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

P1611

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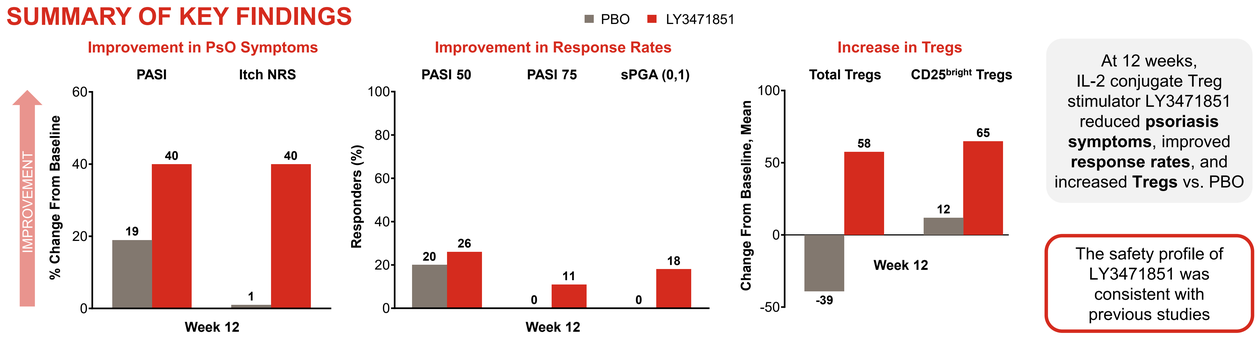
BACKGROUND

- Impaired interleukin (IL)-2 production and dysfunction in regulatory T cell (Treg) biology contribute to the pathogenesis of multiple autoimmune and inflammatory diseases, including psoriasis (Pso)[1]
- Patients with PsO have shown a decrease in either Treg numbers or immunosuppressive functions of Tregs[1]
- LY3471851 (NKTR-358; rezpegaldesleukin) is a polyethylene glycol conjugate of recombinant human IL-2 that, in human studies, has been shown to selectively stimulate Treg expansion and suppressive function[2,3]

OBJECTIVE

- To report the efficacy, safety, and biologic effects of LY3471851 in a Phase 1b, double-blind, placebo-controlled study (NCT04081350) of patients with PsO

SUMMARY OF KEY FINDINGS



At 12 weeks, IL-2 conjugate Treg stimulator LY3471851 reduced **psoriasis symptoms**, improved **response rates**, and increased **Tregs** vs. PBO

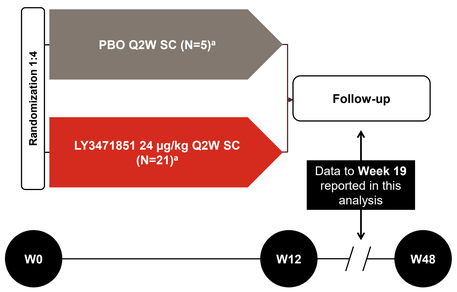
The safety profile of LY3471851 was consistent with previous studies

CONCLUSIONS

- The IL-2 conjugate Treg stimulator, LY3471851, showed a safety profile consistent with previous studies[3]
- In patients treated with LY3471851:
  - Treg numbers increased
  - PASI, sPGA scores, and Itch NRS improved over the treatment period
  - PASI improvement was maintained after drug withdrawal up to Week 19

METHODS

Study Design



[a] Total of 7 doses/patient

Key Eligibility Criteria

- Age 18-70 years
- Plaque PsO involving ≥10% body surface area in the affected skin[a]
- Candidates for systemic therapy or phototherapy
- ≥2 similar and evaluable lesions
- Static Physician's Global Assessment (sPGA) score ≥3
- Psoriasis Area and Severity Index (PASI) ≥12

[a] Other than the face and scalp

Assessments

- Efficacy: PASI, sPGA, and Itch Numeric Rating Scale (NRS)
- Safety: Treatment-emergent adverse effects and injection site reactions
- Pharmacodynamics: Flow cytometry and epigenetic markers

Statistical Analysis

- Observed data were summarized using descriptive statistics

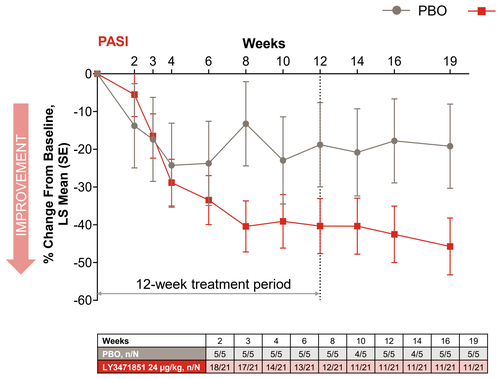
RESULTS

Demographics and Baseline Characteristics

	PBO (N=5)	LY3471851 24 µg/kg (N=21)
Age, years	42.6 (15.1)	47.5 (13.4)
Sex, n (%)		
Female	2 (40.0)	9 (42.9)
Male	3 (60.0)	12 (57.1)
Race, n (%)		
White	5 (100)	14 (66.7)
Black	0	2 (9.5)
Asian	0	3 (14.3)
American Indian or Alaska Native	0	1 (4.8)
Other	0	1 (4.8)
Ethnicity, n (%)		
Hispanic or Latino	0	2 (9.5)
Not Hispanic or Latino	5 (100)	19 (90.5)
PASI	31.6 (8.0)	29.3 (6.2)
sPGA score	3.4 (0.6)	3.2 (0.4)
Itch NRS	6.2 (3.0)	7.9 (1.9)
Prior medications, n (%)	4 (80.0)	16 (76.2)

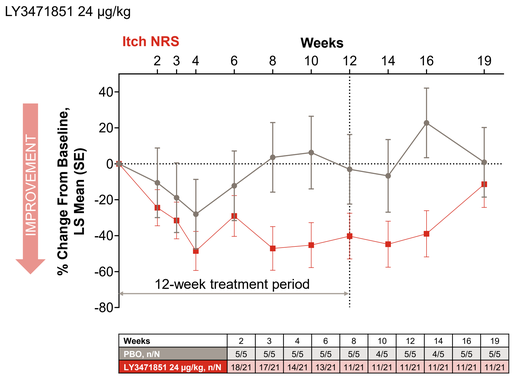
Data are mean (SD) unless stated otherwise

PASI Improved With LY3471851 vs. PBO and Was Maintained up to Week 19



Weeks	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
LY3471851 24 µg/kg, n/N	18/21	17/21	14/21	13/21	12/21	11/21	11/21	11/21	11/21	11/21

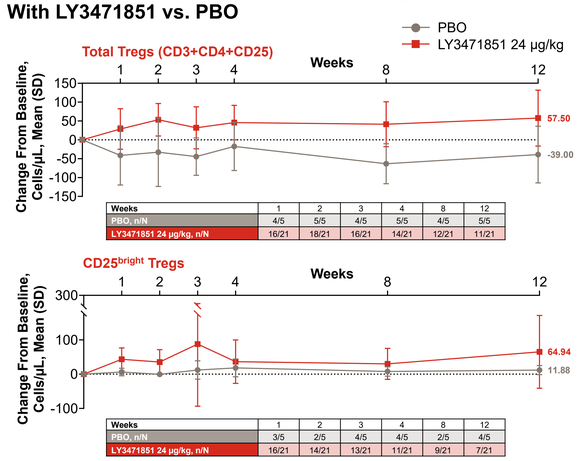
At Week 12, Itch NRS Improved With LY3471851 vs. PBO



Weeks	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
LY3471851 24 µg/kg, n/N	18/21	17/21	14/21	13/21	11/21	11/21	11/21	11/21	11/21	11/21

Note: n=number of patients with assessments at the visit; N=number of patients in the adjusted Intent-to-Treat set with assessments up to the visit

At Week 12, Total Tregs and CD25^{bright} Tregs Increased With LY3471851 vs. PBO

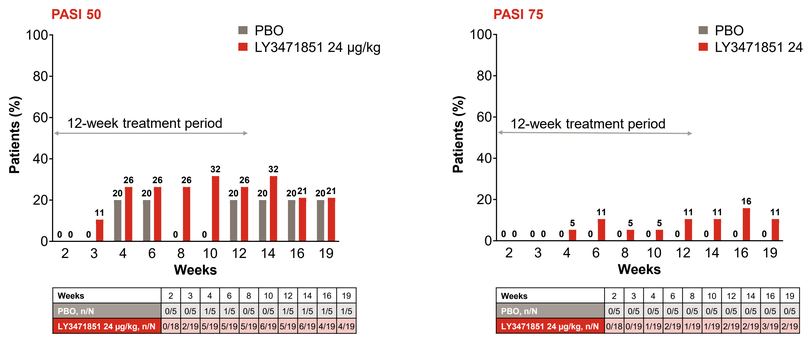


Weeks	1	2	3	4	8	12
PBO, n/N	4/5	5/5	4/5	5/5	4/5	5/5
LY3471851 24 µg/kg, n/N	16/21	18/21	16/21	14/21	12/21	11/21

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

Notes: n=number of patients with assessments at the visit; N=number of patients in the pharmacodynamic analysis set with assessments up to the visit. Samples taken at Weeks 2, 4, 8, and 12 are trough samples, and samples taken at Weeks 1 and 3 correspond to approximate LY3471851 maximum drug concentration (C_{max})

At Week 12, 26% of LY3471851-Treated Patients Achieved PASI 50 and 11% Achieved PASI 75; Response Rates Were Maintained up to Week 19

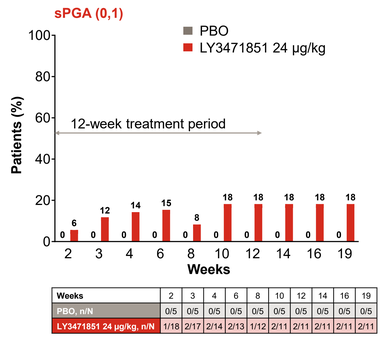


Weeks	2	3	4	6	8	10	12	14	16	19
PBO, n/N	0/5	0/5	1/5	1/5	0/5	0/5	1/5	1/5	1/5	1/5
LY3471851 24 µg/kg, n/N	0/18	2/19	5/19	5/19	5/19	6/19	5/19	6/19	4/19	4/19

Weeks	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
LY3471851 24 µg/kg, n/N	0/18	0/19	1/19	2/19	1/19	1/19	2/19	2/19	3/19	2/19

Note: n=number of responders at the visit; N=number of patients in the adjusted Intent-to-Treat set with assessments up to the visit

At Week 12, sPGA Scores Improved With LY3471851 vs. PBO



Weeks	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
LY3471851 24 µg/kg, n/N	1/18	2/17	2/14	2/13	1/12	2/11	2/11	2/11	2/11	2/11

AEs and Injection Site Reactions

AEs, n (%) # Events	PBO (N=5)	LY3471851 24 µg/kg (N=21)
AEs	0	14 (66.7) 34
Infections and infestations	0	6 (28.6) 7
General disorders and administration site conditions	0	4 (19.0) 8
Skin and subcutaneous tissue disorders	0	3 (14.3) 3
Blood and lymphatic system disorders	0	2 (9.5) 3
Investigations (eosinophil count increased)	0	2 (9.5) 2
Musculoskeletal and connective tissue disorders	0	2 (9.5) 5
Respiratory, thoracic and mediastinal disorders	0	2 (9.5) 2
Gastrointestinal disorders	0	1 (4.8) 2
Neoplasms benign, malignant and unspecified[a]	0	1 (4.8) 1
Renal and urinary disorders	0	1 (4.8) 1
Severe AEs	0	1 (4.8) 1[a]
SAEs	0	0
Deaths	0	0
AEs leading to study discontinuation	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[b]	0	1 (4.8) 1
Injection site reactions,[c] # events	0	28

[a] Exacerbation of psoriasis; [b] Including cysts and polyps; [c] Solicited reports

- The majority of injection site reactions were mild or moderate in severity

REFERENCES

1. Nussbaum L, et al. *Br J Dermatol*. 2021;184:14-24.
2. Dixit N, et al. *J Transl Autoimmun*. 2021;4:100103.
3. Fanton C, et al. *J Transl Autoimmun*. 2022;5:100152.

ABBREVIATIONS

AE=adverse event; CD=cluster of differentiation; C_{max}=maximum drug concentration; IL=interleukin; LS=least squares; NRS=Numeric Rating Scale; PASI=Psoriasis Area and Severity Index; PASI 50/75=≥50%/75% improvement from baseline in PASI; PBO=placebo; PsO=psoriasis; Q2W=every 2 weeks; SAE=serious AE; SC=subcutaneous; SD=standard deviation; SE=standard error; sPGA=static Physician's Global Assessment; Treg=regulatory T cell; W=Week

DISCLOSURES

- **S. Forman** has served as a speaker, consultant, advisory board member, and/or investigator for: AbbVie, Aclaris, Asana BioSciences, AstraZeneca, Athenex, Celgene, Cutanea, Eli Lilly and Company, Incyte Corporation, Innovaderm Research, Novartis, Pfizer, Promius Pharma, Regeneron, UCB Pharma, Valeant Pharmaceuticals, and XBiotech; **C. Schmitz**, **A. Budelsky**, **R. Benschop**, **K. Jackson**, **H. Zou**, **P. Klekotka**, and **A. Nirula** are employees and shareholders of: Eli Lilly and Company; **B. Kotzin** and **J. Zalevsky** are employees and shareholders of: Nektar
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