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

P1242

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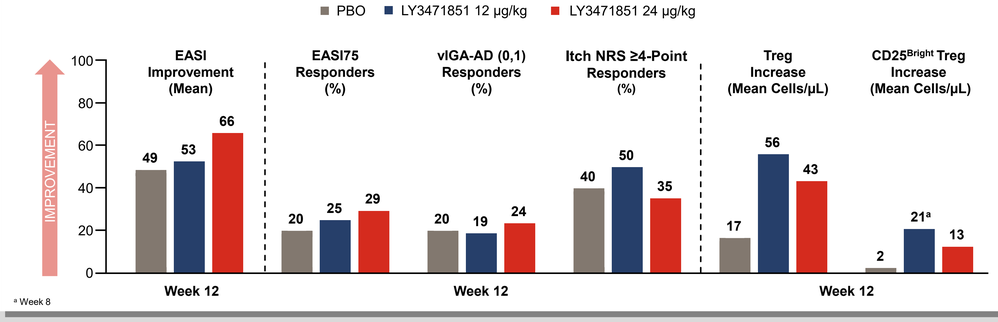
BACKGROUND

- Decreased regulatory T cell (Treg) numbers or impaired immunosuppressive function contribute to the pathogenesis of multiple autoimmune and inflammatory diseases, including atopic dermatitis (AD)[1]
- LY3471851 (NKTR-358; rezpegaldesleukin) is a polyethylene glycol conjugate of recombinant human interleukin (IL)-2 that, in human studies, has been shown to selectively stimulate Treg expansion and suppressive function[2,3]
  - This could result in beneficial clinical outcomes in patients with inflammatory diseases such as AD

OBJECTIVE

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

SUMMARY OF KEY FINDINGS



[a] Week 8

IL-2 conjugate Treg stimulator LY3471851 reduced **atopic dermatitis symptoms** and increased **Tregs** at 12 weeks vs. PBO

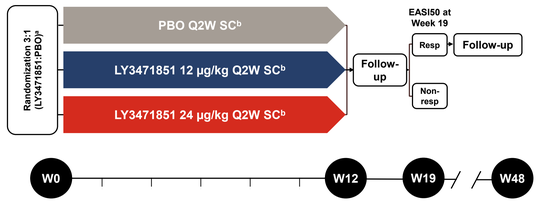
No SAEs or severe AEs were reported with LY3471851; the safety profile supports further clinical development in patients with AD

CONCLUSIONS

- The IL-2 conjugate Treg stimulator, LY3471851, had a safety profile at the doses studied that supports further clinical development of LY3471851 in patients with AD
- A trend toward dose-dependent improvement was observed in EASI and vIGA-AD scores and EASI75, vIGA-AD (0,1), and Itch NRS ≥4-point improvement responder rates with LY3471851 vs. placebo through 12 weeks of treatment
- Improvements with LY3471851 24 µg/kg were sustained during follow-up to 48 weeks
- Total Tregs and CD25^{bright} Tregs increased with LY3471851 vs. placebo up to Week 12

METHODS

Study Design[a]



[a] Full study design is not shown; the LY3471851 10 µg/kg cohort is not included in this analysis
[b] Total of 7 doses/patient

Key Eligibility Criteria

- Age 18-70 years
- Moderate-to-severe AD involving ≥10% body surface area in the affected skin
- History of inadequate response or intolerance to topical medications
- vIGA-AD™ ≥3
- Eczema Area and Severity Index (EASI) ≥16

Assessments

- Efficacy:
  - Change from baseline in EASI
  - Proportion of patients who achieved 75% improvement from baseline in EASI score (EASI75)
  - Proportion of patients who achieved vIGA-AD of 0 (clear) or 1 (almost clear)
  - Durability of vIGA-AD (0,1) response in Week 16 vIGA-AD (0,1) responders
  - Proportion of patients who achieved ≥4-point improvement in Itch Numeric Rating Scale (NRS)
- Safety: Treatment-emergent adverse effects and injection site reactions
- Pharmacodynamics: Flow cytometry and epigenetic markers

Statistical Analyses

- Analyses were from interim data cut-off of May 10, 2022 for efficacy and September 17, 2021 for pharmacodynamics and safety using descriptive statistics
- Response rates used non-responder imputation for missing data

RESULTS

Demographics and Baseline Characteristics

	PBO (N=10)[a]	LY3471851 12 µg/kg (N=16)	LY3471851 24 µg/kg (N=17)
Age, years	42.5 (19.8)	47.9 (17.5)	37.5 (16.4)
Sex, n (%)			
Female	6 (60.0)	11 (68.8)	7 (41.2)
Male	4 (40.0)	5 (31.3)	10 (58.8)
Race, n (%)			
White	6 (60.0)	11 (68.8)	14 (82.4)
Black	3 (30.0)	3 (18.8)	3 (17.6)
Asian	1 (10.0)	2 (12.5)	0
American Indian or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Other	0	0	0
Ethnicity, n (%)			
Hispanic or Latino	0	3 (18.8)	7 (41.2)
Not Hispanic or Latino	10 (100)	13 (81.3)	10 (58.8)
EASI	24.8 (7.1)	23.4 (11.3)	22.1 (6.3)
vIGA-AD, n (%)			
0 (Clear)	0	0	0
1 (Almost clear)	0	0	0
2 (Mild)	0	0	0
3 (Moderate)	5 (50.0)	9 (56.3)	11 (64.7)
4 (Severe)	5 (50.0)	7 (43.8)	6 (35.3)
Itch NRS	8.5 (1.3)	7.8 (2.1)	7.4 (2.5)
Prior medications, n (%)	10 (100)	15 (93.8)	13 (76.5)

Data are mean (SD) unless stated otherwise
[a] 1 site was terminated due to quality issues and subjects were excluded from the analyses (1 subject in the PBO group)

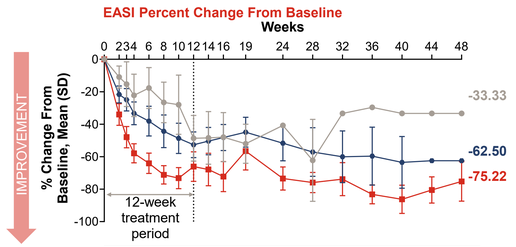
AEs and Injection Site Reactions

AEs, n (%) # Events	PBO (N=10)	LY3471851 12 µg/kg (N=16)	LY3471851 24 µg/kg (N=17)
AEs	8 (80.0) 13	9 (56.3) 16	13 (76.5) 28
Infections and infestations	2 (20.0) 2	4 (25.0) 5	7 (41.2) 11
Gastrointestinal disorders	3 (30.0) 4	1 (6.3) 1	3 (17.6) 3
Investigations[a]	0	0	4 (23.5) 4
Nervous system disorders	0	2 (12.5) 2	2 (11.8) 2
General disorders and administration site conditions	1 (10.0) 1	1 (6.3) 1	2 (11.8) 2
Eye disorders	0	2 (12.5) 2	0
Skin and subcutaneous tissue disorders	0	1 (6.3) 1	1 (5.9) 1
Musculoskeletal and connective tissue disorders	1 (10.0) 20	0	1 (5.9) 1
Postoperative wound infections	0	0	1 (5.9) 1
Renal and urinary disorders	0	0	1 (5.9) 1
Respiratory, thoracic and mediastinal disorders	0	0	1 (5.9) 1
Injury, poisoning and procedural complications	2 (20.0) 2	1 (6.3) 1	1 (5.9) 1
Metabolism and nutrition disorders	1 (10.0) 1	1 (6.3) 1	0
Gastroesophageal reflux disease	1 (10.0) 1	0	0
Blood and lymphatic system disorders	0	1 (6.3) 1	1 (5.9) 1
Injection site discoloration	0	1 (6.3) 1	0
Immune system disorders	0	1 (6.3) 1	0
Severe AEs	3 (30.0) 4	0	0
SAEs	2 (20.0) 3	0	0
Deaths	0	0	0
AEs leading to study discontinuation	0	1 (6.3) 2[b]	3 (17.6) 3[c]
Injection site reactions,[d] # events	1	43	34

[a] Increase in eosinophil count, hepatic enzymes, lymphocyte count, and weight; [b] Nausea and headache; [c] Abscess limb, eosinophil count increase, and urticaria; [d] Solicited reports

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

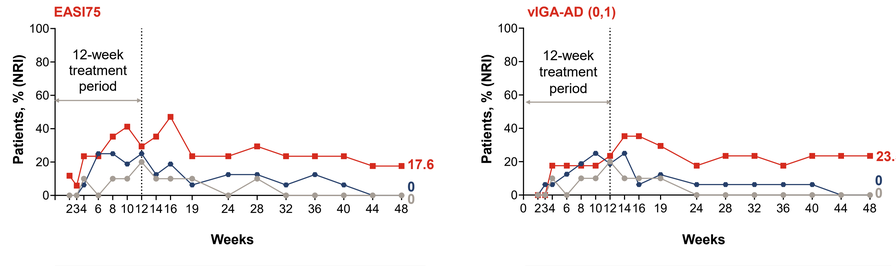
Dose-Dependent Trend in EASI Percent Change From Baseline Was Observed With LY3471851 vs. PBO up to Week 48



Weeks	0	2	3	4	6	8	10	12	14	16	19	24	28	32	36	40	44	48
PBO, n	10	8	6	8	6	8	5	6	4	4	5	1	2	1	1	1	1	1
LY3471851 12 µg/kg, n	16	16	15	15	14	14	12	12	12	12	12	7	5	4	4	3	1	1
LY3471851 24 µg/kg, n	17	16	15	14	14	13	12	11	12	12	12	7	8	8	6	6	6	6

Note: n=number of patients with assessments at the visit

Dose-Dependent Trend in EASI75 and vIGA-AD (0,1) Responders Was Seen With LY3471851 vs. PBO up to Week 48



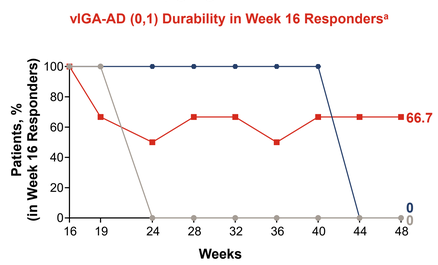
Weeks	0	2	3	4	6	8	10	12	14	16	19	24	28	32	36	40	44	48
PBO, n	10	0	0	1	0	1	1	2	1	1	1	0	1	0	0	0	0	0
LY3471851 12 µg/kg, n	16	0	0	1	4	4	3	4	2	3	1	2	2	1	2	1	0	0
LY3471851 24 µg/kg, n	17	2	1	4	4	6	7	5	6	8	4	4	5	4	4	4	3	3

Weeks	0	2	3	4	6	8	10	12	14	16	19	24	28	32	36	40	44	48
PBO, n	10	1	1	2	1	2	0	4	2	1	0	0	1	0	1	1	0	0
LY3471851 12 µg/kg, n	16	0	0	1	4	4	3	4	2	3	1	2	2	1	2	1	0	0
LY3471851 24 µg/kg, n	17	2	1	4	4	6	7	5	6	8	4	4	5	4	4	4	3	3

Note: n=number of responders

PBO (N=10) LY3471851 12 µg/kg (N=16) LY3471851 24 µg/kg (N=17)

A High Percentage of Week 16 vIGA-AD (0,1) Responders Maintained Response to Week 48 With LY3471851 24 µg/kg

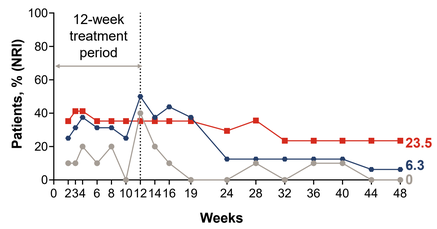


Weeks	16	19	24	28	32	36	40	44	48
PBO, n	1	1	0	0	0	0	0	0	0
LY3471851 12 µg/kg, n	1	1	1	1	1	1	1	0	0
LY3471851 24 µg/kg, n	6	4	3	4	4	3	4	4	4

Note: n=number of responders
[a] Analysis includes patients who achieved vIGA-AD (0,1) at Week 16

PBO (N=1) LY3471851 12 µg/kg (N=1) LY3471851 24 µg/kg (N=6)

Dose-Dependent Trend in Itch NRS Responders Was Seen With LY3471851 vs. PBO up to Week 48

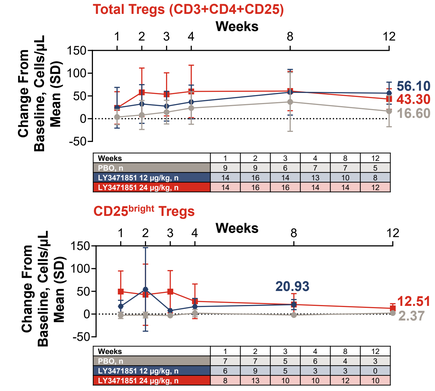


Weeks	0	2	3	4	6	8	10	12	14	16	19	24	28	32	36	40	44	48
PBO, n	10	1	1	2	1	2	0	4	2	1	0	0	1	0	1	1	0	0
LY3471851 12 µg/kg, n	16	4	5	6	5	5	4	8	6	7	6	2	2	2	2	2	1	1
LY3471851 24 µg/kg, n	17	6	7	7	6	6	6	6	6	6	5	6	4	4	4	4	4	4

Note: n=number of responders

PBO (N=10) LY3471851 12 µg/kg (N=16) LY3471851 24 µg/kg (N=17)

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



Weeks	1	2	3	4	8	12
PBO, n	9	9	6	7	7	5
LY3471851 12 µg/kg, n	14	16	14	13	10	8
LY3471851 24 µg/kg, n	14	16	16	14	14	12

Weeks	1	2	3	4	8	12
PBO, n	7	7	5	6	4	3
LY3471851 12 µg/kg, n	6	9	5	3	3	0
LY3471851 24 µg/kg, n	8	13	10	10	12	10

Notes: n=number of patients with assessments at 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})

PBO (N=11) LY3471851 12 µg/kg (N=16) LY3471851 24 µg/kg (N=17)

REFERENCES

1. Agrawal R, et al. *Curr Probl Dermatol*. 2011;41:112-124.
2. Dixit N, et al. *J Transl Autoimmun*. 2021;4:100103.
3. Fanton C, et al. *J Transl Autoimmun*. 2022;5:100152.

ABBREVIATIONS

AD=atopic dermatitis; AE=adverse event; EASI=Eczema Area and Severity Index; EASI50=50% improvement from baseline in EASI score; EASI75=75% improvement from baseline in EASI score; IL=interleukin; Non-resp=non-response; NRI=non-responder imputation; NRS=Numeric Rating Scale; PBO=placebo; Resp=response; Q2W=once every 2 weeks; SAE=serious AE; SC=subcutaneous; SD=standard deviation; Treg=regulatory T cell; W=Week

DISCLOSURES

- **S. Schleicher** has been a primary investigator for: AbbVie, Allergan, Amgen, Asana BioSciences, AstraZeneca, Castle Biosciences, Cutanea, Dignity Sciences, Dr Reddy's Laboratories, Eli Lilly and Company, Encube Ethicals, Exeltis, Ferndale Pharma Group, Foamix Pharmaceuticals, Fougera Pharmaceuticals, Galderma, Genentech, GlaxoSmithKline, Glenmark Pharmaceuticals, Helix BioMedix, IntraDerm, NFlection Therapeutics, Novan, Novartis, Oculus PharmaCare, ParaPRO, Pfizer, Quinnova Pharmaceuticals, Qurient, Regeneron, Sol-Gel Technologies, Taro Pharmaceutical Industries, Tolmar, Valeant Pharmaceuticals, and Vyome Therapeutics; **B. Kotzin** and **J. Zalevsky** are employees and shareholders of: Nektar; **C. Schmitz**, **A. Budelsky**, **R. Benschop**, **K. Jackson**, **H. Zou**, **P. Klekotka**, and **A. Nirula** are employees and shareholders of: Eli Lilly and Company
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