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

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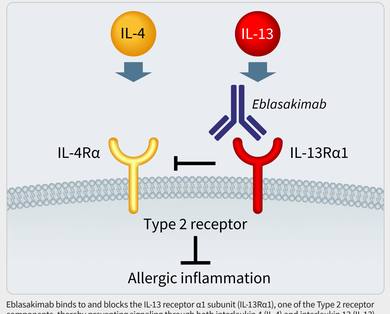
BACKGROUND

- Key inflammatory mediators of atopic dermatitis (AD) include interleukin-4 (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 atopic dermatitis.[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 in poster #P0343, while patient reported outcomes are presented in poster #P0342.
- 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

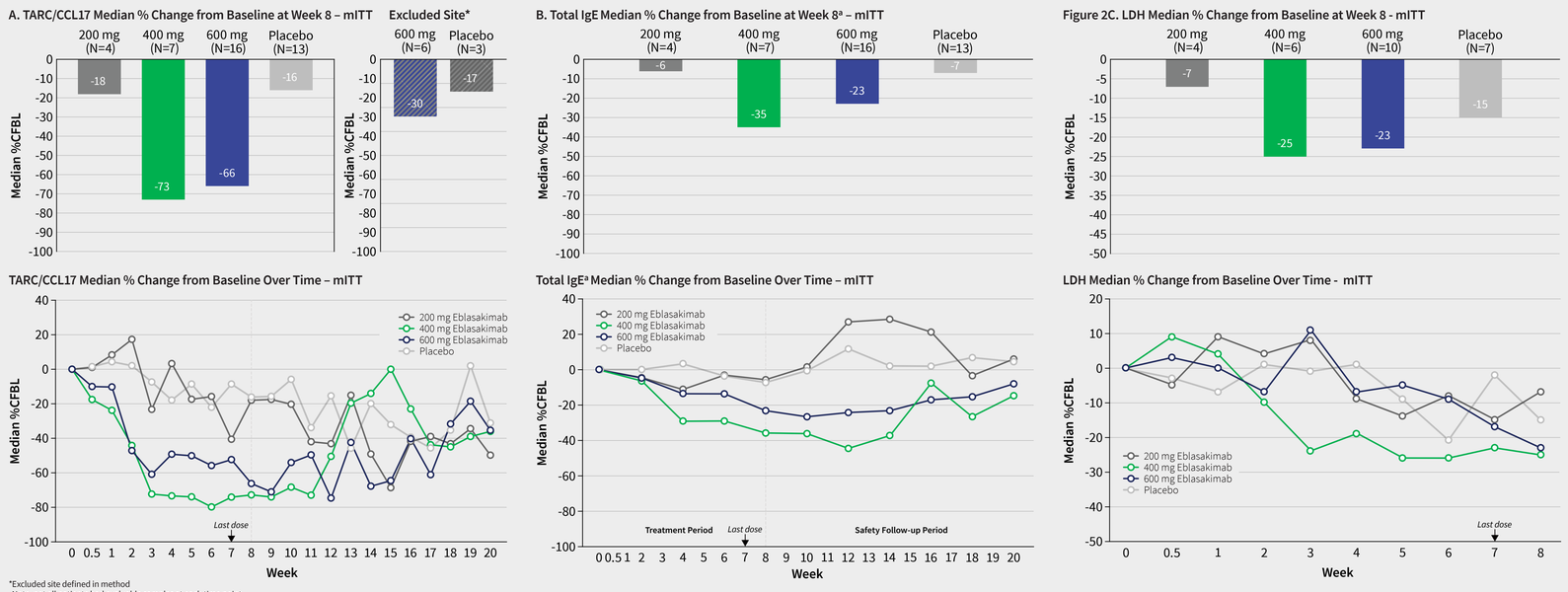
- A total of 40 patients were included in the mITT population analysis and received either eblasakimab at 200 mg (N=4), 400 mg (N=7), 600 mg (N=16), or placebo (N=13) (**Table 1**).
- Patient demographics and baseline characteristics for the mITT population were generally similar across dose cohorts, 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**).
- The Excluded site* set was markedly different from the mITT set at baseline with substantially lower serum TARC/CCL17 (**Table 1**), serum IgE (**Table 1**), and EASI scores (Poster #0343) showing lower extent and severity of disease. Other notable differences included older age and lower IGA and BSA. Participants at this site had no atopic disease history but reported other comorbidities including diabetes and hypertension (Poster #0342).
- Baseline biomarker levels from the Excluded site* were, on average, within the reference range for individuals without AD, except for TARC/CCL17 levels, which were slightly elevated (**Table 1**).
- In the mITT population, 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).
- At the Excluded site*, median % changes from baseline in total IgE, TARC/CCL17, and LDH level with 600 mg eblasakimab were substantially less than those of the corresponding mITT 600 mg dose group and similar to placebo at week 8 (P=0.272 vs. placebo for TARC/CCL17; **Figure 2A** and data not shown).

Table 1. Patient Demographics and Baseline Characteristics

		mITT				Excluded site*	
		Eblasakimab 200mg (N=4)	Eblasakimab 400mg (N=7)	Eblasakimab 600mg (N=16)	Placebo (N=13)	Eblasakimab 600mg (N=6)	Placebo (N=3)
Age, Mean (SD)		32.5 (5.26)	29.4 (4.89)	34.0 (13.39)	34.2 (11.27)	56.7 (17.92)	59.0 (22.27)
Male, n (%)		3 (75.0%)	5 (71.4%)	12 (75.0%)	10 (76.9%)	1 (16.7%)	1 (33.3%)
Race, n (%)	Asian	4 (100%)	7 (100%)	7 (43.8%)	8 (61.5%)	0	0
	Black	0	0	1 (6.2%)	0	1 (16.7%)	0
	White	0	0	8 (50.0%)	3 (23.1%)	5 (83.3%)	3 (100.0%)
	Other	0	0	0	2 (15.4%)	0	0
Ethnicity, n (%)	Not Hispanic or Latino	4 (100%)	7 (100%)	15 (93.8%)	13 (100.0%)	0	2 (66.7%)
BMI (kg/m^2), Mean		25.8 (2.95)	25.3 (5.08)	26.3 (8.23)	25.8 (4.88)	30.8 (6.17)	25.2 (1.98)
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	677 (1,124) 268	76 (88) 76
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	466 (340) 366	446 (244) 446
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	180.3 (37.69) 173	143.3 (36.30) 138

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]mITT: eblasakimab 600 mg (n=14), Placebo (n=12); Excluded site: Placebo (n=2)
[c]Data are derived from the full analysis set from the safety population for LDH
[d]mITT: eblasakimab 200 mg (n=5), eblasakimab 400 mg (n=8), Placebo (n=14); Excluded site: Placebo (n=2)

Figure 2. Changes from Baseline to Week 8 in Atopic Dermatitis Biomarkers



*Excluded site defined in method
Note: not all patients had evaluable samples at each time point.
[a]Day 15 was the first post-baseline time point assessed for IgE.
[b]Data are derived from the full analysis set from the safety population for LDH and EOS.
[c]Data collected to Week 8
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.

CONCLUSIONS

- 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] (see also Poster #P0343), itch and sleep loss (see Poster #P0342).
  - 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.

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.
- Analyses were performed on 3 populations:
  - Modified intent-to-treat population (mITT) – the intent-to-treat population excluding 9 patients at one clinical site that were markedly different from the mITT set at baseline (see next bullet) and were excluded in a pre-specified sensitivity analysis that was defined prior to unblinding.
  - *Excluded site- Further data are presented from a prespecified subgroup of patients from an excluded site with atypical AD. This excluded site consisted of the 9 patients noted above at one clinical site that were markedly different from the mITT set at baseline due to characteristics including older age, lower scores on AD measures, lack of atopic disease history, and higher rates of diabetes and hypertension (see Posters #P0343 and #P0342).
  - Safety population- all randomized patients who received at least 1 dose of study drug.
- 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 and 400 mg groups for TARC and IgE were descriptively described due to small sample size.

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AUTHOR DISCLOSURES

F. Cevikbas and K.A. Veverka are employees of ASLAN Pharmaceuticals; A. Ward is a former employee of ASLAN Pharmaceuticals. J.P. Thyssen is an advisor for AbbVie, Almirall, Arena Pharmaceuticals, Coloplast, OM Pharma, Aslan Pharmaceuticals, Union Therapeutics, Eli Lilly & Co, LEO Pharma, Pfizer, Regeneron, and Sanofi-Genzyme, a speaker for AbbVie, Almirall, Eli Lilly & Co, LEO Pharma, Pfizer, Regeneron, and Sanofi-Genzyme, and received research grants from Pfizer, Regeneron, and Sanofi-Genzyme; E. Simpson reports personal fees from AbbVie, Amgen, Arena Pharmaceuticals, ASLAN Pharmaceuticals, Boston Consulting Group, Collective Acumen, LLC (CA), Dermira, Eli Lilly, Evidera, ExcerptaMedica, Forte Bio RX, Galderma, GlaxoSmithKline, Incyte, Janssen, Kyowa Kirin Pharmaceutical Development, Leo Pharm, Medscape LLC, Merck, Pfizer, Physicians World LLC, Regeneron, Roivant, Sanofi-Genzyme, Trevi therapeutics, Valeant, WebMD (these potential conflicts of interest have been reviewed and managed by OHSU). Dr. Simpson also reports grants (or serves as Principal investigator role) from AbbVie, Amgen, Arcutis, ASLAN Pharmaceuticals, Castle Biosciences, CorEvitas, Dermavant, Dermira, Eli Lilly, Incyte, Kymab, Kyowa Hakko Kirin, Leo Pharmaceuticals, Pfizer, Regeneron, Sanofi, and Target RWE (these potential conflicts of interest have been reviewed and managed by OHSU); S.T.G. Thng holds of stock or stock options and has received funding, medical writing, and article processing charges from ASLAN Pharmaceuticals, and has participated in a Data Safety Monitoring." Board.