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

THU0054

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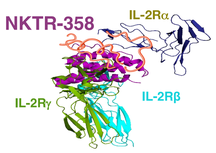
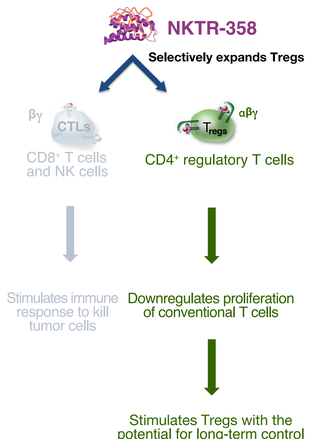
# BACKGROUND

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



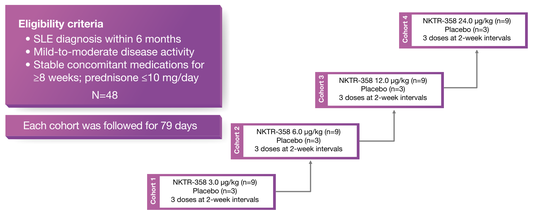

- Compared with native IL-2, PEG conjugation:
  - Alters the binding profile of NKTR-358, eliciting a lower binding affinity for IL-2Rβ and a different binding bias for IL-2Rα and IL-2Rβ
  - Imparts selectivity for the stimulation of regulatory T cells (Tregs) over conventional T cells (Tcons)
  - Increases the half-life
- NKTR-358 has shown:
  - Activity in animal models of systemic lupus erythematosus (SLE) and cutaneous hypersensitivity[1]
  - Selective stimulation of Tregs in a single ascending dose (SAD) study in healthy volunteers[2]




# 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)




## 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

## 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

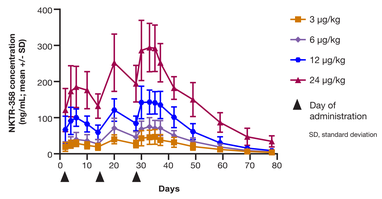
## Safety

### 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

## Pharmacokinetics

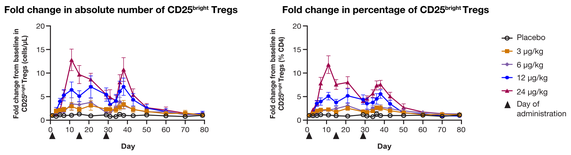
### NKTR-358 demonstrated dose proportional PK with repeated dosing




- 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

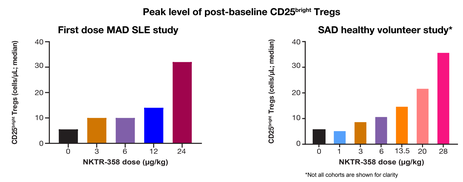
## Changes in numbers and percentages of Tregs

### NKTR-358 elicited sustained, dose-dependent increases in the absolute numbers and percentages 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

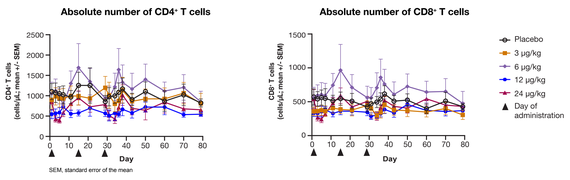
### Similar induction of CD25$^{bright}$ Tregs in healthy volunteers and patients with SLE following treatment with NKTR-358




- 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

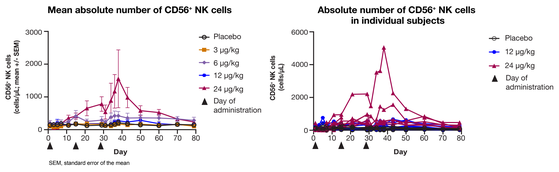
## Changes in Tcon and NK cell numbers

### No overall changes in Tcon cell numbers with NKTR-358




- 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

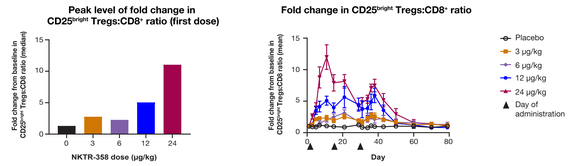
### NKTR-358 treatment led to low-level increases in the numbers of CD56$^+$ NK cells in most patients




- 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)

## Changes in Treg expansion after multiple administrations

### NKTR-358 maintained selectivity for Treg expansion after multiple administrations




- 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)

# 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

# REFERENCES

1. Langowski J, *et al.* Poster presented at the *American College of Rheumatology* Annual Meeting 2017: 2715.
2. Fanton C, *et al.* Poster presented at the *American College of Rheumatology* Annual Meeting 2019: 0098.

# ACKNOWLEDGEMENTS

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# DISCLOSURES

**CF, SS, ND, LL, JZ, BK:** shareholders of Nektar Therapeutics; employees of Nektar Therapeutics. **VC:** grant/research support from Nektar Therapeutics for conducted studies; speaker bureaus: >5 years ago. **RL:** grant/research support for industry-sponsored trials; consultant for Gilead, Exagen, Myriad Rheumatology; speaker bureaus: Sanofi/Genzyme, Regeneron, Bristol-Myers Squibb, AbbVie. **RF:** grant/research support from Nektar Therapeutics to Northwell Rheumatology to conduct this study; consultant for Nektar Therapeutics. **ID** has no disclosures.