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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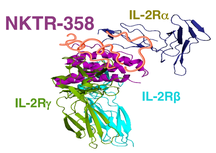
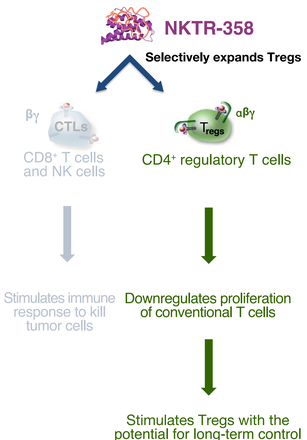
BACKGROUND

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



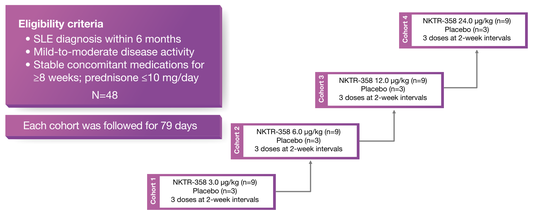
- Compared with native IL-2, PEG conjugation:
  - Alters the binding profile of NKTR-358, eliciting a lower binding affinity for IL-2Rβ and a different binding bias for IL-2Rα and IL-2Rβ
  - Imparts selectivity for the stimulation of regulatory T cells (Tregs) over conventional T cells (Tcons)
  - Increases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

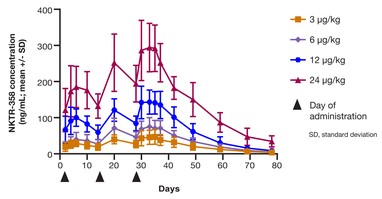
Safety

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

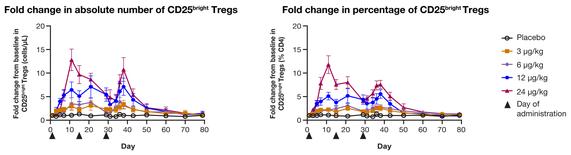
NKTR-358 demonstrated dose proportional PK with repeated dosing



- 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

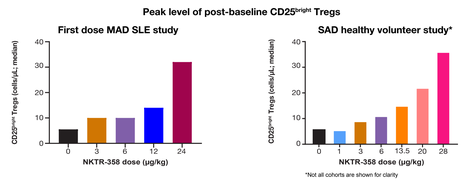
Changes in numbers and percentages of Tregs

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

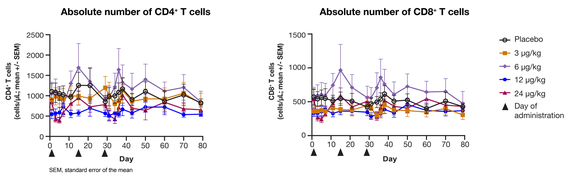
Similar induction of CD25^{bright} Tregs in healthy volunteers and patients with SLE following treatment with NKTR-358



- 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

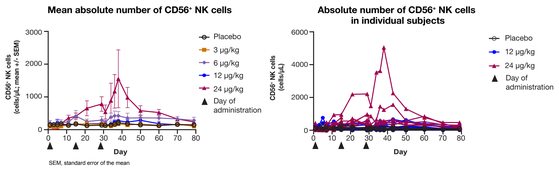
Changes in Tcon and NK cell numbers

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

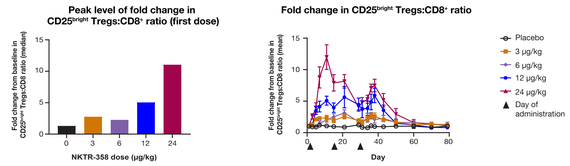
NKTR-358 treatment led to low-level increases in the numbers of CD56$^+$ NK cells in most patients



- 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.