Selective Expansion of Regulatory T-Cells in Humans by a Novel IL-2 Conjugate T-reg Stimulator, NKTR-358, Being Developed for the Treatment of Autoimmune Diseases

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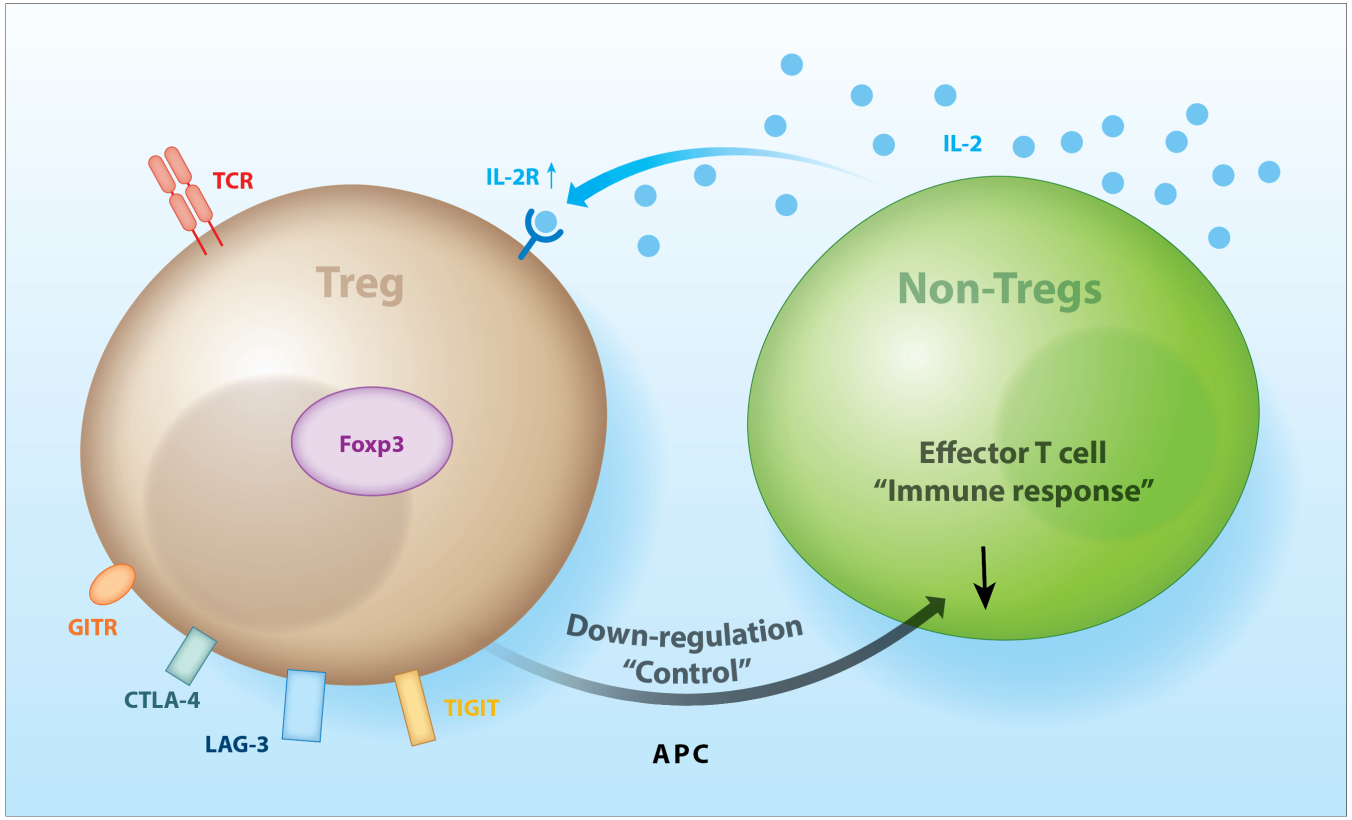
Disclosures

- C. Fanton, S. Siddhanti, N. Dixit, L. Lu, T. Gordi, J. Zalevsky, B. Kotzin are employees of Nektar Therapeutics and own shares of the company

- D. Dickerson is an employee of PRA Healthsciences

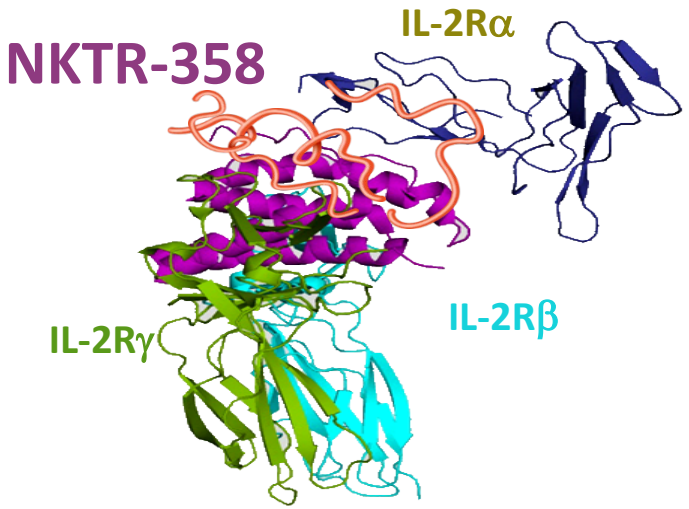
IL-2 is Critical for Treg Expansion, Function and Control of Immune Responses by Tregs



Many autoimmune disorders, including SLE, are associated with:

- Reduced Treg numbers
- Impaired Treg function
- Reduced systemic IL-2

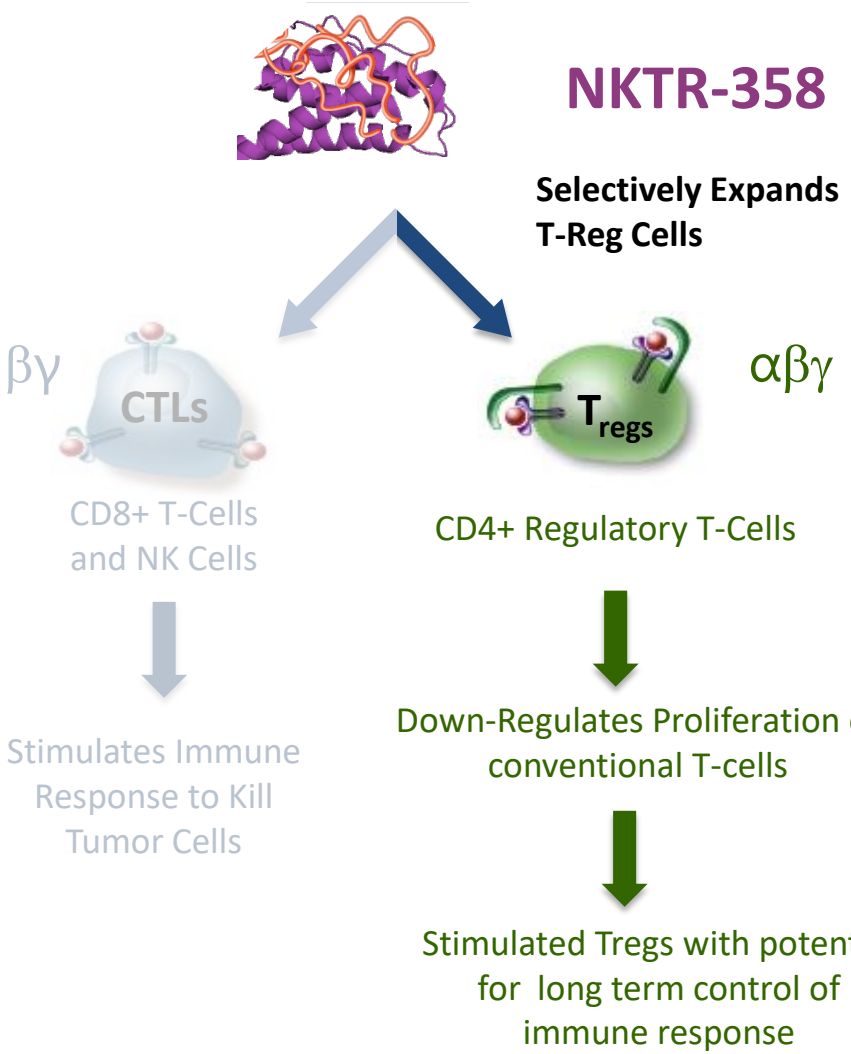
NKTR-358: PEG-conjugated rhIL-2 Selectively Induces Regulatory T-cells (Tregs) and Their Suppressive Activity



PEG-conjugation:

- Alters binding profile of NKTR-358 (vs IL-2) with lower binding affinity to IL-2Rβ and different binding bias for IL-2Rα & IL-2Rβ
- Imparts selectivity for effect on Tregs over Tcons (vs IL-2)
- Increases half life (vs IL-2)

NKTR-358 has shown activity in animal models of SLE and cutaneous hypersensitivity



NKTR-358: Single Ascending Dose Study Objectives

Assess the effects of subcutaneous administration of single-ascending doses of NKTR-358 in healthy volunteers on:

Primary

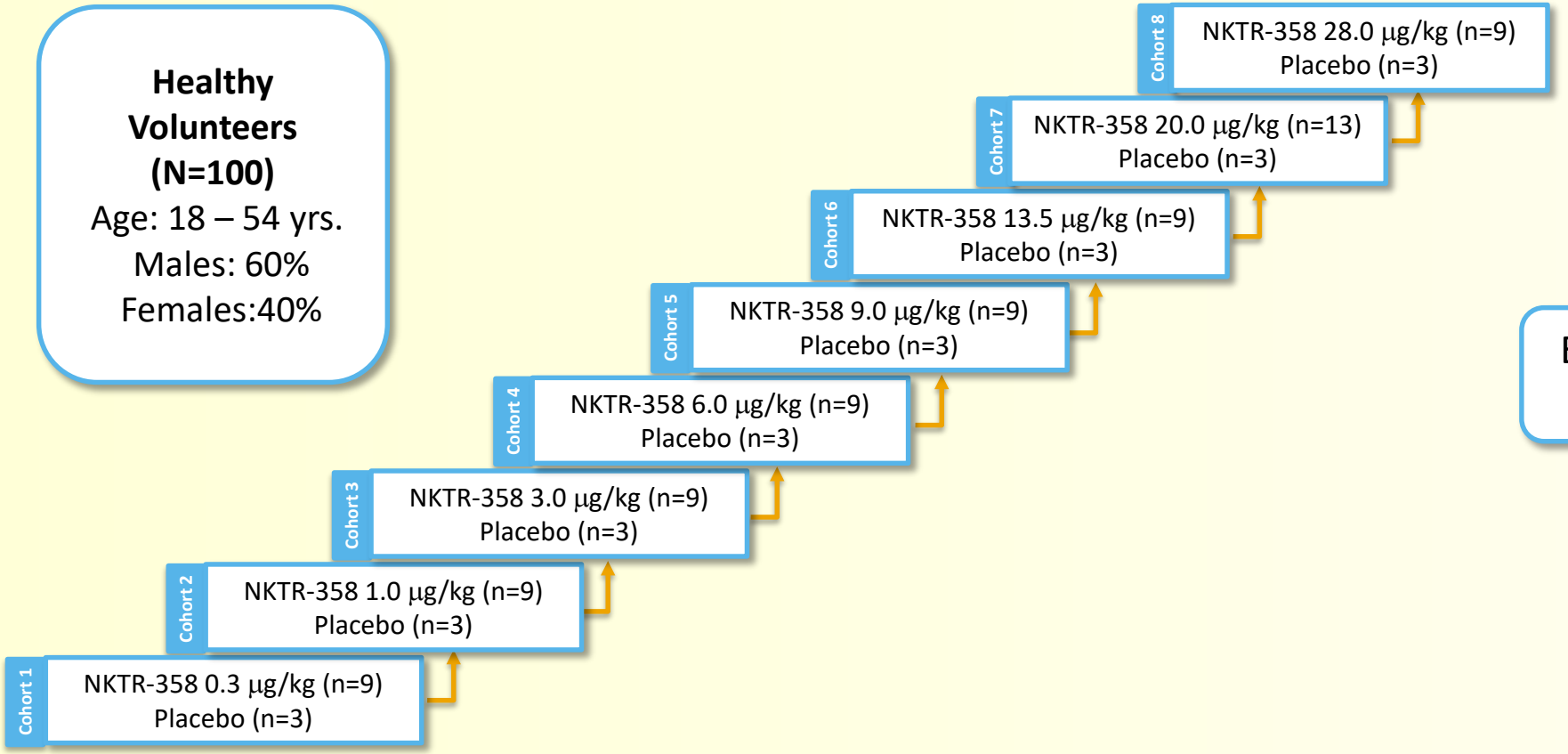
- Safety and tolerability in subjects as evaluated by:
  - Adverse events
  - Vital signs
  - Clinical laboratory
  - Cytokine levels

Secondary

- Time course and extent of changes in the numbers and activity of Tregs, Tcons, and NK cells and subsets
- Pharmacokinetics (PK) of NKTR-358
- Other immunological effects: cytokine levels, peripheral blood cell populations, serum proteins and gene expression

Study Design: Randomized Double-blind Study of Subcutaneous Single Ascending Doses of NKTR-358 in Healthy Volunteers

Healthy Volunteers (N=100)
Age: 18 – 54 yrs.
Males: 60%
Females:40%



Each cohort followed for 50 days

Study Enrolled and Follow-up Complete

NKTR-358 SAD Study Results: NKTR-358 was Safe and Well Tolerated in Healthy Volunteers

- No dose-limiting toxicities, deaths, or AEs leading to study discontinuation
- No clinically significant vital sign, ECG, or physical examination abnormalities
- Adverse events primarily limited to mild or moderate (Grade 1 or 2) injection site reactions
- 4 subjects experienced Grade 1 mild events of headache
- 1 subject at the highest dose tested (28.0 µg/kg) experienced mild (Grade 1) signs and symptoms of vomiting, diarrhea, anorexia, tachycardia, and myalgia attributed to elevated cytokine levels
- No anti-drug antibodies detected

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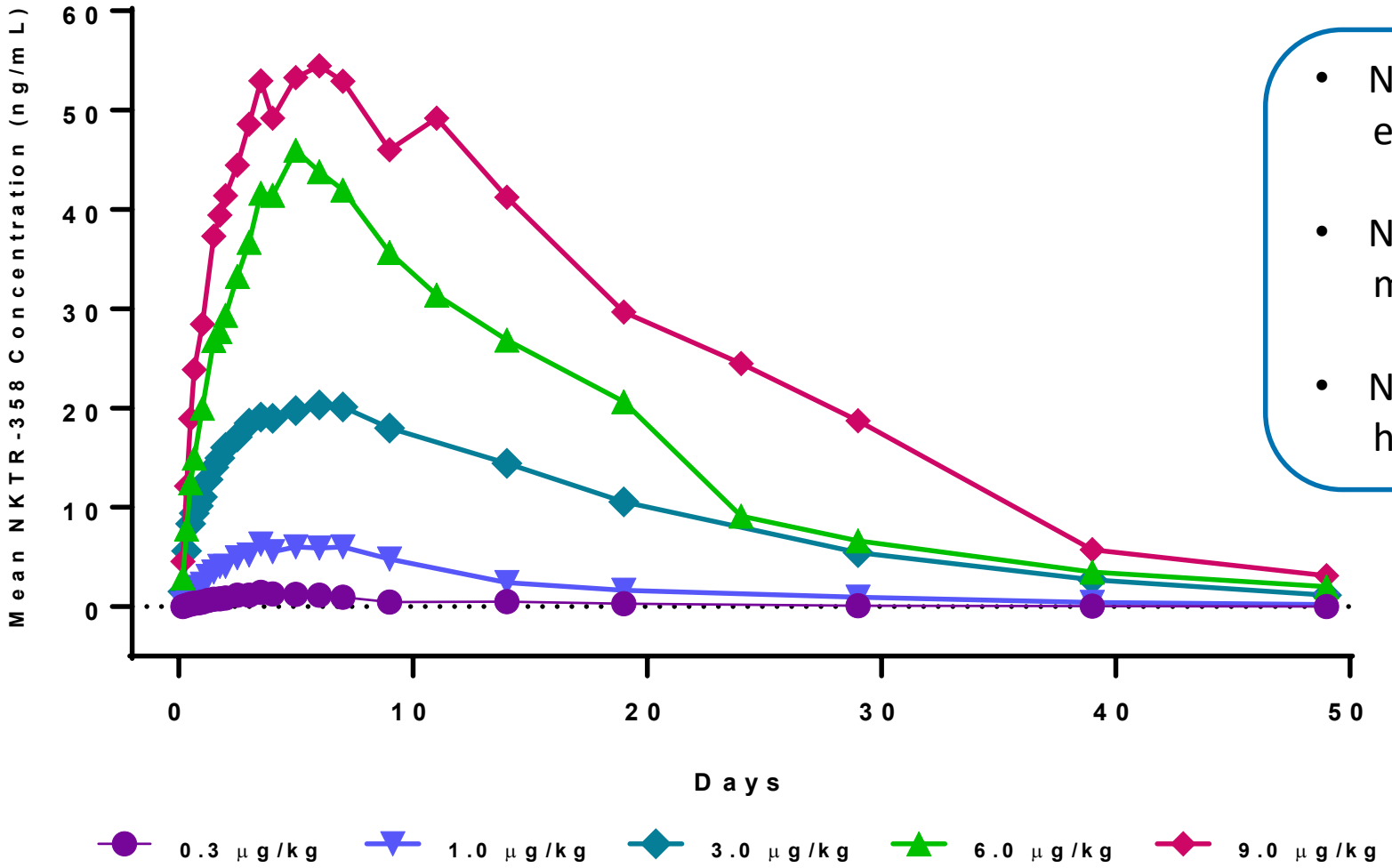
NKTR-358 Concentration Curves Indicate Dose Proportional Pharmacokinetics*



- NKTR-358 Cmax and AUC values exhibited a dose proportional increase
- NKTR-358 concentrations reached maximum levels in 4-6 days
- NKTR-358 has an estimated elimination half-life of 8-9 days

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Not all cohorts are shown for clarity

*PK analyses preliminary and in progress

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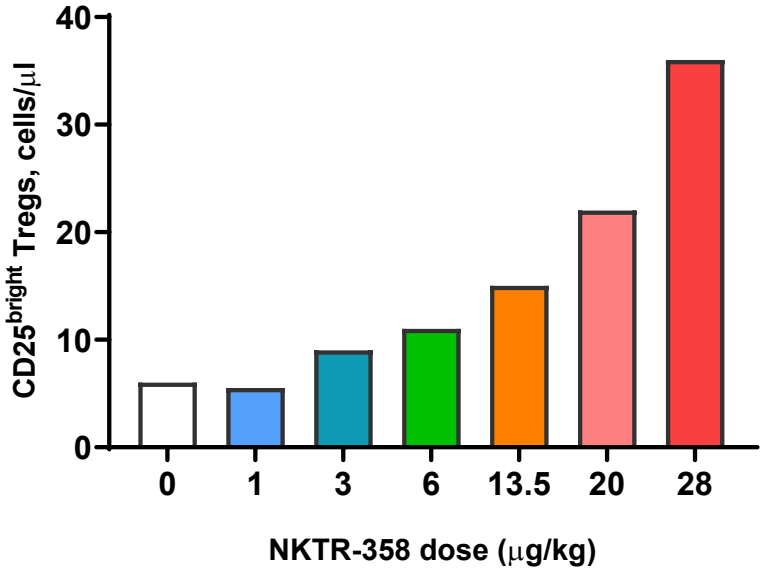
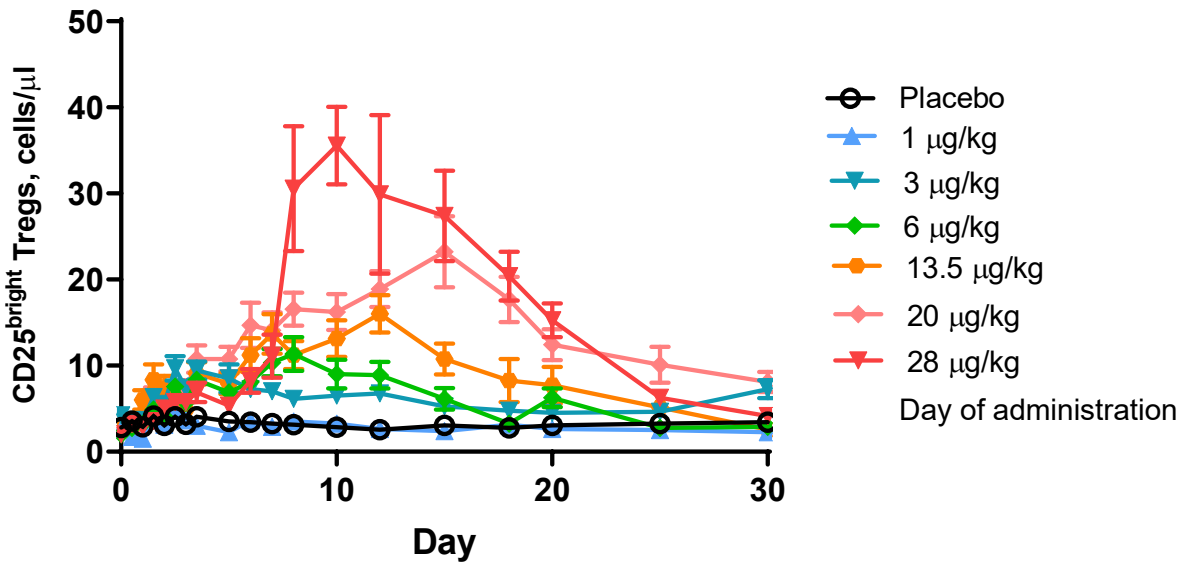
NKTR-358 Leads to Sustained, Dose-dependent Increases in CD25^{bright} Tregs

Median peak effect of CD25^{bright} Tregs



Absolute numbers of CD25^{bright} Tregs



- At 28 µg/kg NKTR-358:
  - 17-fold mean peak increase in numbers of CD25^{bright} Tregs above predose value
  - Treg levels peak at Days 10-12 and do not return to baseline until Days 20-25 following administration
- Increase in Treg activation markers ICOS and CTLA4 were observed at doses ≥13.5 µg/kg

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Not all cohorts are shown for clarity

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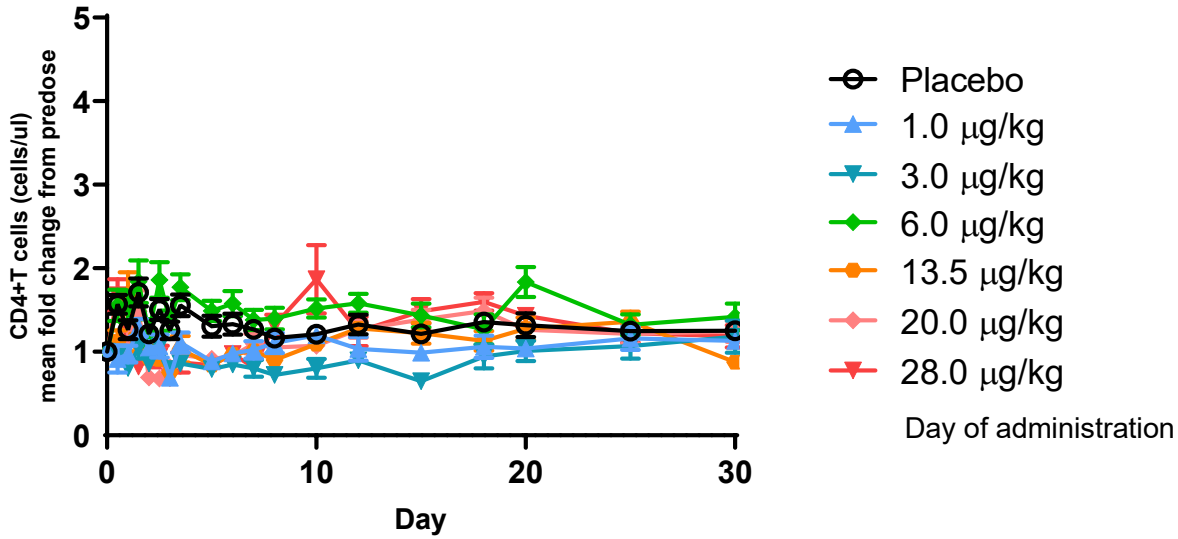
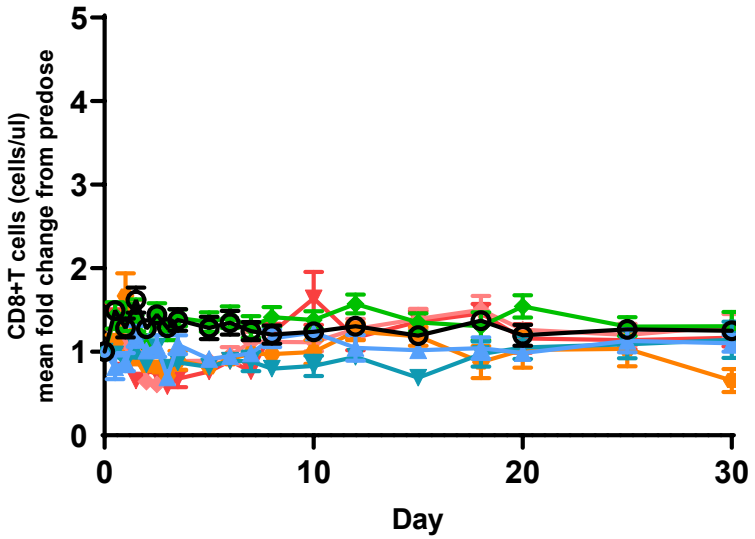
NKTR-358: No Changes in Numbers of Tcon Cells and Low-level Increases in Numbers of CD56+ NK Cells

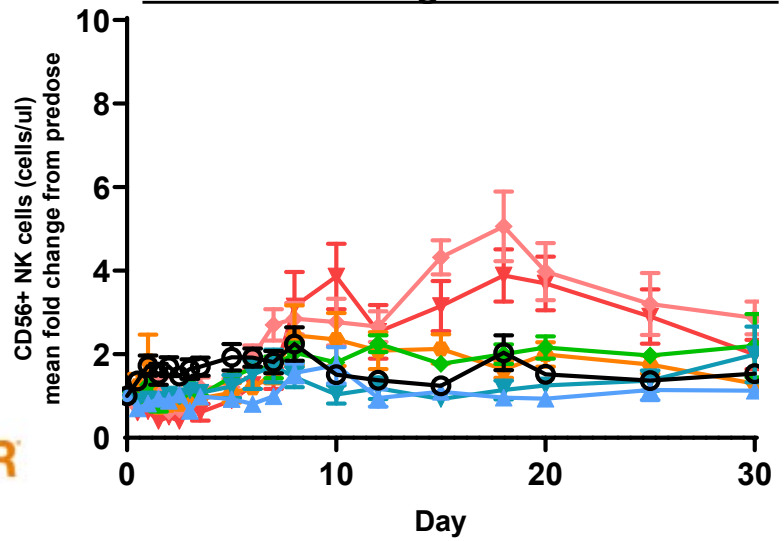
Mean fold change of CD4+ cells



Mean fold change of CD8+ cells



Mean fold change of CD56+ NK cells



Not all cohorts are shown for clarity

NKTR-358 SAD Study: Conclusions

- Safe and well tolerated in this first in human study
- Preliminary data suggest dose proportional pharmacokinetics and prolonged exposure with a half-life of 8-9 days
- Marked and selective dose-dependent expansion of $CD25^{bright}$ Treg cells
- No measurable changes in numbers and percentages of CD4+ and CD8+ Tcons at all doses and low-level increases of NK cell numbers at highest doses tested
- Data provide strong support for studying NKTR-358 in autoimmune and inflammatory diseases
- NKTR-358 is currently being studied in a multiple ascending dose clinical trial in patients with SLE and additional studies in other inflammatory diseases are planned

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