

Evaluation of the Mechanism of Action of MTX-101, a Novel Regulatory T cell Modulator, in a Phase 1b Clinical Study for Adults with Stage 3 Type 1 Diabetes

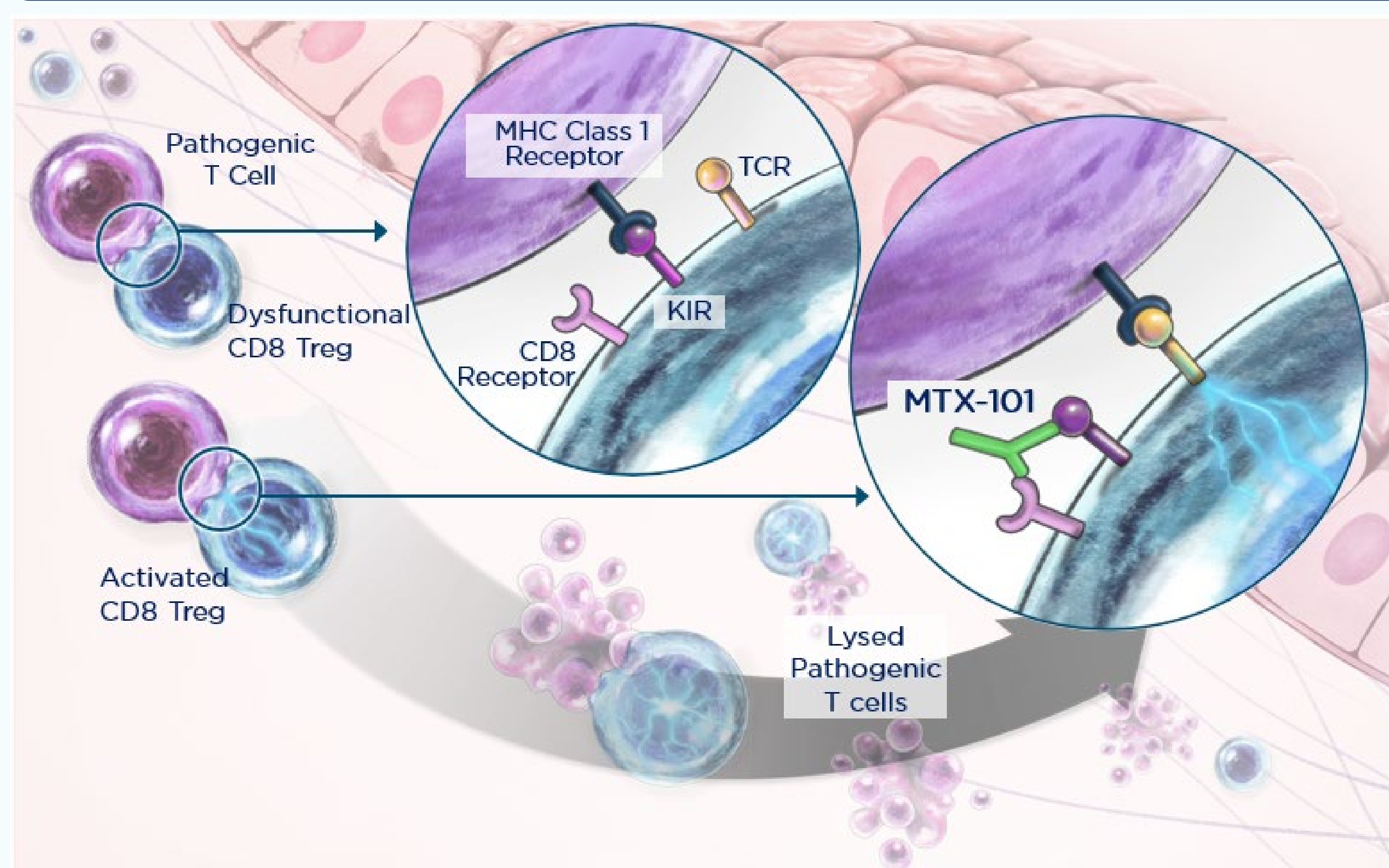
Jason W. Chien, Catherine J. McMahan, Jean S. Campbell, Roxana E. Rojas, Heather Wroe, Jasmine C. Labuda, Daniel R. Boster, Daniel T. Patton, Eyayu K. Belay, Allison R. O'Rourke, Meghan E. Maurer, Cong Tan, Sean K. Summers, Kaelen S. Encarnacion, Nadine M. Morgan, Monica M. Childs, Kristi L. Manjarrez, Kristine M. Swiderek, John M. Wentworth, Courtney A. Crane

Background

Regulatory CD8 T cells (CD8 Treg) are responsible for the selective killing of pathogenic T cells to maintain peripheral immune tolerance. In patients with type 1 diabetes (T1D) that respond to immunotherapies, CD8 Treg prevalence is increased following dosing and correlates with durable treatment effect. CD8 Treg appear dysfunctional in patients with autoimmune diseases, including T1D, in part due to expression of inhibitory KIR receptors which serve as autoimmune checkpoints.

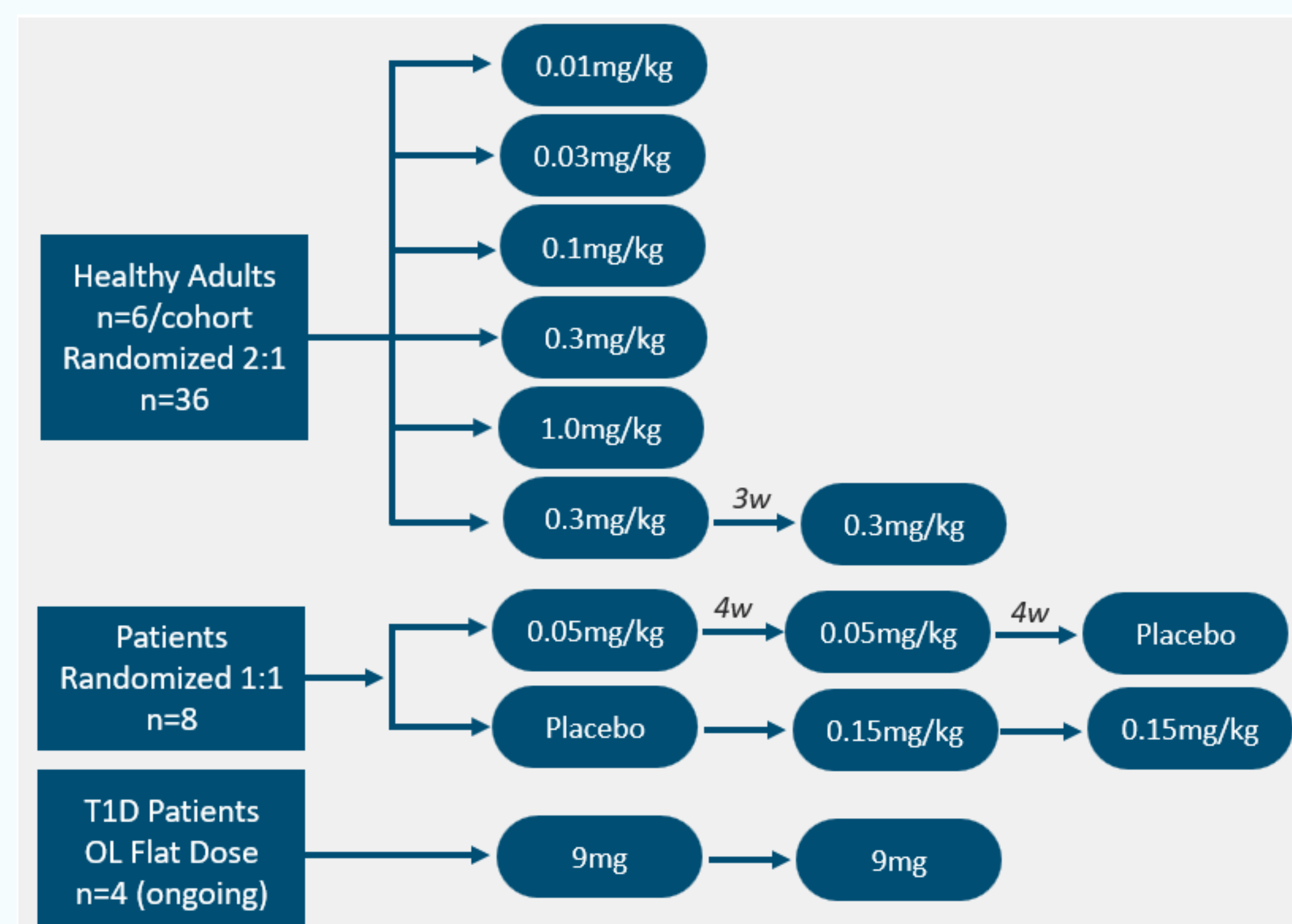
This study sought to evaluate the postulated mechanism of action for a novel CD8 Treg modulator, MTX-101, that restores CD8 Treg killing of pathogenic T cells by disrupting the binding of inhibitory KIR expressed by CD8 Treg to its ligand. Analyses illustrate the effects of selective modulation of the CD8 Treg network for the first time in humans.

Therapeutic Hypothesis



Model of the postulated mechanism of action for MTX-101. MTX-101, a bispecific antibody targeting inhibitory KIR and CD8, supports TCR restricted CD8 Treg activation and cytolytic capacity, restoring immune tolerance and preventing downstream inflammation and tissue destruction.

Study Schema



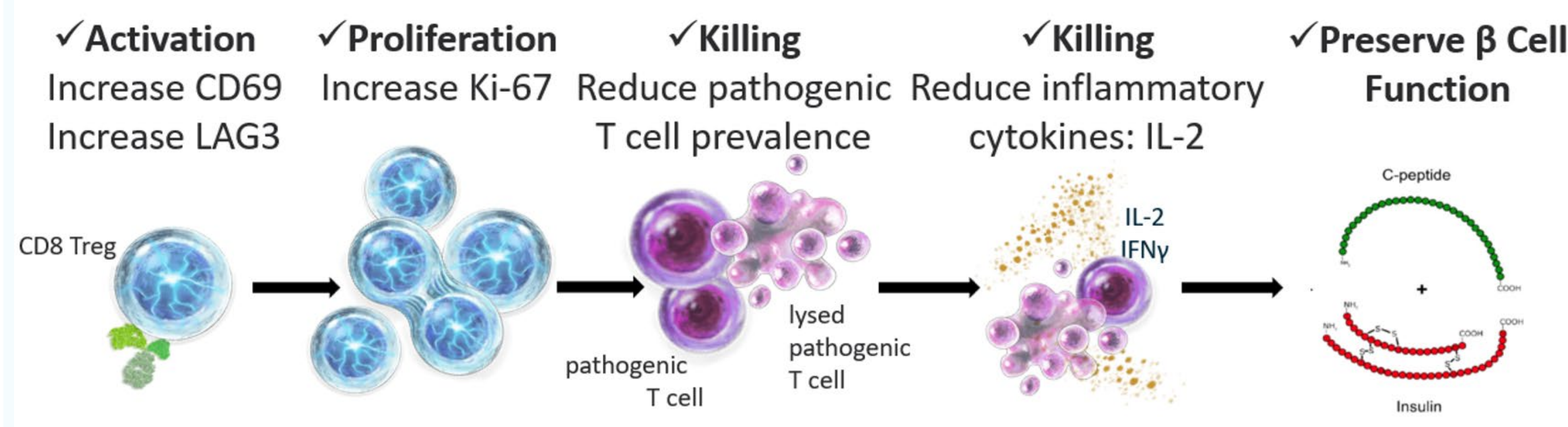
Patient Eligibility:

- Stage 3 T1D: 18-45 yrs, T1D-related autoantibody, C-peptide >0.2nmol/L, HbA1C<10%
- Celiac: Physician-diagnosed for >3mo, CeD-related autoantibody, on strict GFD ≥1mo

Study Objectives:

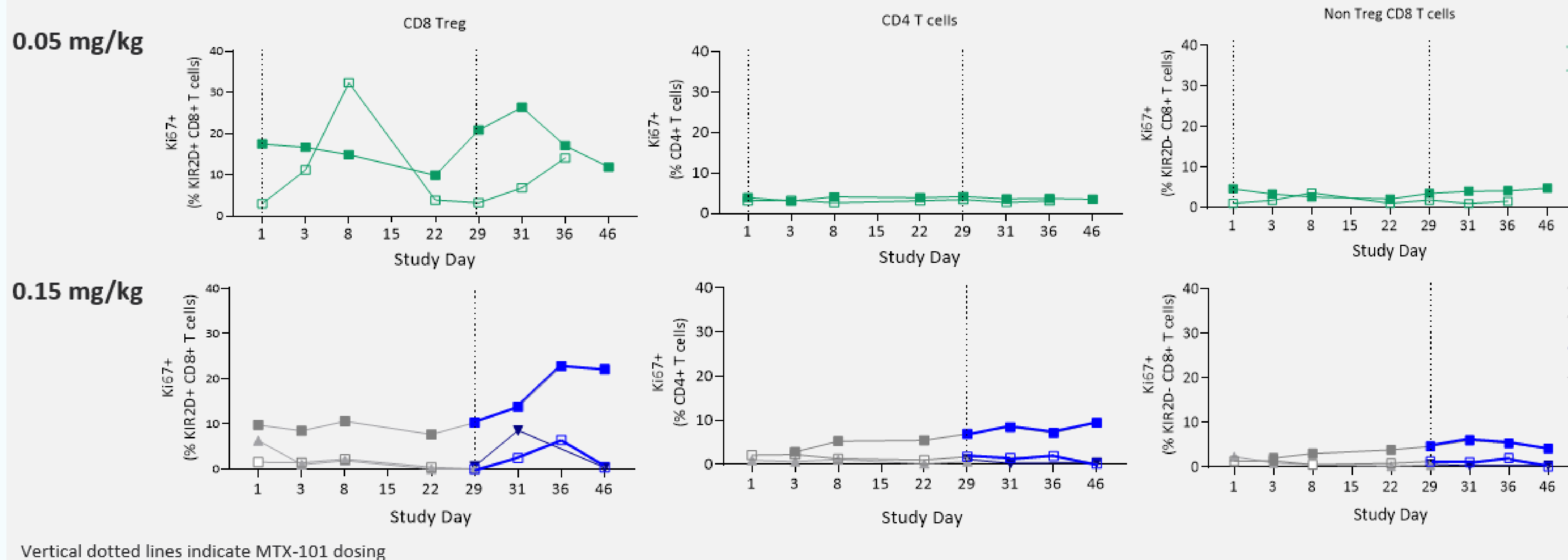
- Safety
- PK, Receptor Occupancy
- PD: selective CD8 Treg activation, proliferation and targeted pathogenic T cell killing
- T1D patients: MMTT C-peptide assessed at 3mo and 6mo

Postulated Mechanism of Action in Patients



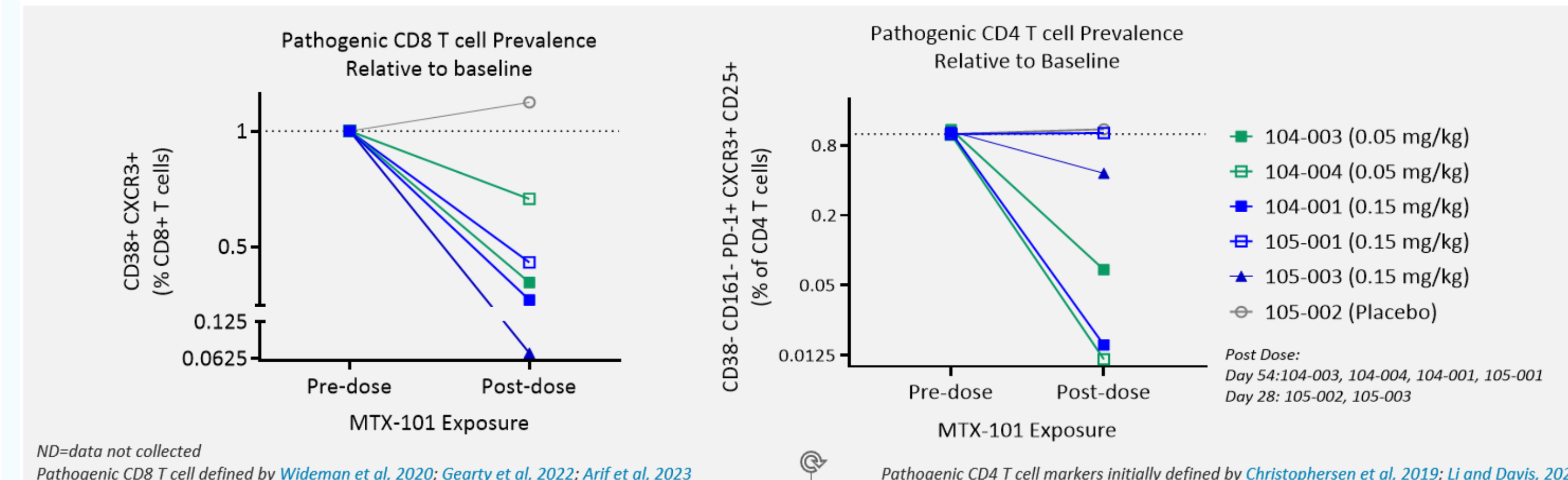
MTX-101 Selectively Induces CD8 Treg Proliferation

No observed proliferation in other immune cell populations in T1D patients

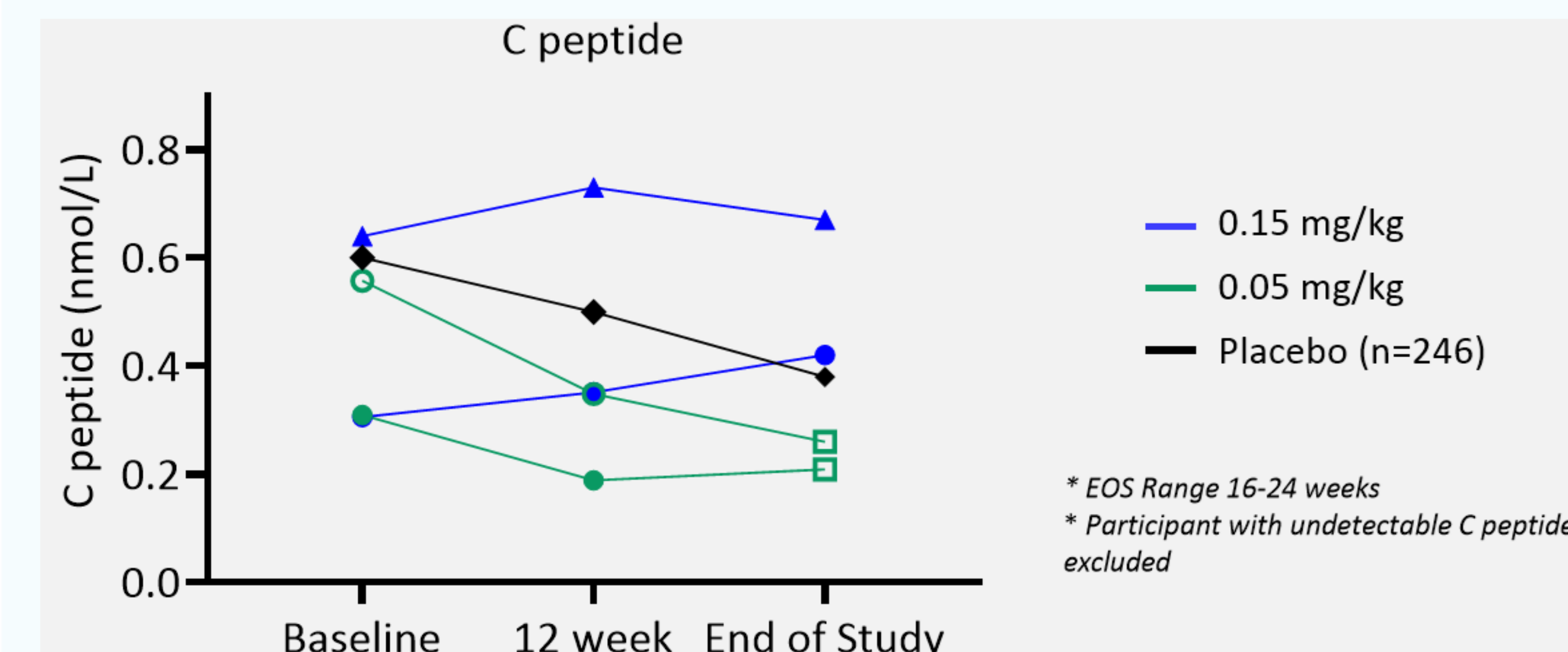


Reduction of Pathogenic CD4 and CD8 T Cells

Pathogenic T cell prevalence is reduced following MTX-101 dosing in Stage 3 T1D Patients



MTX-101 Effect on C-Peptide



Summary

- MTX-101 can shift the treatment paradigm in Stage 3 T1D patients
- MTX-101 is the first CD8 Treg modulator for Stage 3 T1D to preserve C-peptide and delay progression of a disease where daily insulin injections are the standard of care for symptom management
- 38 adult participants, including 4 Celiac and 10 T1D patients, treated with MTX-101 in Ph1 study
- Consistent findings that MTX-101 restores the activation of CD8 Treg and the selective reduction of pathogenic T cells
- Strong mechanistic readthrough with notable maintenance of C-peptide after a single dose

MTX-101 can safely and selectively modulate the CD8 Treg network to restore durable immune homeostasis and preserve endogenous insulin production