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NEW PATHWAYS TO SMARTER MEDICINE™

2020 EULAR European Congress of Rheumatology

Results from a Phase 1b Multiple-Ascending Dose Study of NKTR-358:
"NKTR-358, a novel IL-2 conjugate, stimulates high levels of regulatory T cells in patients with systemic lupus erythematosus" Fanton C., et al.

Dr. Jonathan Zalevsky - Chief R&D Officer
Brian Kotzin - SVP, Clinical Development and Head of Immunology at Nektar
Jennifer Ruddock - SVP, Strategy and Corporate Affairs

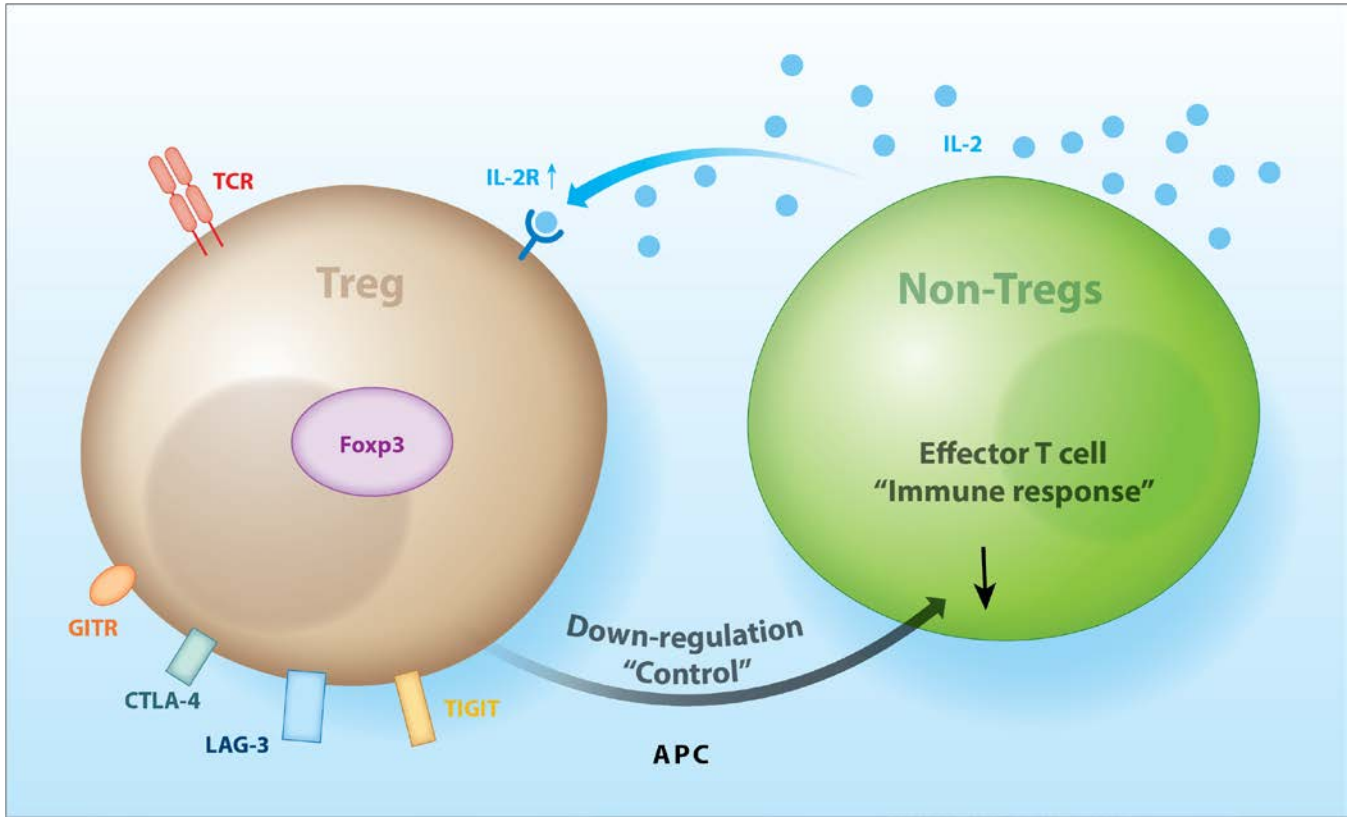
Investor & Analyst Call June 5, 2020

This presentation includes forward-looking statements regarding Nektar's proprietary drug candidates, the timing of the start and conclusion of ongoing or planned clinical trials, the timing and outcome of regulatory decisions, and future availability of clinical trial data. Actual results could differ materially and these statements are subject to important risks detailed in Nektar's filings with the SEC including the Form 10-Q filed on May 8, 2020. Nektar undertakes no obligation to update forward-looking statements as a result of new information or otherwise.

Autoimmune diseases intrinsically reflect a distorted Teff/Treg balance

The goal in autoimmune diseases is to restore a proper Treg/Teff balance

IL-2 is the main cytokine promoting Tregs' survival and function



Mice rendered deficient in IL-2 or IL-2R have no Tregs and develop severe inflammation and multiorgan autoimmunity

Many autoimmune disorders, including SLE, are associated with:

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

IL-2 has the potential to regulate the Teff/Treg balance by promoting Tregs

Interleukin-2 mechanisms of action are well understood

IL-2 stimulates and expands Tregs

- **control of the effector T cell mediated autoimmune response**

IL-2 blocks the differentiation of Tfh cells

- control of the effector antibody mediated autoimmune response

IL-2 blocks the differentiation of pro-inflammatory Th17 cells

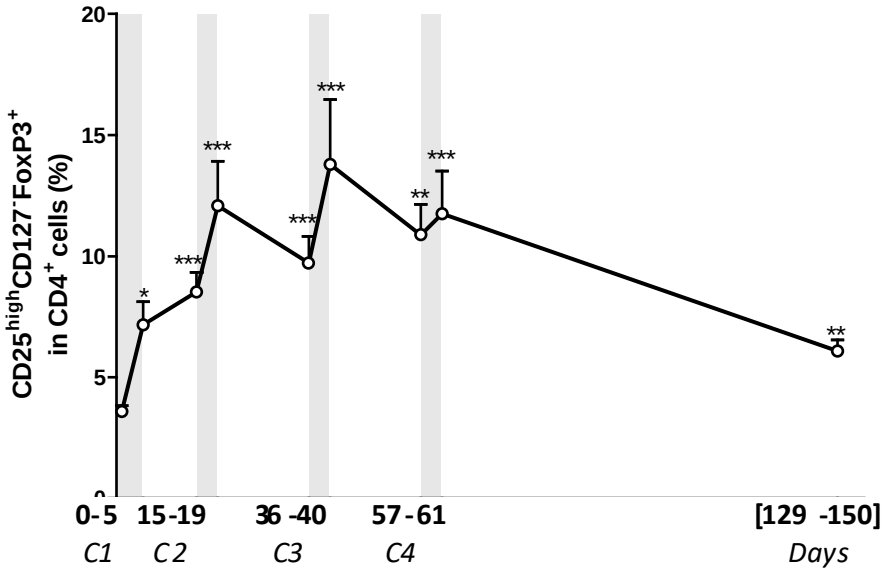
- control of inflammation

These properties have contributed to positive pre-clinical results obtained in >30 experimental autoimmune and inflammatory diseases (including T1D, EAE and SLE)

Klatzmann & Abbas; Nature Reviews Immunology 2015

Low-dose IL-2 PoC in an autoimmune disease: vasculitis

Tregs



The NEW ENGLAND JOURNAL of MEDICINE

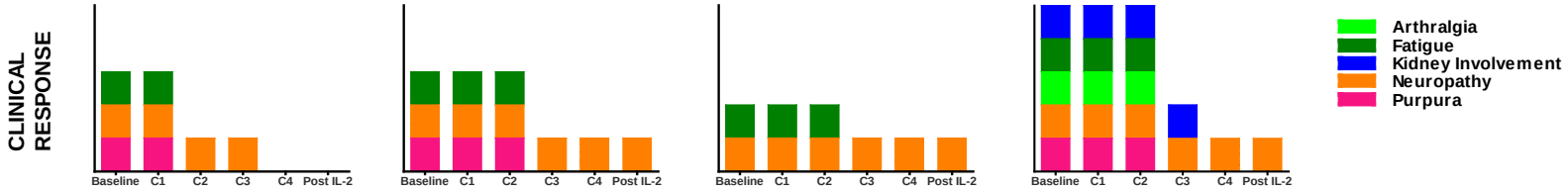
ORIGINAL ARTICLE

Regulatory T-Cell Responses to Low-Dose Interleukin-2 in HCV-Induced Vasculitis

David Saadoun, M.D., Ph.D., Michelle Rosenzwajg, M.D., Ph.D., Florence Joly, Ph.D., Adrien Six, Ph.D., Fabrice Carrat, M.D., Ph.D., Vincent Thibault, Pharm.D., Damien Sene, M.D., Ph.D., Patrice Cacoub, M.D., and David Klatzmann, M.D., Ph.D.

- 10 patients treated: 1.5 - 3 million IU/day
- Very well tolerated
- Excellent Treg induction
- Clinical improvements in 8/10 patients

Clinical response



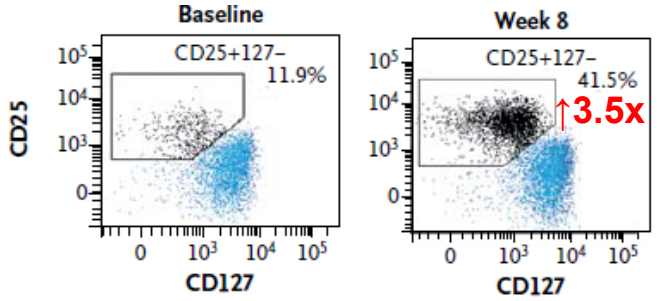
We also showed that low-dose IL-2 has anti-inflammatory effects

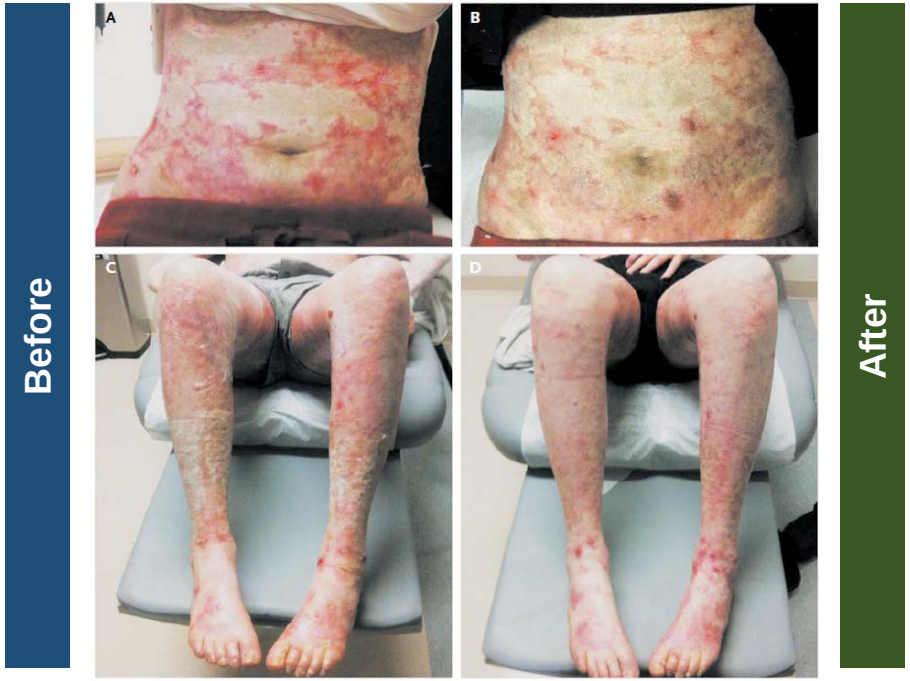
Saadoun, *NEJM 2011; Rosenzwajg*, J. *Autoimmunity 2015*

Low-Dose IL-2 PoC in an allo-immune inflammatory disease: chronic graft-versus-host disease (cGVHD)

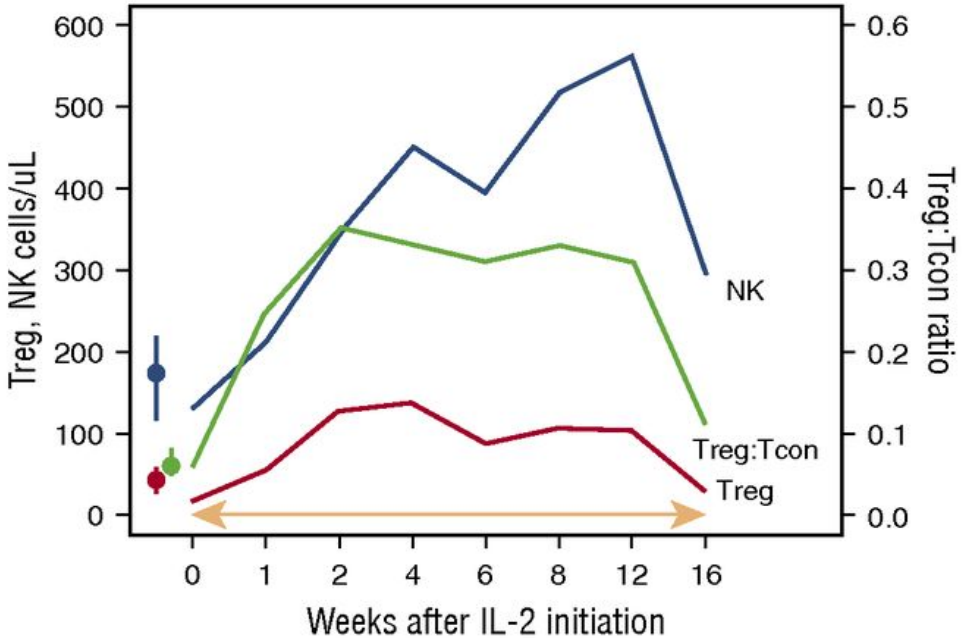
- **Daily s.c. IL-2 delivery of 1 MIU/m2**
  - patients following stem-cell transplant, median age of 49.5 years
  - 20/35 patients demonstrate (incomplete) clinical response
  - Reduction in steroid usage, improved skin pathology, liver function
- Continued administration does not lead to further Treg expansion
  - Continued IL-2 administration required for Treg increase
  - Responders have higher baseline Treg:Tcon ratios

3-5x increase in blood Treg cells





Treg, NK expansion following IL-2 treatment



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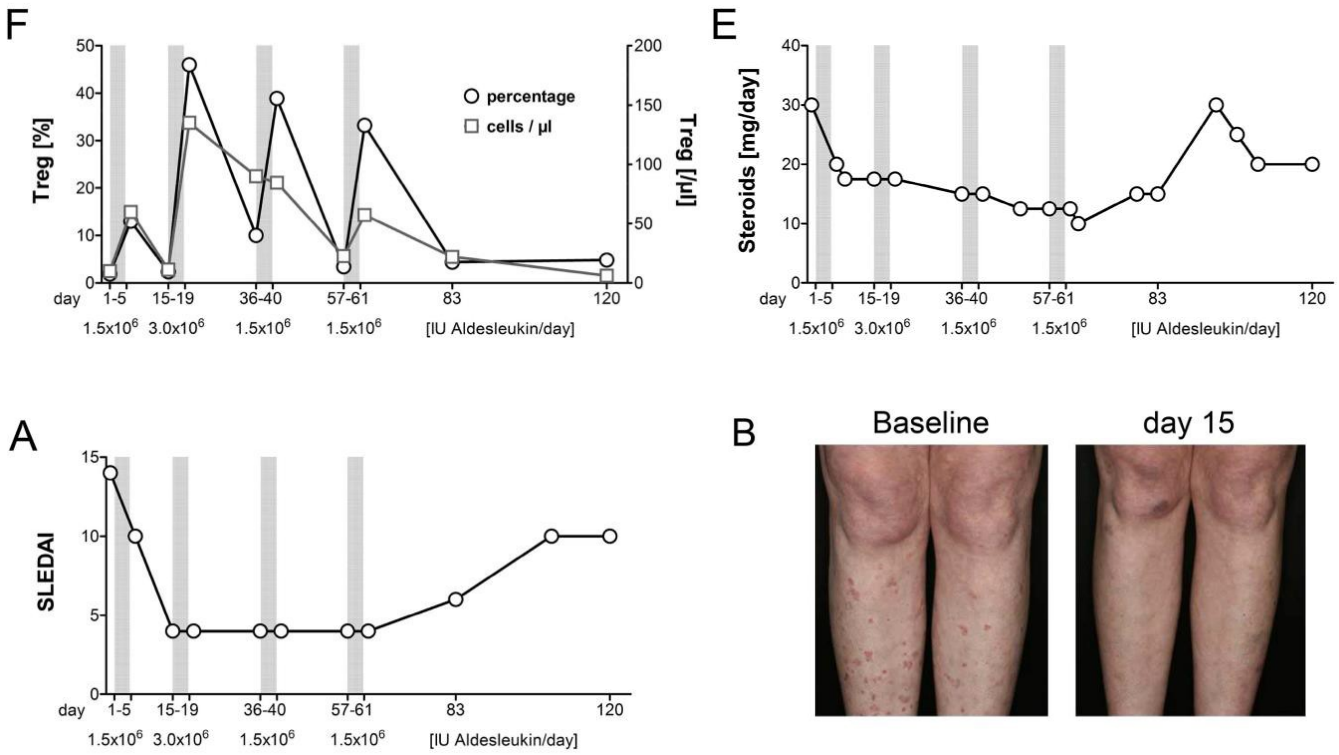
Koreth, *NEJM 2011;* Koreth, *Blood* 2016

Clinical remission in refractory SLE patient treated with low-dose IL-2

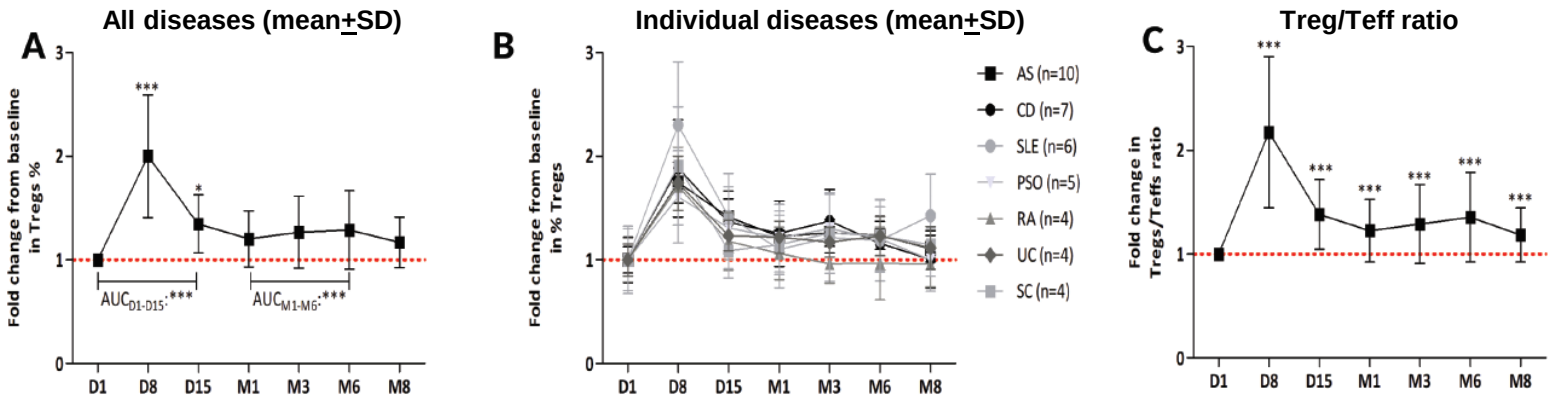


- 36-year-old female patient with SLE with high disease activity at baseline
  - Active arthritis with clinical and laboratory signs of myositis, rash, hypocomplementaemia and elevated anti dsDNA antibodies (SELENA-SLEDAI 14).
- First treatment cycle with low-dose IL-2:
  - Signs of arthritis, active skin eruptions and laboratory signs of myositis disappeared (figure 1A–C) and myalgia also improved 3 weeks later.
- Following three cycles:
  - Organ manifestations remained absent, disease activity remained low (SELENA-SLEDAI 4) (figure 1A–C)
- Daily dose of glucocorticosteroids could be reduced step by step (figure 1E).
- Clinical response associated with cyclic and treatment-related increases of the CD25++Foxp3+CD127lo Treg population (figure 1F).

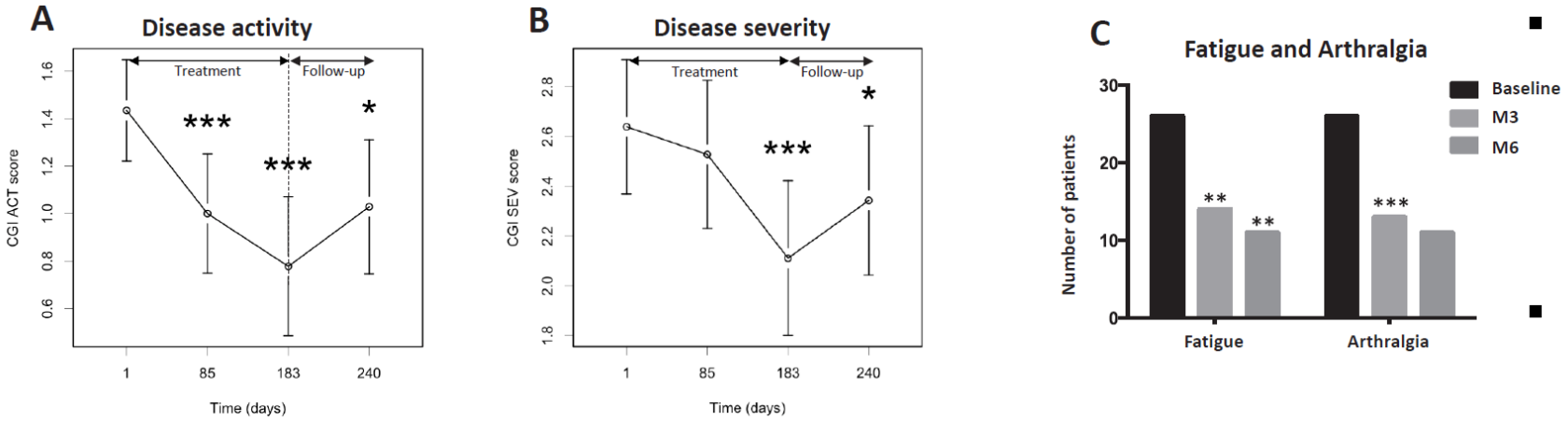
SOURCE: :Ann Rheum Dis. 2015 Apr;74(4):791-2. doi: 10.1136/annrheumdis-2014-206506. Epub 2015 Jan 21.

Immunological and clinical effects of low-dose interleukin-2 across 11 autoimmune diseases

Change in Tregs (%CD4) from day 1 to month 8



Change in Clinical Endpoints from day 1 to month 8



- LD-IL2 daily (induction) then q2W for 6mo (maintenance)
  - 46 patients across 11 autoimmune diseases
  - Mild-to-moderate rheumatoid arthritis, ankylosing spondylitis, SLE, psoriasis, Behcet's disease, granulomatosis with polyangiitis, Takayasu's disease, Crohn's disease, UC, autoimmune hepatitis, sclerosing cholangitis
  - Well tolerated across all diseases
- Specific Treg expansion and activation to similar levels in all patients across indications,
  - Concomitant medications, including corticosteroids and NSAIDs, did not impact observed Treg increases
- Significant reduction in clinical endpoints across the 11 autoimmune diseases

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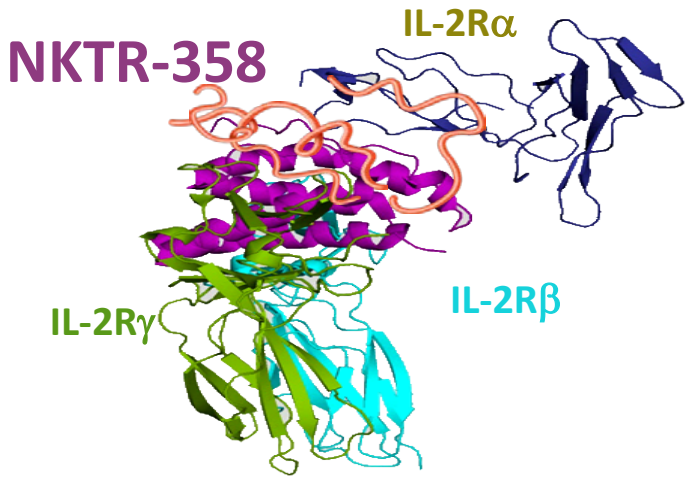
SOURCE: :Ann Rheum Dis. 2019 Nov; 78:209-17. doi: 10.1136/annrheumdis-2018-214229.

NKTR-358: A PEG-conjugated rhIL-2 that Selectively Induces Tregs and their Suppressive Activity

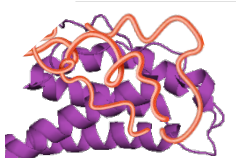


Compared with native IL-2, PEG conjugation:

- Alters the binding profile of NKTR-358, eliciting a lower binding affinity for IL-2Rβ and a different binding bias for IL-2Rα and IL-2Rβ
- Imparts selectivity for the stimulation of regulatory T cells (Tregs) over conventional T cells (Tcons)
- Increases the half-life

NKTR-358 has shown:

- Activity in animal models of systemic lupus erythematosus (SLE) and cutaneous hypersensitivity
- Selective stimulation of Tregs in a single ascending dose (SAD) study in healthy volunteers



NKTR-358

Selectively expands Tregs

βγ

CTLs

$CD8^+$ T cells and NK cells

Stimulates immune response to kill tumor cells

T_{regs}

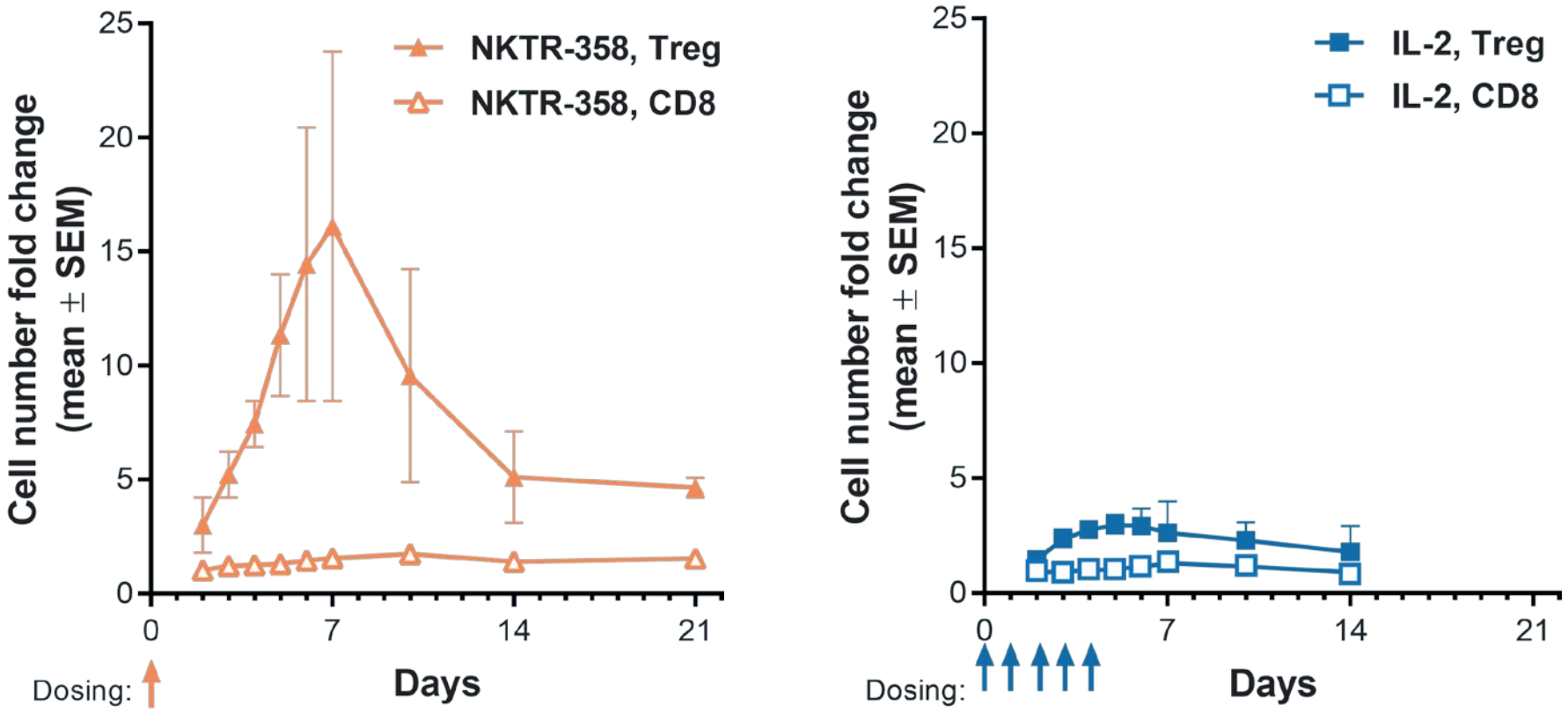
αβγ

$CD4^+$ regulatory T cells

Downregulates proliferation of conventional T cells

Stimulates Tregs with the potential for long-term control of the immune response

NKTR-358 preferentially expands Tregs in non-Human primates

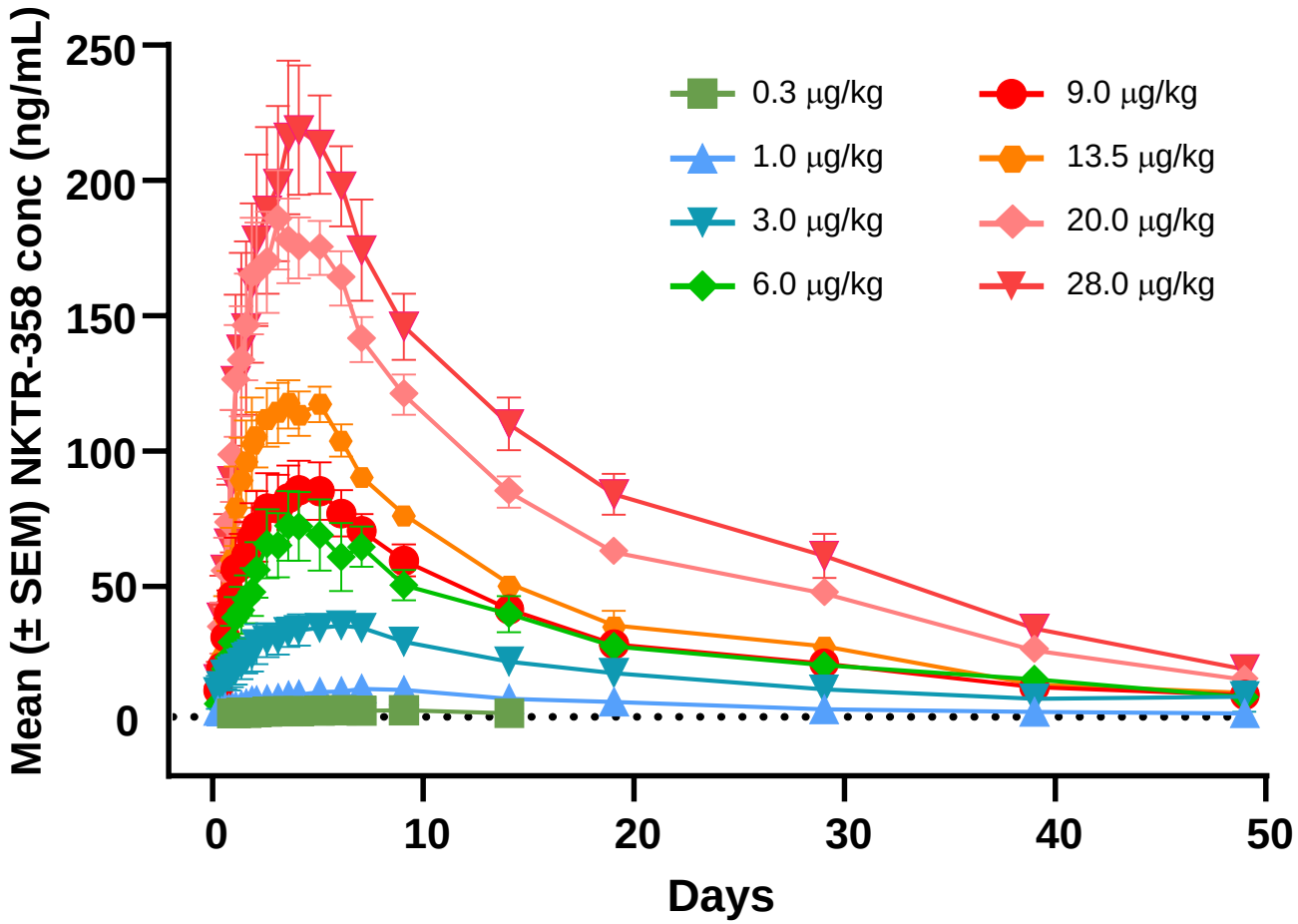


Cynomolgus monkeys administered:

- NKTR-358 (25 µg/kg) single dose, or,
- recombinant human IL-2 (5 µg/kg) daily on 5 consecutive days

SOURCE: 13th Annual World Congress on Inflammation 2017, Langowski et. al.

NKTR-358 concentration curves indicate dose proportional Pharmacokinetics

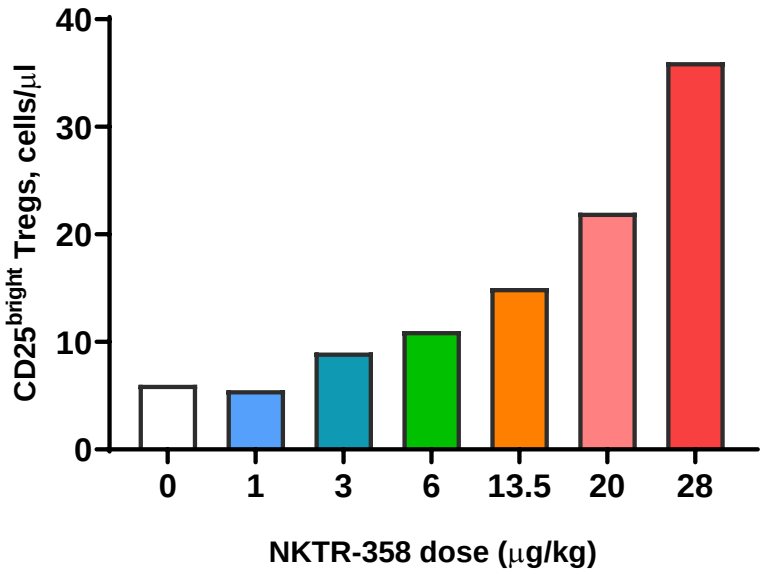


- NKTR-358 Cmax and AUC values exhibited a dose proportional increase
- NKTR-358 concentrations reached maximum levels in 5-7 days
- NKTR-358 has an estimated elimination half-life of 8-11 days
  - half-life of IL-2 in human serum is ~5-7 minutes

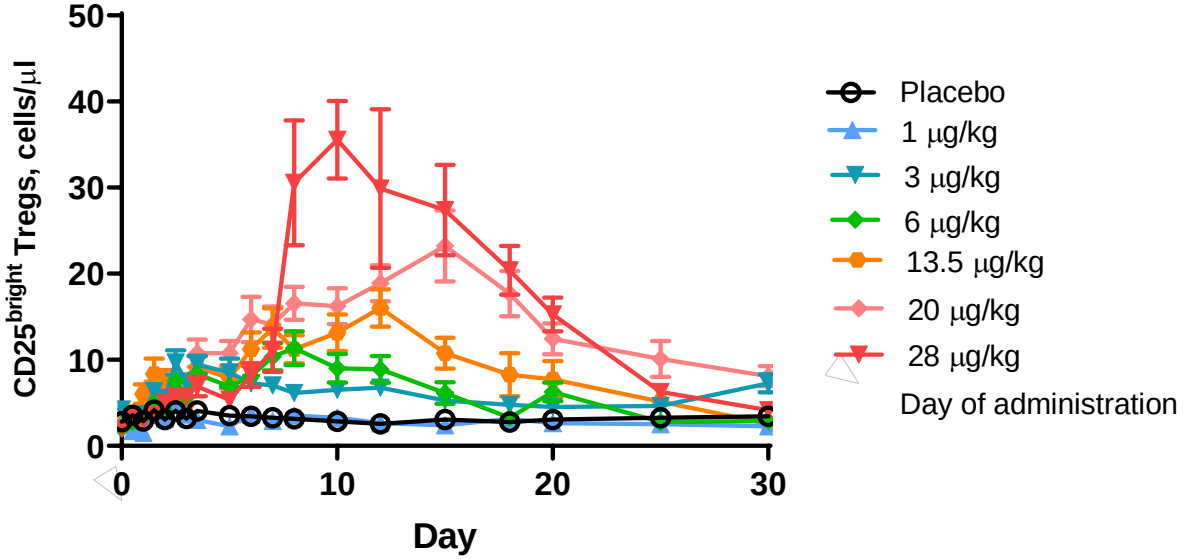
SOURCE: Promise of IL-2 Therapy, Nov 2019, Paris France
EULAR 2019 Congress

EULAR 2019: NKTR-358 leads to sustained, dose-dependent increases in CD25^{bright} Tregs

Median peak effect of CD25^{bright} Tregs



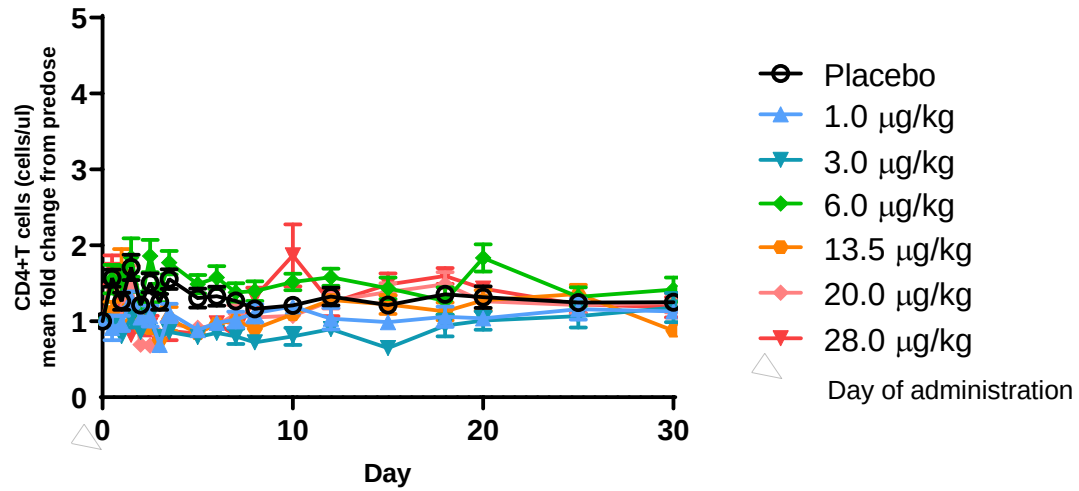
Absolute numbers of CD25^{bright} Tregs



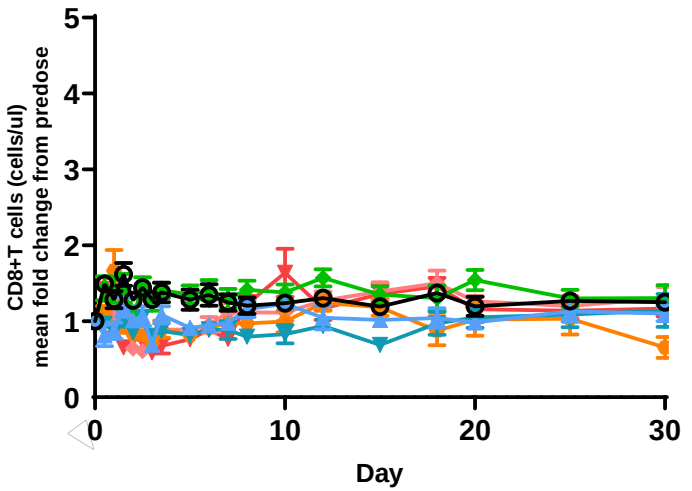
- At 28 µg/kg NKTR-358:
  - 17-fold mean peak increase in numbers of CD25^{bright} Tregs above predose value
  - Treg levels peak at Days 10-12 and do not return to baseline until Days 20-25 following administration
- Increase in Treg activation markers ICOS and CTLA4 were observed at doses ≥13.5 µg/kg

EULAR 2019: NKTR-358: No changes in numbers of Tcon cells and low-level increases in numbers of CD56+ NK Cells

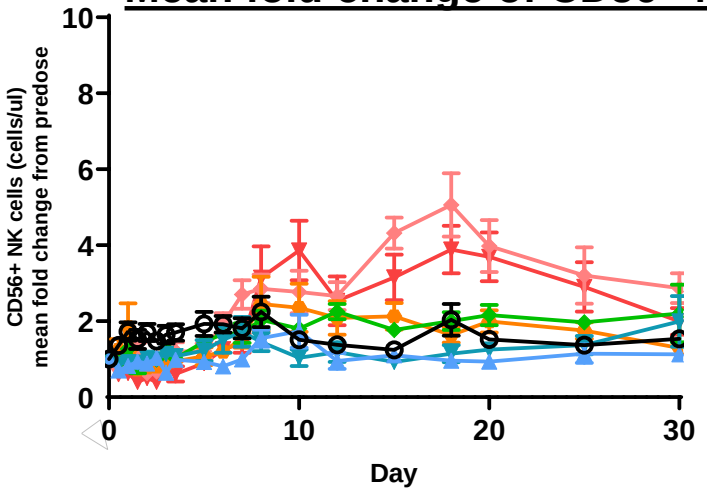
Mean fold change of CD4+ cells



Mean fold change of CD8+ cells



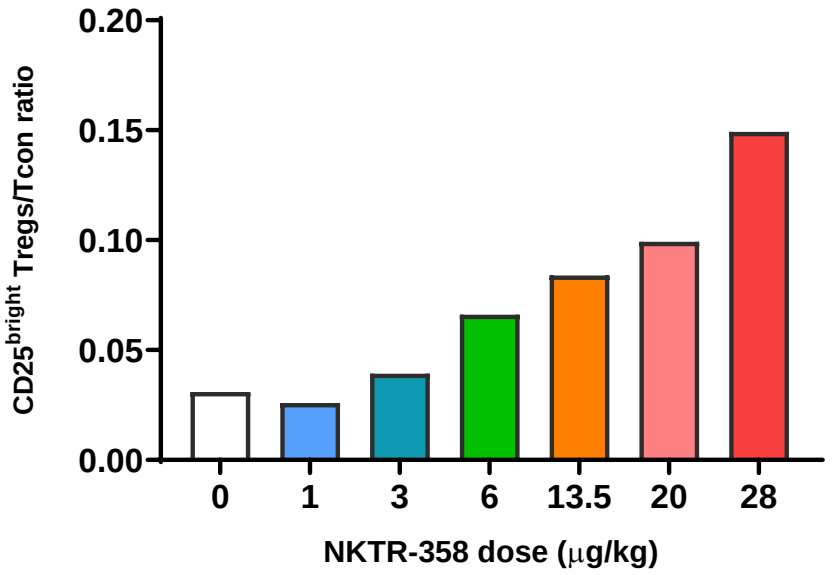
Mean fold change of CD56+ NK cells



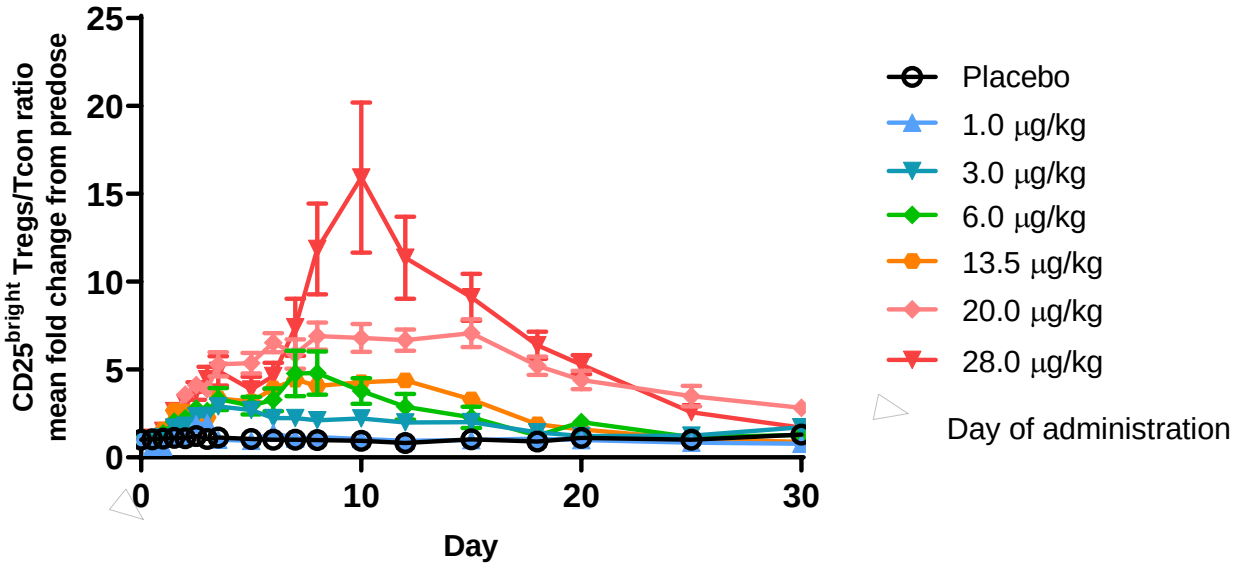
Not all cohorts are shown for clarity

EULAR 2019: NKTR-358 selectively induces Tregs in a dose-dependent manner

Median peak effect of CD25^{bright} Treg/Tcon ratio



Mean Fold change in CD25^{bright} Tregs/Tcon cell ratio



- NKTR-358 administration leads to 15-fold increase in mean peak Treg:Tcon ratio over baseline at 28 μg/kg

In this analysis Tcon cells are defined as CD8+ Tcells; Not all cohorts are shown for clarity

THU0054

NKTR-358, a novel IL-2 conjugate, stimulates high levels of regulatory T cells in patients with systemic lupus erythematosus

Christie Fanton[1], Suresh Siddhanti[1], Neha Dixit[1], Lin Lu[1], Vishala Chindalore[2], Robert Levin[3], Isam Diab[4], Richard Furie[5], Jonathan Zalevsky[1], Brian Kotzin[1]

[1]Nektar Therapeutics, San Francisco, CA; [2]Pinnacle Research, Anniston, AL; [3]Clinical Research of West Florida, Clearwater, FL; [4]Paramount Medical Research, Middleburg Heights, OH; [5]Northwell Health, Great Neck, NY

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METHODS
Study design

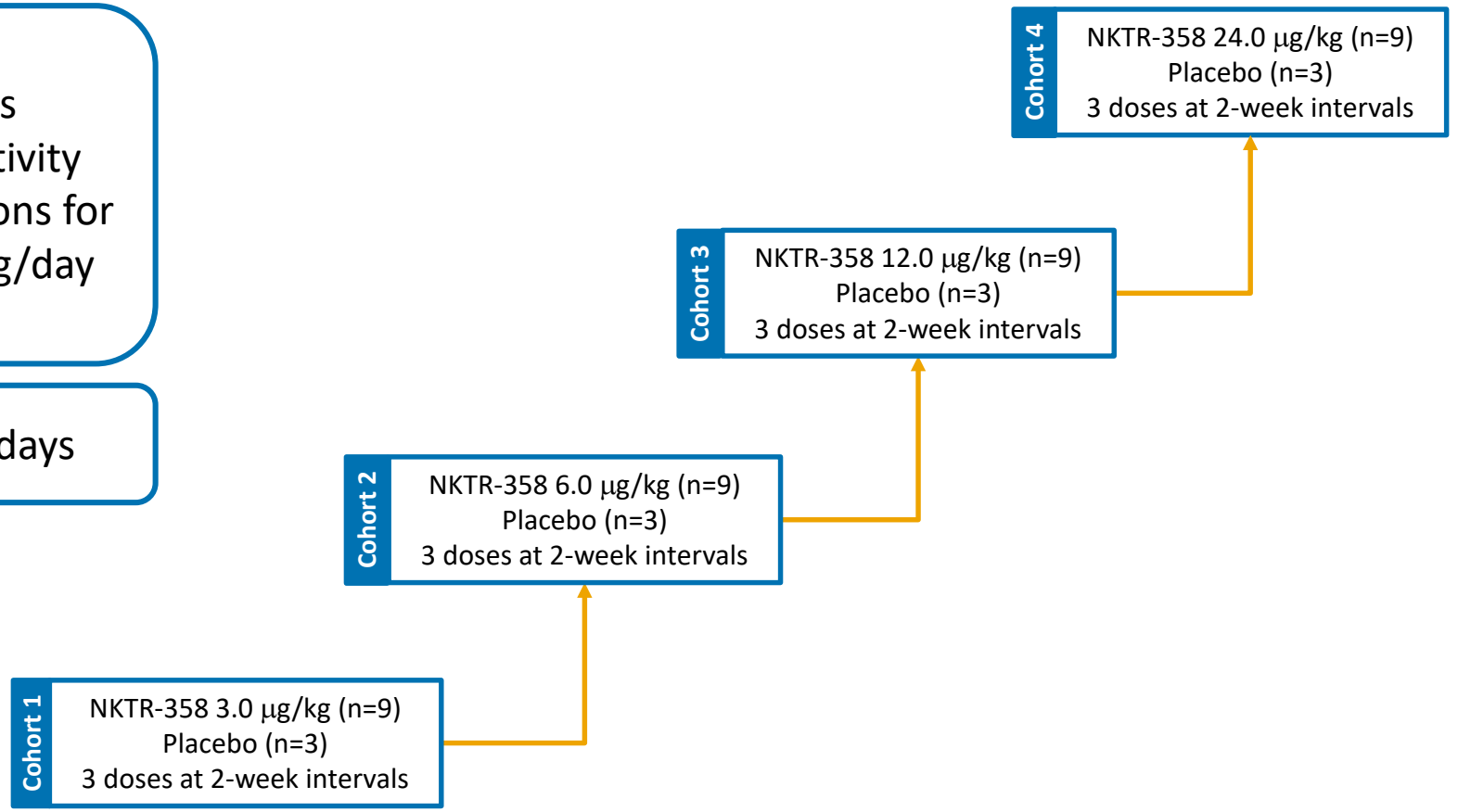
A randomized, double-blind, multiple ascending dose (MAD) Phase 1b study of subcutaneous NKTR-358 in patients with mild-to-moderate SLE (NCT03556007)

Eligibility criteria

- SLE diagnosis within 6 months
- Mild-to-moderate disease activity
- Stable concomitant medications for ≥8 weeks; prednisone ≤10 mg/day

N=48

Each cohort was followed for 79 days



METHODS
Study objectives

Primary

Safety and tolerability of NKTR-358 as evaluated by:

- Adverse events
- Vital signs
- Clinical laboratory evaluations

Secondary

- Time course and change in number and activity of Tregs, Tcons, NK cells and subsets
- PK of NKTR-358
- Change in cytokine levels, peripheral blood cell populations, serum proteins and gene expression
- Change in disease activity based on SLEDAI and CLASI scores*

CLASI, cutaneous lupus erythematosus disease area severity index; NK, natural killer; PK, pharmacokinetics; SLEDAI, systemic lupus erythematosus disease activity index; Tcons, conventional T cells; Tregs, regulatory T cells

*This Phase 1b study design, including small numbers of patients, low entry disease activity, and short treatment duration is unlikely to support adequate assessment of disease activity effect

METHODS
Assay methodology

- Immunophenotyping by multicolor flow cytometry was performed to quantify multiple immune cell subsets, using whole blood collected at multiple time points pre- and post-NKTR-358 administration
  - **$CD25^{bright}$ Tregs:** A $CD4^+$ $FoxP3^+$ $CD25^+$ Treg subpopulation with the highest CD25 expression; expected to have the highest suppressive capacity
  - **$CD4^+$ T cells:** $CD3^+$ $CD4^+$ conventional T cells
  - **$CD8^+$ T cells:** $CD3^+$ $CD8^+$ conventional T cells
  - **NK cells:** $CD3^-$ $CD56^+$ NK cells
- Plasma concentrations of NKTR-358 were measured by a validated indirect sandwich ligand binding assay with a lower limit of quantitation of 1.0 ng/mL

RESULTS
Baseline demographics and disease characteristics

	NKTR-358 (n=36)	Placebo (n=12)
Age, mean years (SD)	47.2 (12.5)	47.8 (8.3)
Female (%)	34 (94.4)	12 (100)
Body mass index, mean (SD)	26.9 (3.0)	26.7 (4.6)
Disease duration, months	9.5 (8.9)	14.3 (9.7)
SLEDAI score (SD, min–max)	6.0 (2.8, 0–10)	5.2 (2.7, 2–10)
CLASI activity score (SD, min–max)	4.1 (4.7, 0–22)	2.7 (3.2, 0–9)
Baseline medication, n (%)		
Prednisone	12 (33.3)	4 (33.3)
Hydroxychloroquine	24 (66.7)	6 (50.0)
Methotrexate	4 (11.1)	0
Mycophenolate mofetil	1 (2.8)	2 (16.7)
Azathioprine	5 (13.9)	0

CLASI, cutaneous lupus erythematosus disease area severity index; SD, standard deviation; SLEDAI, systemic lupus erythematosus disease activity index

RESULTS
Safety

NKTR-358 was safe and well tolerated in patients with SLE

- No dose-limiting toxicities, deaths, or clinically significant vital signs, electrocardiogram, or physical examination abnormalities were observed
- Adverse events were primarily mild or moderate (Grade 1 or 2) injection site reactions
- One patient in the lowest dose cohort (3 μg/kg) experienced a serious adverse event of migraine
  - This occurred 3 weeks after the last dose of NKTR-358 and was deemed not related to study drug by the investigator
- Three patients discontinued treatment
  - One patient in the highest dose cohort (24 μg/kg) discontinued NKTR-358 after the second dose due to elevated eosinophil levels, with no clinical sequelae
  - One patient withdrew from NKTR-358 and one patient withdrew consent, both unrelated to adverse events
- One patient in the highest dose cohort (24 μg/kg) demonstrated transient and mild (Grade 1) symptoms of a flu-like syndrome after the second and third doses that were considered related to study drug; no clinically relevant changes in hematology, chemistry, or cytokine levels were associated with either episode, and both episodes resolved within 24 hours without treatment
- No antidrug antibodies were detected throughout the entire 79 days of follow-up

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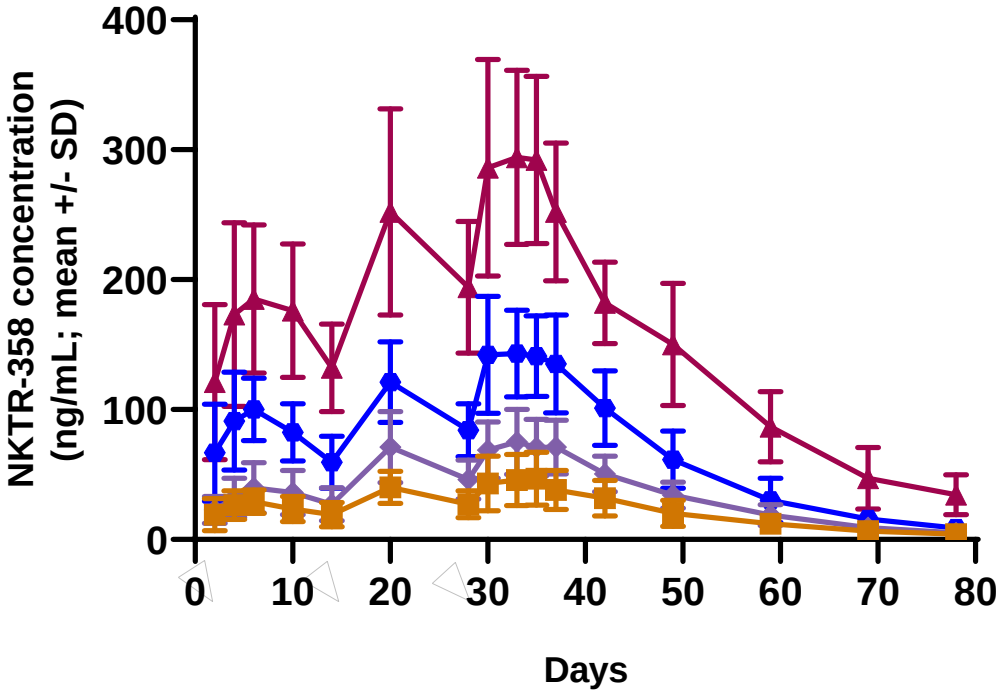
RESULTS
Pharmacokinetics

NKTR-358 demonstrated dose proportional PK with repeated dosing



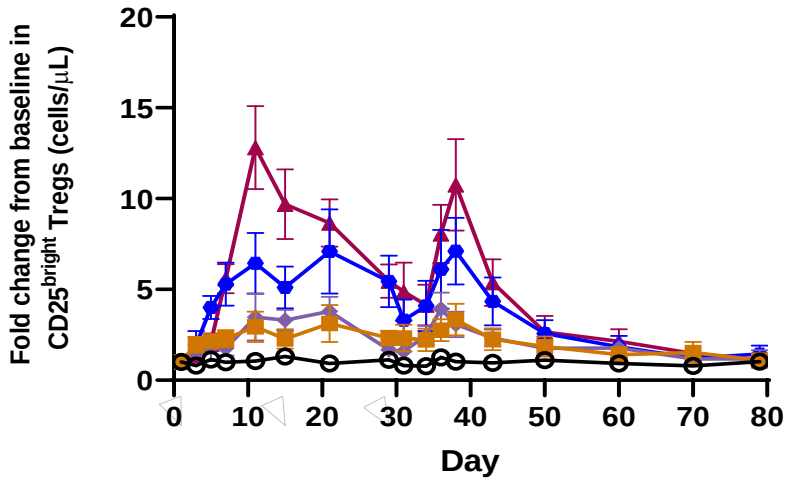
- Cmax and AUC values exhibited dose-proportional increases with repeated dosing of NKTR-358
- NKTR-358 plasma concentrations reached maximum levels in 3–6 days
- NKTR-358 had an estimated terminal half-life of 10–13 days
- Results were similar to those observed in healthy volunteers in the SAD study[2]
  - Maximum concentration reached at 5–7 days
  - Estimated half-life of 8–11 days

SD, standard deviation

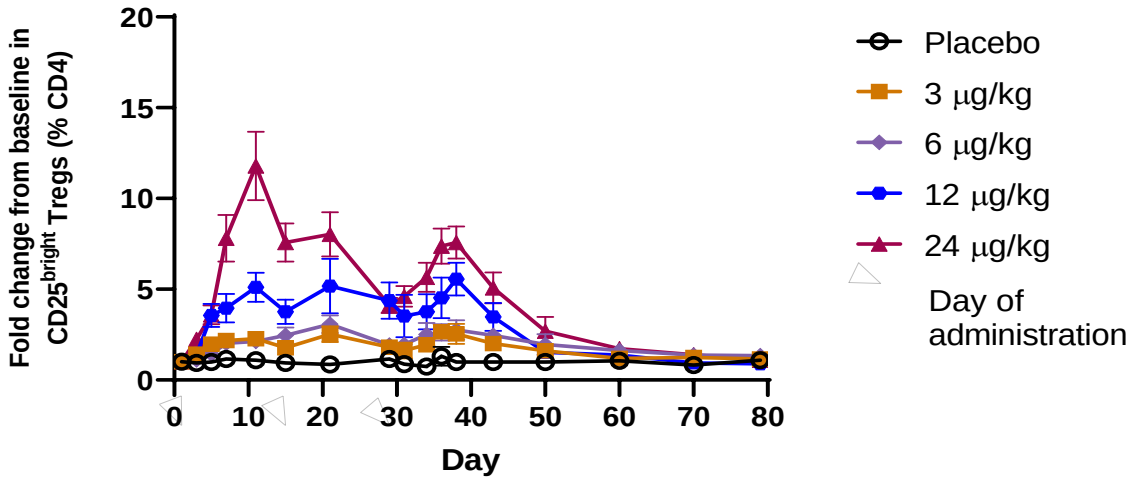
RESULTS
Changes in numbers and percentages of Tregs

NKTR-358 elicited sustained, dose-dependent increases in the absolute numbers and percentages of CD25^{bright} Tregs

Fold change in absolute number of CD25^{bright} Tregs



Fold change in percentage of CD25^{bright} Tregs



- At 24 μg/kg NKTR-358, a maximum 12-fold mean peak increase (above baseline levels) in number and percentage of CD25^{bright} Tregs was observed, suggesting a large increase in the most suppressive Treg population
- The dose-dependent increase in CD25^{bright} Tregs was maintained through multiple administrations of NKTR-358
- In both MAD and SAD studies:
  - CD25^{bright} Treg levels peaked on Day 10 following first administration of NKTR-358
  - Treg levels remained above baseline for 25–30 days following administration of the last dose of NKTR-358 at 24 μg/kg (MAD) or 28 μg/kg (SAD)
  - Treg activation markers CD25, CTLA4, and Helios increased at doses ≥12 μg/kg

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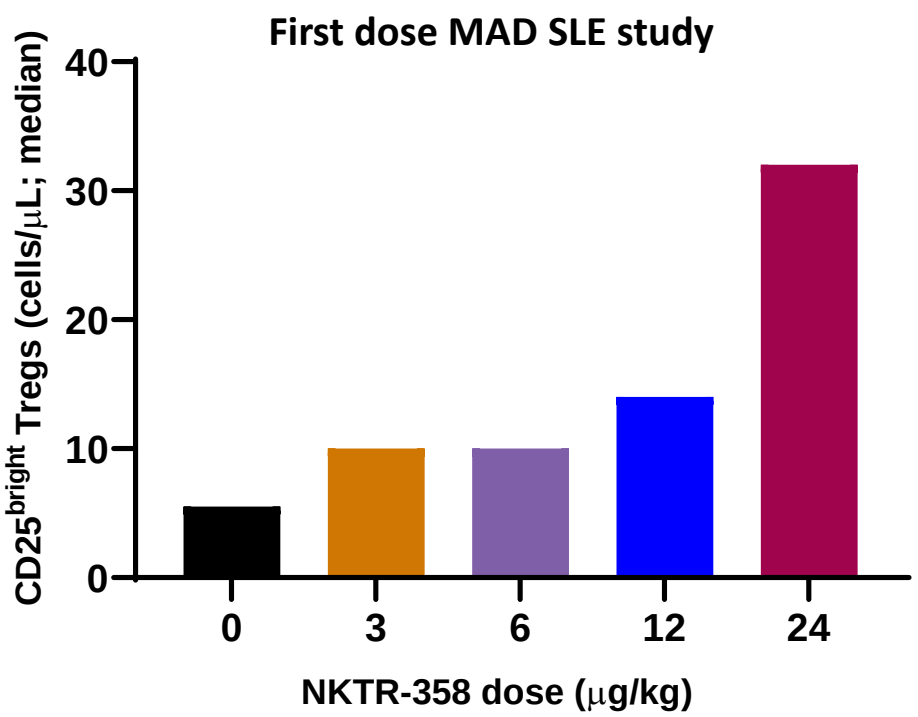
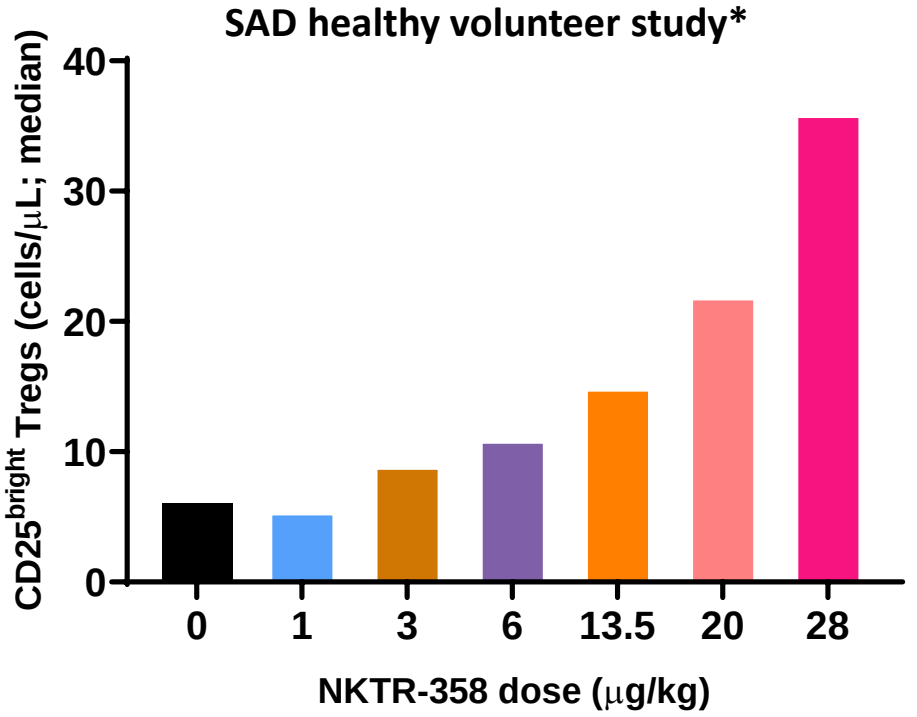
RESULTS
Changes in numbers and percentages of Tregs

Similar induction of CD25^{bright} Tregs in healthy volunteers and patients with SLE following treatment with NKTR-358

Peak level of post-baseline CD25^{bright} Tregs





*Not all cohorts are shown for clarity

- The increase in Tregs observed with 24 μg/kg NKTR-358 in the SLE population was comparable to that observed at 28 μg/kg NKTR-358 in the population of healthy volunteers

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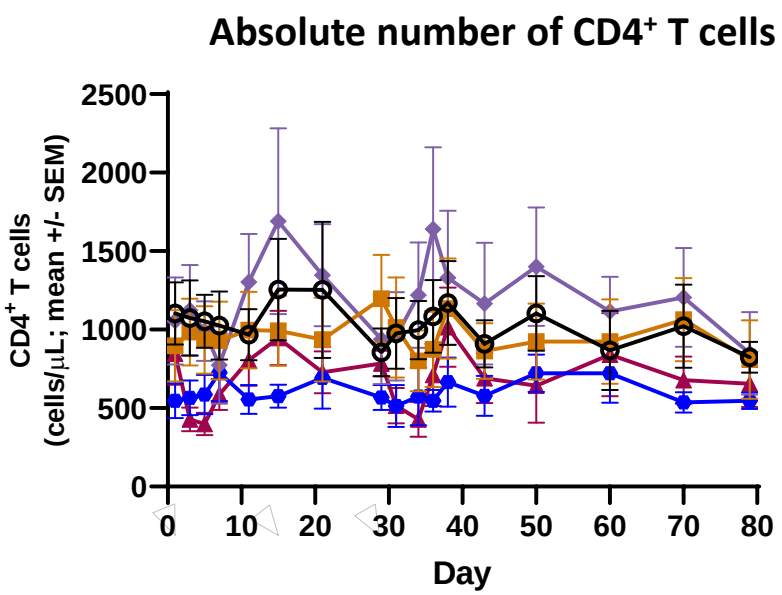
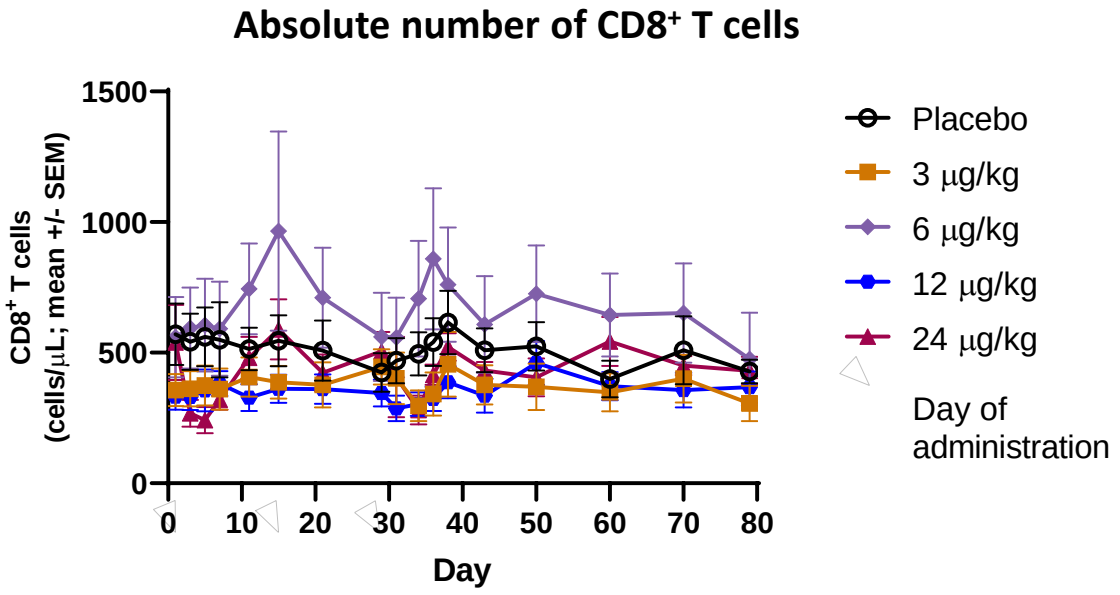
RESULTS
Changes in Tcon and NK cell numbers

No overall changes in Tcon cell numbers with NKTR-358



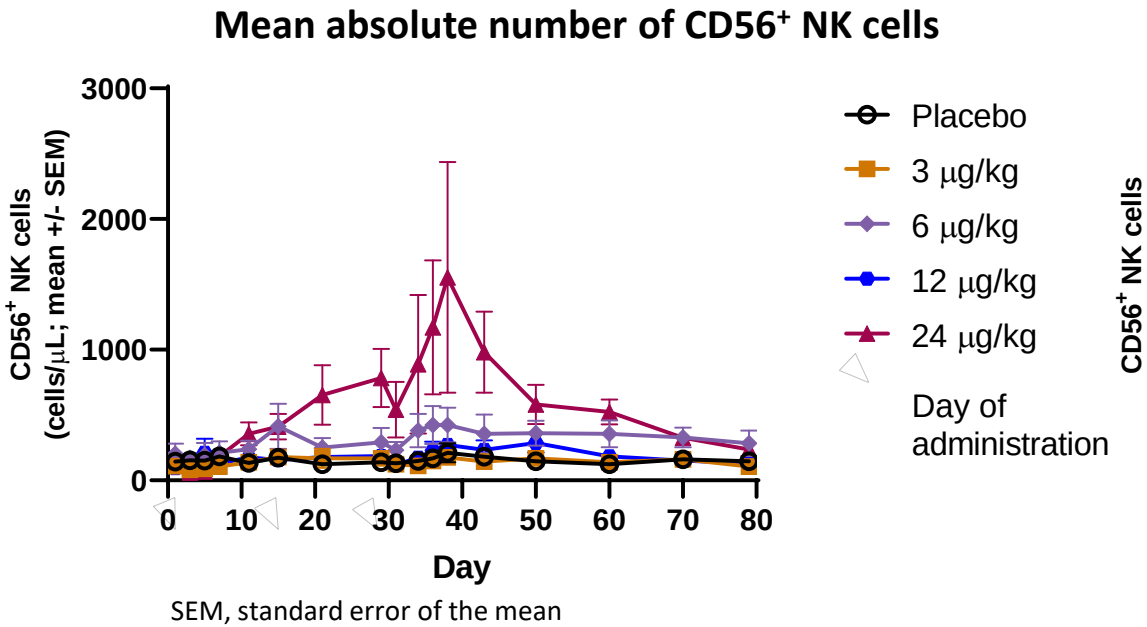


SEM, standard error of the mean

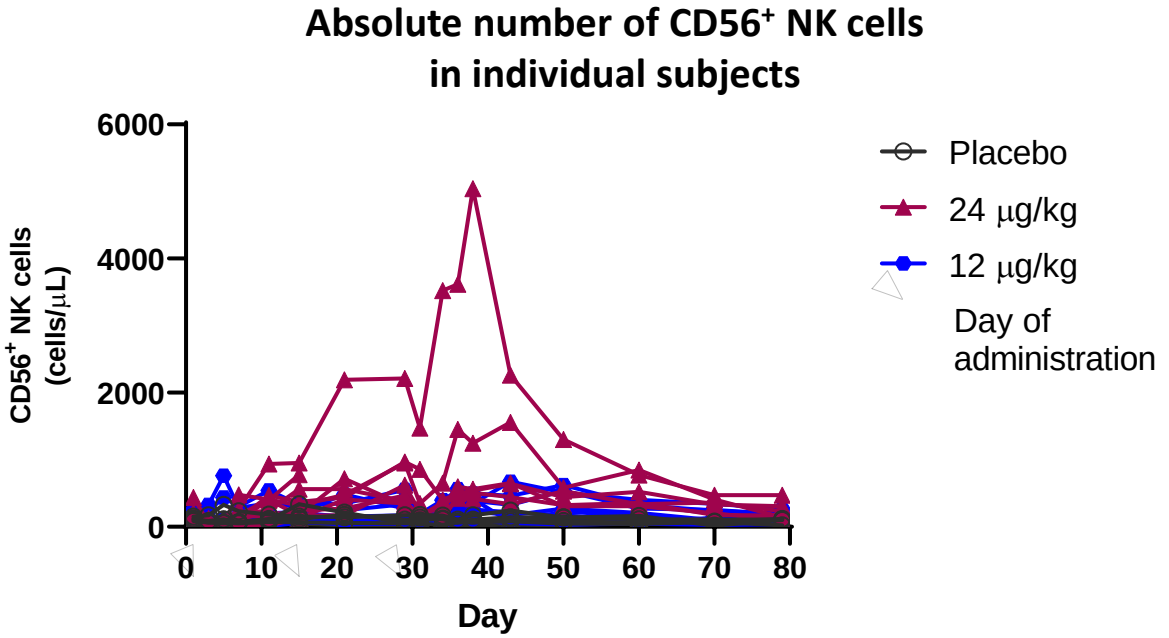
- At 24 μg/kg NKTR-358, a transient decrease in cell numbers was observed 5 days post-first and -third doses, consistent with observations at 20 and 28 μg/kg in the SAD study
- Elevated levels of T cells in the 6 μg/kg cohort were driven by two patients with higher numbers of T cells throughout the dosing period; this was not observed in higher-dose cohorts

RESULTS
Changes in Tcon and NK cell numbers

NKTR-358 treatment led to low-level increases in the numbers of CD56$^+$ NK cells in most patients



SEM, standard error of the mean

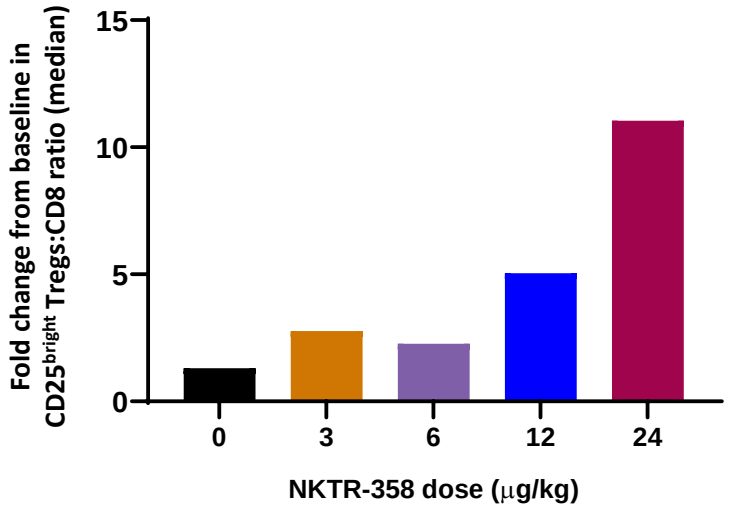


- The increase observed in the mean absolute number of CD56$^+$ NK cells at 24 µg/kg NKTR-358 is driven by an increase in two patients
  - The change in mean absolute number of NK cells for other patients at 24 µg/kg NKTR-358 was similar to that observed in the SAD healthy volunteer study at the highest dose (28 µg/kg)

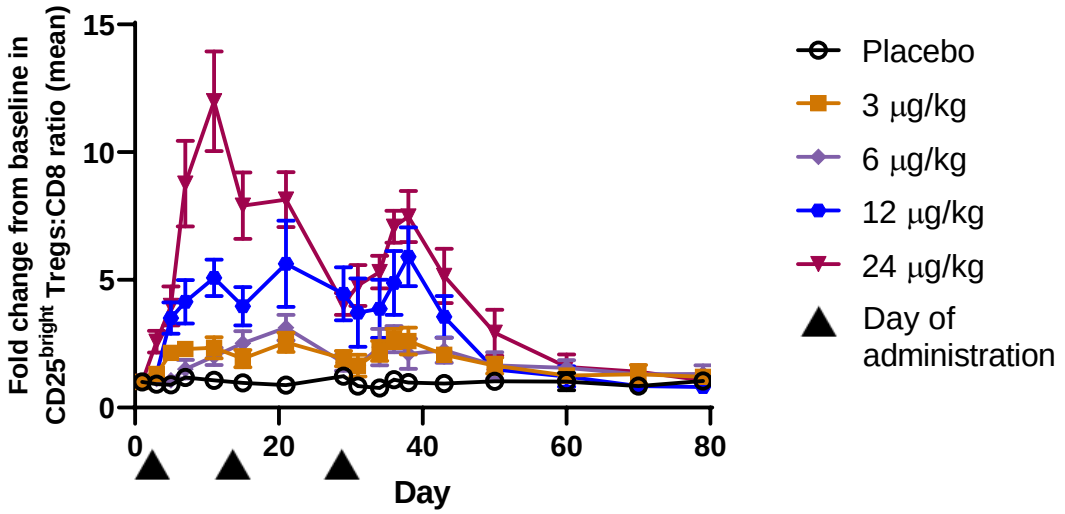
RESULTS
Changes in Treg expansion after multiple administrations

NKTR-358 maintained selectivity for Treg expansion after multiple administrations

Peak effect of fold change in CD25^{bright} Tregs:CD8^{+} ratio (first dose)



Fold change in CD25^{bright} Tregs:CD8^{+} ratio



- NKTR-358 administration resulted in selective expansion of Tregs to levels similar to those observed in the SAD healthy volunteer study
- At 24 μg/kg NKTR-358 in the MAD study:
  - 12-fold increase in mean peak Tregs:Tcon ratio was observed from baseline after the first administration
  - 7-fold increase in mean peak Tregs:Tcon ratio was observed from baseline after the third administration (data available for only 6 patients)

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CONCLUSIONS

- NKTR-358 was safe and well tolerated in patients with mild-to-moderate SLE
  - Safety profile was similar between single and repeat administrations
- Data show dose-proportional pharmacokinetics and prolonged exposure, with a half-life of 10–13 days
- NKTR-358 elicited a marked and selective, dose-dependent expansion of $CD25^{bright}$ Tregs in patients with mild-to-moderate SLE, which was maintained through multiple administrations
  - Similar extent and magnitude of induction as observed in the SAD study in healthy volunteers
- There were no consistent increases in $CD4^{+}$ and $CD8^{+}$ Tcons at all doses
- Low-level increases in NK cell numbers occurred in some patients at the highest dose tested
- These data further validate prior results in healthy volunteers and provide strong support for continued testing in patients with SLE and other inflammatory diseases. A Phase 2 trial of NKTR-358 in patients with SLE is planned

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Poster

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Poster presented at the European E-Congress of Rheumatology (EULAR) June 3–6, 2020

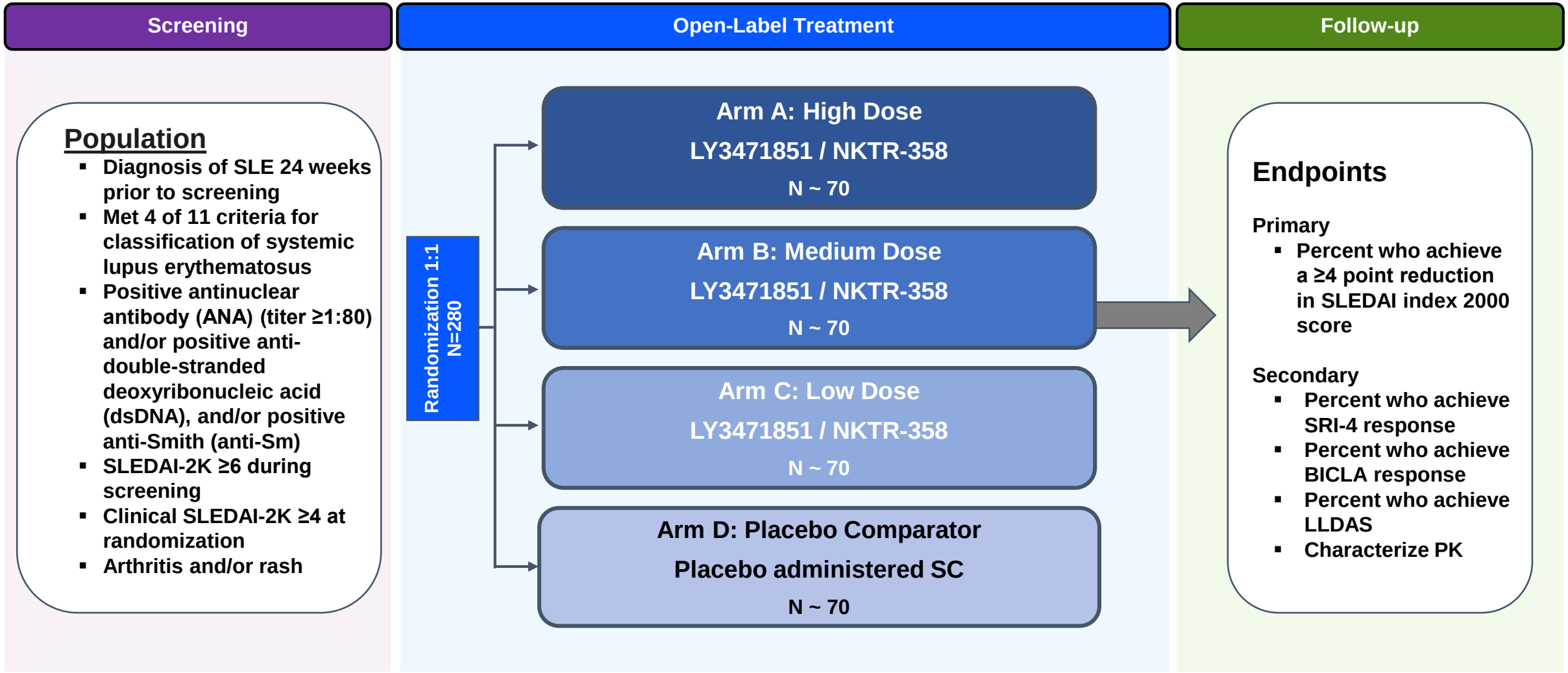
Corresponding author: Jonathan Zalevsky: jzalevsky@nektar.com

NKTR-358: Development program with Lilly advancing into multiple auto-immune conditions

NKTR-358: An IL-2 Pathway T-Regulatory Cell Stimulator

- Lilly to initiate Phase 2 study in lupus (SLE) in H2 2020
- Lilly is conducting two additional Phase 1b studies in Psoriasis and Atopic Dermatitis
- Lilly to start an additional Phase 2 study in new auto-immune disease in H2 2020
- Lilly to run the clinical development program through registrational trials and assume manufacturing
- Nektar Economics:
  - $150 million upfront payment
  - Up to $250 million in development and regulatory milestones
  - Maximum development cost sharing – Nektar 25%/Lilly 75%
  - Significant double-digit royalties (Nektar has co-promote option in U.S.)

Systemic Lupus Erythematosus Phase 2 Study Design



SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SRI: Systemic Lupus Erythematosus Responder Index; BICLA: BILAG-based Combined Lupus Assessment; LLDAS: Lupus Low Disease Activity State

Q&A Session

- Dr. Jonathan Zalevsky
  - Chief Research and Development Officer
- Dr. Brian Kotzin
  - SVP of Clinical Development
- Jennifer Ruddock
  - SVP of Strategy and Corporate Affairs

(Link to Poster: https://www.nektar.com/download_file/792/0)