NKTR-358: a selective, first-in-class IL-2 pathway agonist which increases number and suppressive function of regulatory T cells for the treatment of immune inflammatory disorders

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Introduction

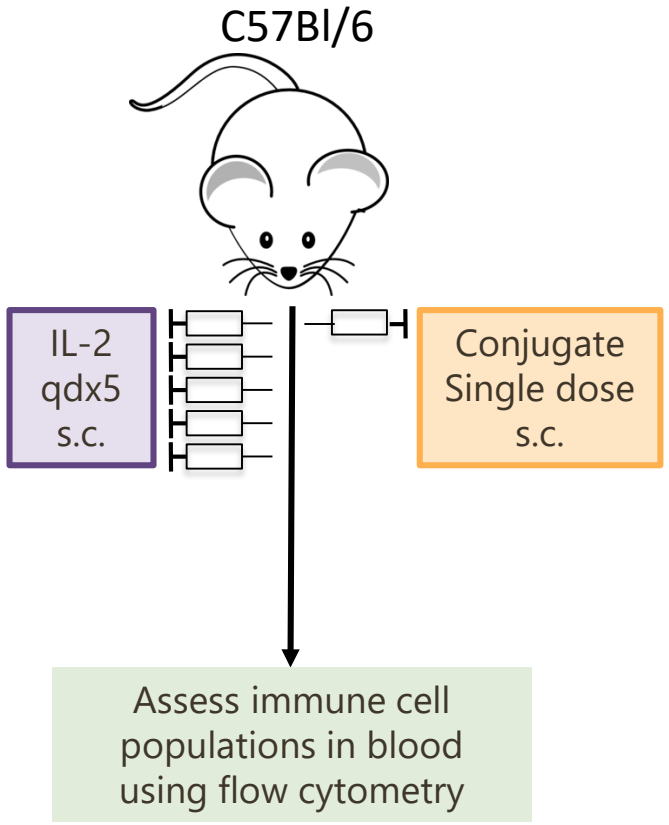
- A progressive imbalance of regulatory T cells (Tregs) relative to conventional T cells (Tcon) is shared by many autoimmune diseases

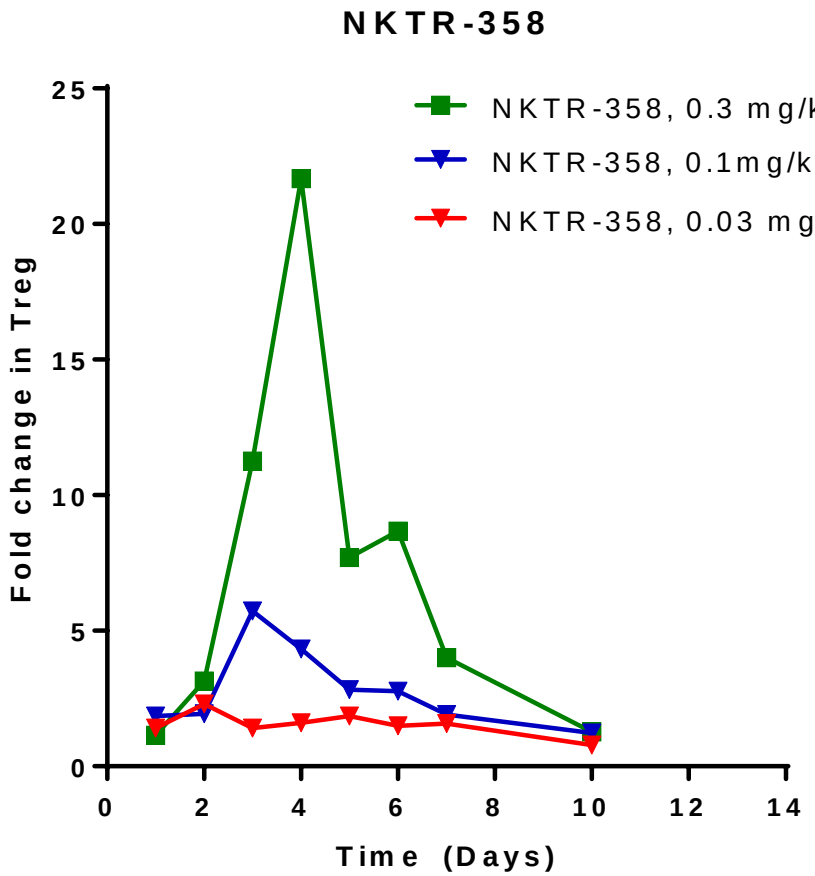
- Enhanced sensitivity of Tregs to IL-2 supports use of low-dose IL-2 therapy
  - Low-dose IL-2 therapy hampered by poor pharmacokinetics, AEs, short-lived effects
  - Magnitude of Treg mobilization ultimately limited by elicitation of Tcon
  - Clinical benefit demonstrated in GVHD, SLE and other indications

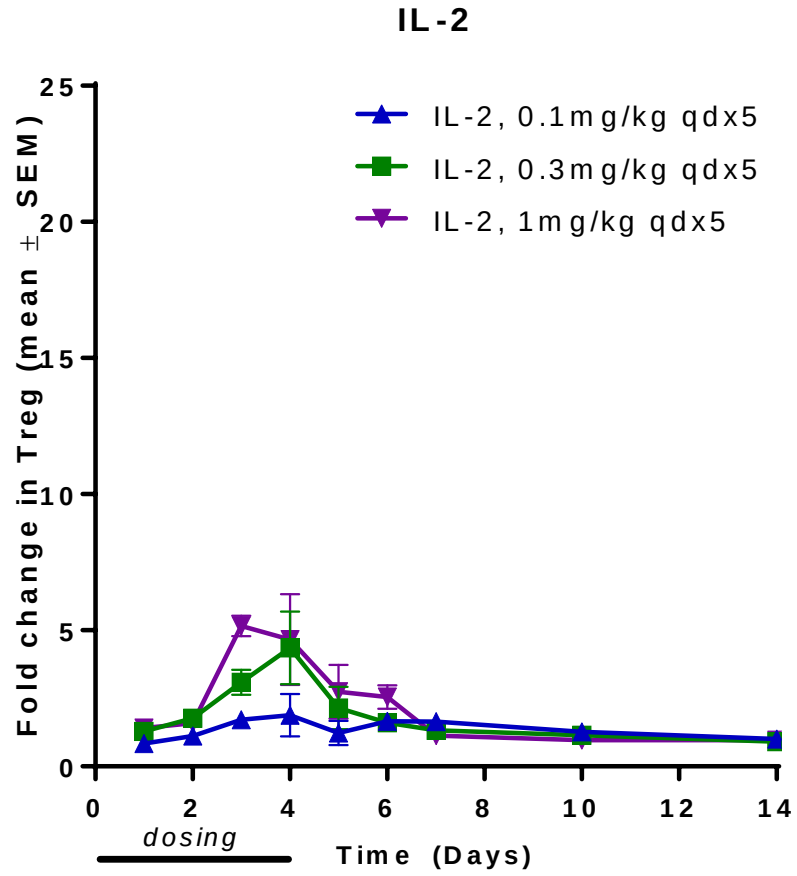
NKTR-358

- Potential first-in-class therapeutic for direct manipulation of Tregs
- Biotherapeutic born from Nektar's extensive development experience with IL-2 and polymer conjugation
- Preferential increase in number and activity of Tregs, minimal action on non-Tregs
- Utilizes the FDA-approved aldesleukin sequence
- Monthly or twice monthly self-administered subcutaneous product
- In development for autoimmune and allergy indications

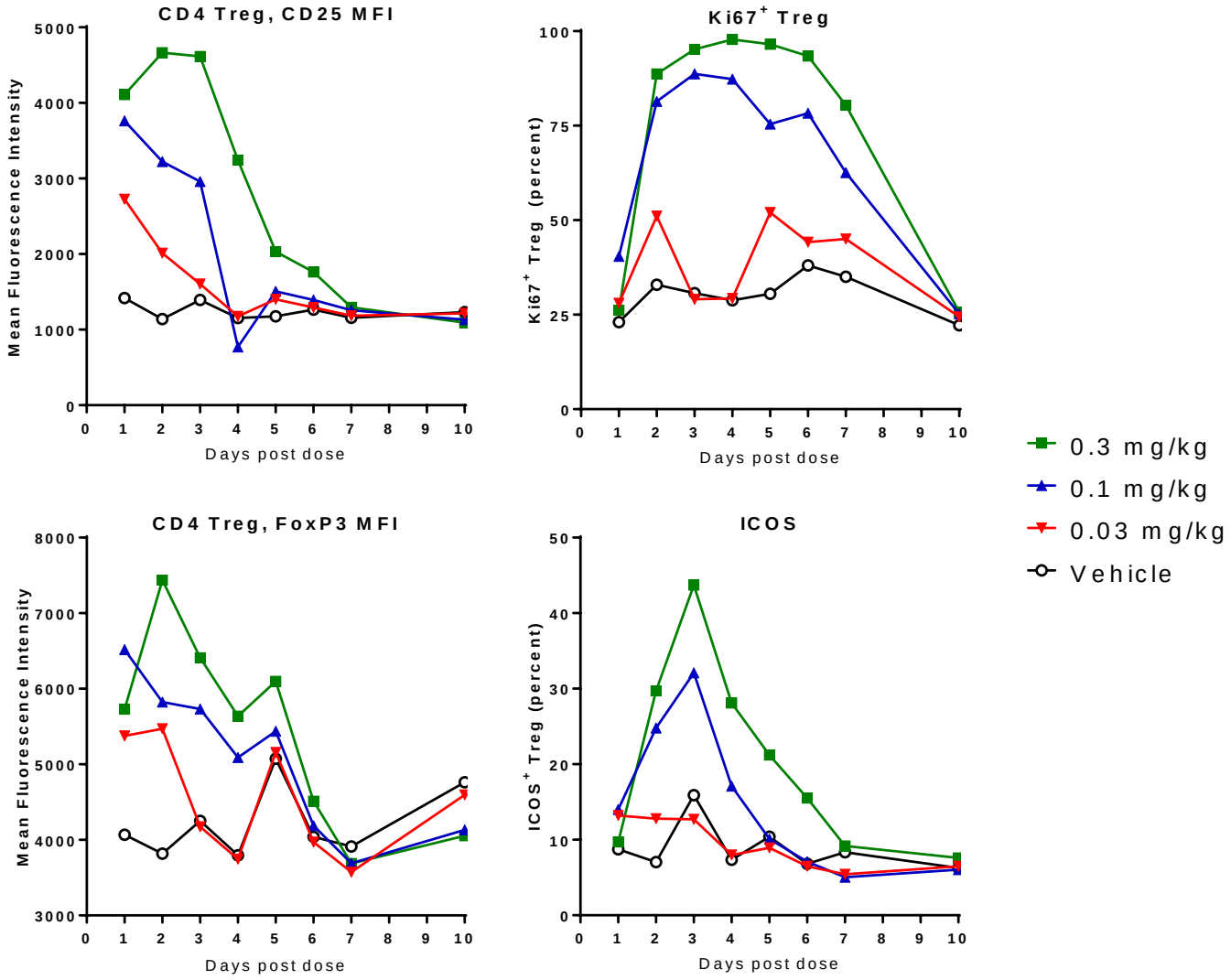
NKTR-358 was identified by an *in vivo* screen







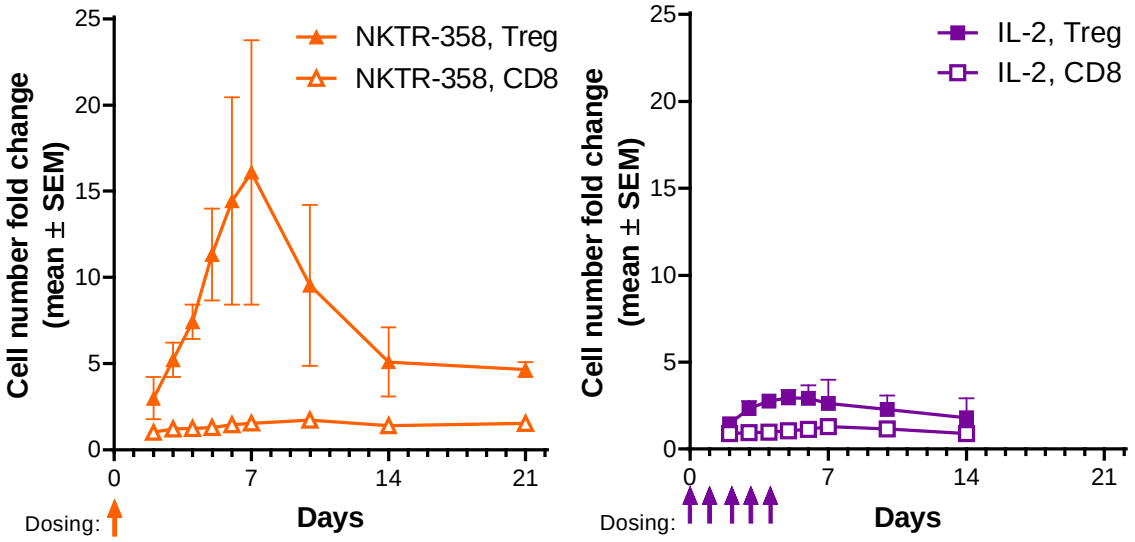
NKTR-358 promotes Treg proliferation and activation



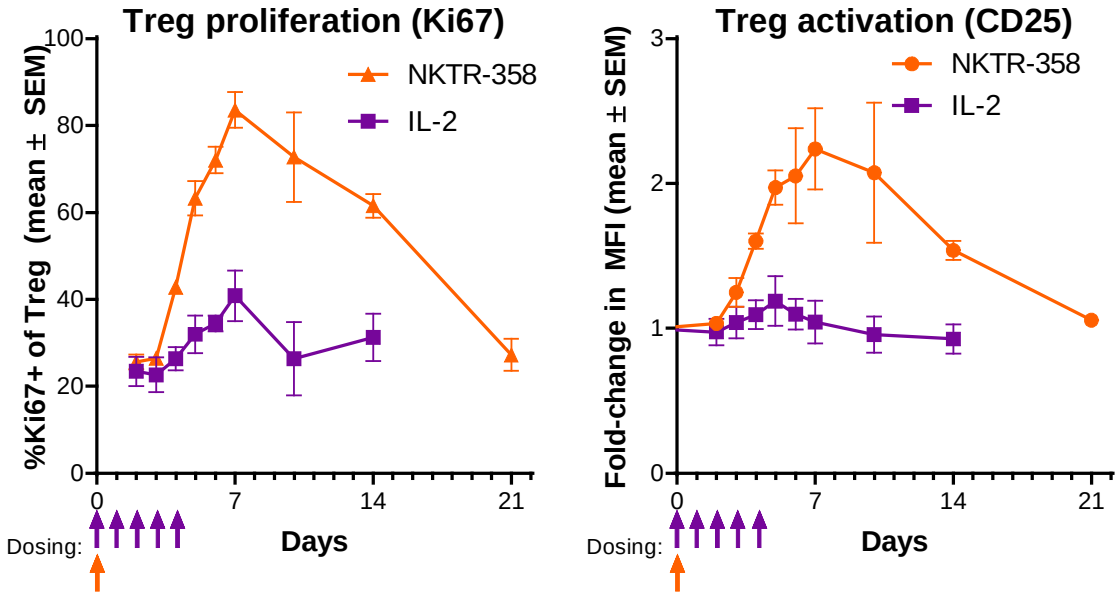
- Single subcutaneous NKTR-358 administration in mice
- Induction of proliferation and activation markers
  - Helios, GITR, CTLA-4, CD39, CD73, OX40, and PD-1 (not shown)
  - Similar effect in blood and spleen

Preferential Treg expansion in non-human primates

Treg, CD8 in blood

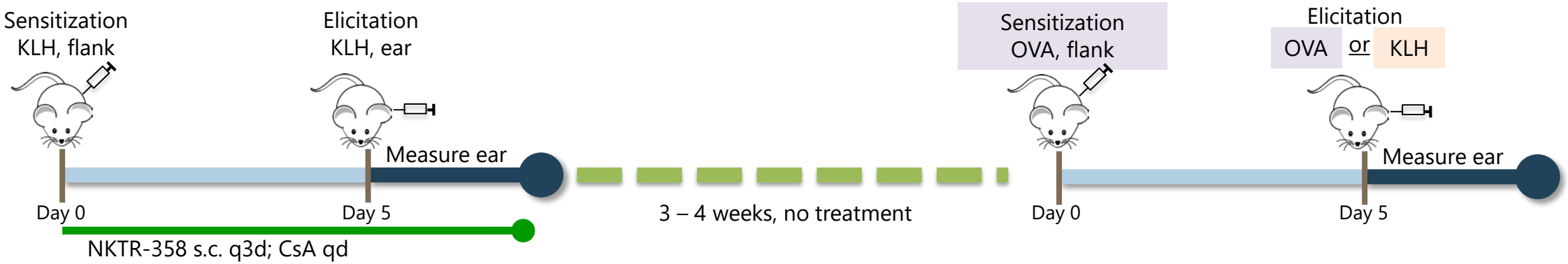


Treg activation

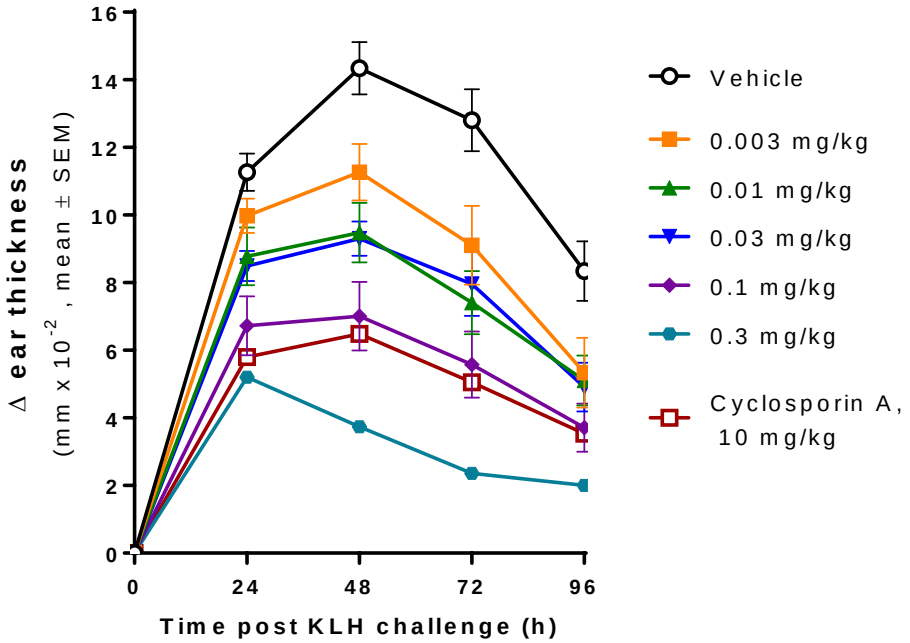


Cynomolgus monkey : 1M + 1F
25µg/kg : NKTR-358 single dose *vs.* qdx5 for IL-2

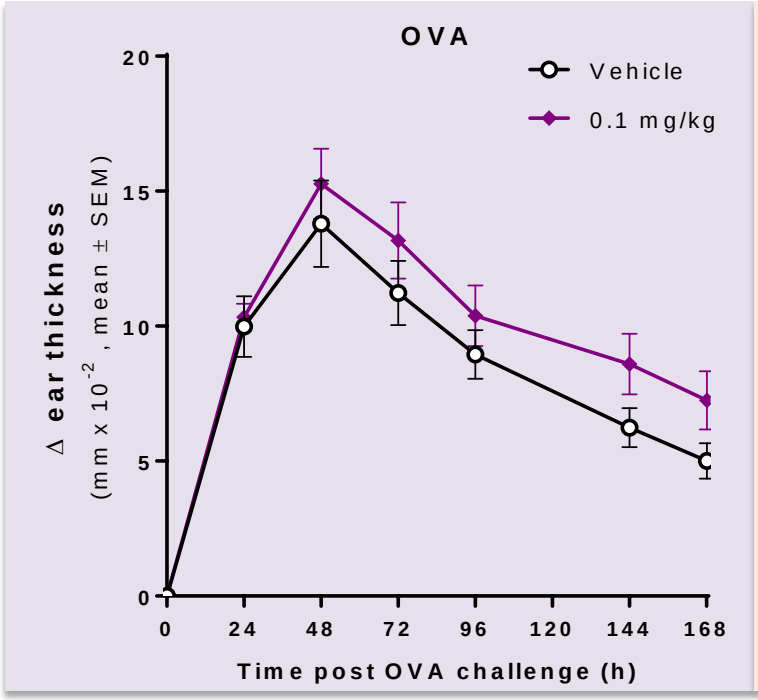
NKTR-358 suppresses antigen-driven inflammation

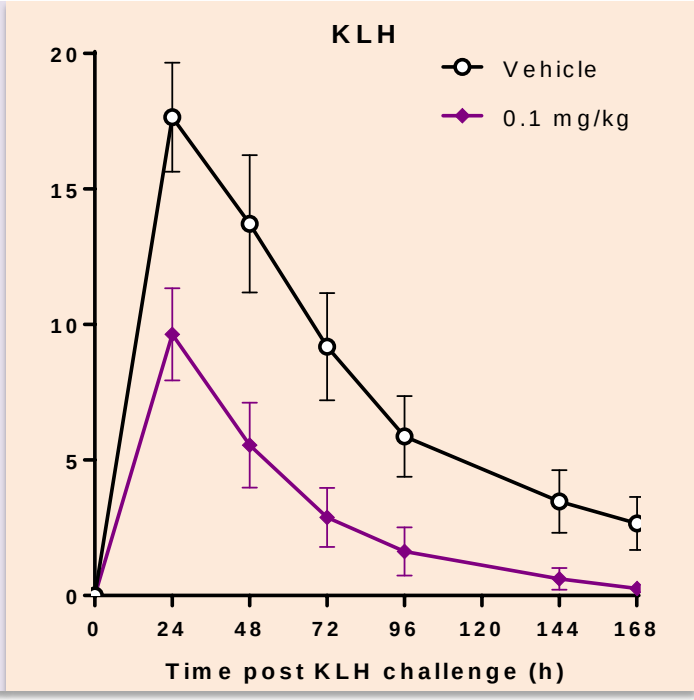


Primary efficacy

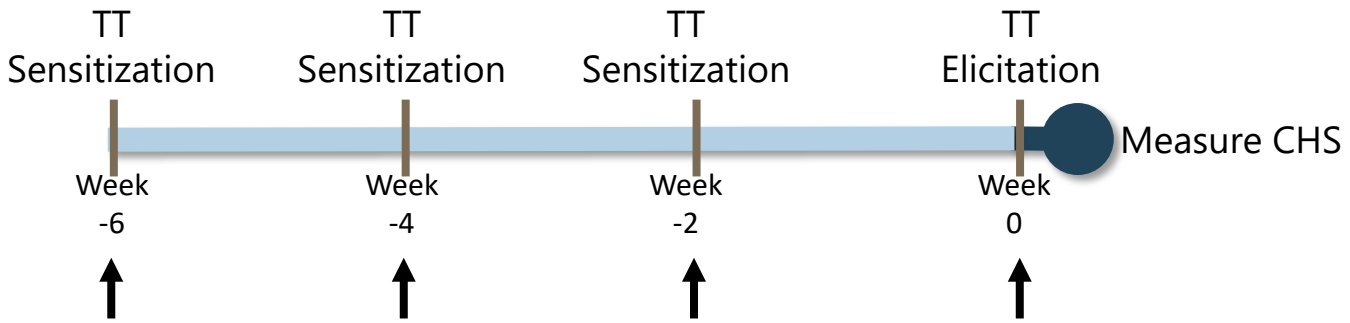


Rechallenge : Antigen-specific Treg memory

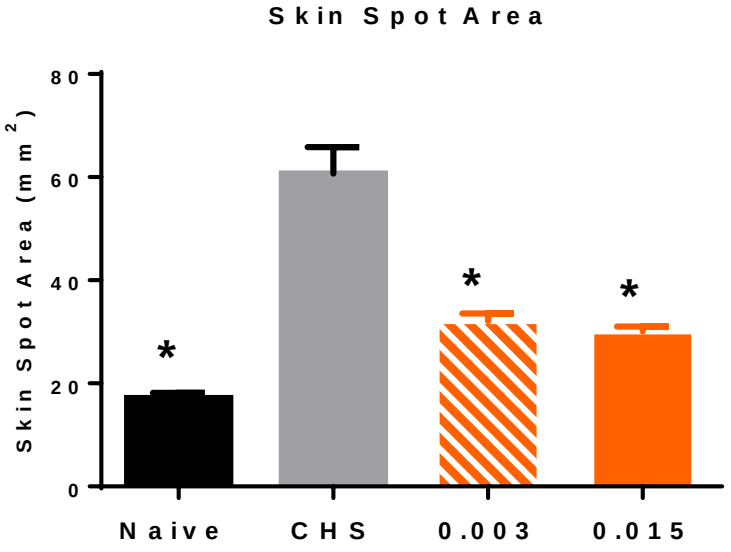


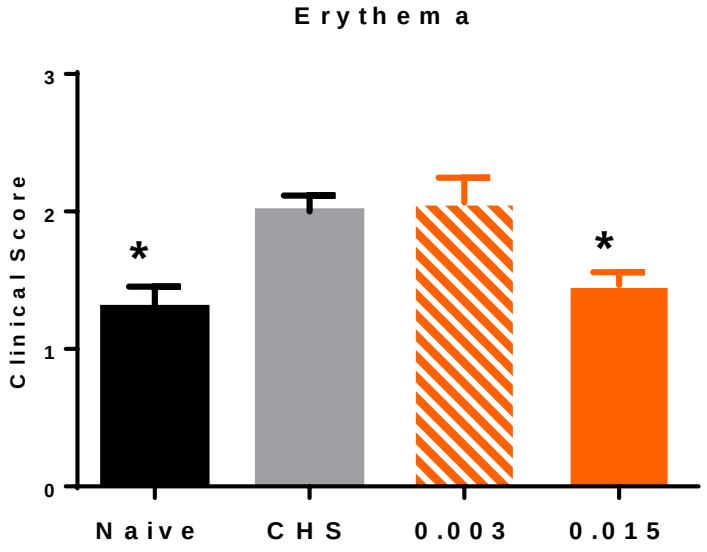


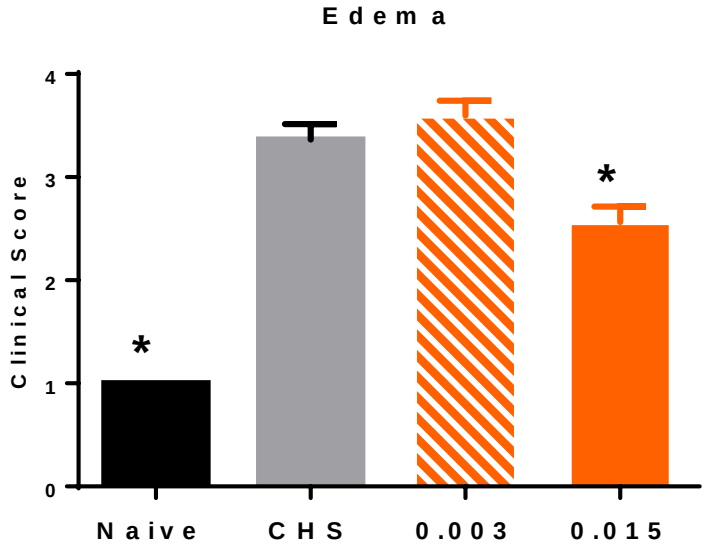
NKTR-358 suppresses antigen-driven inflammation in a primate model of cutaneous hypersensitivity



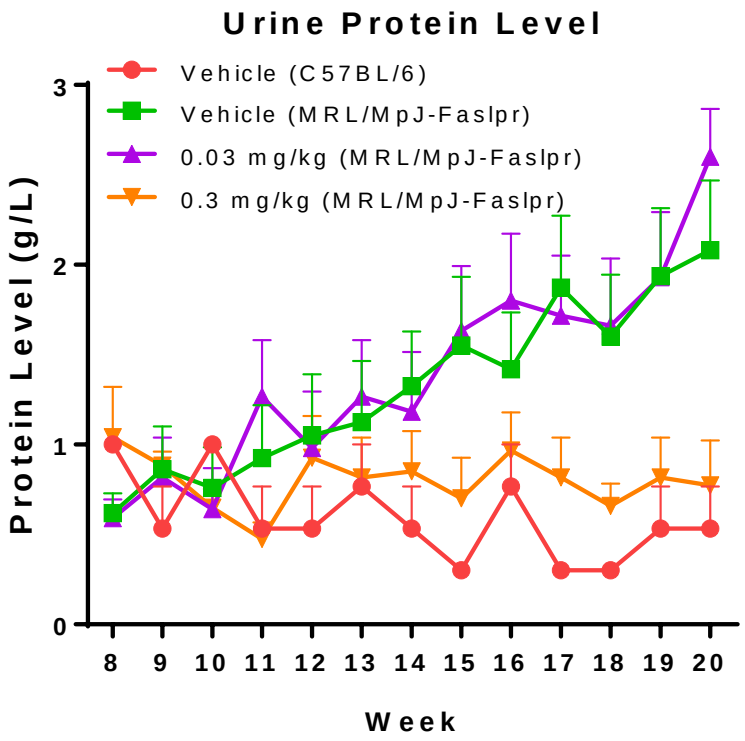
CHS: Cutaneous Hypersensitivity
TT: Tetanus Toxoid
Arrows: NKTR-358 s.c., 0.003 & 0.015 mg/kg q2w
*: $p < 0.05$ vs CHS, ANOVA

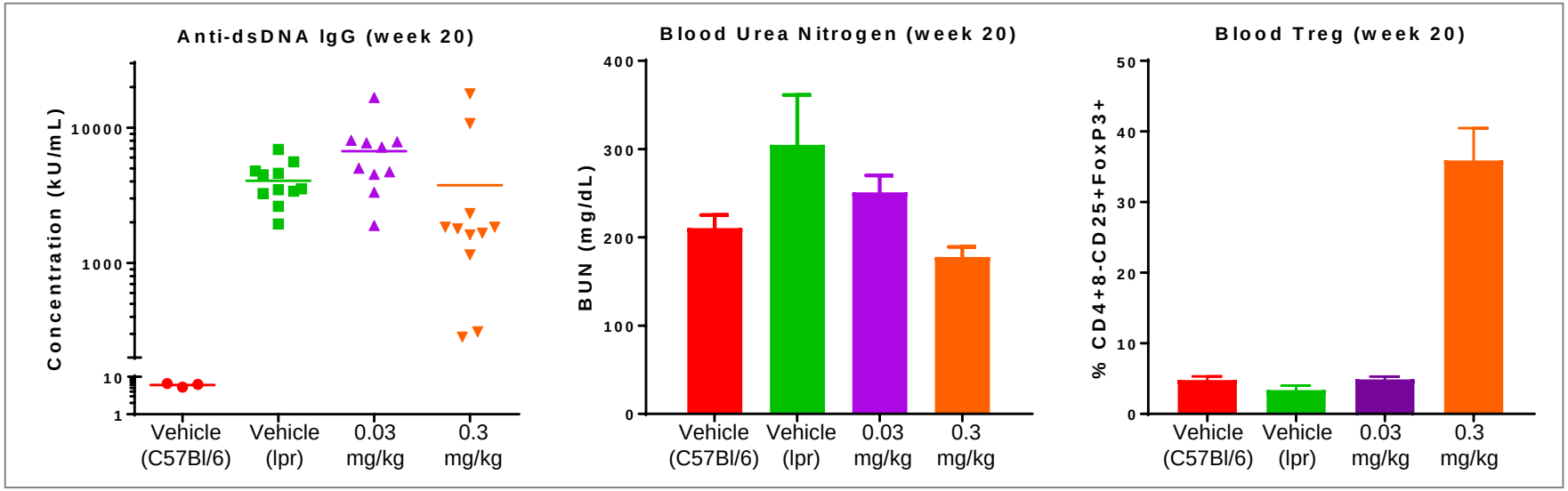






NKTR-358 is efficacious in a mouse model of SLE





- NKTR-358 demonstrated dose-dependent efficacy on multiple parameters in mouse SLE
- 0.3 mg/kg (q3d, week 8-20) reduces urine protein and blood urea nitrogen to naïve mouse parameters
- Efficacy is consistent with Treg elevation

Summary

- Nektar's immune-regulatory cytokine drug NKTR-358 induces profound Treg effects
  - Greater magnitude of total Treg cell increase than IL-2
  - Highly selective for Tregs with limited effects on non-Treg cells
  - Increased Treg suppressive capacity
  - Prolonged activation and proliferation of Treg in higher species

- Phase I Single Ascending Dose trial initiated March 2017
  - Primary readouts are Treg mobilization, functional activity, PK and safety
  - Goal is to establish a range of dose levels to be advanced into a Multiple Ascending Dose trial in patients with SLE