

NKTR-358: A Selective Regulatory T Cell Inducing Agent for the Treatment of Autoimmune and Inflammatory Diseases

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NEKTAR

Lilly

Introduction

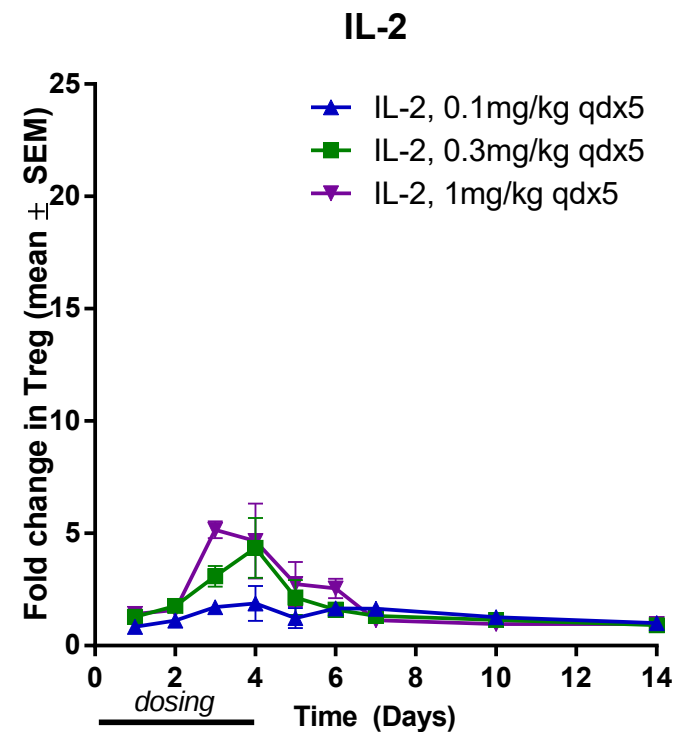
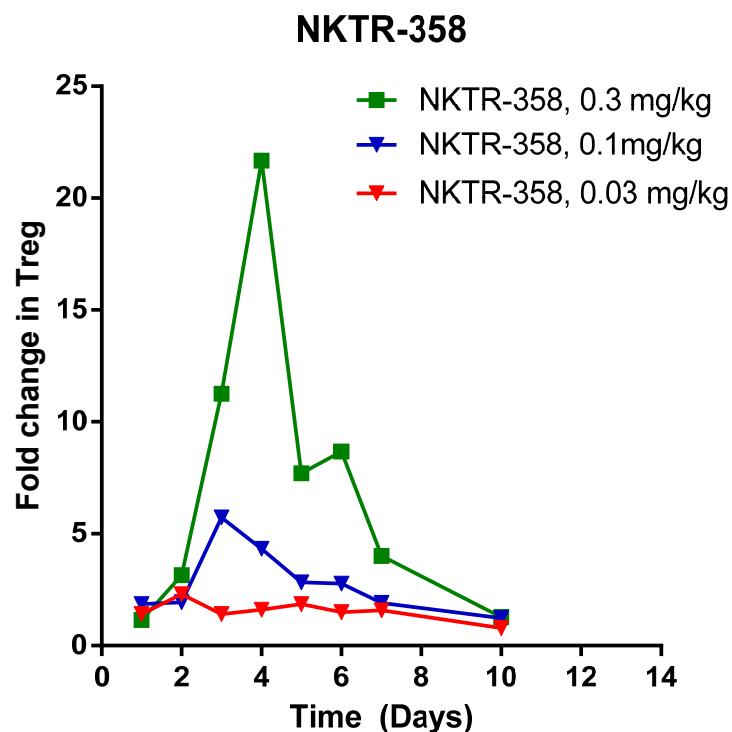
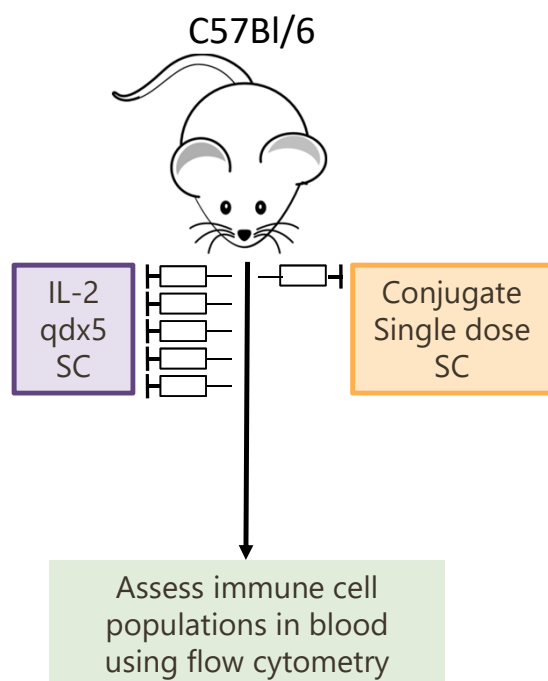
- A progressive imbalance of regulatory T cells (Tregs) relative to conventional T cells (Tcon) is shared by many autoimmune diseases
- Enhanced sensitivity of Tregs to IL-2 supports use of low-dose IL-2 therapy
 - Low-dose IL-2 therapy hampered by poor pharmacokinetics, AEs, short-lived effects
 - Magnitude of Treg mobilization ultimately limited by elicitation of Tcon
 - Clinical benefit demonstrated in GVHD, psoriasis, SLE and other indications

NKTR-358

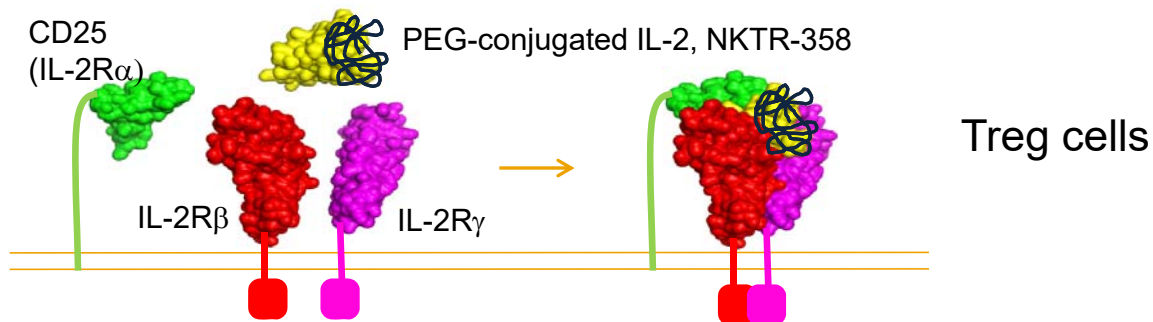
- Preferential increase in number and activity of Tregs, minimal action on non-Tregs
 - Potential first-in-class therapeutic for direct manipulation of Tregs
- Biotherapeutic born from Nektar's extensive development experience with IL-2 and polymer conjugation
- Utilizes the FDA-approved aldesleukin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

Nektar and Eli Lilly entered into a co-development agreement for NKTR-358 in August 2017

NKTR-358 was Discovered by In Vivo Screening

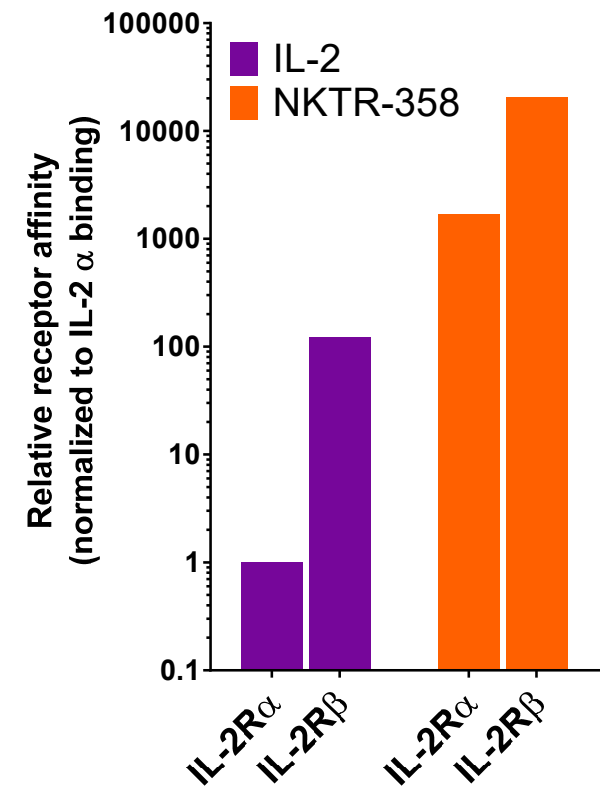


NKTR-358 has Attenuated Affinity to IL-2 Receptors

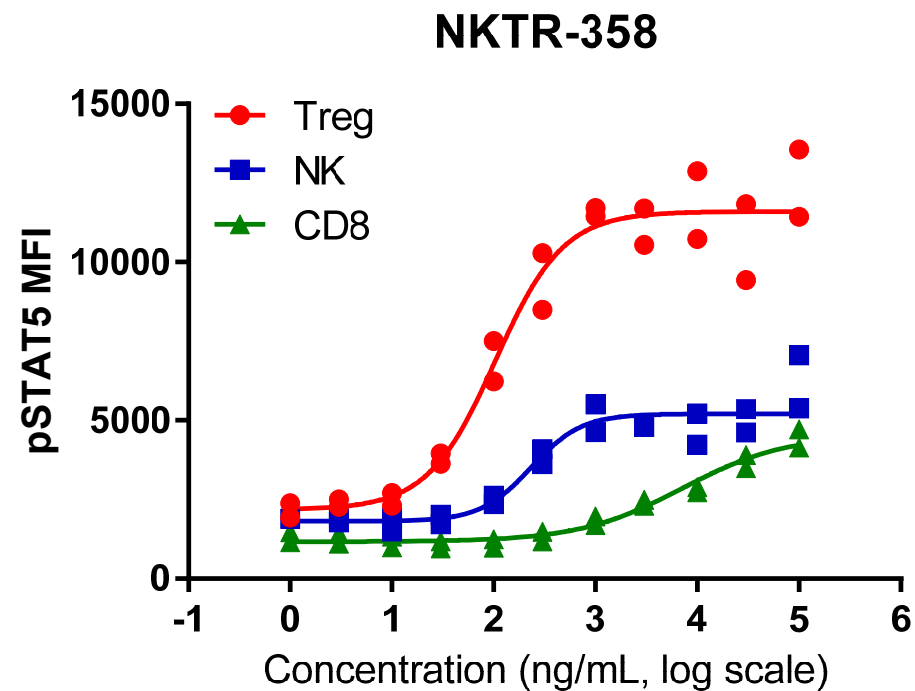
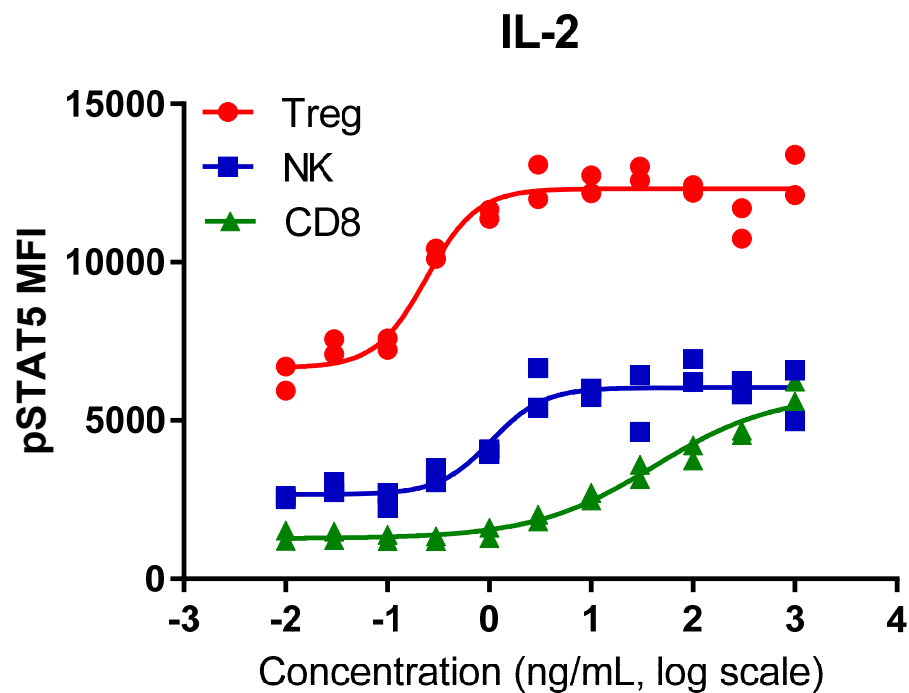


- PEG-conjugation reduces binding affinity of NKTR-358 relative to IL-2
- Relative to IL-2, NKTR-358 has:
 - Lower binding affinity to IL-2R β
 - Different binding bias for IL-2R α & IL-2R β

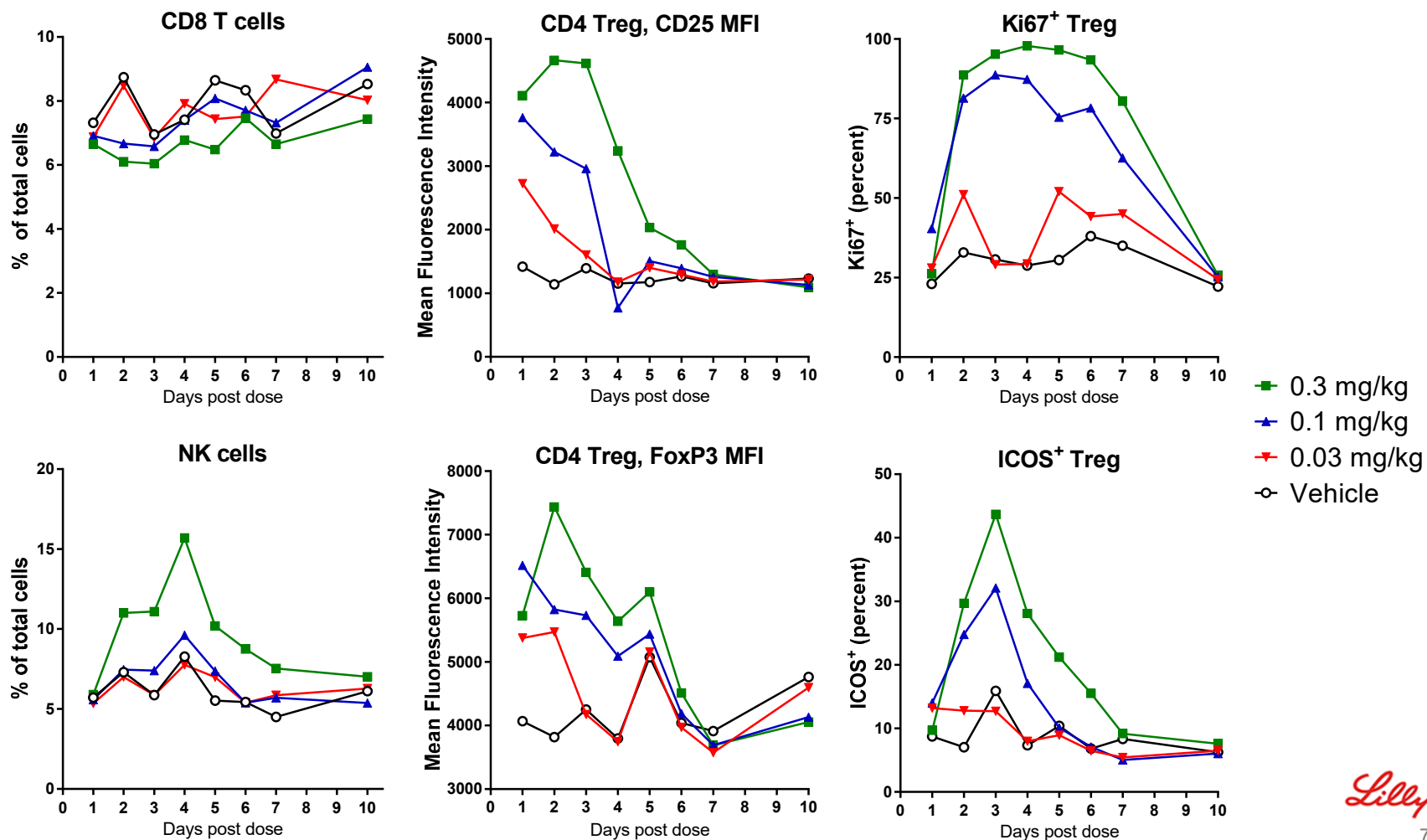
Receptor Binding



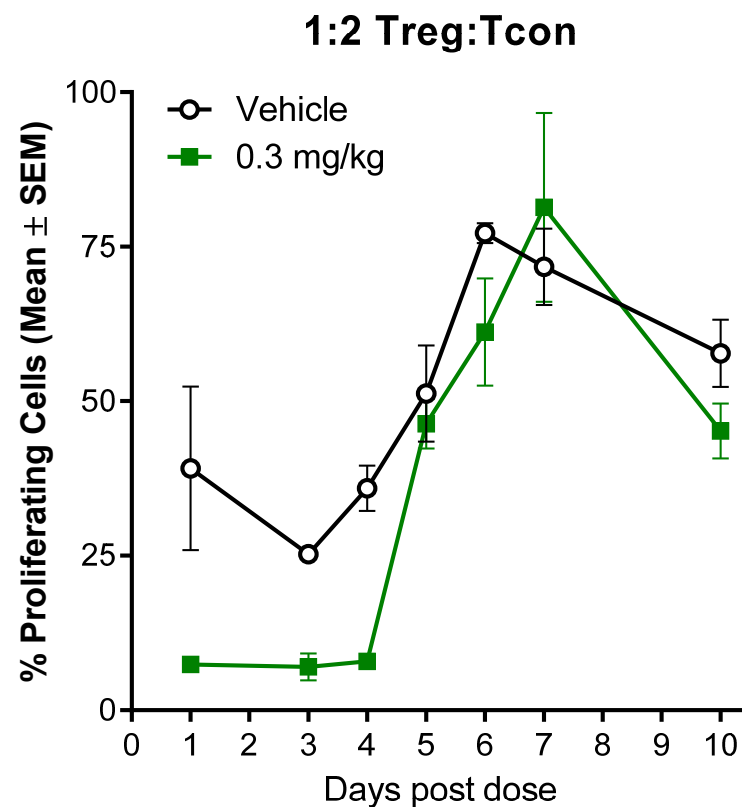
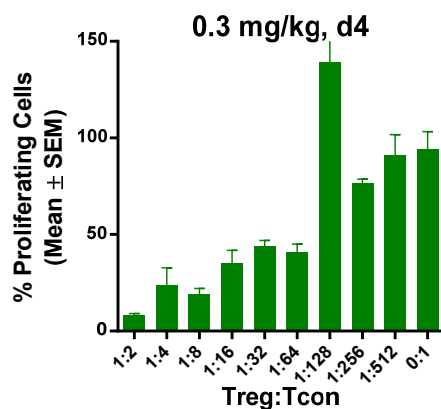
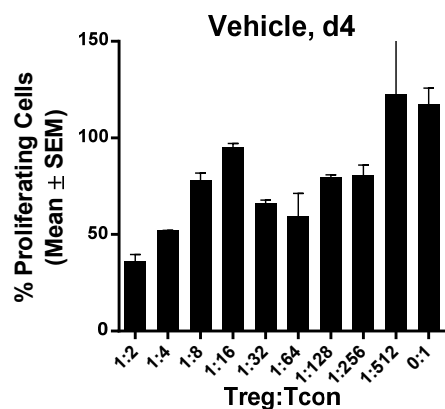
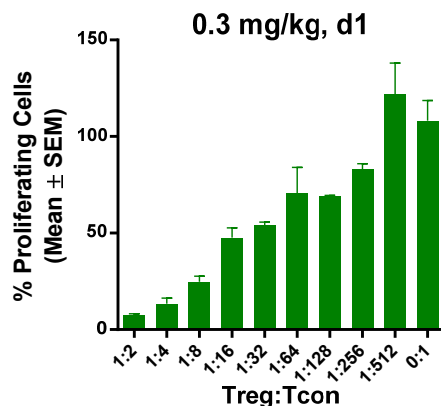
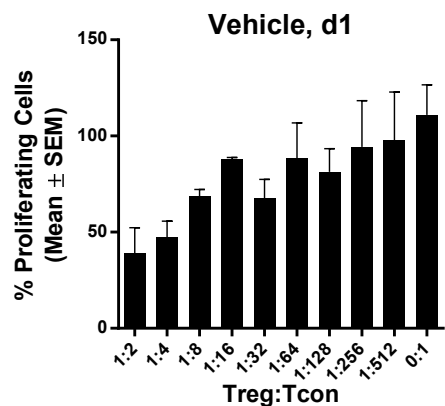
NKTR-358 Favors Activation of Treg Over Tcon



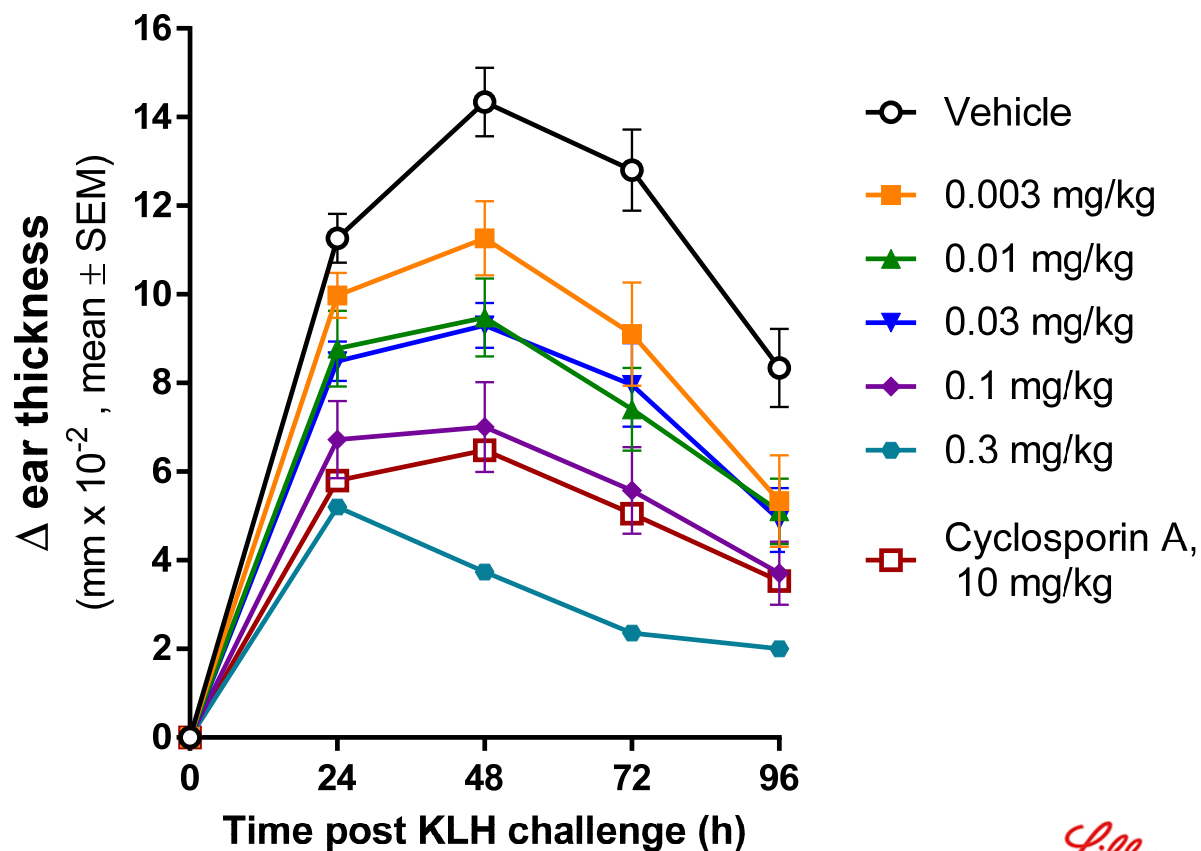
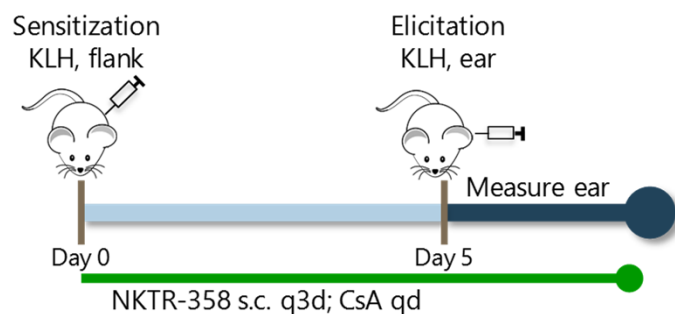
NKTR-358 Promotes Selective Treg Activation



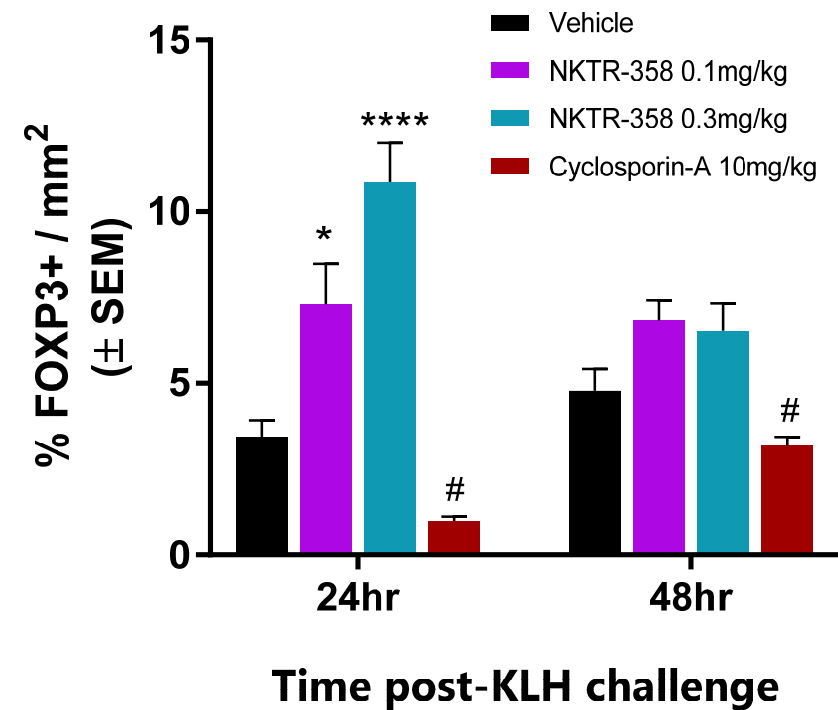
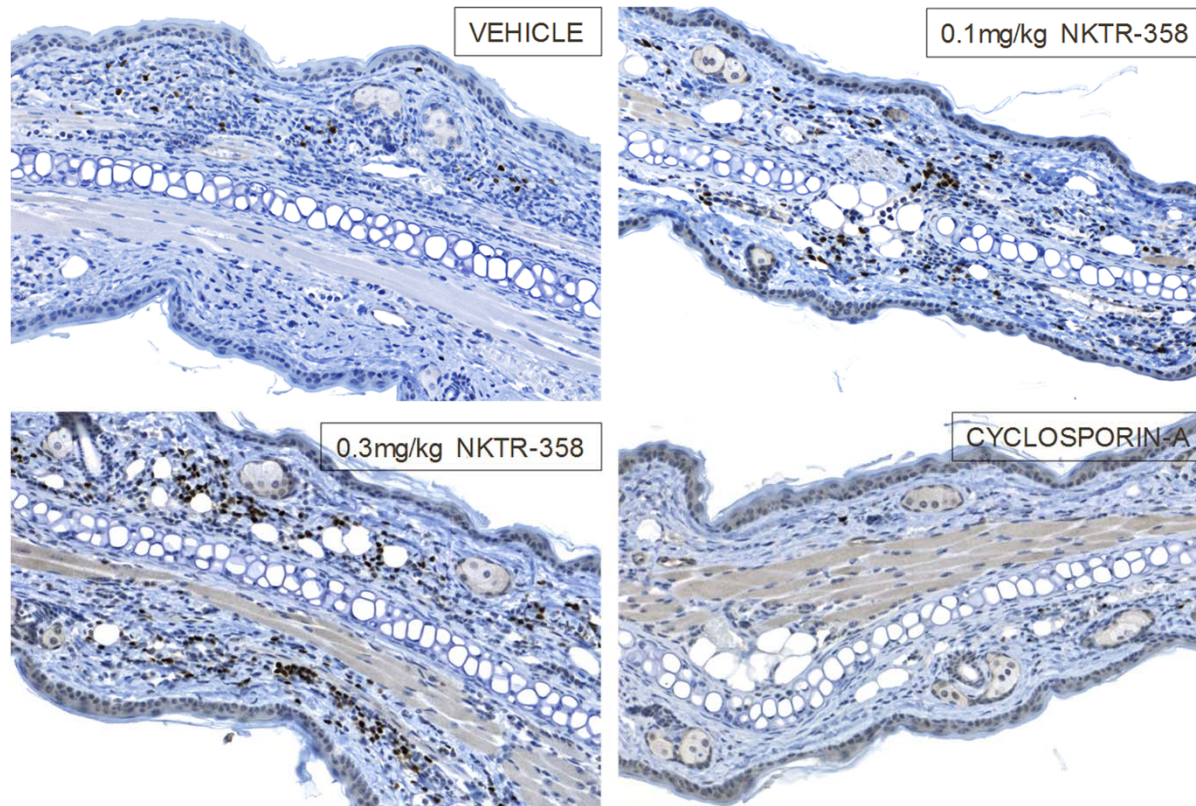
NKTR-358 Promotes Treg Suppressive Function



NKTR-358 Suppresses Inflammation in Mouse DTH



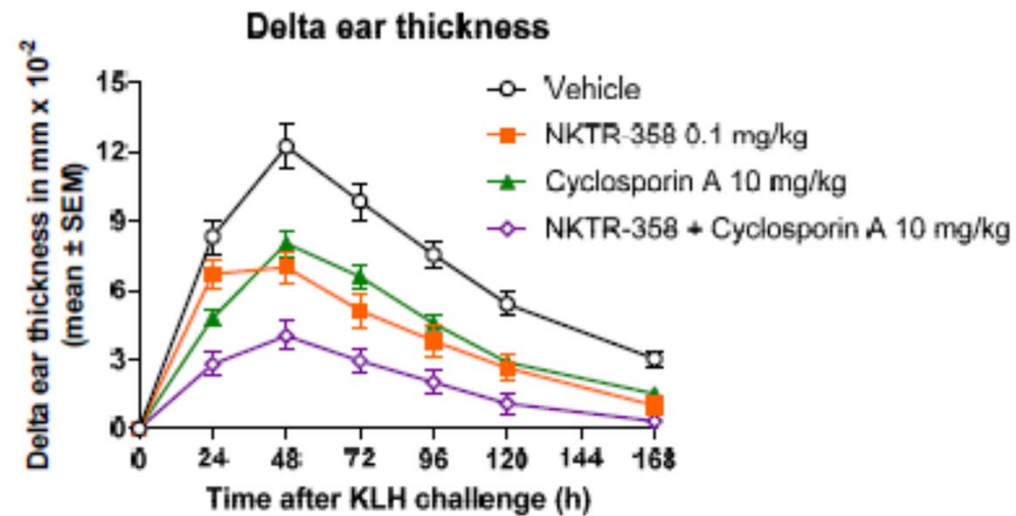
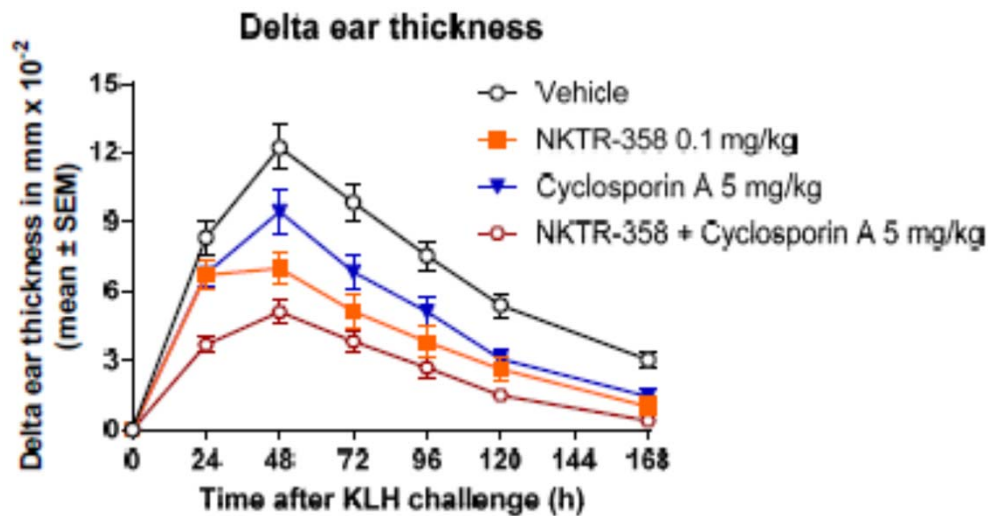
NKTR-358 Promotes Treg Infiltration in Mouse DTH



*p<0.05, ****p<0.0001 vs Vehicle w.r.t. same timepoint
One-way ANOVA (Bonferroni's post-test)

#p<0.001, unpaired t-test vs Vehicle w.r.t. same timepoint

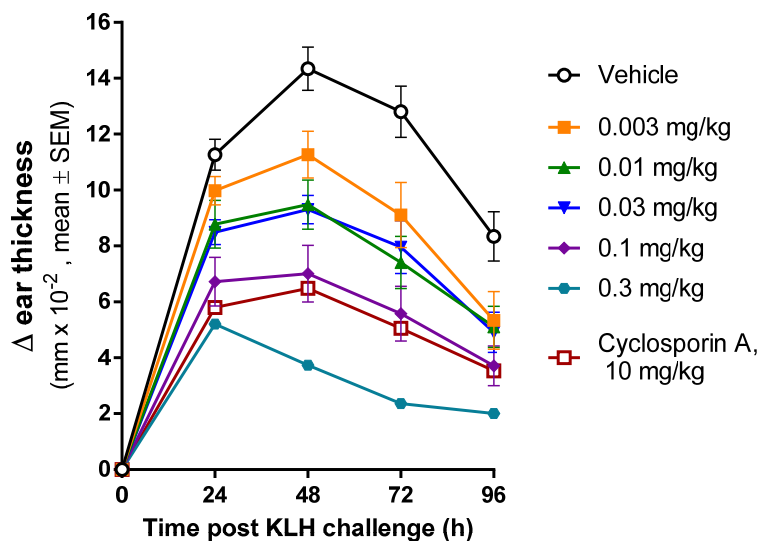
Combination of NKTR-358 + Anti-Inflammatory: Synergy of Non-Overlapping MOAs



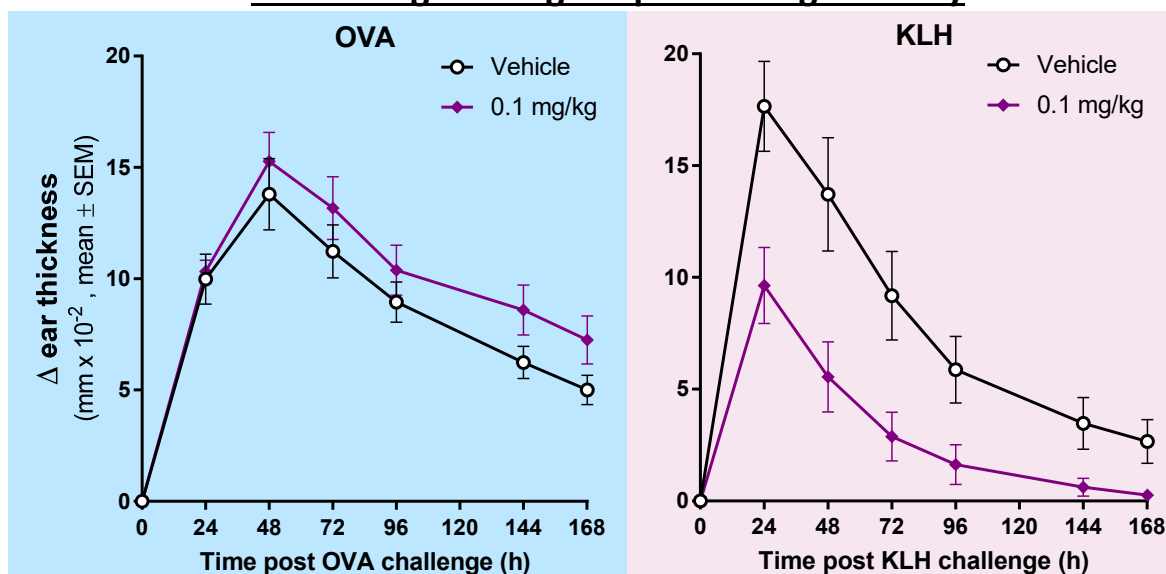
NKTR-358 Promotes Antigen-Specific Treg Memory



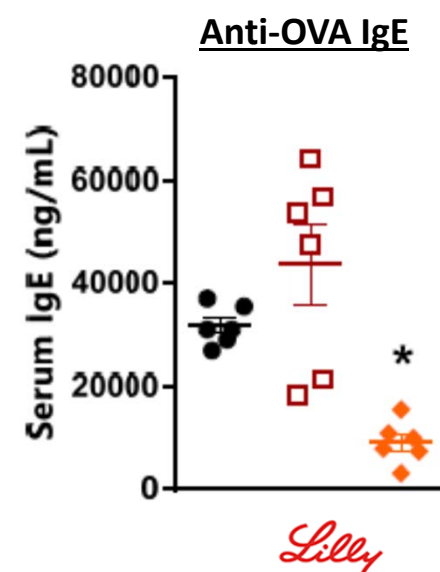
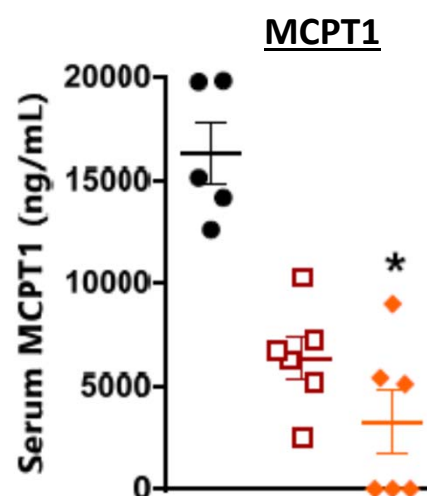
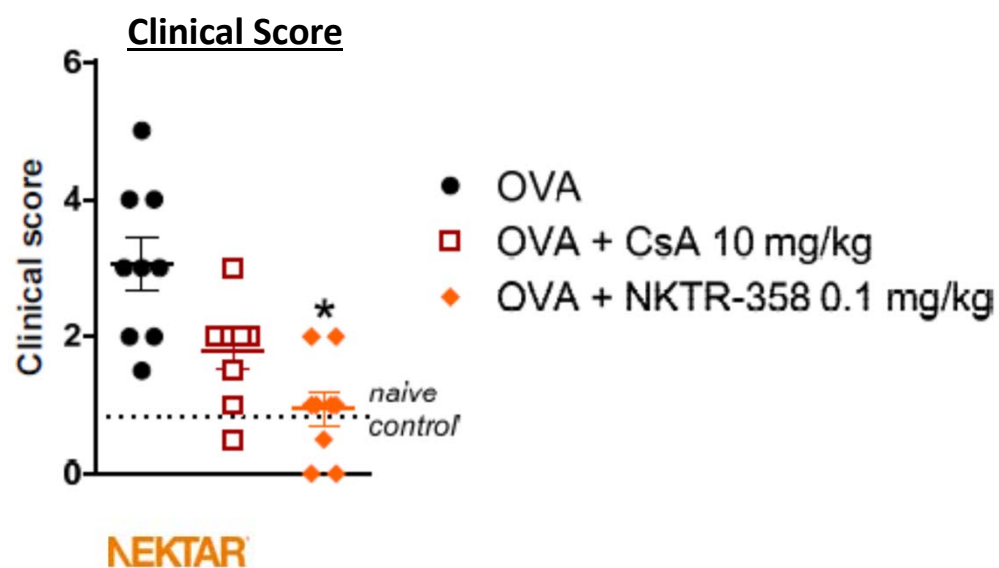
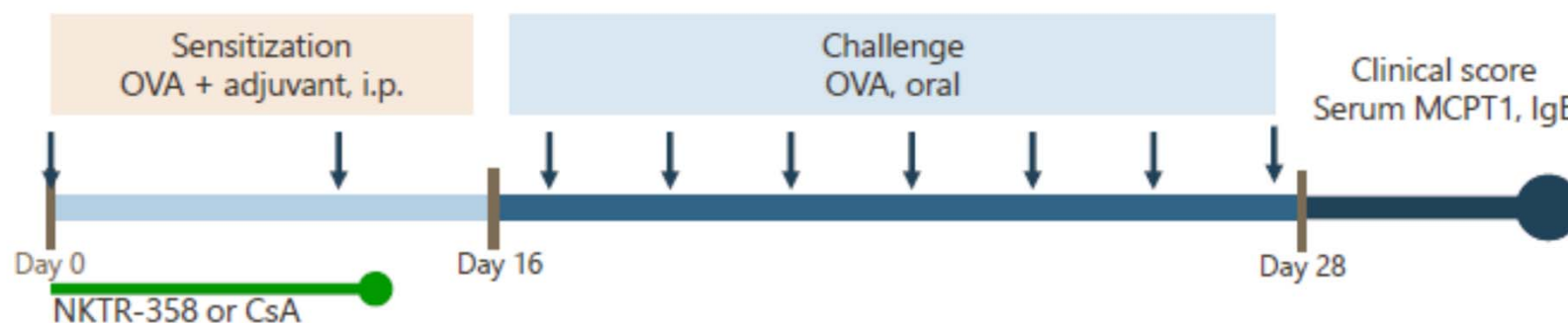
Primary efficacy



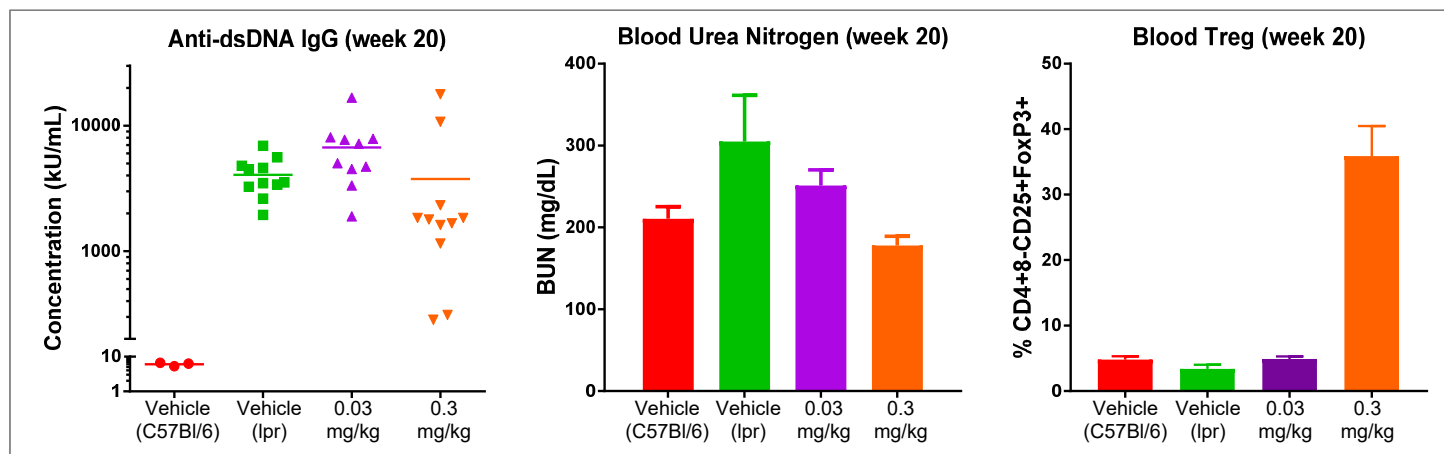
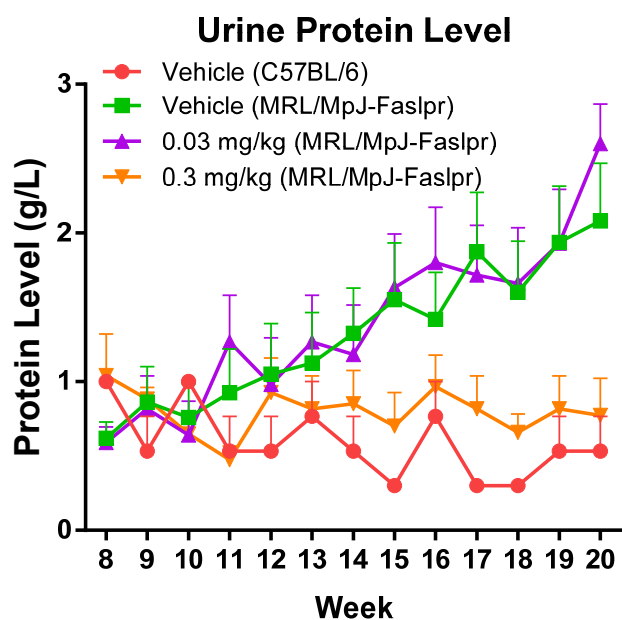
Rechallenge : Antigen-specific Treg memory



NKTR-358 Efficacy in OVA-Induced Food Allergy in Mice



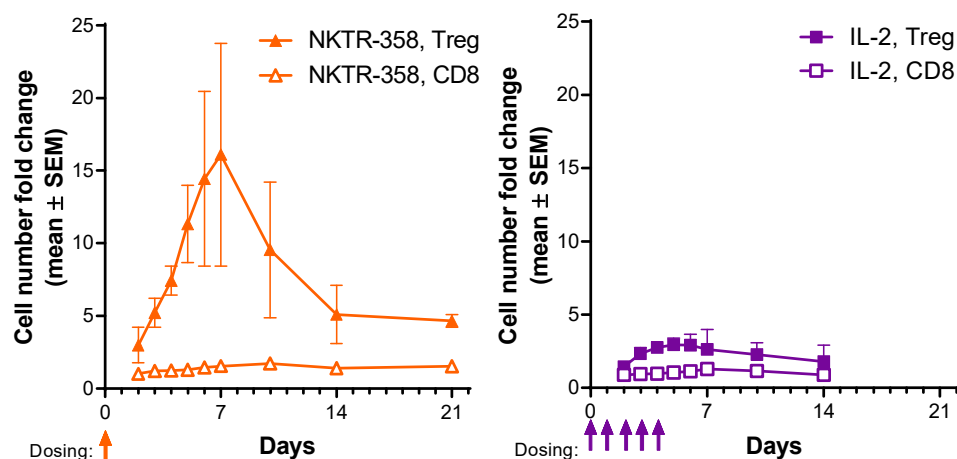
NKTR-358 Efficacy in Mouse SLE



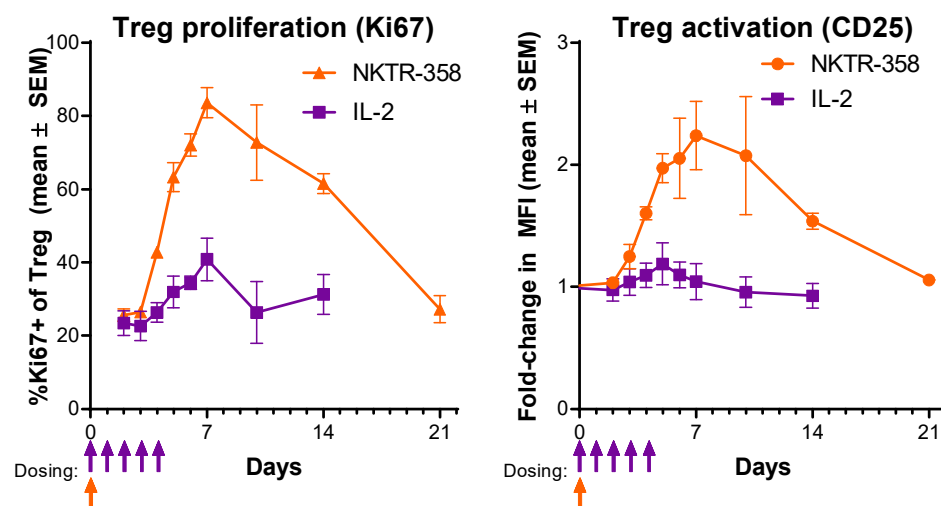
- NKTR-358 demonstrated dose-dependent efficacy on multiple parameters in mouse SLE
- 0.3 mg/kg (q3d, week 8-20) reduces urine protein and blood urea nitrogen to naïve mouse parameters
- Efficacy is consistent with Treg elevation

Preferential and Sustained Treg Expansion in NHP

Treg, CD8 in blood

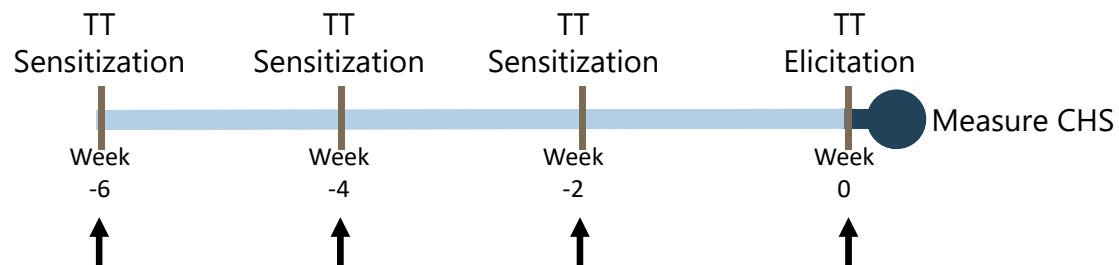


Treg activation



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

NKTR-358 Suppresses Inflammation in Monkey DTH



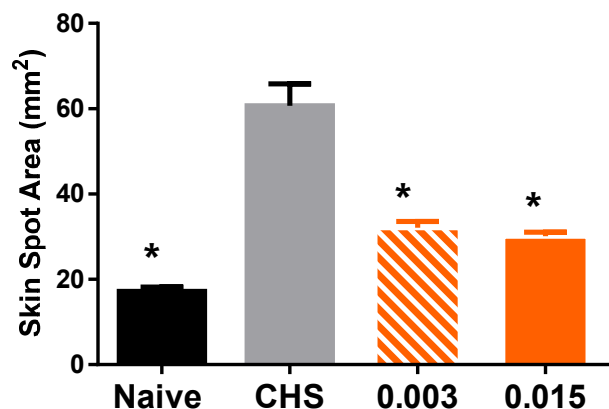
CHS: Cutaneous Hypersensitivity

TT: Tetanus Toxoid

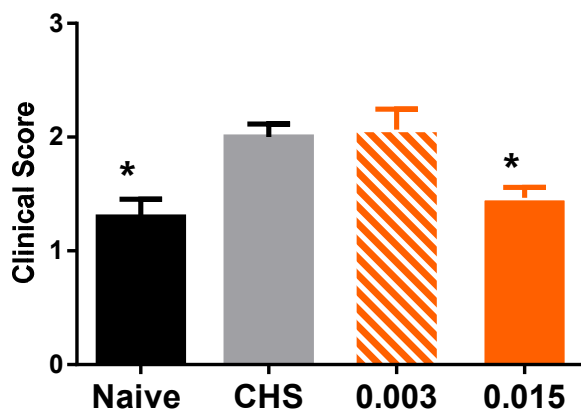
Arrows: NKTR-358 s.c., 0.003 & 0.015 mg/kg q2w

*: $p < 0.05$ vs CHS, ANOVA

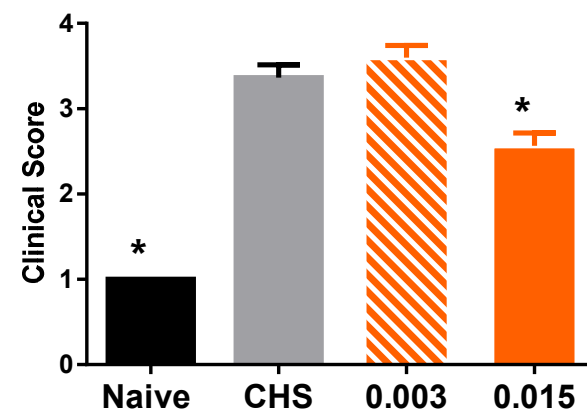
Skin Spot Area



Erythema



Edema



Development Status of NKTR-358

- Phase I Single Ascending Dose trial initiated March 2017
 - Primary readouts are Treg mobilization and activity, Treg/Tcon selectivity ratio, PK and safety
 - Goal is to establish a range of dose levels to be advanced into a clinical trial in patients with SLE
- Phase I Multiple Ascending Dose trial in SLE Patients Q2 2018
- Nektar and Lilly plan multiple indications in Phase II

Summary of NKTR-358

- NKTR-358 is an immune-regulatory cytokine drug being developed by Nektar and Lilly that 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 and induction of long-lived Treg memory
 - Prolonged activation and proliferation of Treg in higher species
- Clinical development ongoing for the treatment of autoimmune and chronic inflammatory indications