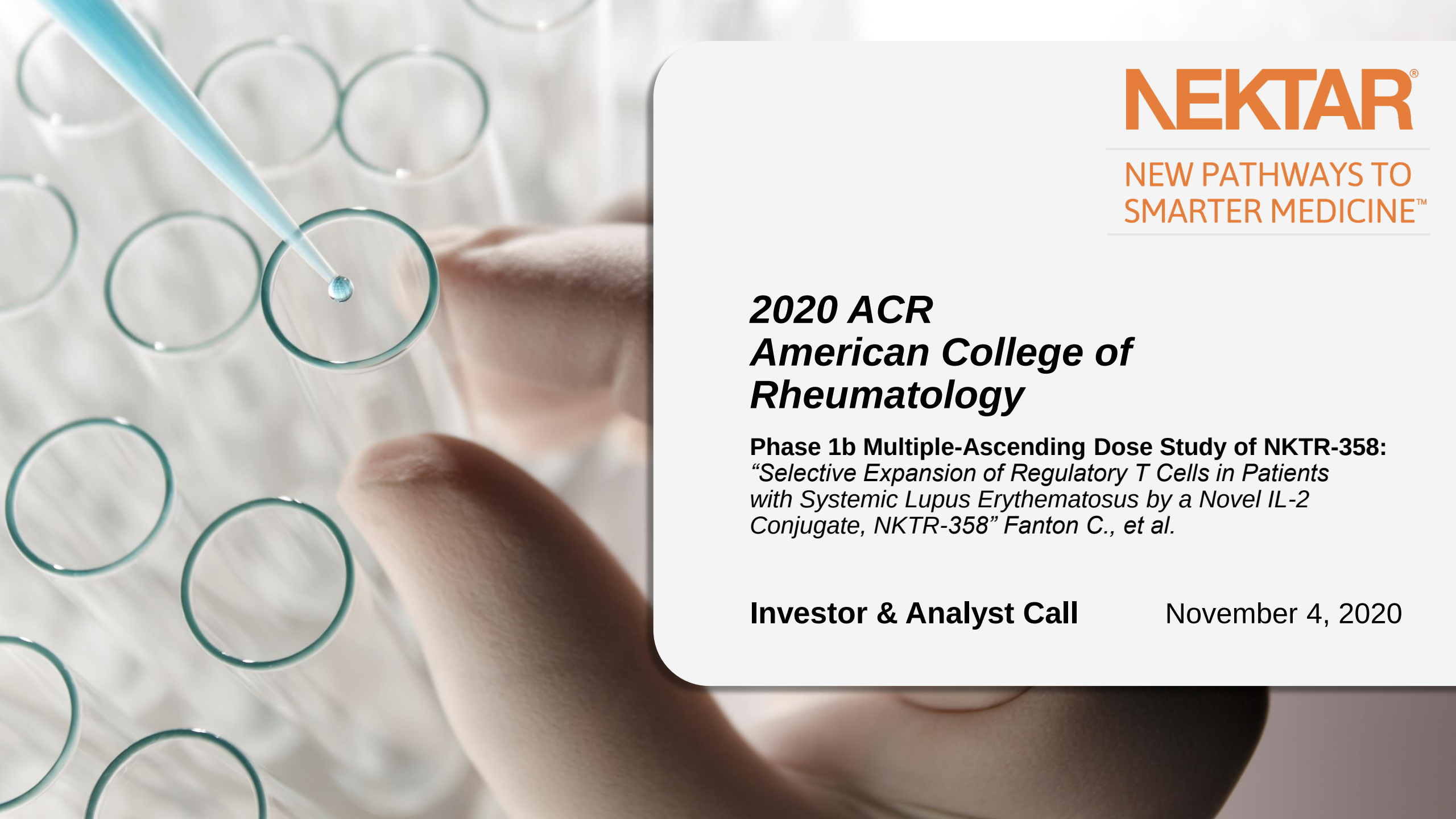




NEKTAR[®]

NEW PATHWAYS TO
SMARTER MEDICINE™

**2020 ACR
American College of
Rheumatology**

Phase 1b Multiple-Ascending Dose Study of NKTR-358:
*“Selective Expansion of Regulatory T Cells in Patients
with Systemic Lupus Erythematosus by a Novel IL-2
Conjugate, NKTR-358” Fanton C., et al.*

Investor & Analyst Call

November 4, 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 August 8, 2020. Nektar undertakes no obligation to update forward-looking statements as a result of new information or otherwise.

Today's Speakers and Agenda



Dr. David Klatzmann

Professor of Immunology,
Department of Inflammation-
Immunopathology-Biotherapy,
Sorbonne University and
Medical School



Dr. Jonathan Zalevsky

Chief Research and
Development Officer
Nektar Therapeutics

- **T Regulatory Cell Biology and Experiences in Auto-Immune Disorders with Low-Dose IL-2**
 - *David Klatzmann, M.D.*
- **ACR 2020: "Selective Expansion of Regulatory T Cells in Patients with Systemic Lupus Erythematosus by a Novel IL-2 Conjugate, NKTR-358"**
 - *Jonathan Zalevsky, Ph.D., Nektar Therapeutics*
- **Q&A Session**



Dr. David Klatzmann

Dr. David Klatzmann is a professor of Immunology at the Sorbonne University and Medical School in Paris, France. He also serves as chairman of the Inflammation-Immunopathology-Biotherapy Department.

Klatzmann received his MD and PhD from the Pierre & Marie Curie Medical School. His research interests include translational Immunology with focus on Treg cells, for which he was awarded funding from the European Research Council (ERC Advanced Grant) in 2012. He jointly discovered the AIDS virus and pioneered research on low-dose IL-2 immunotherapies.

Regulatory T Cell Biology and Experiences in Auto-Immune Disorders with Low-Dose IL-2

David Klatzmann, M.D

Interleukin-2 mechanisms of action are well understood

IL-2 stimulates and expands regulatory T cell (Treg)

- **control of the effector T cell (Teff) mediated auto-immune response**

IL-2 blocks the differentiation of Tfh cells

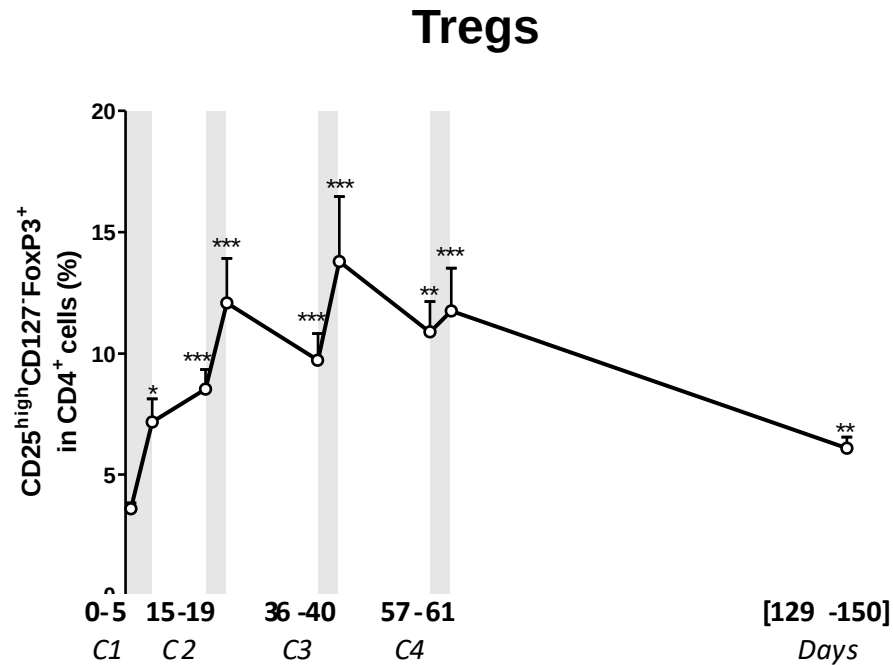
- control of the effector antibody mediated auto-immune response

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 auto-immune and inflammatory diseases (including T1D, EAE and SLE)

Low-dose IL-2 PoC in an auto-immune disease: vasculitis



The NEW ENGLAND JOURNAL of MEDICINE

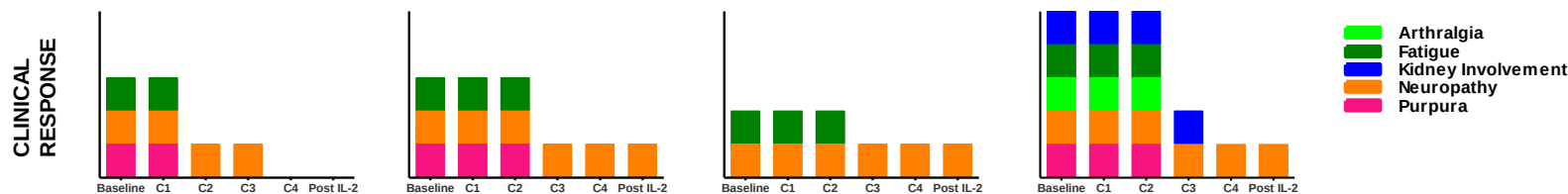
ORIGINAL ARTICLE

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

David Saadoun, M.D., Ph.D., Michelle Rosenzweig, 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

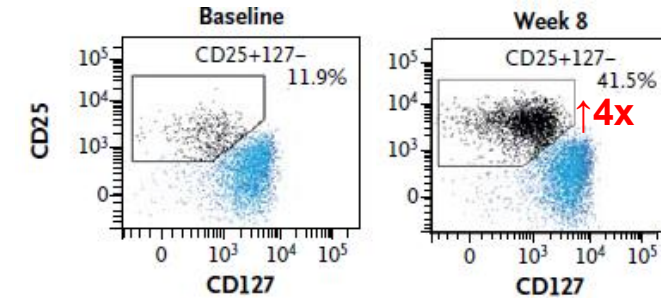
Low-Dose IL-2 PoC in an allo-immune inflammatory disease: chronic graft-versus-host disease (cGVHD)

- **Daily s.c. IL-2 delivery of 1 MIU/m²**
 - 20/35 patients demonstrate (incomplete) clinical response
 - Reduction in steroid usage, improved skin pathology, liver function

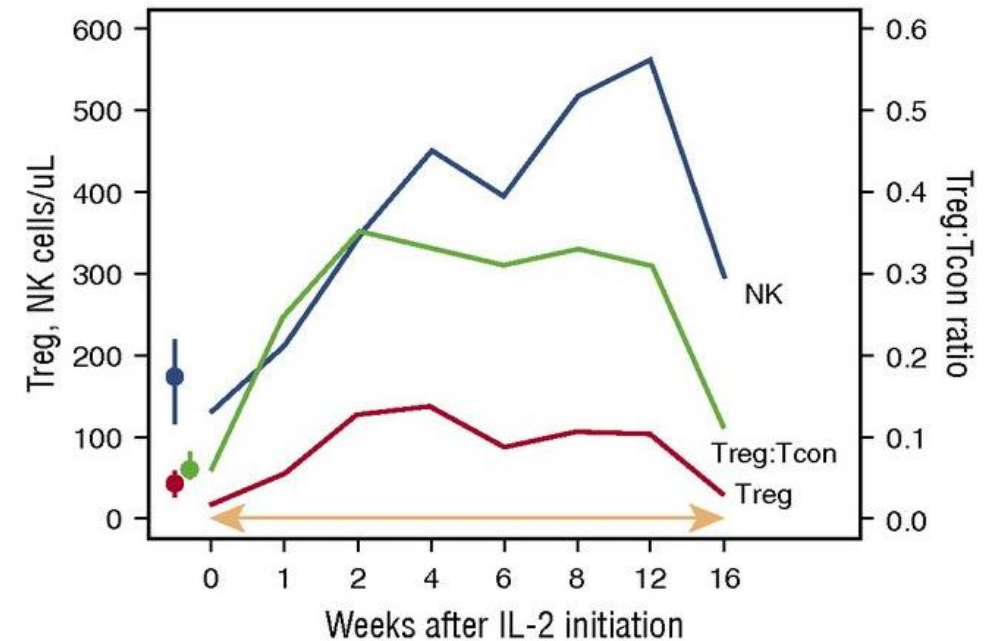


Koreth, *NEJM* 2011; Koreth, *Blood* 2016

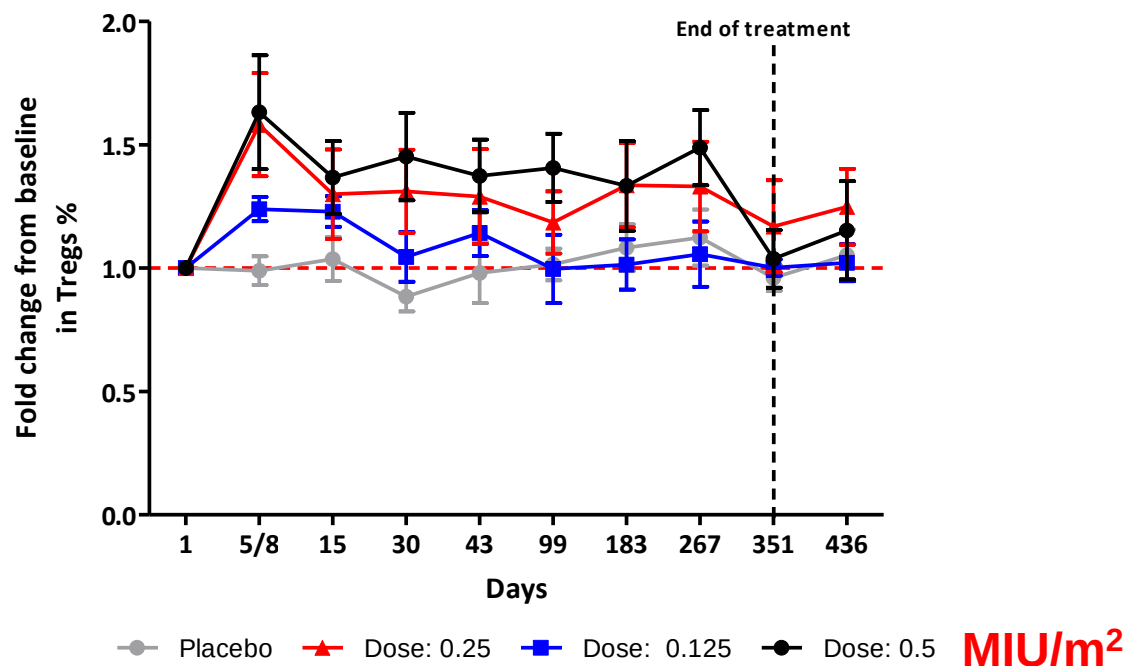
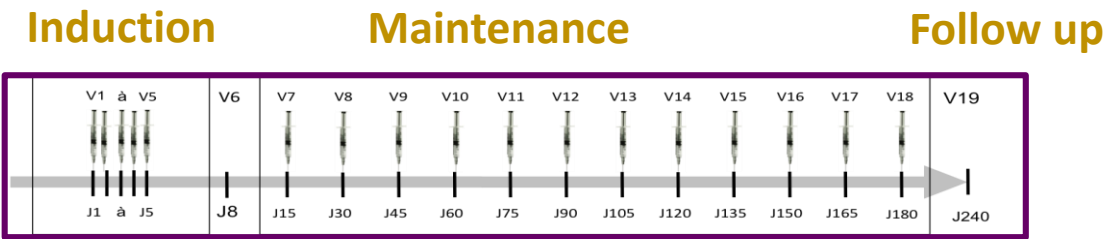
3-5x increase in blood Treg cells



Treg, NK expansion following IL-2 treatment

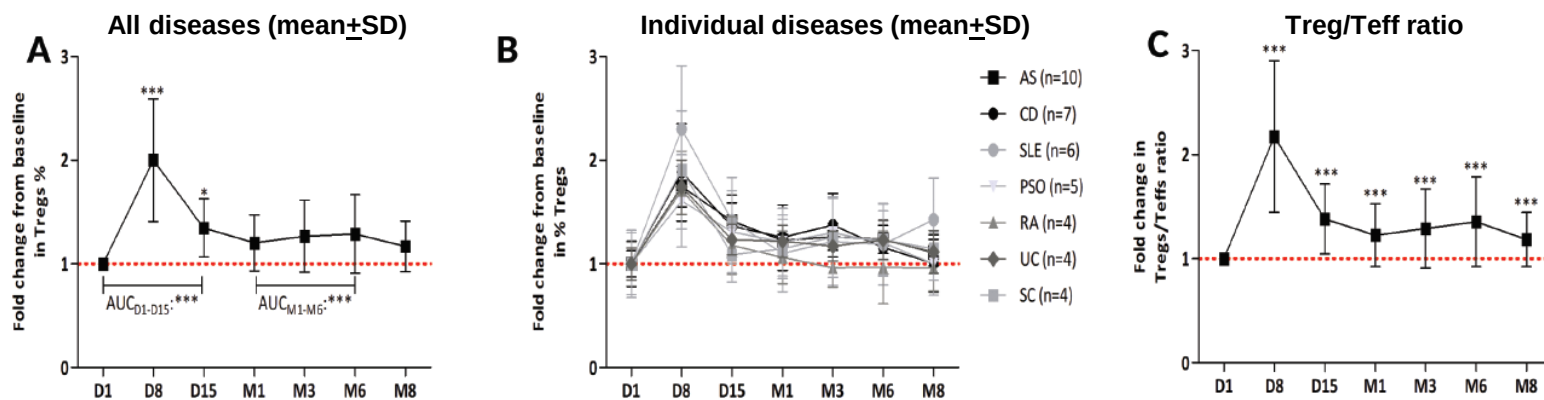


Dose-dependent Treg increase during a 1-year treatment in children with T1D (DF-IL2-child study)



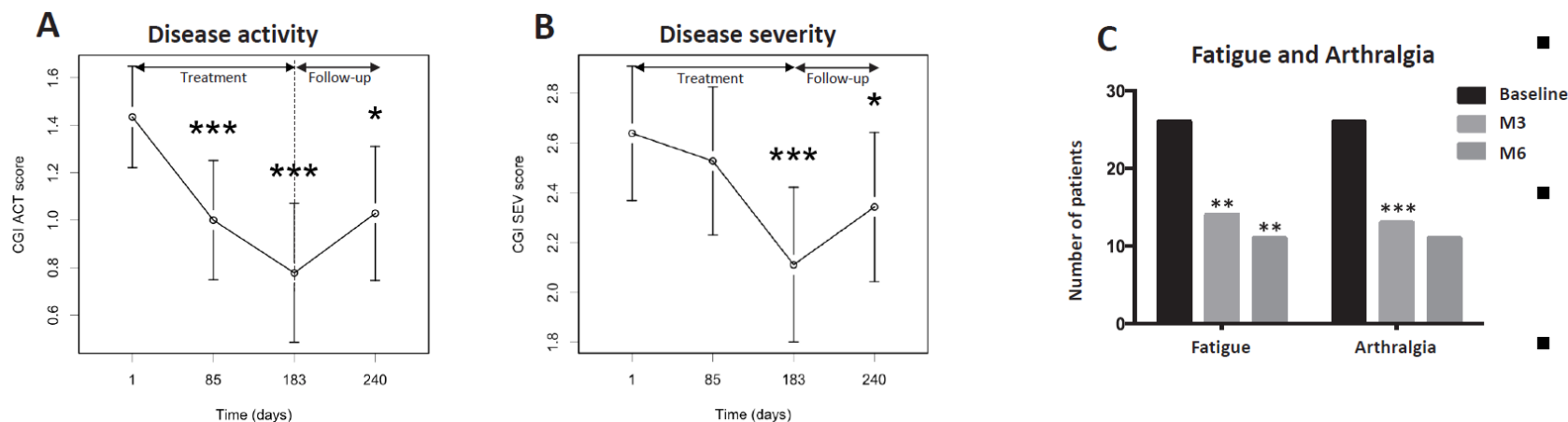
TRANSREG STUDY: Immunological and clinical effects of low-dose interleukin-2 across 11 auto-immune diseases

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



- Low-dose IL-2 daily (induction) then q2W for 6mo (maintenance)
 - 40 patients across 11 auto-immune diseases
 - Mild-to-moderate rheumatoid arthritis, ankylosing spondylitis, SLE, psoriasis, Behcet's disease, granulomatosis with polyangiitis, Takayasu's disease, Crohn's disease, UC, auto-immune hepatitis, sclerosing cholangitis

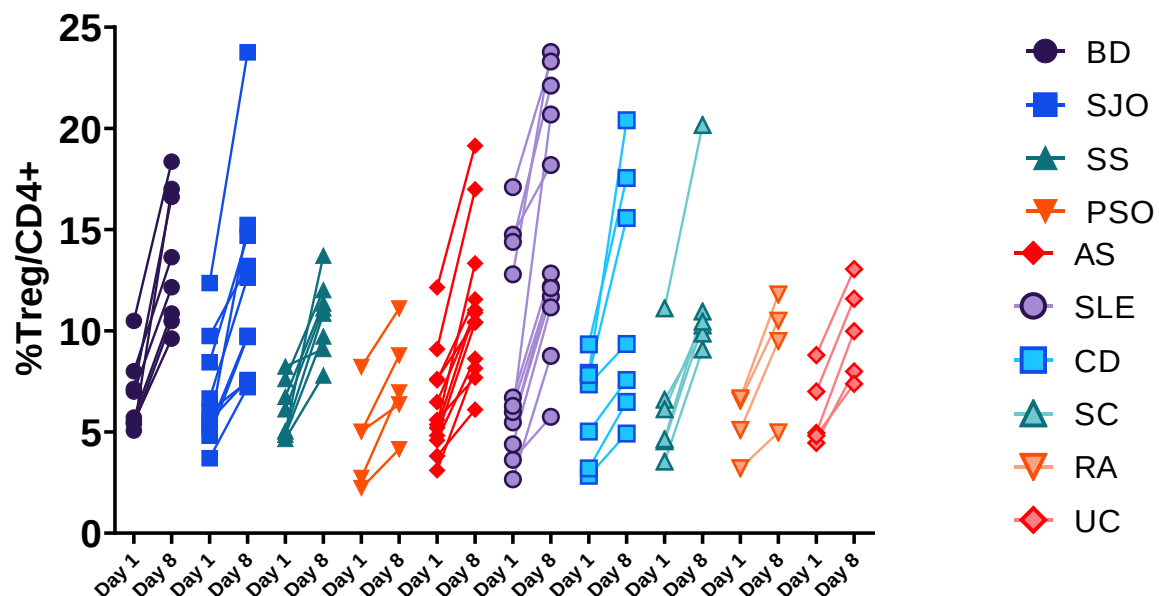
Change in Clinical Endpoints from day 1 to month 8



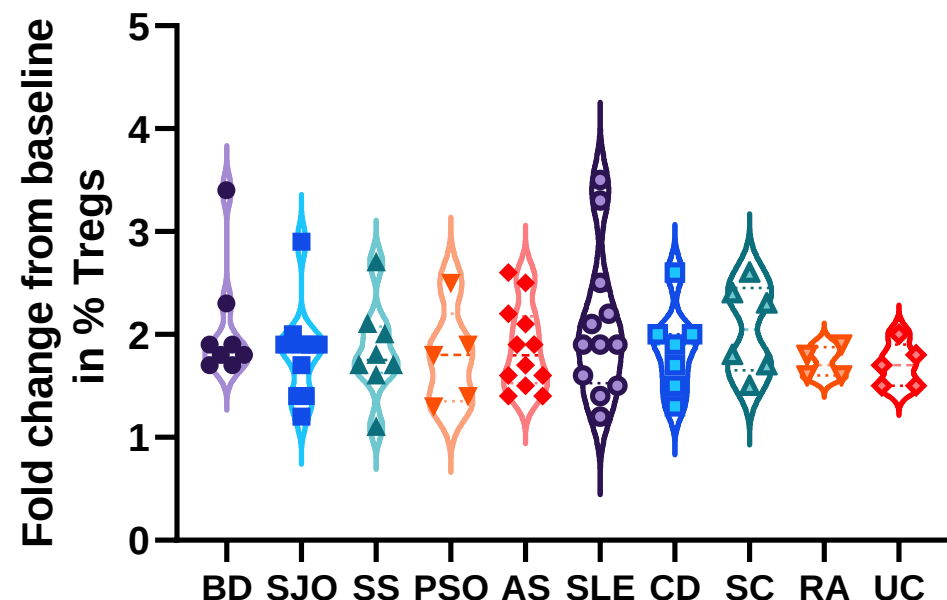
- Well tolerated across all diseases
- Specific Treg expansion and activation to similar levels in all patients across indications
 - concomitant medications, including corticosteroids and NSAIDs, did not impact observed Treg increases
- Significant reduction in clinical endpoints across the 11 auto-immune diseases

TRANSREG STUDY: Significant increase of Tregs observed independent of pathology

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

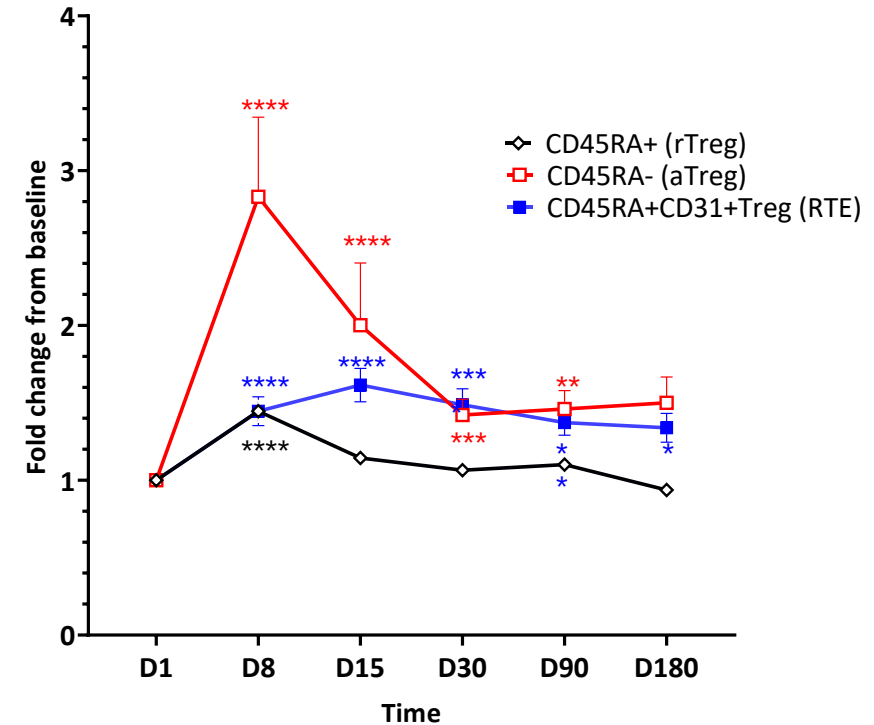
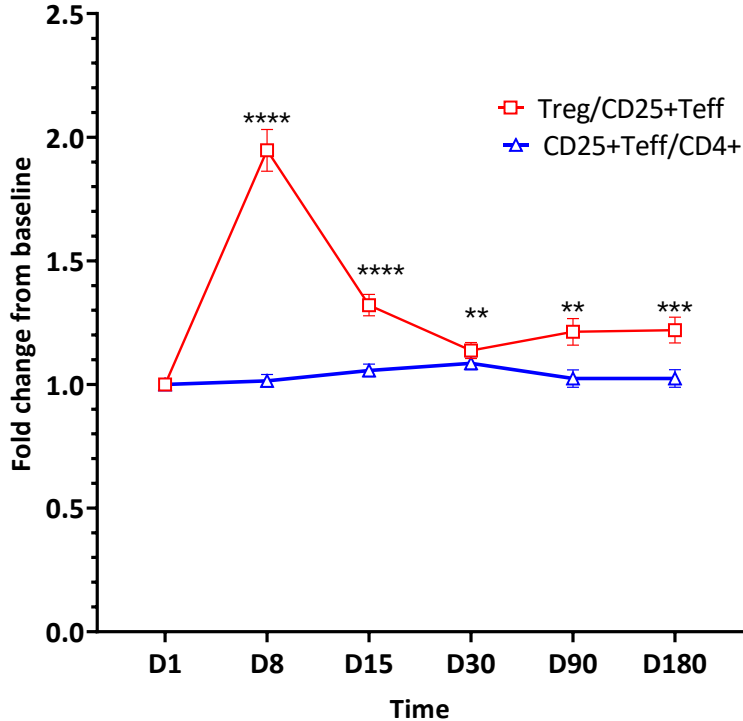


Fold change in % Tregs



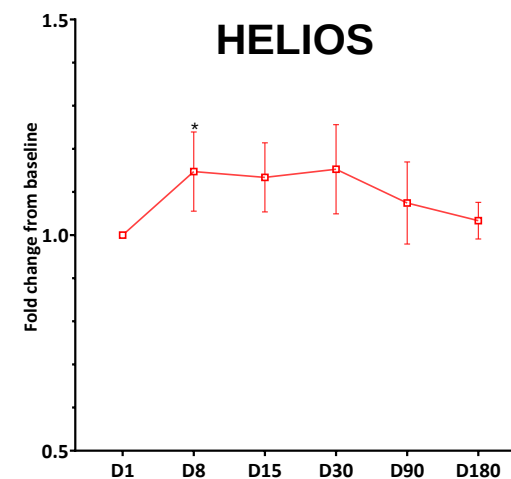
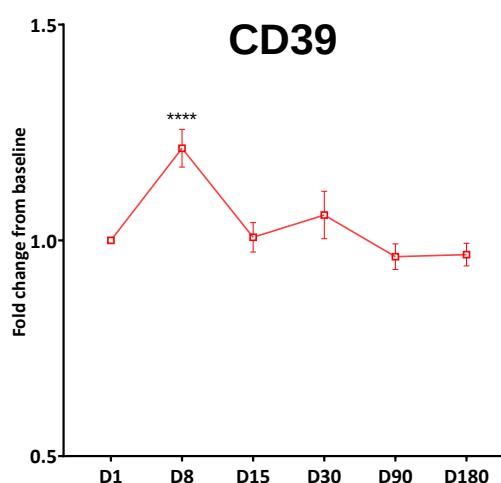
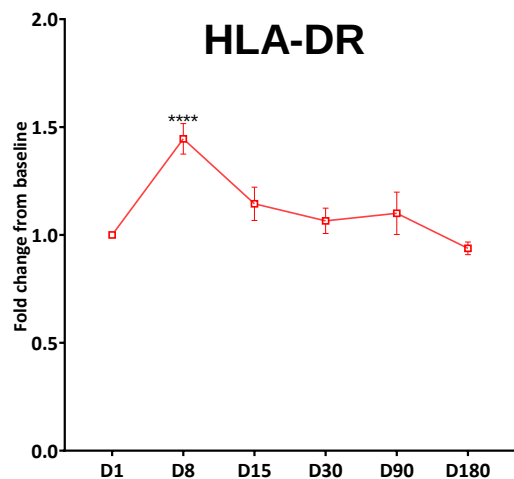
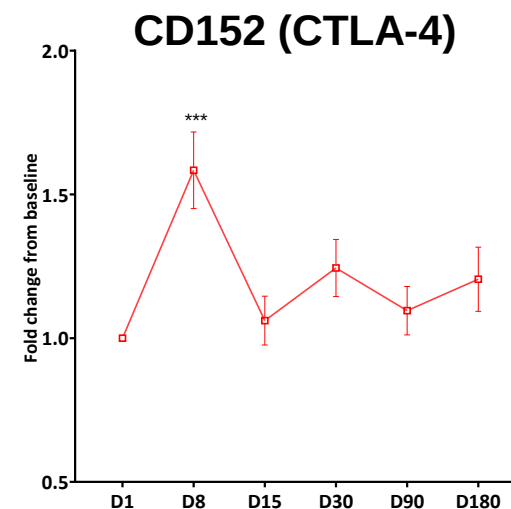
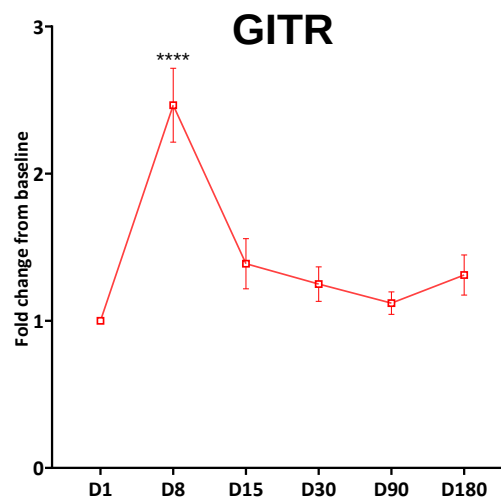
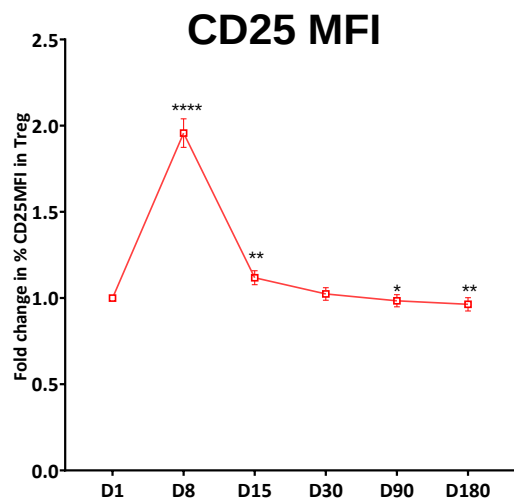
- Significant increase of Tregs was observed at day-8 independent of the pathology
- No significant difference in Treg increase was seen between pathologies
 - Mean increase by pathology: 70% to 100%

Treg selectivity after Low-Dose IL-2 induction and maintenance periods



- Low-dose IL-2 selectively activates and expands Tregs without activating CD25^{lo/+}Foxp3⁻ CD4⁺ Teff cells, which translates into a significant increase in Treg to CD25^{lo/+}Foxp3⁻CD4⁺ Teffs cell ratio
- Both naïve and activated/memory Treg populations expanded after low-dose IL-2

TRANSREG STUDY: Update on 80 patients across 13 auto-immune diseases



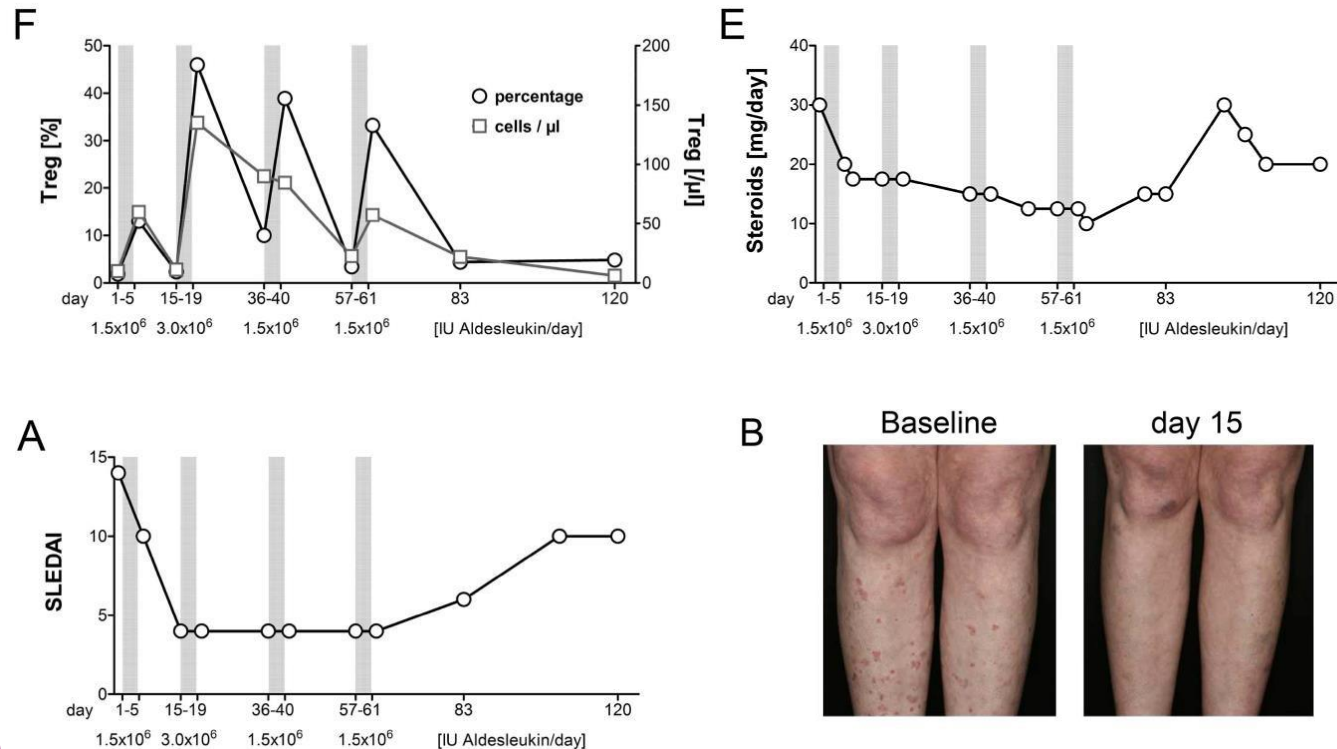
TRANSREG STUDY: Update on 80 patients across 13 auto-immune diseases

Pathology	Clinical Response (CGI)	% Response
Sclerosing Cholangitis	0/6	0%
Rheumatoid Arthritis	1/4	25%
Ankylosing Spondylitis	5/12	42%
Psoriasis	3/5	60%
Ulcerative Colitis	3/5	60%
Behcet's Disease	5/8	63%
Sjogren syndrome	6/9	67%
Systemic Lupus Erythematosus	8/12	67%
Crohn's Disease	5/7	71%
Systemic sclerosis	5/7	71%
Autoimmune Hepatitis	1/1	100%
Takayasu's Disease	1/1	100%
Granulomatosis with Polyangitis	1/1	100%

Clinical Global Impression (CGI):

- CGI was selected as a clinical evaluation method that could work across our heterogeneous group of diseases
- CGI was originally developed for use in clinical trials to provide a brief, stand-alone assessment of the clinician's view of the patient's global functioning prior to and after initiating a study medication

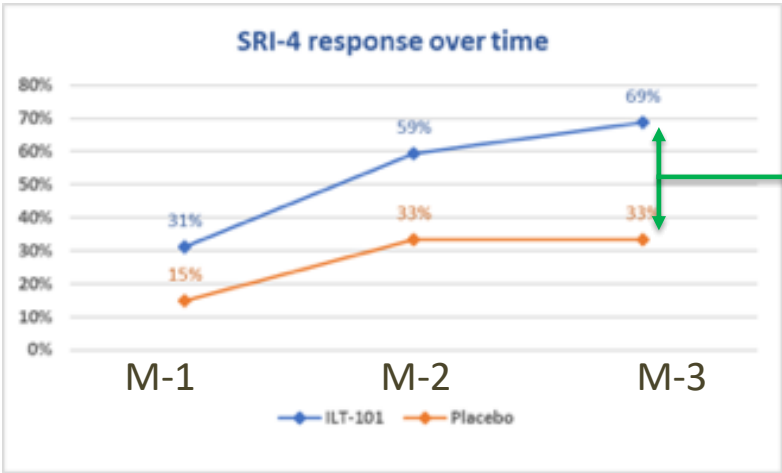
Clinical remission in refractory SLE patient treated with low-dose IL-2



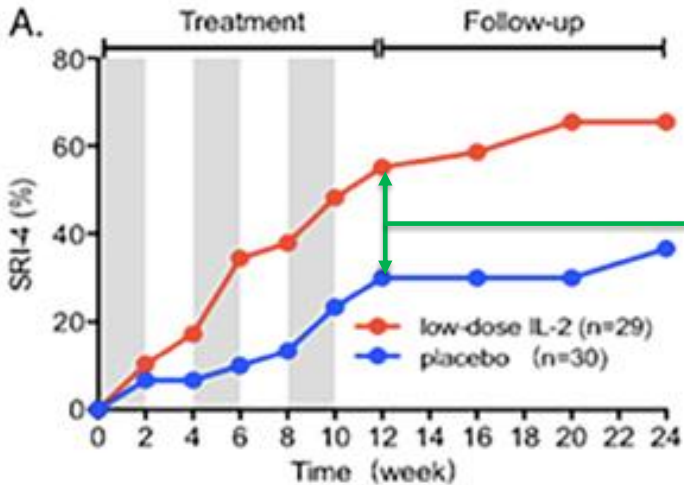
- 36-year-old female patient with SLE with high disease activity at baseline
 - Active arthritis with clinical and laboratory signs of myositis, rash, hypocomplementaemia and elevated anti dsDNA antibodies (SELENA-SLEDAI 14).
- First treatment cycle with low-dose IL-2:
 - Signs of arthritis, active skin 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).

Low-Dose IL-2 efficacy in two RCT in SLE

LUPIL-2



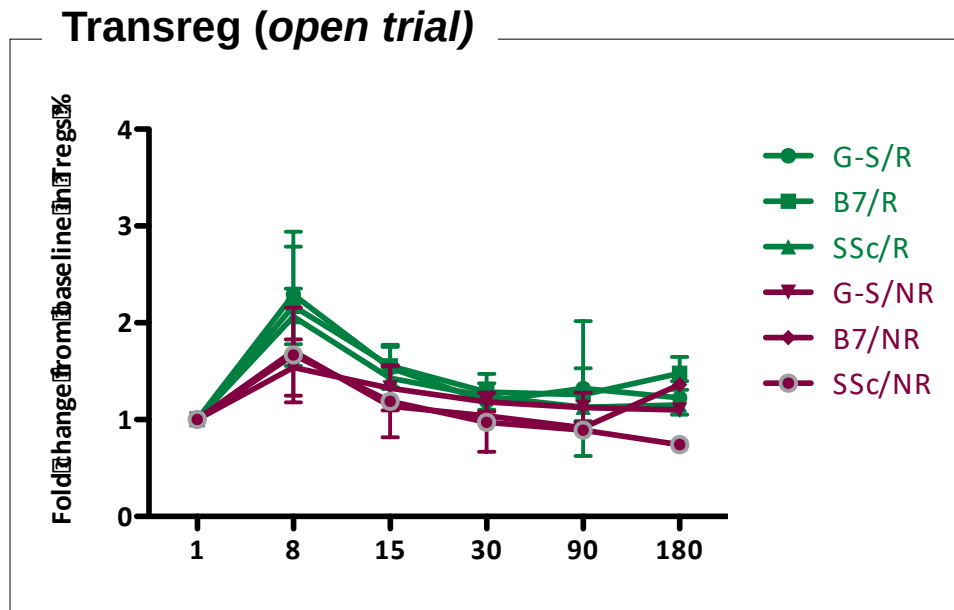
$\Delta = 36\%$ at M3



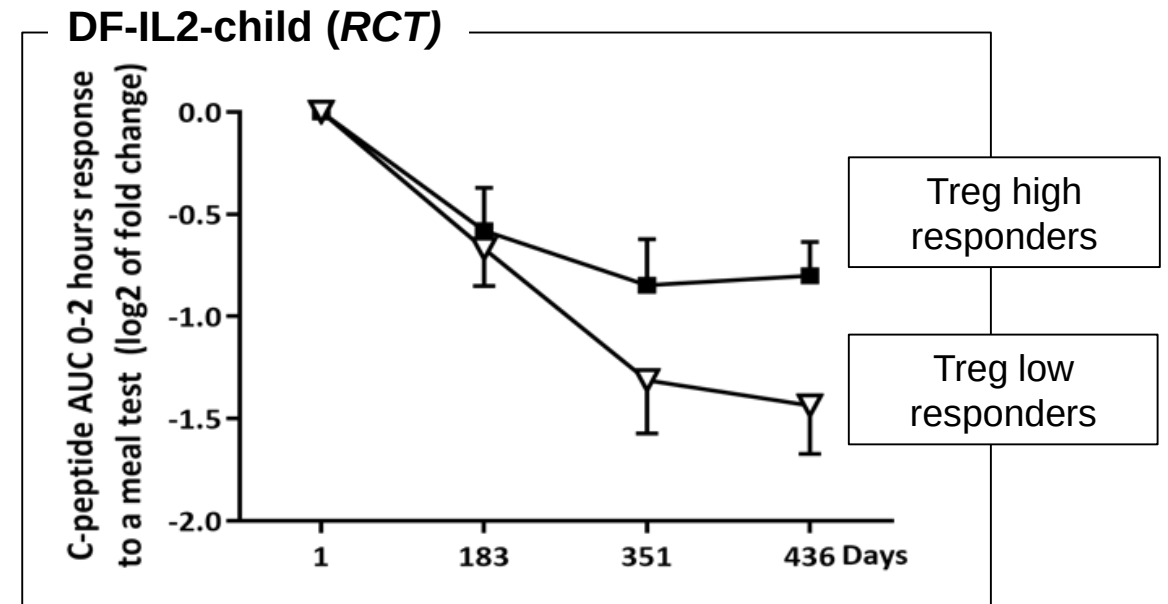
$\Delta = 30\%$ at M3

Clinical efficacy is correlated with Treg expansion and activation

Treg increase in clinical Responders (R) vs non-responders (NR)

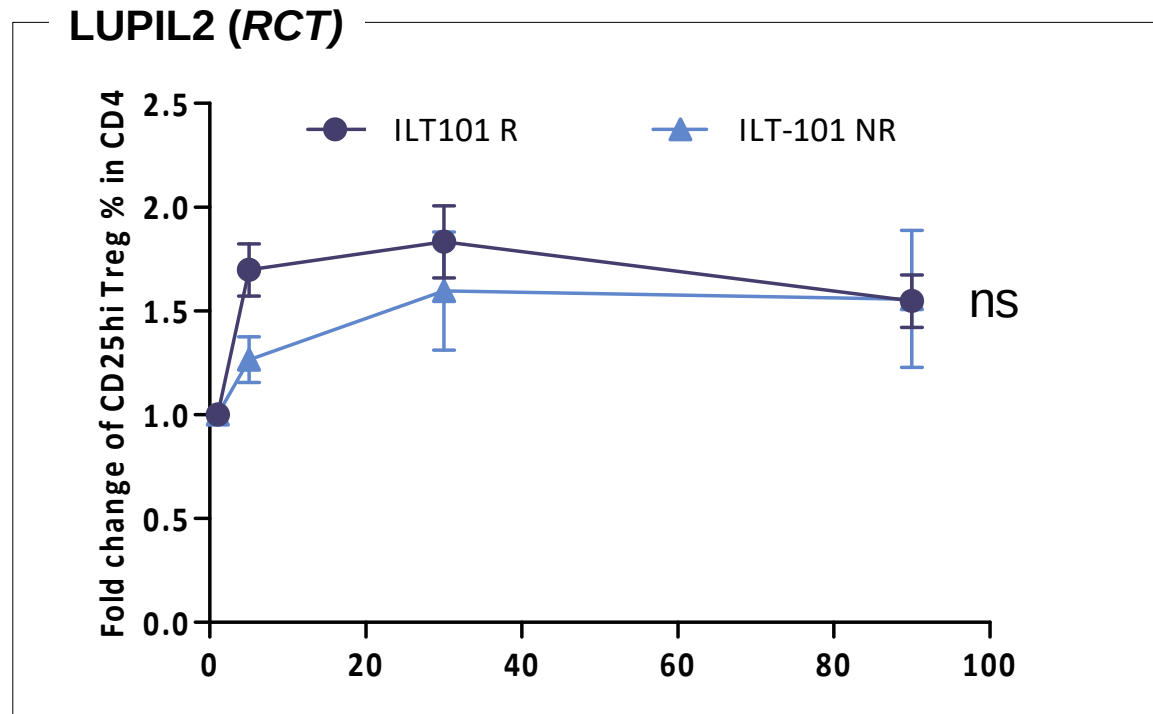


Clinical response in high vs low Treg responders



Clinical efficacy is correlated with Treg expansion and activation

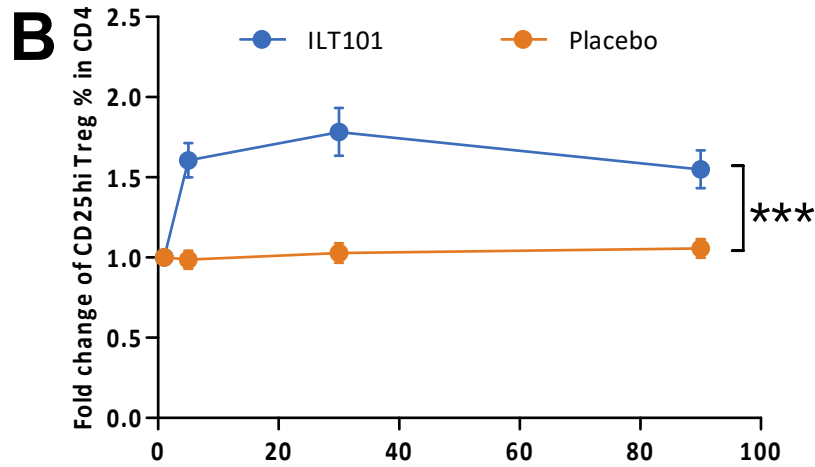
Treg increase in clinical responders (R) vs non-responders (NR)



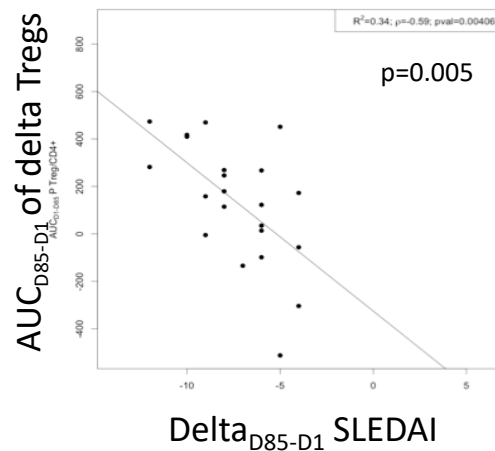
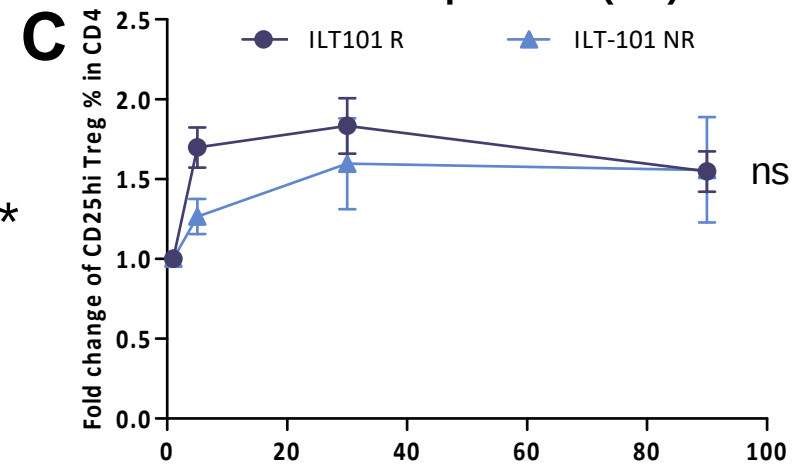
Clinical efficacy is correlated with Treg expansion and activation

LUPIL2 (RCT)

Treg increase with ILT101 vs Placebo



Treg increase in clinical responders (R) vs non-responders (NR)



- Clinical response to low dose IL-2 is correlated to the Treg response

Conclusions

- **IL-2 represents a first-in-class Treg agonist**
 - **with an excellent safety profile**
 - **with a well understood mechanism of action**
 - **with indication of efficacy in open and phase-II trials**
 - **with indications that efficacy is correlated to the level of expansion and activation of Tregs**

Clinical Stage Engineered IL-2 Pathway Agonists in Development for Auto-immune Disease

	NKTR-358	AMG592 ¹	RG7835 ²	DEL106/CC92252 ¹	PT101 ¹
Company	 NEKTAR / Lilly	 AMGEN	 Roche	 Bristol Myers Squibb™	 PANDION THERAPEUTICS
Description	Native IL-2 Stable PEGylation	IL-2 mutein Fc Fusion	IL-2 mutein IgG Fusion	IL-2 mutein Fc Fusion	IL-2 mutein Fc Fusion
Stage	Phase 2	Phase 1b/2	Phase 1b	Phase 1b	Phase 1
S.C. Route of Administration	✓	✓	✓	✓	✓
Preferential binding to high affinity (αβγ) IL-2R	✓	✓	✓	✓	✓
Mutations reduce binding to med affinity (βγ) IL-2R	✗	✓	✓	✓	✓
Expansion of CD4-Tregs Significant fold increase above baseline	✓ Observed in Single and Repeat Dosing Studies	✓ Single Dose Only	No clinical data disclosed	✓ Single Dose Only	No clinical data disclosed
Tolerability	✓ Repeat Dosing	✓ Single Dose Only	No clinical data disclosed	✓ Single Dose Only	No clinical data disclosed
Anti-drug Antibodies Detected in Clinical Setting	✗ None in 50-day follow-up in both Single Dose and Repeat Dose Studies	✓* Reported with single dose	No clinical data disclosed	✓* Reported with single dose	No clinical data disclosed

SOURCES: 1. The Promise of Interleukin-2 Therapy for autoimmune and inflammatory diseases, allergy, transplantation and cancer (<https://www.il-2-2019.com/>); *Detail was derived through QA session by company presenter; 2. Peterson LB, Bell CJM, Howlett SK, et al. A long-lived IL-2 mutein that selectively activates and expands regulatory T cells as a therapy for autoimmune disease. *J Autoimmun.* 2018;95:1-14. doi:10.1016/j.jaut.2018.10.017



"Selective Expansion of Regulatory T Cells in Patients with Systemic Lupus Erythematosus by a Novel IL-2 Conjugate, NKTR-358"

Jonathan Zalevsky, PhD

Selective Expansion of Regulatory T Cells in Patients with Systemic Lupus Erythematosus by a Novel IL-2 Conjugate, NKTR-358

Christie Fanton¹, Richard Furie², Neha Dixit¹, Cat Haglund¹, Lin Lu¹, Suresh Siddhanti¹, Vishala Chindalore³, Robert Levin⁴, Islam Diab⁵, Brian Kotzin¹, Jonathan Zalevsky¹

¹Nektar Therapeutics, Inc., San Francisco, CA; ²Division of Rheumatology, Northwell Health, Great Neck, NY;

³Pinnacle Research Group, Anniston, AL; ⁴Clinical Research of West Florida, Clearwater, FL;

⁵Paramount Medical Research and Consulting, Middleburg Heights, OH



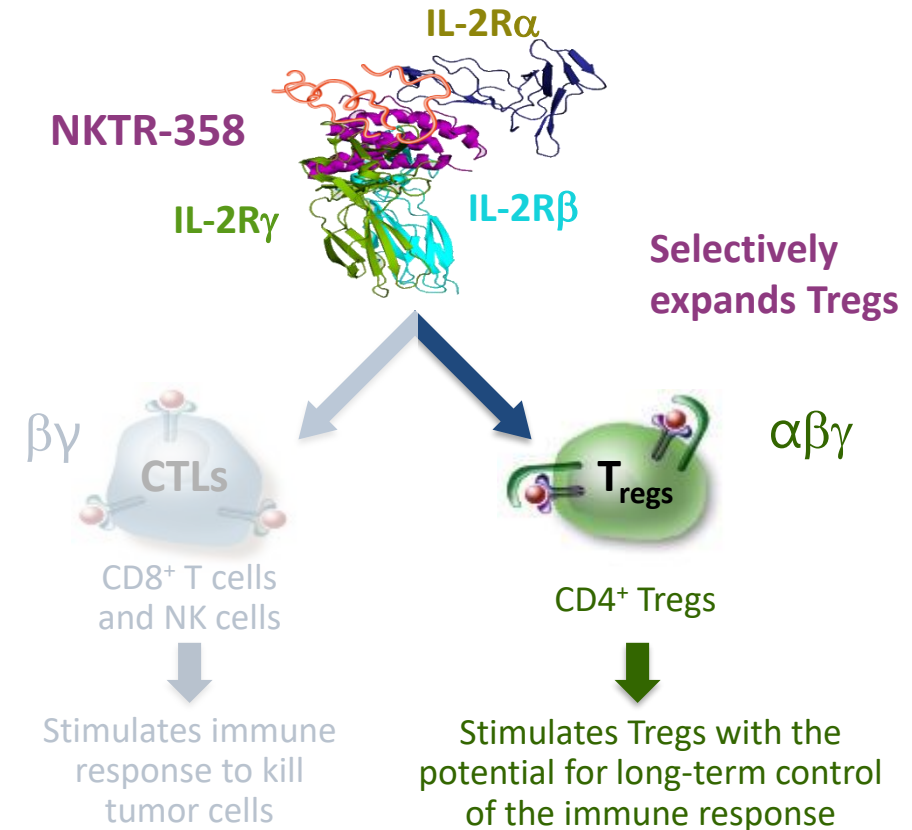
Poster presented by Prof. Richard Furie at ACR Convergence Virtual Meeting, November 5–9, 2020.



BACKGROUND

- Compared with recombinant human interleukin-2 (IL-2), PEG-conjugated NKTR-358 has:¹
 - An altered binding profile, with a lower binding affinity for IL-2R β and a different binding bias for IL-2R α and IL-2R γ
 - Selectivity for stimulating regulatory T cells (Tregs) over conventional T cells (Tcons)
 - An increased half-life
- NKTR-358 has shown:
 - Activity in animal models of systemic lupus erythematosus (SLE) and cutaneous hypersensitivity²
 - Selective stimulation of Tregs in a single-ascending dose (SAD) study in healthy volunteers³

NKTR-358: A PEG-conjugated rhIL-2 that selectively induces Tregs and their suppressive activity



CTL, cytotoxic T lymphocyte; IL-2R, interleukin-2 receptor; NK, natural killer; rh, recombinant human; Treg, regulatory T cell.

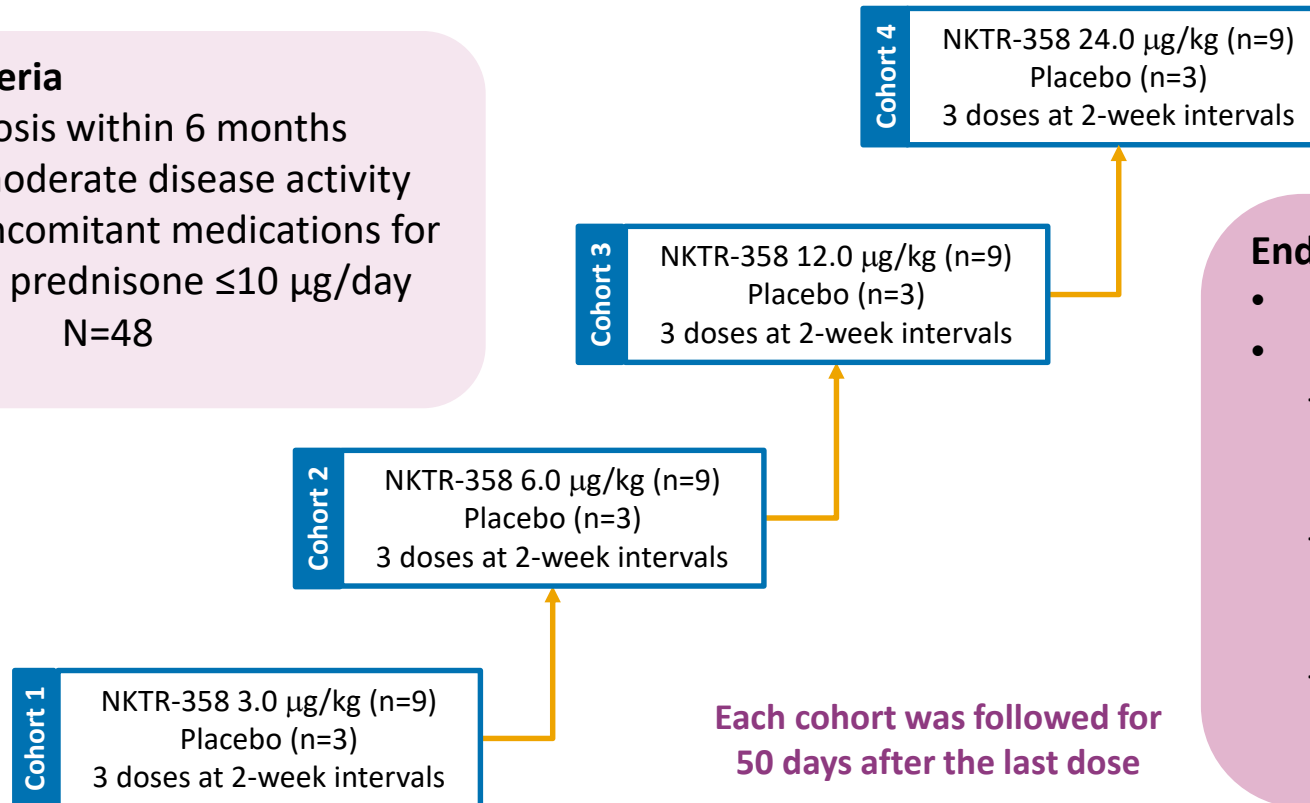
METHODS

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 $\mu\text{g}/\text{day}$
- N=48



Endpoints

- **Primary:** Safety and tolerability
- **Secondary:**
 - Time course and change in number and activity of Tregs, Tcons, NK cells and subsets
 - Change in cytokine levels, peripheral blood cell populations, serum proteins and gene expression
 - Change in disease activity based on SLEDAI, CLASI-A, and joint scores*

CLASI-A, cutaneous lupus erythematosus disease area and severity index–activity; NK, natural killer; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index; Tcon, conventional T cell; Treg, regulatory T cell.

*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

Assessments

- Immunophenotyping by multicolor flow cytometry 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⁺ Tcons
 - **CD8⁺ T cells:** CD3⁺ CD8⁺ Tcons
 - **Natural killer (NK) cells:** CD3⁻ CD56⁺⁺⁺ CD16⁻ (bright) , CD3⁻ CD56⁺ CD16⁺ (dim), and CD3⁻ CD56⁺ (total)
- Epigenetic modifications were evaluated with the Epiontis ID qPCR-based assay to monitor methylation status of the Treg-specific demethylation region (TSDR) of the *FoxP3* gene, using whole blood collected at multiple time points pre- and post-NKTR-358 administration
- Gene expression was measured with the NanoString platform, with whole blood collected at multiple time points pre- and post-NKTR-358 administration
- Post-hoc analyses were performed for change in cutaneous lupus erythematosus disease area and severity index–activity (CLASI-A) score for individual patients following NKTR-358 treatment

RESULTS

Baseline demographics and disease characteristics

	NKTR-358 (n=36)	Placebo (n=12)
Age, years, mean (SD)	47.2 (12.5)	47.8 (8.3)
Female, n (%)	34 (94.4)	12 (100)
Body mass index, mean (SD)	26.9 (3.0)	26.7 (4.6)
Disease duration, months, mean (SD)	9.5 (8.9)	14.3 (9.7)
SLEDAI score, mean (SD, min–max)	6.0 (2.8, 0–10)	5.2 (2.7, 2–10)
CLASI-A score, mean (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-A, cutaneous lupus erythematosus disease area and severity index–activity; SD, standard deviation; SLEDAI, systemic lupus erythematosus disease activity index.

RESULTS

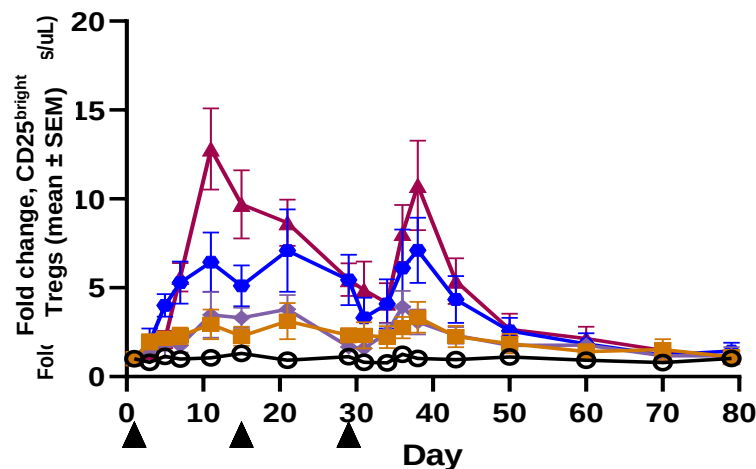
Safety and tolerability

- No dose-limiting toxicities, deaths, or clinically significant vital sign, 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 3 weeks after the last dose of NKTR-358; it was not considered related to the study drug
- Three patients discontinued treatment (one patient [24 µg/kg] due to elevated eosinophil levels, with no clinical sequelae; two patients for reasons unrelated to adverse events)
- One patient in the highest dose cohort (24 µg/kg) demonstrated transient and mild (Grade 1) flu-like symptoms after the second and third doses that were considered related to the 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 50 days of follow-up

RESULTS

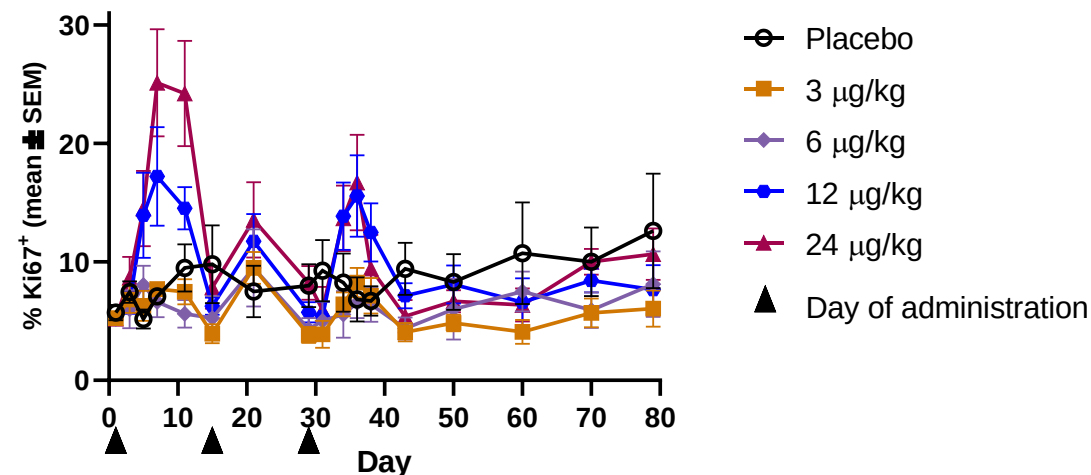
NKTR-358 led to sustained, dose-dependent increases in the number and proliferation of CD25^{bright} Tregs

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



SEM, standard error of the mean; Treg, regulatory T cell.

Proliferation (% Ki67⁺) of CD25^{bright} Tregs

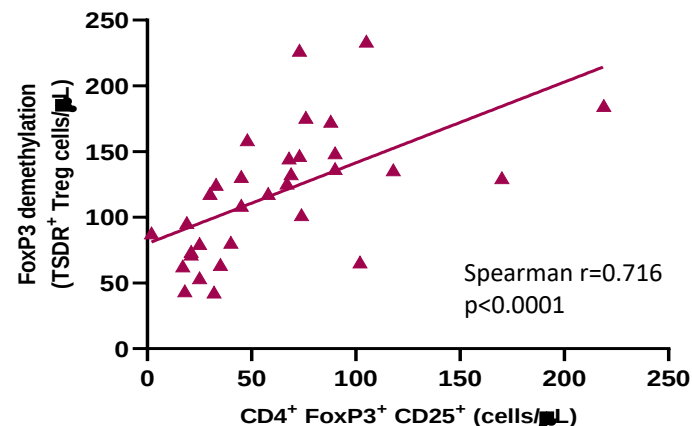


- NKTR-358 (24 µg/kg) resulted in: ±
 - Maximum 12-fold mean peak increase over baseline in number of CD25^{bright} Tregs
 - Treg levels peaked at Day 10 after the first NKTR-358 dose and remained above baseline for 20–30 days following the last dose
 - Maximum 5-fold mean peak increase over baseline in Ki67⁺ CD25^{bright} Tregs
- Treg increases observed with NKTR-358 in SLE patients were comparable with those seen at 28 µg/kg in healthy volunteers
- No overall changes in Tcon cell numbers were observed following NKTR-358 administration (data not shown)

RESULTS

Identification of NKTR-358-induced Tregs supported by correlation with demethylation status of *FoxP3* gene

Correlation of Treg number with *FoxP3* demethylation at 24 µg/kg



Each data point represents an individual blood sample from nine NKTR-358-treated patients where data were available for both flow cytometry and demethylation assays.

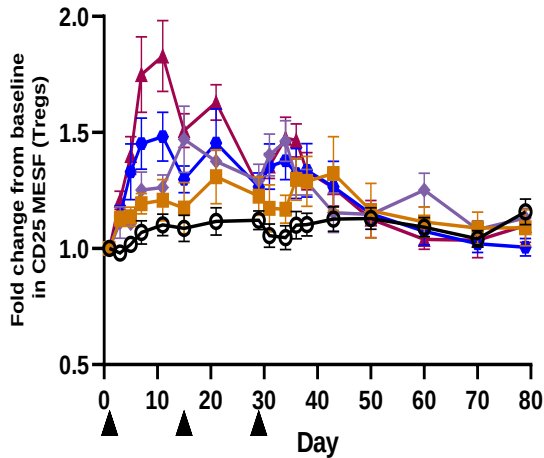
TSDR, Treg-specific demethylated region; Treg, regulatory T cell.

- An epigenetically active (demethylated) *FoxP3* gene is observed solely in Tregs and not in activated (non-Treg) CD4⁺ Tcons¹
- After treatment with ≥6 µg/kg NKTR-358, a significant correlation was observed between NKTR-358-induced Tregs identified by flow cytometry (CD4⁺ CD25⁺ FoxP3⁺ cells) and Tregs identified by epigenetic analysis (percentage of demethylation of *FoxP3* TSDR)

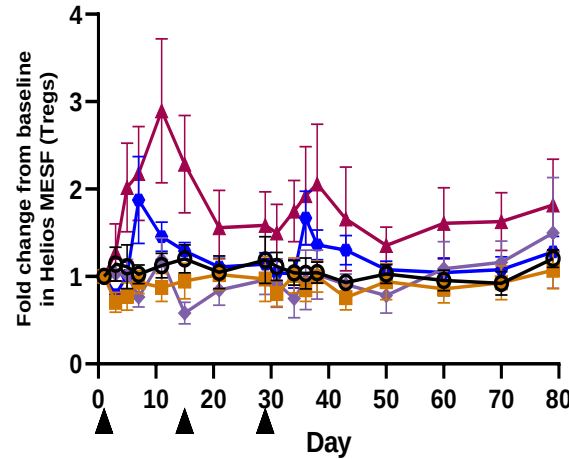
RESULTS

NKTR-358 ($\geq 12 \mu\text{g/kg}$) elicited a dose-dependent induction of Treg activation markers

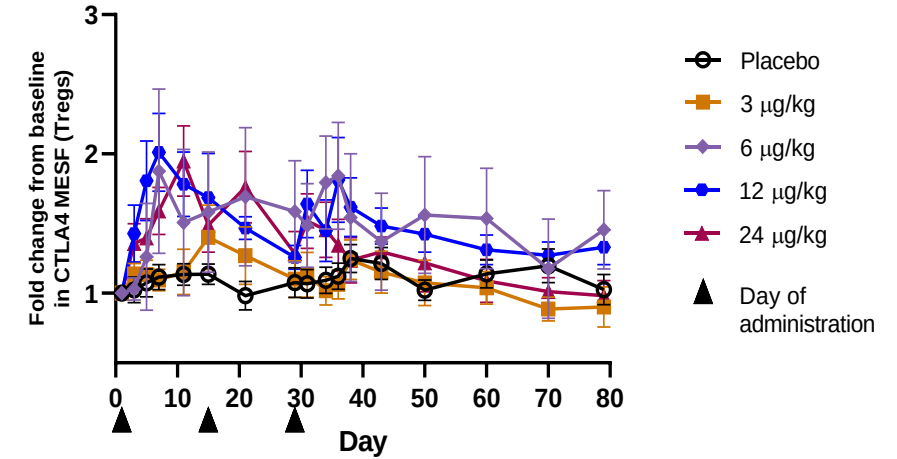
Expression of CD25 on total Tregs



Expression of Helios on total Tregs



Expression of CTLA-4 on total Tregs



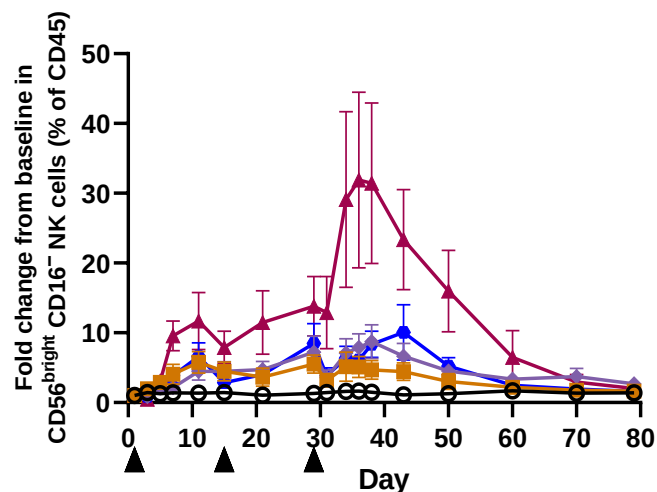
CTLA4, cytotoxic T-lymphocyte-associated protein 4; MESF, molecules of equivalent soluble fluorochrome; Treg, T regulatory cell.

- A sustained induction of markers associated with increased suppressive Treg function was observed at 12 and 24 $\mu\text{g/kg}$ NKTR-358
- The magnitude of increase was similar to the change observed in the SAD study in healthy volunteers

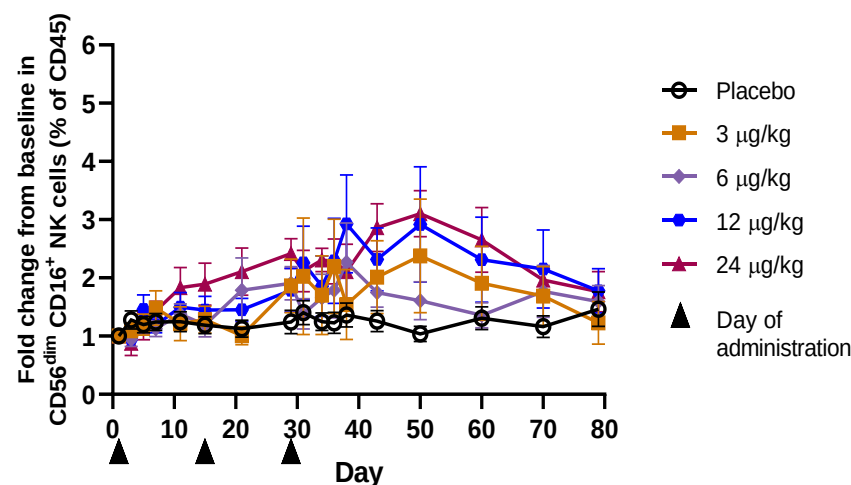
RESULTS

NKTR-358 led to low-level increases in CD56⁺ NK cells in most patients at 24 µg/kg

Fold change in frequency (% CD45) of
CD56^{bright} CD16⁻ NK cells



Fold change in frequency (% CD45) of
CD56^{dim} CD16⁺ NK cells



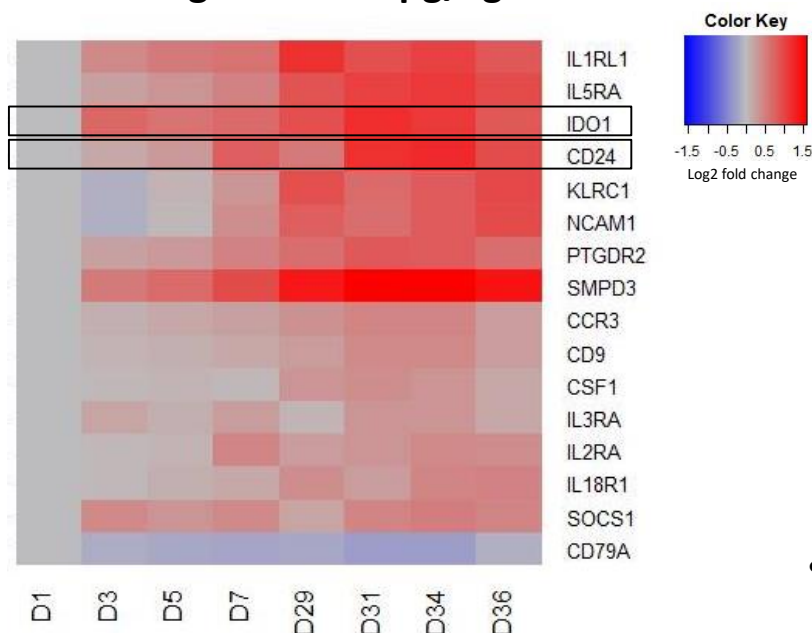
NK, natural killer.

- NKTR-358 treatment led to low-level increases in total CD56⁺ NK cells in most patients at 24 µg/kg, with the increase driven by two outlier individuals
- The CD56^{bright} population was more sensitive to NKTR-358 than the CD56^{dim} population, showing greater induction following NKTR-358 administration
- The ratio of CD56^{bright} to CD56^{dim} NK cells increased 16-fold over predose at 24 µg/kg

RESULTS

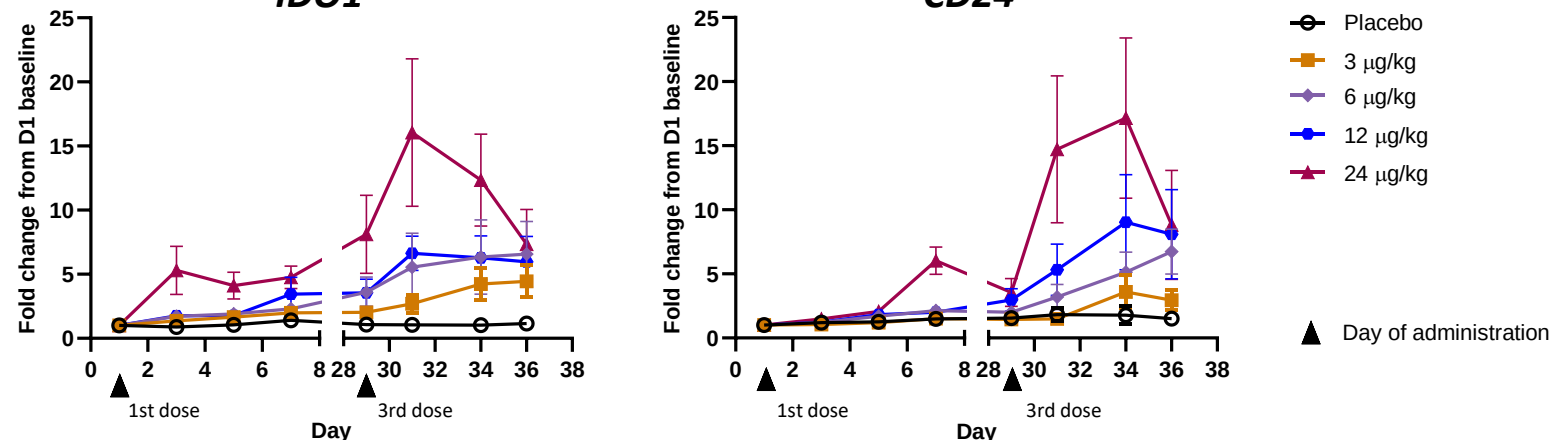
NKTR-358 led to the dose-dependent induction of genes associated with regulating immune processes and Treg function

Pattern of differential expression of genes at 24 µg/kg



NanoString mRNA expression analysis
(Pan-Cancer Immune Profiling 770 gene panel).

Dose-dependent changes in two genes

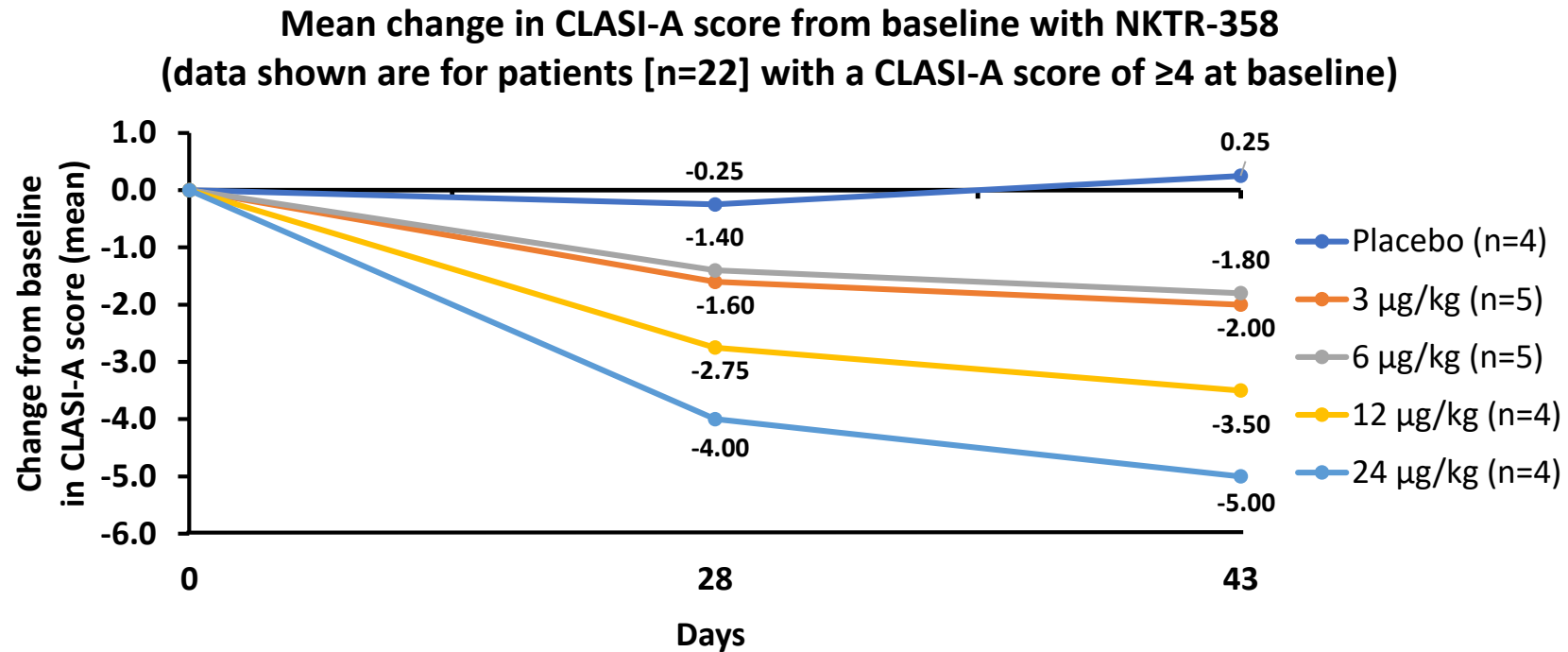


RNA samples were collected after the 1st and 3rd administration.
D1, day 1.

- NKTR-358 elicited an increase in the number and magnitude of differentially expressed genes associated with Treg regulation
- Some of the differentially expressed genes overlap with those reported previously in healthy volunteers
- Repeat administration with NKTR-358 showed further induction in most dose-dependent genes

RESULTS

NKTR-358 demonstrated a dose-dependent reduction in CLASI-A score*



CLASI-A, CLASI-A, cutaneous lupus erythematosus disease area and severity index–activity.

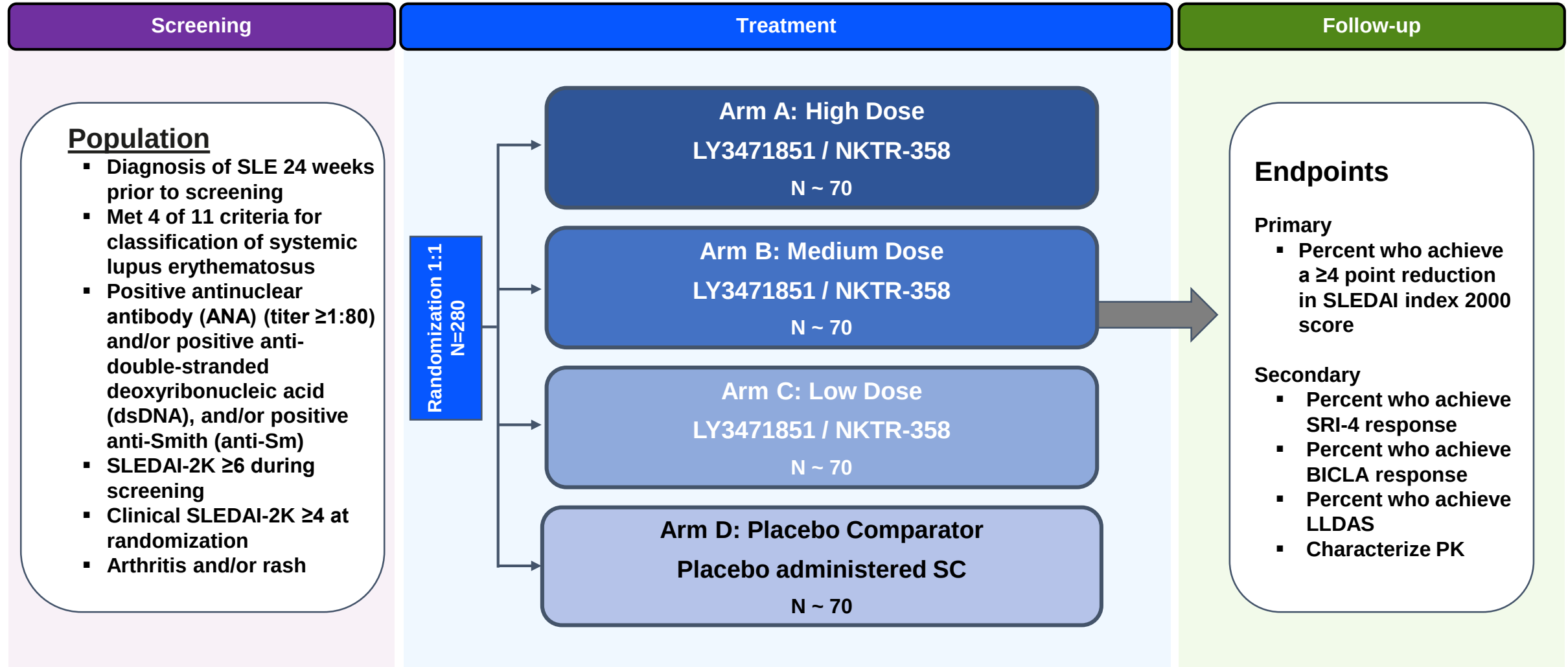
- One patient (24 µg/kg) experienced a reduction in CLASI-A score from 22 at baseline to 5 by Day 43 (2 weeks after last dose)
- Seven of 18 patients had a ≥ 4 -point reduction in CLASI-A score from baseline by Day 43
- No observed changes in SLEDAI or joint scores were noted due to the short treatment duration in this study

*In this small subset of patients, primarily with mild disease and short treatment duration.

CONCLUSIONS

- NKTR-358 was safe and well tolerated, with a similar safety profile for single and repeat doses
- A selective, dose-dependent expansion of CD25^{bright} Tregs was observed, which was maintained through multiple NKTR-358 administrations
 - Treg induction was further supported by a correlation between the number of Tregs and the extent of demethylated *FoxP3*
 - Increases in Treg activation markers (CD25, Helios, and CTLA-4) and genes associated with Treg regulation were observed with NKTR-358
- Low-level increases in NK cell numbers occurred in most patients at the highest NKTR-358 dose; the CD56^{bright} population was more sensitive than the CD56^{dim} population
- A dose-dependent reduction in CLASI-A score was seen with NKTR-358 treatment, which warrants further exploration
- These data provide strong support for continued testing of NKTR-358 in patients with SLE and other inflammatory diseases
 - A Phase 2 trial of NKTR-358 in patients with SLE is currently recruiting (NCT04433585)

Systemic Lupus Erythematosus Phase 2 Study Design



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

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

- Lilly initiated Phase 2 study in lupus (SLE) in Summer of 2020
- Lilly is conducting two additional Phase 1b studies in Psoriasis and Atopic Dermatitis
- Lilly is planning to start an additional Phase 2 study in ulcerative colitis
- Lilly now conducting clinical development program through registrational trials and is assuming 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.)



Q&A Session



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