Eblasakimab, a Monoclonal Antibody Targeting IL-13Rα1 Reduces Serum Biomarkers Associated with Atopy and Correlated with Disease Severity in Patients With Moderate-to-Severe Atopic Dermatitis

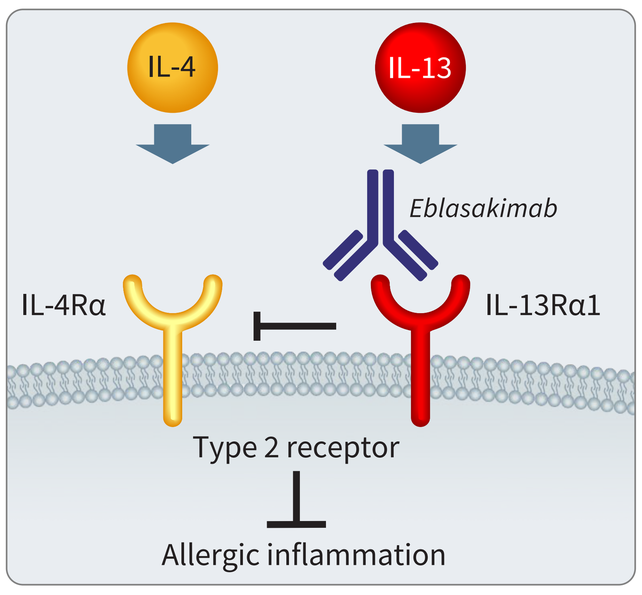
Ferda Cevikbas[1], Eric Simpson[2], Alison Ward[1], Steven Tien Guan Thng[3], Karen A. Veverka[1]

1. ASLAN Pharmaceuticals, California and Singapore. 2. Department of Dermatology, Oregon Health & Science University, Portland, OR, USA.
3. Skin Research Institute of Singapore, Agency for Science Technology & Research, Singapore; National Skin Center, Singapore

Background

- Key inflammatory mediators of atopic dermatitis (AD) include interleukin (IL)-4 and IL-13, which both signal through a shared type 2 receptor, a heterodimer comprising IL-4Rα and IL-13Rα1.[1,2]
- Eblasakimab, a first-in-class, fully human monoclonal antibody binds IL-13Rα1 with high affinity and blocks the signaling of IL-4 and IL-13 through the type 2 receptor[3] (Figure 1).
- Elevated serum levels of specific biomarkers are associated with increased disease severity and exacerbations of AD.[4-8]
  - These biomarkers include thymus and activation regulated chemokine (TARC/CCL17), total immunoglobulin E (IgE), lactate dehydrogenase (LDH).
  - Reference range levels for these biomarkers in individuals without AD have been reported in the range of:
    - » TARC/CCL17: 200 pg/mL[9]
    - » Total IgE: 150 to 1,000 UI/mL (usually accepted upper limit is between 150 and 300 UI/mL)[10]
    - » LDH: 105 to 333 U/L.[11]
  - TARC/CCL17 is a chemokine involved in developing acute and chronic lesions in AD and serves as a biomarker for disease severity.[12]
  - IgE binds several immune cells and plays a role in the release of inflammatory mediators and antigen presentation in AD.[5]
  - LDH is an enzyme found in most cells and is known to be a marker of inflammation, but it also has been shown to correlate with levels of TARC/CCL17 and total IgE in patients with AD.[7]
- In a recent randomized multiple ascending dose (MAD) study [NCT04090229] eblasakimab demonstrated significant improvements in key measures of disease severity vs. placebo in patients with moderate-to-severe AD.[13]
- Clinically relevant primary and secondary endpoint data are presented separately.
- In the same study, pharmacodynamic assessments were performed to analyze AD biomarker levels in response to eblasakimab treatment in patients with moderate-to-severe AD.

Figure 1. Eblasakimab Mechanism of Action



Eblasakimab binds to and blocks the IL-13 receptor α1 subunit (IL-13Rα1), one of the Type 2 receptor components, thereby preventing signaling through both interleukin 4 (IL-4) and interleukin 13 (IL-13), key drivers of allergic inflammation in atopic dermatitis.
IL-4, Interleukin-4; IL-4Rα, interleukin-4 receptor α; IL-13, interleukin-13; IL-13Rα1, interleukin-13 receptor α1 subunit

Objective

- To investigate the pharmacodynamic effect of weekly eblasakimab administration on biomarkers of allergic inflammation (TARC/CCL17, total IgE and LDH) in patients with moderate-to-severe AD.

Results

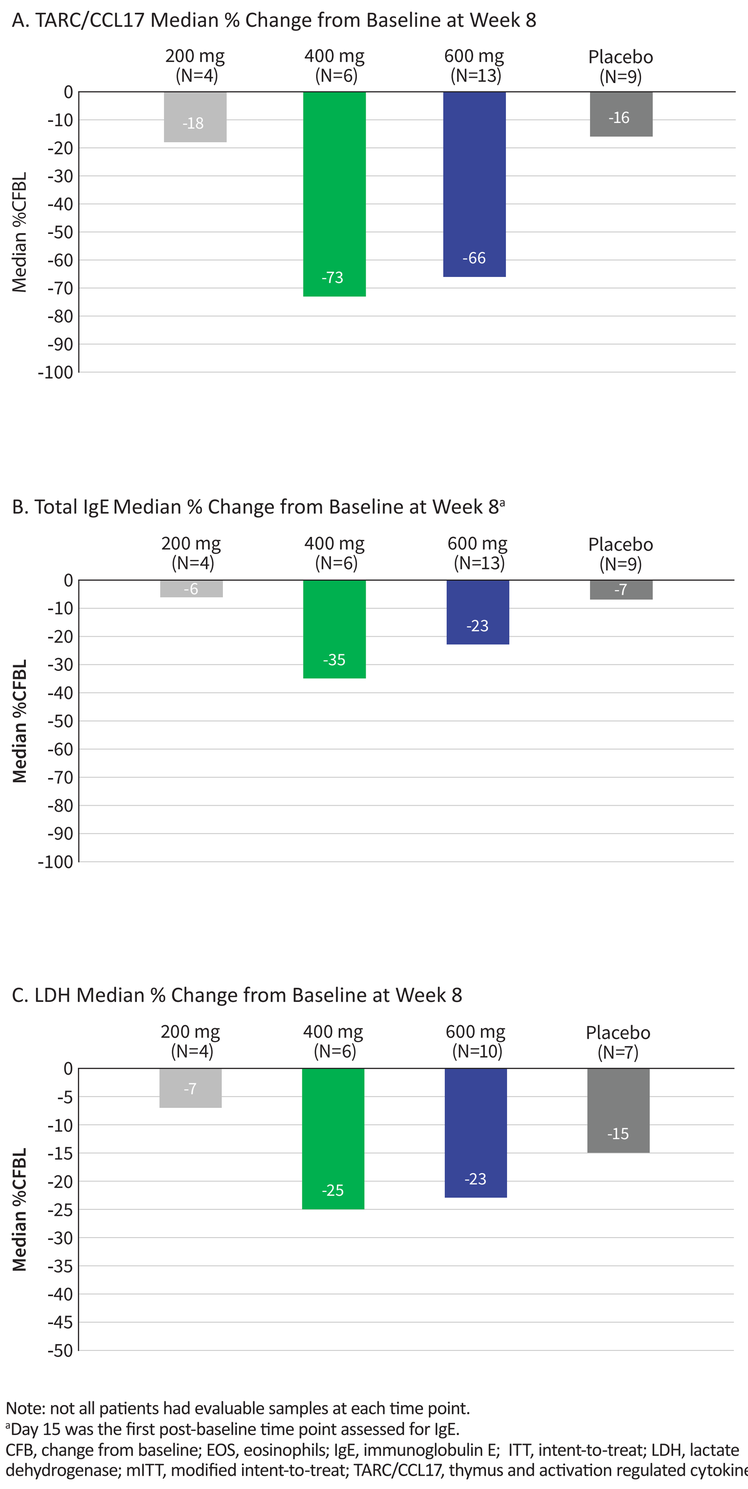
Table 1. Patient Demographics and Baseline Characteristics

		Eblasakimab 200 mg (N=4)	Eblasakimab 400 mg (N=7)	Eblasakimab 600 mg (N=16)	Placebo (N=13)
Age, Mean (SD)		32.5 (5.3)	29.4 (4.9)	34.0 (13.4)	34.2 (11.3)
Male, n (%)		3 (75.0%)	5 (71.4%)	12 (75.0%)	10 (76.9%)
Race, n (%)	Asian	4 (100%)	7 (100%)	7 (43.8%)	8 (61.5%)
	Black	0	0	1 (6.2%)	0
	White	0	0	8 (50.0%)	3 (23.1%)
	Other	0	0	0	2 (15.4%)
Ethnicity, n (%)	Not Hispanic or Latino	4 (100%)	7 (100%)	15 (93.8%)	13 (100.0%)
BMI (kg/m²), Mean		25.8 (3.0)	25.3 (5.1)	26.3 (8.3)	25.8 (4.9)
Total IgE (kU/L)[a,b]	Mean (SD) Median	15,891 (14,993) 12,278	23,297 (28,508) 10,660	8,660 (7,178) 6,468	8,706 (8,175) 7173
TARC/CCL17 (pg/mL)[b]	Mean (SD) Median	6,097 (6,247) 5,556	18,310 (40,556) 2262	4,223 (5,186) 2128	5,056 (6,842) 2398
LDH (U/L)	Mean (SD)[c,d] Median	571.8 (378.07) 429	679.1 (255.46) 687	418.9 (290.32) 306	432.4 (187.07) 419

BMI, body mass index; IgE, immunoglobulin E; TARC/CCL17, thymus and activation regulated chemokine, LDH, lactate dehydrogenase, SD, standard deviation.
[a]kU/L=IU/mL [b]eblasakimab 600 mg (N=14), Placebo (N=12) [c]Data are derived from the full analysis set from the safety population for LDH [d]eblasakimab 200 mg (N=5), eblasakimab 400 mg (N=8), Placebo (N=14)

- A total of 40 patients were included in the analysis and received either eblasakimab at 200 mg (N=4), 400 mg (N=7), 600 mg (N=16), or placebo (N=13) (**Table 1**).
- Patient demographics and baseline characteristics were generally similar across dose cohorts, with a slightly younger population in the 400 mg group, a higher proportion of Asian patients in the 200 mg and 400 mg groups, and some differences in the level of elevation of biomarkers, particularly for TARC/CCL17 and total IgE (**Table 1**).
- Eblasakimab reduced levels of pharmacodynamic markers IgE, TARC/CCL17, and LDH in the 400 mg and 600 mg dose groups after 8 weeks of once-weekly treatment, with a significant difference between 600 mg vs. placebo for TARC/CCL17 (least squares [ls] mean of -62.23 vs -17.83, *P*<0.001) (**Figure 2A-C**).
  - Reductions from baseline were observed as early as the first post- baseline assessment for TARC/CCL17 (day 4), IgE (day 15) and LDH (day 15).
  - In general, serum biomarkers remained suppressed in the eblasakimab groups for 4-6 weeks following the last dose.
  - End-of-study values for total IgE and TARC/CCL17 were no different than placebo, a trend also observed for LDH (data not shown).

Figure 2. Changes from Baseline to Week 8 in AD Biomarkers



Note: not all patients had evaluable samples at each time point.
[a]Day 15 was the first post-baseline time point assessed for IgE.
CFB, change from baseline; EOS, eosinophils; IgE, immunoglobulin E; ITT, intent-to-treat; LDH, lactate dehydrogenase; mITT, modified intent-to-treat; TARC/CCL17, thymus and activation regulated cytokine.

Methods

- A placebo-controlled, double-blind, multiple ascending dose Phase 1b study was conducted in which patients with moderate-to-severe AD received either eblasakimab (200, 400, 600 mg) or placebo administered subcutaneously once weekly for 8 weeks, with a 12-week safety follow-up period.
- Key inclusion criteria were:
  - Chronic AD present for ≥3 years before screening visit
  - Eczema Area and Severity Index score ≥16 at screening and baseline
  - Investigator Global Assessment score ≥3 (scale of 0 to 4) at screening and baseline
  - ≥10% body surface area of AD involvement at screening and baseline
- Blood samples were taken at pre-specified time points to assess levels of TARC/CCL17, total IgE, and LDH.
  - TARC/CCL17 levels were measured in duplicate using an enzyme-linked immunosorbent assay (ELISA) assay.
  - Total IgE concentrations were determined in duplicate using the validated ImmunoCap Total IgE assay (Thermo Fisher Scientific).
  - LDH was determined as part of routine laboratory safety monitoring.
  - Samples were analyzed and reported by a local testing laboratory following their protocols and procedures.
- Mean percent changes from baseline in levels of each biomarker are reported.
  - Inferential statistical analysis was performed for TARC/CCL17 and IgE for 600 mg vs. placebo groups at Week 8 only using an ANCOVA model fitting the Week 8 %CFBL as the response variable, and treatment (eblasakimab or placebo) and the baseline biomarker score as covariates, with a prespecified 1-sided 5% significance level.
  - Results for LDH as well as for the 200 mg and 400 mg groups for TARC and IgE were descriptively described due to small sample size.

Conclusion

- In this small Phase 1b multiple ascending dose study, eblasakimab, a monoclonal IL-13Rα1 directed antibody, reduced circulating levels of AD-associated pharmacodynamic biomarkers TARC/CCL17, total IgE and LDH.
  - In this study, biomarker responses were greatest in the 400 mg and 600 mg dose groups and were not further reduced at the higher dose group.
  - Among the biomarkers analyzed, TARC/CCL17 and LDH showed the greatest decrease from baseline levels with eblasakimab treatment.
  - This general suppression of biomarker levels supports the clinical responses and improvements in patient-reported outcomes observed in this trial, as evidenced by reductions in measures of AD severity[13] (reported separately, poster WCD), itch and sleep loss (reported separately, poster WCD).
  - Limitations of the analysis include differences in baseline levels of biomarkers between groups, small n values, the presence of outliers, and a non-homogenous patient population.
- These biomarker results are consistent with findings in the literature reported for other approved AD treatments[14] and show the utility of these markers for characterizing reductions in disease severity in a moderate-to-severe AD population.
- These data along with the clinical results of the trial support the further investigation of eblasakimab for the treatment of moderate-to-severe AD.
- A Phase 2b dose-finding trial is currently underway to evaluate the safety and efficacy of eblasakimab to treat moderate-to-severe atopic dermatitis.

References: 1. Dubin C, *et al. Expert Rev Clin Immunol.* 2021;17(8):835-852. **2.** Junttila IS. *Front Immunol.* 2018;9:888. **3.** Redpath NT, *et al. Biochem J.* 2013;451(2):165-175. **4.** Liddiard K, *et al. BMC Mol Biol.* 2006;7:45. **5.** Wollenberg A, *et al. World Allergy Organ J.* 2021;14(3):100519. **6.** Punnonen J, *et al. J Allergy Clin Immunol.* 1997;100(6 Pt 1):792-801.**7.** Kogawa K, *et al. J Cutan Immunol Allergy.* 2022;5:133–135. **8.** Simon D, *et al. Allergy.* 2004;59(6):561-570. **9.** Kakinuma, T, *et al. J Allergy Clin Immunol.* 2001;107(3):535-541. **10.** Laurent, J, *et al. Ann Med Interne* (Paris). 1985;136(5):419-422. **11.** https://www.ucsfhealth.org/medical-tests/lactate-dehydrogenase-test#:~:text=Normal%20Results,vary%20slightly%20among%20different%20laboratories. **12.** Kataoka Y. *J Dermatol.* 2014 Mar;41(3):221-9. **13.** Blauvelt A, *et al. American Academy of Dermatology*; 2022; Boston, MA. **14.** Hamilton, JD, *et al. Clin Exp Allergy.* 2021;51(7):915-931.

Acknowledgement: This study was funded by ASLAN Pharmaceuticals LTD. The authors thank the patients and other investigators who participated in this study.
Sponsor: ASLAN Pharmaceuticals Ltd.