Neutralizing interleukin-13 with tralokinumab reduces abundance of *S. aureus* in adolescents with atopic dermatitis

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Objectives

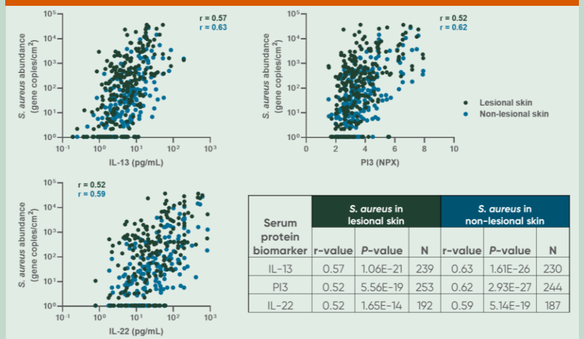
- To assess *S. aureus* abundance in lesional and non-lesional skin of adolescents with moderate-to-severe AD in the ECZTRA 6 trial
- To determine the impact of IL-13 neutralization on *S. aureus* abundance in adolescents with AD

Results

S. aureus abundance by key biomarkers at baseline

- *S. aureus* abundance (gene copies/cm^2) strongly positively correlated with AD-associated serum biomarkers IL-13, IL-22, and Elafin/PI3 at baseline in both lesional and non-lesional skin (**Figure 2**)

Figure 2. Correlation of *S. aureus* abundance and relevant biomarkers at baseline in lesional and non-lesional skin

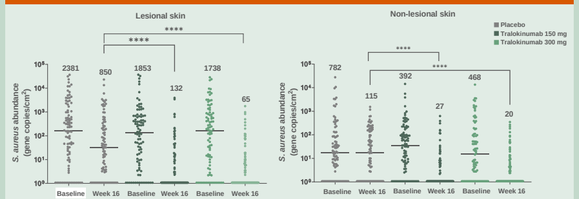


Serum protein biomarker	*S. aureus* in lesional skin			*S. aureus* in non-lesional skin		
	r-value	*P*-value	N	*r*-value	*P*-value	N
IL-13	0.57	1.06E-21	239	0.63	1.61E-26	230
PI3	0.52	5.56E-19	253	0.62	2.93E-27	244
IL-22	0.52	1.65E-14	192	0.59	5.14E-19	187

Effect of tralokinumab treatment on *S. aureus* abundance and status

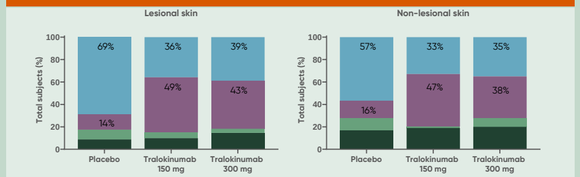
- *S. aureus* abundance (gene copies/cm^2) was significantly lower at Week 16 in both lesional and non-lesional skin of patients receiving tralokinumab (150 mg and 300 mg) compared to those receiving placebo (**Figure 3**)
- From baseline to Week 16, 49% of patients receiving tralokinumab 150 mg and 43% of patients receiving tralokinumab 300 mg went from *SA*$^+$ to *SA*$^-$ lesional skin, compared to 14% receiving placebo (**Figure 4**)
  - Similar reductions were observed in the percentage of tralokinumab-treated patients with *SA*$^+$ non-lesional skin

Figure 3. *S. aureus* abundance in lesional and non-lesional skin



****P<0.0001 for Mann-Whitney test comparing median values at Week 16 between treatment groups. Dots represent individual patients; line shows median; values above are mean.

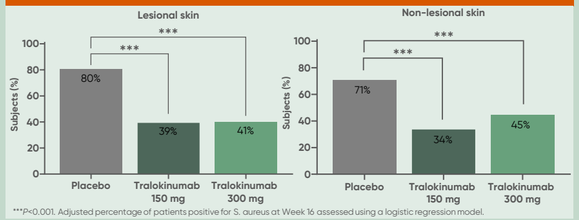
Figure 4. Change in *S. aureus* status in lesional and non-lesional skin from baseline to Week 16



Percentage of patients with *S. aureus* values at both baseline and Week 16 by *S. aureus* status.

- At Week 16, after adjusting for baseline *S. aureus* status and any rescue use, the percentage of tralokinumab-treated (both 150 mg and 300 mg) patients who were *SA*$^+$ was significantly lower compared to placebo in both lesional and non-lesional skin (**Figure 5**)
- A higher proportion of patients negative for *S. aureus* at baseline achieved EASI-75 at Week 16, however tralokinumab treatment improved AD severity regardless of baseline *S. aureus* status relative to placebo (**Table 2**)
- There was a positive correlation between reduction in *S. aureus* abundance and improvement in EASI from baseline to Week 16 (**Figure 6**)

Figure 5. Patients positive for *S. aureus* in lesional and non-lesional skin at Week 16

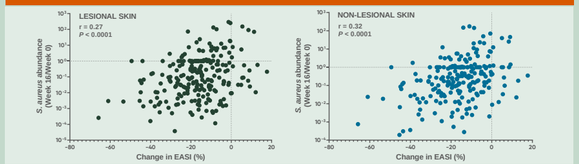


***P<0.001. Adjusted percentage of patients positive for S. aureus at Week 16 assessed using a logistic regression model.

Table 2. EASI response at Week 16 in patients according to baseline *S. aureus* abundance

SA status at baseline	Tralokinumab 150 mg		Tralokinumab 300 mg		Placebo	
	Negative (N=15)	Positive (N=76)	Negative (N=13)	Positive (N=70)	Negative (N=13)	Positive (N=75)
EASI at baseline	20.1	32.0	27.0	27.9	18.6	27.3
EASI at Week 16	3.6	10.4	4.0	8.0	5.8	16.4
EASI change	-16.9	-18.1	-21.5	-15.6	-12.0	-10.6
EASI % change	-79.2	-65.4	-83.5	-67.7	-71.4	-39.3
EASI-75 (%)	60.0	37.1	53.8	39.7	38.5	20.3

Figure 6. Change in *S. aureus* abundance compared to change in EASI from baseline to Week 16 in lesional and non-lesional skin



Background

- Patients with atopic dermatitis (AD) are frequently colonized with high levels of *S. aureus*[1]
- Both epidermal barrier disruption and type 2 inflammation are thought to contribute to this dysbiosis in patients with AD[2]
- Tralokinumab is a high-affinity, monoclonal antibody that targets IL-13, a key driver of type 2 inflammation
- ECZTRA 6 evaluates the efficacy, safety, and tolerability of tralokinumab monotherapy in adolescent patients aged 12 to <18 years with moderate-to-severe AD who are candidates for systemic therapy in a randomized, double-blind, placebo-controlled, parallel-group, multi-center trial
- We evaluated effects of tralokinumab on skin *S. aureus* abundance in adolescents with moderate-to-severe AD in the Phase 3 ECZTRA 6 trial (NCT03526861)

Materials and Methods

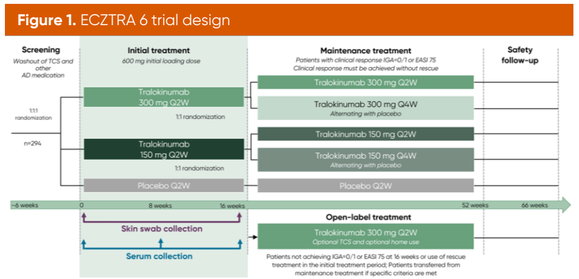
Study design, sample collection, and analyses

- Adolescent patients (aged 12–17 years) were randomized (1:1:1) to receive subcutaneous tralokinumab 150mg or 300mg every 2 weeks (Q2W), or placebo (**Figure 1**)
- Skin swabs collected from 5x10 cm areas of lesional and non-lesional skin on upper extremities, lower extremities, or trunk at baseline and Week 16
- *S. aureus* abundance was assessed by *femA* qPCR

Statistical analyses

- Differences in percentage of subjects positive for *S. aureus* (*SA*$^+$; defined as >1.07 gene copies/cm^2) at Week 16 (tralokinumab 150mg/300mg vs placebo) were assessed using a logistic regression model adjusting for baseline *SA* status and rescue use (any TCI, TCS, or systemic treatment
- Statistical significance of *S. aureus* abundance in lesional and non-lesional skin was calculated using nonparametric Mann-Whitney test using the difference between medians
- Subjects with a baseline *S. aureus* value were included in the analyses
- All statistical tests and *P*-values are nominal

Figure 1. ECZTRA 6 trial design



Conclusions

- In this Phase 3 study in adolescents aged 12–17 years, baseline *S. aureus* abundance strongly positively correlated with levels of key serum biomarkers
- Tralokinumab treatment led to a nominally significant reduction in *S. aureus* abundance and *S. aureus* positive subjects at Week 16
- These data suggest that specific targeting of IL-13 is effective in reducing *S. aureus* abundance in adolescents with moderate-to-severe AD

Baseline and Disease Characteristics

- Baseline demographics and disease characteristics were largely balanced between treatment groups (**Table 1**)

Table 1. Baseline demographics and clinical characteristics

	Tralokinumab 150 mg Q2W (N=98)	Tralokinumab 300 mg Q2W (N=97)	Placebo (N=94)
Mean age, years	14.8	14.6	14.3
Age group, n (%)			
12–14	37 (37.8)	45 (46.4)	49 (52.1)
15–17	61 (62.2)	52 (53.6)	45 (47.9)
Male sex, n (%)	51 (52.0)	47 (48.5)	51 (54.3)
Mean duration of AD, years (SD)	12.7 (3.7)	12.1 (3.7)	12.1 (3.5)
Severe disease (IGA=4), n (%)	44 (44.9)	48 (49.5)	43 (45.7)
Mean EASI (SD)	32.1 (12.9)	31.8 (13.9)	31.2 (14.5)
Mean SCORAD (SD)	67.7 (14.4)	68.3 (13.7)	67.4 (14.9)
Mean CDLQI (SD)	12.9 (6.3)	13.4 (7.3)	13.3 (6.0)
Mean Weekly Average Peak Pruritus NRS (SD)	7.5 (1.6)	7.8 (1.5)	7.5 (1.7)
S. aureus			
n			
Lesional skin	92	90	92
non-lesional skin	90	86	88
Median abundance, gene copies/cm^2			
lesional skin	133.9	159.8	162.7
non-lesional skin	35.2	15.6	17.5
% *S. aureus*$^+$			
lesional skin	83.7	81.1	82.6
non-lesional skin	78.9	70.9	73.9

Abbreviations

AD, atopic dermatitis; CDLQI; Children's Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; N, number of patients with recorded observation; NRS, numerical rating scale; Q2W, every 2 weeks; Q4W, every 4 weeks; *SA*, *S. aureus*; SCORAD, SCORing Atopic Dermatitis; SD, standard deviation; TCS, topical corticosteroid.

References

1. Edslev S, *et al. Acta Derm Venereol.* 2020; 100(12):adv00164. **2.** Biedermann T, *et al. Front Immunol.* 2015;6:353.

Disclosures

LAB has been a consultant for Allakos, Arena Pharmaceuticals, DermTech, Evelo Biosciences, Galderma, Incyte, Janssen, LEO Pharma, Merck, Numab Therapeutics, Pfizer, Rapt Therapeutics, Regeneron, Ribon Therapeutics, Sanofi/Genzyme, Sanofi-Aventis, Stealth BioTherapeutics, Trevi Therapeutics, Union Therapeutics and Xencor. DMC Member: Novartis. Investigator for Abbvie, Astra-Zeneca, DermTech, Kiniksa, Pfizer, Regeneron, and Ribon Therapeutics. **SW** has been a scientific adviser for AbbVie, Almirall, Eli Lilly, GlaxoSmithKline, Kymab, LEO Pharma, Novartis, Pfizer, Regeneron, and Sanofi; has lectured at educational events sponsored by AbbVie, Almirall, Eli Lilly, Galderma, LEO Pharma, Pfizer, Novartis, Regeneron, and Sanofi; has received work-related travel support from AbbVie, LEO Pharma, and Sanofi; and has received institutional research grants from La Roche-Posay, LEO Pharma, Pfizer, and Sanofi. **MT** reports serving as an investigator for AbbVie, Boehringer Ingelheim, Eli Lilly, Galderma, LEO Pharma, Pierre Fabre, and Sanofi-Regeneron; a consultant or advisory board for AbbVie, Eli Lilly, MEDAC, and Sanofi-Regeneron. **HS** has received lecture fees from Kyorin, Kyowa Kirin, LEO Pharma, Maruho, Mitsubishi Tanabe, Sanofi, Taiho, and Tokiwa; and scholarship donations from Esai, Maruho, Mitsubishi Tanabe, and Torii. **ADI** reports personal fees (Speaker fees and Consulting fees) from AbbVie, Arena, Dermavant, Eli Lilly, LEO Pharma, Pfizer, Regeneron, and Sanofi. **LFE** has been a scientific adviser and/or clinical study investigator for AbbVie, Almirall, Asana, Aslan, Dermavant, Eli Lilly, Forte, Galderma, Glenmark, Incyte, LEO Pharma, Novartis, Ortho Dermatologics, Pfizer Inc., Regeneron, and Sanofi Genzyme. **TW** received lecture and/or consultancy fees from AbbVie, Almirall, Galderma, Eli Lilly, Janssen/JNJ, LEO Pharma, Novartis, Pfizer, and Regeneron/Sanofi. **PA**, **AK**, and **MAP** are employees of LEO Pharma A/S. **AP** has been an investigator for : AbbVie, Dermavant, Eli Lilly, and Incyte; Data Safety Monitoring Board for AbbVie and Galderma; and Consultant for Boehringer-Ingelheim, Bristol Myers Squibb, Eli Lilly, LEO Pharma, Novartis, Regeneron, Sanofi/Genzyme, and Seanergy.

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