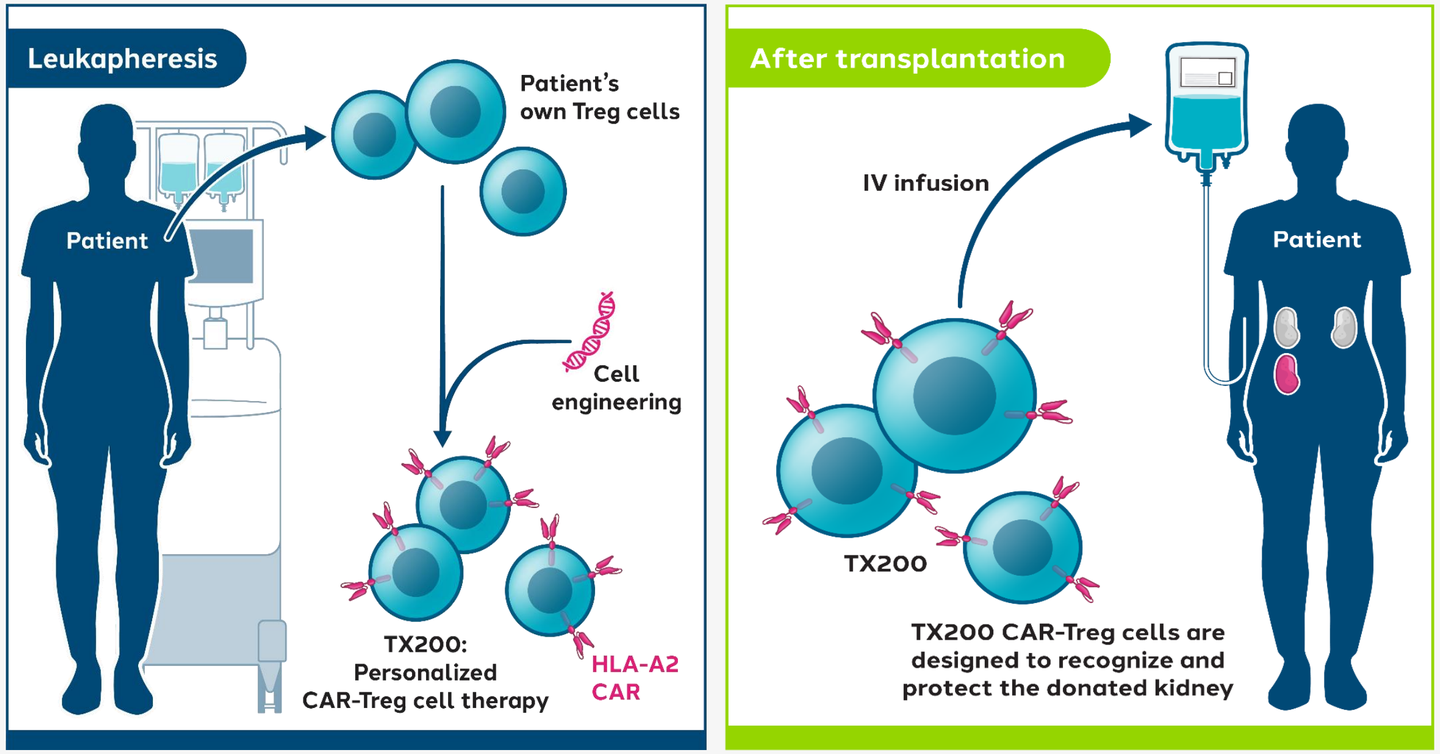
The STEADFAST study was sponsored by Sangamo Therapeutics.





TX200: An investigational CAR-Treg therapy for prevention of immune-mediated rejection in HLA-A2 mismatched kidney transplantation



Goals of TX200 Treatment

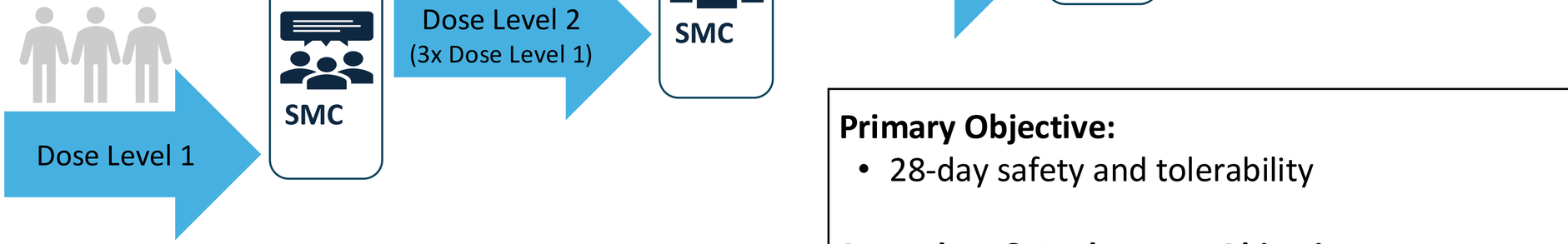
- One-time administration of patient's own regulatory T cells (Tregs) engineered to express a CAR recognizing the HLA-A2 on the transplanted kidney
- Administered approximately 12 weeks post-transplant
- Reduce or eliminate need for lifelong immunosuppressants
- Protect the graft from immune-mediated rejection

CAR=chimeric antigen receptor; HLA-A2 = human leukocyte antigen class I molecule A*02; IV = intravenous; Treg = regulatory T cell.

STEADFAST: A first-in-human Phase I/II study of CAR-Treg therapy in living donor renal transplant patients

8 participants dosed at 4 dose levels in Bayesian study design

TX200 Group



Control Group

Primary Objective:

- 28-day safety and tolerability

Secondary & Exploratory Objectives:

- Long-term safety over 84 weeks study duration
- Biopsy-confirmed acute rejection
- Proof of mechanism (biomarkers)

N = number; SMC = Safety Monitoring Committee.

[1]Received a reduced number of CAR Treg cells, similar to dose level 3

TX200 was well tolerated, and no safety signals were observed

- Median study duration was **88 weeks** (range: 60 – 101 weeks)
- No treatment-emergent adverse events (TEAE) were related to TX200 at any dose-level.

	Dose Level 1 N=3	Dose Level 2 N=1	Dose Level 3 N=1	Dose Level 4 N=3	Control N=3	Overall N=11
Participants with:	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any TEAE	3 (100)	1 (100)	1 (100)	3 (100)	3 (100)	11 (100)
Grade ≥3 TEAE	2 (67)	0	0	0	0	2 (18)
TEAE within 28 days	2 (67)	0	0	1 (33)	2 (67)	5 (46)
Grade ≥3 TEAE within 28 days	1 (33)	0	0	0	0	1 (9)
Any TEAE related to TX200	0	0	0	0	0	0
TEAE leading to study discontinuation	0	0	0	0	0	0
TEAE leading to death	0	0	0	0	0	0

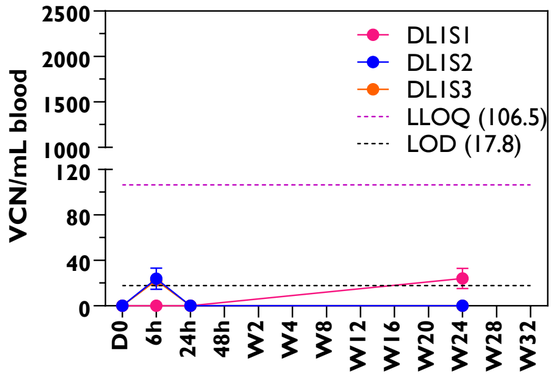
Clinical cut-off date: 22 November 2024.

The most common TEAEs reported by preferred term were nasopharyngitis and diarrhoea, followed by folate deficiency, COVID-19, influenza-like illness, and myalgia – all grade 1 or 2

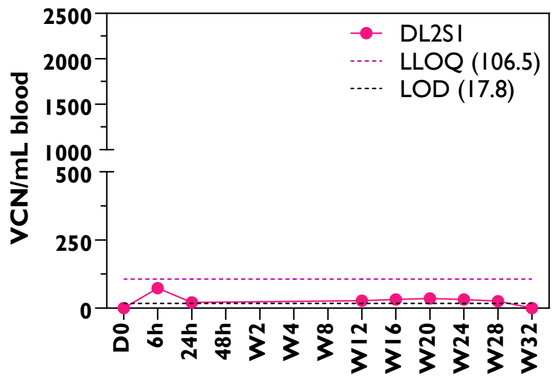
Evidence of TX200 engraftment

TX200 cells were observed in blood for up to 8 months post-TX200 dosing

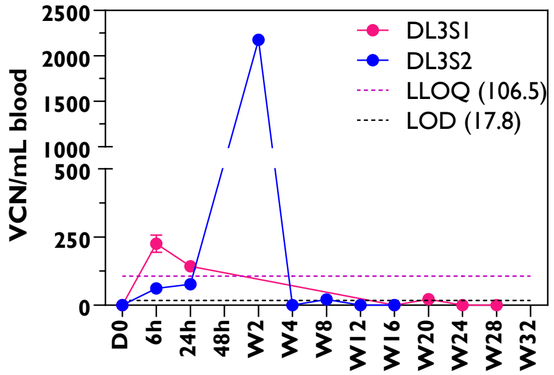
Dose Level 1



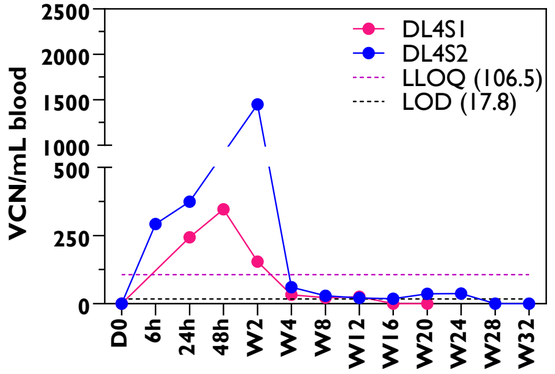
Dose Level 2



Dose Level 3

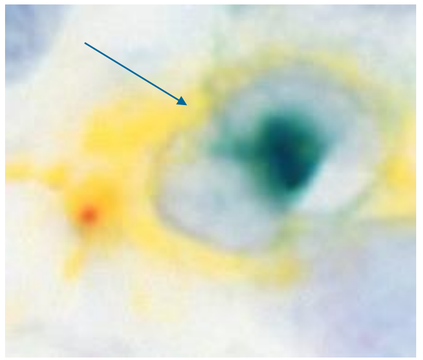


Dose Level 4

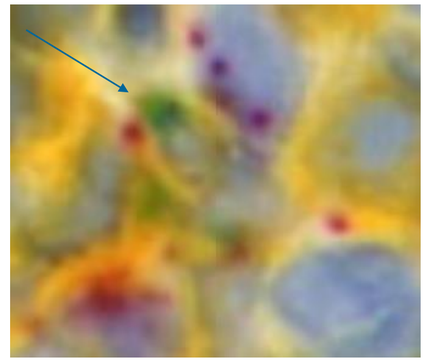


TX200 cells were observed in biopsies at 4 weeks and 6 months post-TX200 dosing

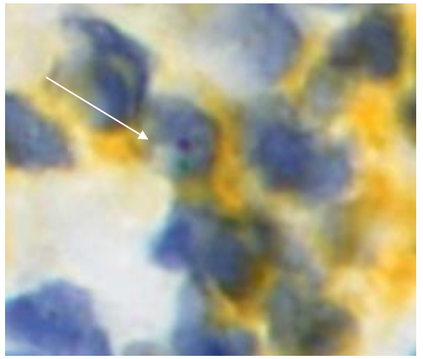
Dose Level 1: 4 weeks
A2 CAR / CD4 / FoxP3



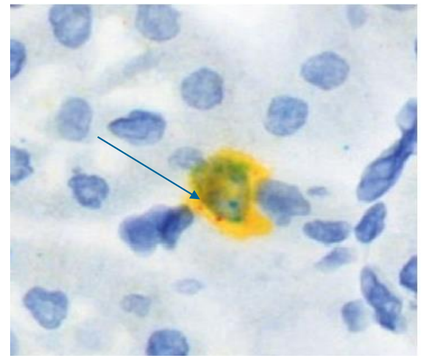
Dose Level 1: 4 weeks
A2 CAR / CD4 / IDO1



Dose Level 1: 6 months
A2 CAR / CD4 / FoxP3



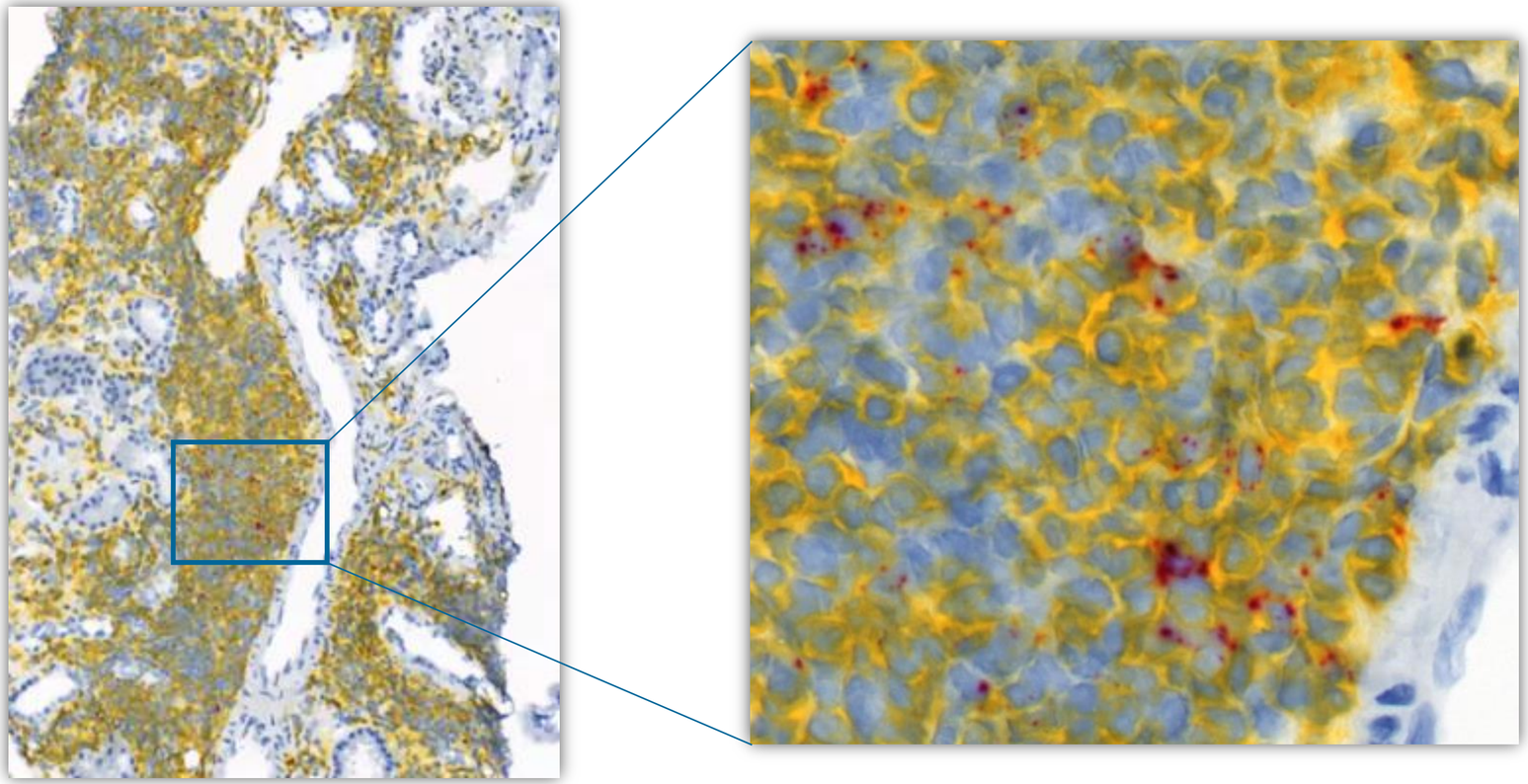
Dose Level 2: 6 months
A2 CAR / CD4 / FoxP3



DL = dose-level; LLOQ = lower limit of quantification; LOD = limit of detection; ml = milliliter; S=subject; VCN=vector copy number; W=week.

Tolerogenic Treg Structures (TOLS) observed at all dose levels

- TOLS in mice are associated with tolerance induction in transplantation[1]
- TOL-like structures were observed in The ONE study conducted at Oxford[2]
- TOL-like structures were detected in biopsies of patients treated with TX200 at all dose levels
- Titration to tacrolimus is ongoing for 5th patient



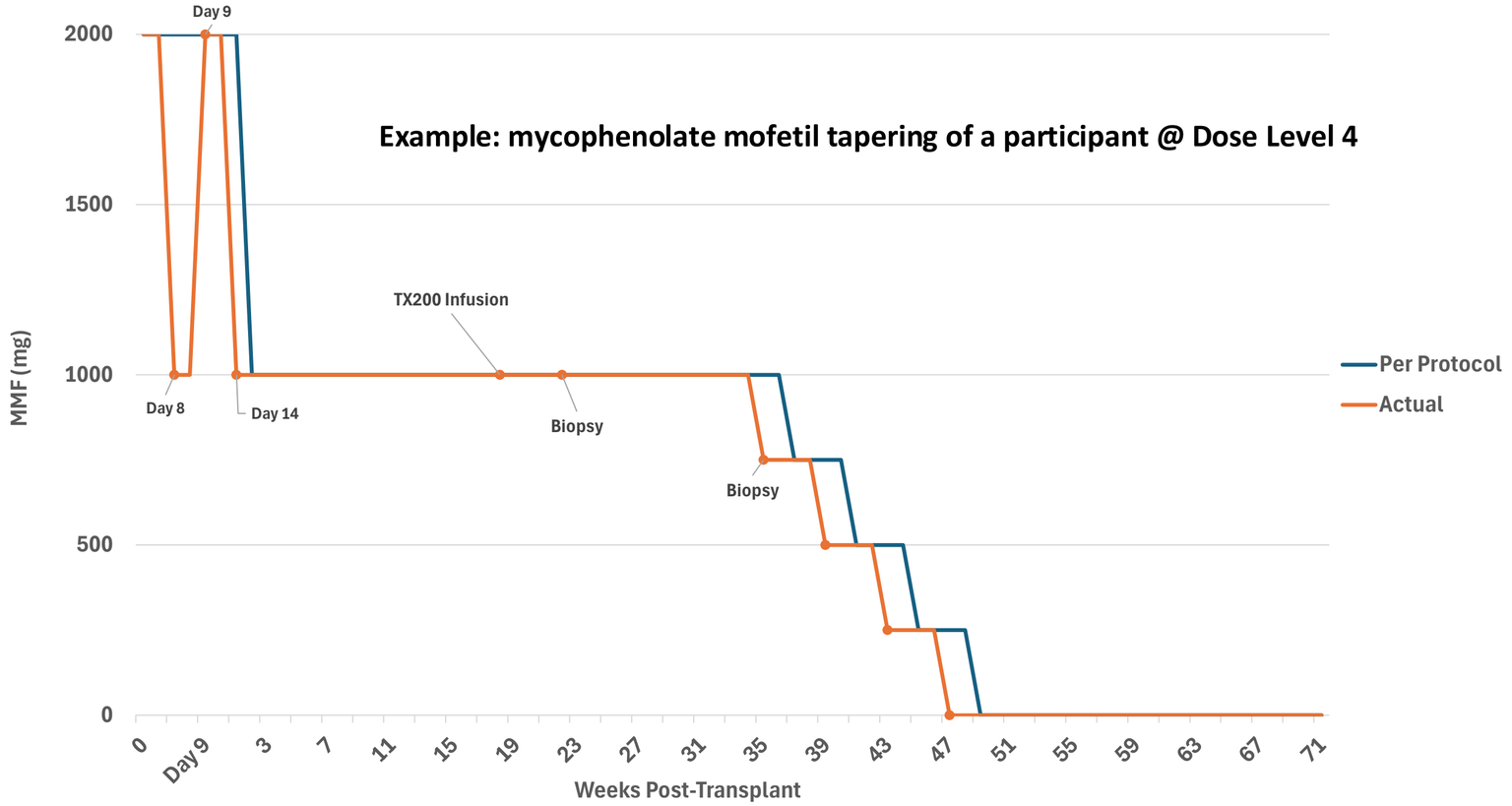
- 4-week biopsy, Dose Level 1
- Example of TOLS around arterial endothelial cell membrane

- Red color is positive FOXP3 RNA staining
- Yellow color is CD4 antibody staining

[1] Rosales et al., Am J Transplant. 2022; 22: 705-716; [2] Harden et al., Am J Transplant.; 2021; 001-9.

Reduction of immunosuppression post-TX200 with no significant inflammatory findings on kidney biopsies

- As of 28 May 2025 data cut, 4 of the 5 participants at Dose Levels 2, 3 and 4 had titrated down to tacrolimus monotherapy.
- No events of Biopsy Confirmed Acute Rejection have been reported for any participant.



* Titration to tacrolimus is ongoing for 5th patient. MMF

TX200 is a promising CAR-Treg therapy to induce tolerance in renal transplantation

- TX200 is well tolerated, and no safety signals were observed in the 8 subjects treated
- Evidence of TX200 cell engraftment in kidney biopsies and blood at 6 and 8 months, respectively
- Evidence of TOLS after TX200 treatment at all dose levels
- Tapering of immunosuppression is feasible following TX200 dosing, and was achieved in 4 of 5 participants at Dose Levels 2, 3 and 4

Overall, data from the STEADFAST study demonstrate that TX200 is safe and well-tolerated, and consistent with proof of mechanism for CAR-Tregs with establishment of a tolerogenic environment in the kidney allograft

We thank the participants in the trial, their families, the investigators and staff at the participating centers.