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Title: Efficacy and Safety of a Selective Regulatory T-Cell Inducing IL-2 Conjugate (LY3471851) in the Treatment of Psoriasis: A Phase 1 Randomised Study

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Introduction

Impaired IL-2 production and dysfunction in regulatory T cell (Treg) biology have been identified as key immunological defects contributing to the pathogenesis of multiple autoimmune and inflammatory diseases including psoriasis (PsO)[1]. Patients (pts) with PsO have shown either a decrease in Treg cell numbers or a reduction in immunosuppressive functions of Treg cells[1]. NKTR-358 (LY3471851) is a polyethylene glycol conjugate of recombinant human IL-2 which selectively stimulates Treg cell expression and activation[2]. Here, we report the efficacy, safety, and biological effects of LY3471851 in a study of patients with PsO.

Materials & methods

In this Phase 1b, double-blind, placebo-controlled study (NCT04081350), pts were randomized to either 24 µg/kg LY3471851 (N=21) or PBO (N=5) dosed bi-weekly, via subcutaneous injections, up to week (W) 12 with a follow-up period of W12-48, data reported here is up to W19. Inclusion criteria at baseline consisted of adult patients who were candidates for systemic therapy or phototherapy, with plaque PsO involving ≥10% body surface area in the affected skin, Static Physician's Global Assessment (sPGA) of ≥3, had at least 2 similar and evaluable lesions, and a Psoriasis Area and Severity Index (PASI) score of ≥12. Efficacy was assessed through PASI, sPGA, and Itch Numeric Rating Scale (Itch NRS). Safety was assessed through Treatment-Emergent Adverse Effects (TEAE), Death, Discontinuation, and Injection Site Reactions (ISR). Pharmacodynamics (PD) were evaluated using flow cytometry and epigenetic markers.

Results

Demographic and disease baseline characteristics are presented in Table 1. LY3471851 treated pts reported an improvement in PASI score at W12, up to W19, relative to PBO (Fig. 1). At W12, 26.3% and 10.5% of LY3471851 treated pts achieved PASI50 and PASI75 respectively, this was maintained up to W19 (Fig. 1). A sustained decrease in change from baseline versus PBO in Itch NRS was observed at W12 in LY3471851 treated pts (-0.8 vs -2.9). For sPGA (0/1) a greater percentage of LY3471851 treated pts were responders, versus PBO, at W12 (18.2% vs 0%). A summary of safety variables and ISR events related to PBO and 24 µg/kg LY3471851 are presented in Table 2. In LY3471851 treated pts, 34 TEAEs occurred, and 4 TEAEs lead to discontinuation. 1 severe TEAE occurred (Exacerbation of PsO), and no deaths occurred in the LY3471851 treated pts. No AEs, severe TEAEs, deaths, or discontinuations occurred in PBO treated pts. The most commonly occurring ISRs reported for LY3471851 treated pts were Erythema (71.4%) and Induration (61.9%). At W12, total Treg cells increased in LY3471851 treated pts, versus PBO, (CFB, 57 vs -39 cells/µL), and CD25bright Treg cells were elevated in the LY3471851 treated pts, relative to PBO (CFB, 65 vs. 12 cells/µL) (Fig.2).

Discussion

The IL-2 conjugate Treg stimulator, LY3471851, showed a consistent safety profile in patients with PsO as previously seen. In pts treated with LY3471851 Treg cells numbers increased, and PASI, sPGA, and Itch NRS scores improved over the treatment period, and PASI improvement was maintained after drug withdrawal up to W19.

[1]Nussbaum L, Chen YL, Ogg GS. *Br J Dermatol*. 2021;184(1):14-24.

[2]Dixit N, Fanton C, Langowski JL, et al. NKTR-358: *J Transl Autoimmun*. 2021;4:100103.

Table 1. Demographic and Disease Baseline Characteristics

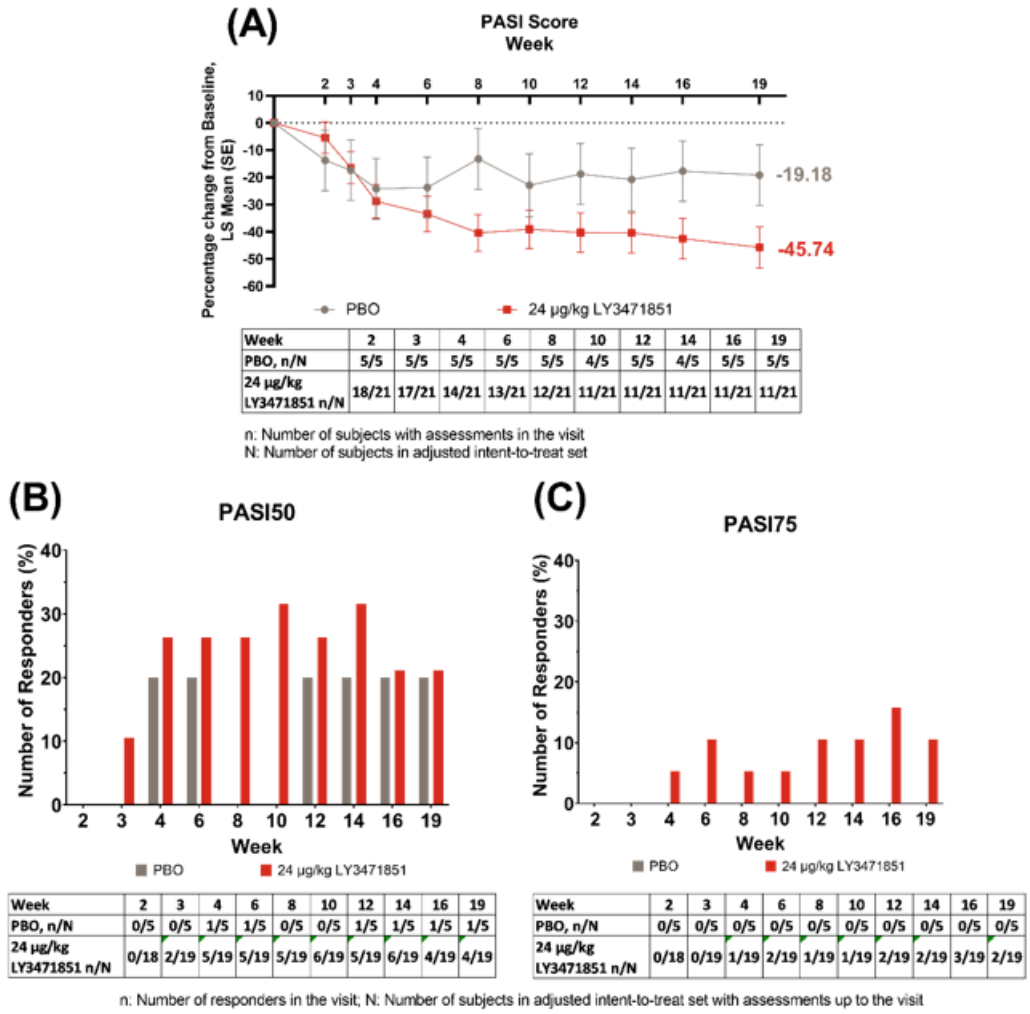
Characteristic	**PBO (N=5)**	**24 µg/kg LY3471851 (N=21)**
Sex, n (%)		
Female	2 (40.0)	9 (42.9)
Male	3 (60.0)	12 (57.1)
Race		
White	5 (100.0)	14 (66.7)
Black or African American	0	2 (9.5)
Asia	0	3 (14.3)
American Indian or Alaska Native	0	1 (4.8)
Other	0	0
Ethnicity, n (%)		
Hispanic or Latino	0	2 (9.5)
Not Hispanic or Latino	5 (100.0)	19 (90.5)
Age (years), Mean (SD)	42.6 (15.1)	47.5 (13.4)
PASI (score), Mean (SD)	31.6 (8.0)	29.3 (6.2)
sPGA (score), Mean (SD)	3.4 (0.5)	3.2 (0.4)
Itch NRS (score), Mean (SD)	6.2 (2.9)	7.9 (1.9)
Any Prior Medications, n (%)	4 (80)	16 (76.2)

PASI = Psoriasis Area and Severity Index (score 0-72); sPGA: static Physician's Global Assessment; NRS: Numeric Rating Scale; PGA: Patient's Global Assessment of Disease Severity.

Table 2. Summary of safety variables and ISR events for PBO and 24 µg/kg LY3471851.

Category	PBO (N=5)	24 µg/kg LY3471851 (N=21)
Adverse Events [n (%) m]	0	14 (66.7) 34
Infections and infestations	0	6 (28.6) 7
Skin and subcutaneous tissue disorders	0	3 (14.3) 3
Blood and lymphatic system disorders	0	2 (9.5) 3
General disorders and administration site conditions	0	4 (19.0) 8
Investigations Eosinophil count increased	0	2 (9.5) 2
Gastrointestinal disorders	0	1 (4.8) 2
Musculoskeletal and connective tissue disorders	0	2 (9.5) 5
Respiratory, thoracic and mediastinal disorders	0	2 (9.5) 5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (4.8) 1
Renal and urinary disorders	0	1 (4.8) 1
Severe Adverse Events [n (%) m]	0	1 (4.8) 1
Adverse Events with Outcome of Death [n (%) m]	0	0
Serious Adverse Events [n (%) m]	0	0
Adverse Events Leading to Discontinuation of Study [n (%) m]	0	4 (19.0) 4
Skin and subcutaneous tissue disorders	0	2 (9.5) 2
Investigations (Eosinophil count increased)	0	1 (4.8) 1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (4.8) 1
Injection Site Reaction [m]	0	28

n = Number of patients; m = Number of events



Week	2	3	4	6	8	10	12	14	16	19
PBO, n/N	5/5	5/5	5/5	5/5	5/5	4/5	5/5	4/5	5/5	5/5
24 µg/kg LY3471851 n/N	18/21	17/21	14/21	13/21	12/21	11/21	11/21	11/21	11/21	11/21

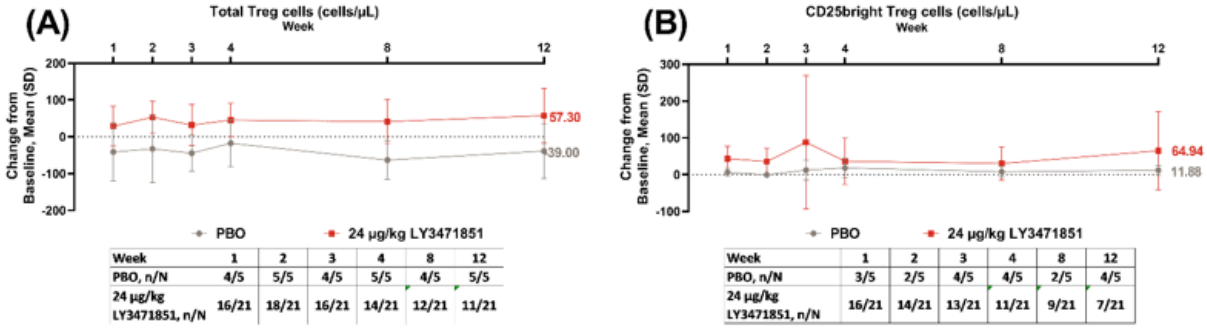
n: Number of subjects with assessments in the visit
N: Number of subjects in adjusted intent-to-treat set

Week	2	3	4	6	8	10	12	14	16	19
PBO, n/N	0/5	0/5	1/5	1/5	0/5	0/5	1/5	1/5	1/5	1/5
24 µg/kg LY3471851 n/N	0/18	2/19	5/19	5/19	5/19	6/19	5/19	6/19	4/19	4/19

Week	2	3	4	6	8	10	12	14	16	19
PBO, n/N	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
24 µg/kg LY3471851 n/N	0/18	0/19	1/19	2/19	1/19	1/19	2/19	2/19	3/19	2/19

n: Number of responders in the visit; N: Number of subjects in adjusted intent-to-treat set with assessments up to the visit

Figure 1. Observed data for (A) Change from Baseline in PASI Score from W12 to W19, in the PBO and 24 µg/kg Cohorts. The proportion of patients who achieved (B) PASI50 and (C) PASI75 response up to W19 in the PBO and 24 µg/kg Cohorts.



Week	1	2	3	4	8	12
PBO, n/N	4/5	5/5	4/5	5/5	4/5	5/5
24 µg/kg LY3471851, n/N	16/21	18/21	16/21	14/21	12/21	11/21

Week	1	2	3	4	8	12
PBO, n/N	3/5	2/5	4/5	4/5	2/5	4/5
24 µg/kg LY3471851, n/N	16/21	14/21	13/21	11/21	9/21	7/21

Figure 2. Change from baseline in (A) total Treg cells and (B) CD25bright Treg cells in the PBO and 24 µg/kg Cohorts. Samples taken at WK 2, 4, 8 and 12 are trough samples and samples taken at WK 1 and 3 correspond to approximate LY Cmax.