Neutralizing interleukin-13 increases skin microbial diversity: results from a Phase 3, randomized, double-blind, placebo-controlled trial of tralokinumab in adult patients with atopic dermatitis

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Introduction

- A healthy skin barrier supports the growth of commensal bacteria that protect the host from pathogenic bacteria and their virulence factors
- In atopic dermatitis (AD), recent studies have pointed to a lack of microbial diversity in lesional and non-lesional skin
- People with AD have high levels of *Staphylococcus aureus* colonizing both lesional and non-lesional skin[1]
- Dysregulation of the skin microbiome in AD is believed to be influenced by epidermal barrier disruption and Th2-driven inflammation, in which the IL-13 cytokine plays a major role
- Tralokinumab is a fully human, high-affinity monoclonal antibody that neutralizes the IL-13 cytokine, and has been shown to improve signs and symptoms in adults with moderate-to-severe AD[2,3]

Objective

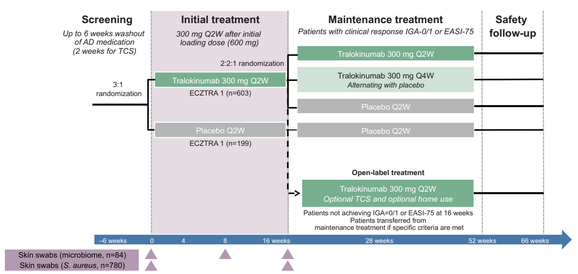
- To examine the impact of tralokinumab treatment on microbial diversity in lesional skin of adults with moderate-to-severe AD from the Phase 3 ECZTRA 1 trial (NCT03131648)

Methods

Study design (Figure 1)

- Bacteria were collected from areas (5 x 10 cm) of lesional skin
- *S. aureus* and overall bacterial abundance was assessed in subjects in ECZTRA 1 (n=780) at Baseline and Week 16 using qPCR of the femA gene and the 16S rRNA using the Ba04230906 and Ba04230899 assays from Thermo Fischer, respectively
- Microbiome profiling was done in 84 subjects (59 on tralokinumab and 25 on placebo) at selected sites from ECZTRA 1 at Baseline, Week 8, and Week 16
- Relative microbial abundance and Shannon diversity were assessed based on DNA sequencing of 16S ribosomal RNA V3-V4 regions
- A total of 30,276 amplicon sequence variants (ASVs) representing known taxa were identified from 205 samples. After filtering for ASVs found in more than one sample, a total of 9,130 ASVs were used for analysis representing 21 phyla, 468 genera and 791 species
- Serum biomarkers were also measured (IL-13 and IL-22 in Singulex Erenna Array; CCL17 by ELISA)

Figure 1. ECZTRA 1 trial design and microbiome sample collection.



AD, atopic dermatitis; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; Q2W, every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroid.

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Results

Baseline characteristics

Table 1. Baseline demographics and clinical characteristics for randomized subjects in parent study (ECZTRA 1) and in the skin swab subgroup.

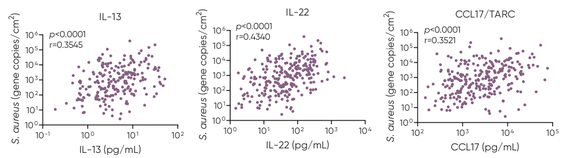
Characteristic	All randomized (N=802)	Skin swab (microbiome) subgroup (N=84)	
		Tralokinumab Q2W (n=59)	Placebo (n=25)
Age			
Mean (SD)	38.8 (14.1)	39.9 (13.8)	36.8 (13.1)
Sex, n (%)			
Male	474 (59.1)	37 (62.7)	16 (64.0)
Female	328 (40.9)	22 (37.3)	9 (36.0)
Race, n (%)			
White	564 (70.3)	48 (81.4)	22 (88.0)
Black	59 (7.4)	2 (3.4)	1 (4.0)
Asian	160 (20.0)	8 (13.6)	2 (8.0%)
IGA, n (%)			
Moderate Disease	391 (48.8)	23 (39.0)	14 (56.0)
Severe Disease	407 (50.7)	36 (61.0)	11 (44.0)
EASI			
Mean (SD)	32.4 (13.8)[a]	35.6 (14.7)	32.8 (13.1)
SCORAD			
Mean (SD)	70.6 (12.9)[c]	74.2 (13.1)	72.1 (10.5)
DLQI			
Mean (SD)	16.9 (7.0)[b]	17.7 (6.6)[d]	18.3 (6.6)
Worst Daily Pruritus NRS (weekly average)			
Mean (SD)	7.7 (1.4)[c]	8.1 (1.4)	8.1 (1.2)

[a]n=798; [b]n=785; [c]n=793; [d]n=57

S. aureus abundance

- At Baseline, *S. aureus* abundance was moderately correlated with IL-13, IL-22, and CCL17/TARC serum levels based on a non-parametric Spearman correlation **(Figure 2)**

Figure 2. *S. aureus* abundance correlates with select biomarkers at Baseline



- Patients with the greatest reduction in *S. aureus* abundance from Baseline to Week 16 also had the greatest improvement in EASI score **(Figure 3)**

Figure 3. Correlation of change in *S. aureus* abundance with change in EASI score

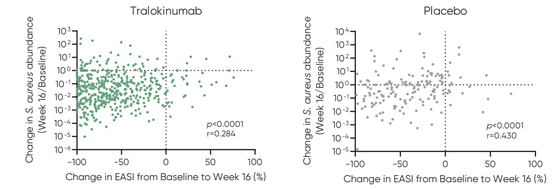
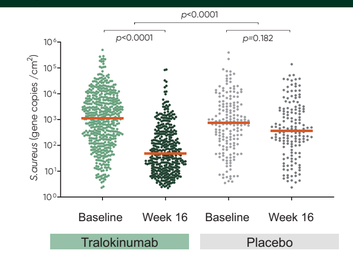
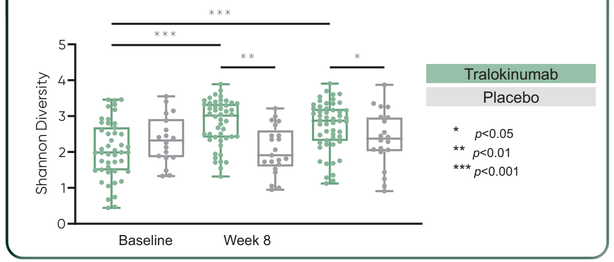


Figure 4. Treatment with tralokinumab led to a greater reduction in *S. aureus* abundance in lesional skin relative to placebo at Week 16



- A 10-fold greater reduction from Baseline was seen for tralokinumab versus placebo in the full population (ratio=0.09; *P*<0.0001) at Week 16 **(Figure 4)**
- Use of rescue therapy did not impact the results

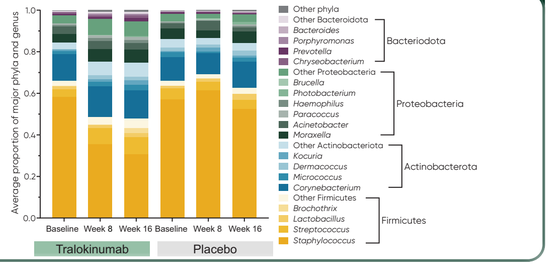
Figure 5. Treatment with tralokinumab led to increased Shannon diversity



Microbiome diversity

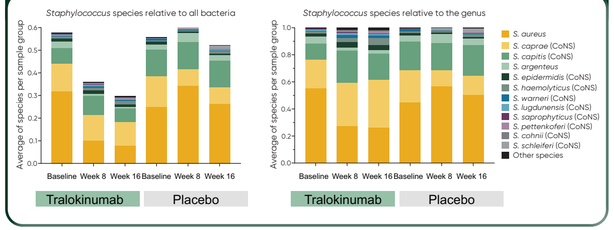
- The tralokinumab group showed a significant increase in microbial diversity over time and relative to the placebo group at Week 8 and Week 16 **(Figure 5)**
- The results are presented as Shannon diversity index, which is a quantitative measure of how many bacterial species are present on the skin and also accounts for the phylogenetic relations between the different species

Figure 6. Relative abundance of the most dominant phyla and genera over time



- Relative abundance of major phyla and genera remained stable for patients receiving placebo, while the relative abundance of *Staphylococcus* was reduced 47.5% from Baseline for the tralokinumab group **(Figure 6)**

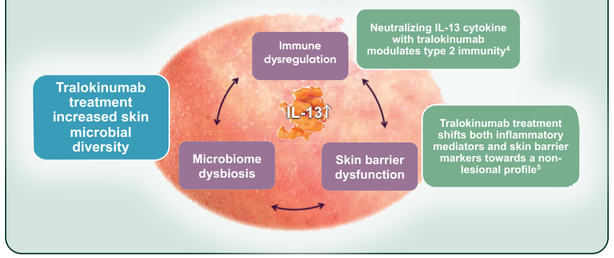
Figure 7. Relative abundance of the most dominant *Staphylococcus* species over time



- At the species level, the overall decrease in the relative abundance of *Staphylococcus* was primarily due to decreased relative abundance of *S. aureus*, from comprising almost 32% of all bacteria at Baseline to less than 8% of all bacteria at Week 16 **(Figure 7)**
- Relative abundance also decreased for *S. argenteus*, a pathogenic hemolysin-producing species associated with *S. aureus*, from 5% of *Staphylococcus* at Baseline to 2% at Week 16
- In contrast, the relative abundance of commensal coagulase-negative staphylococci (CoNS), such as *S. epidermidis* and *S. capitis*, were moderately increased

Conclusions

- Tralokinumab treatment was associated with decreased abundance of *S. aureus* and increased microbial diversity in lesional skin
  - The results support that neutralization of the IL-13 cytokine contributes to improving the hallmarks of AD by shifting the microbial diversity on AD lesional skin towards commensal flora



References

1. Ogonowska P et al. *Front. Microbiol.* 2021; 11:567090; **2.** Wollenberg A et al. *Br J Dermatol.* 2020 Sep 30. doi: 10.1111/bjd.19574. Online ahead of print; **3.** Silverberg et al. *Br J Dermatol.* 2020 Sep 30. doi: 10.1111/bjd.1957 **3.** Online ahead of print; **4.** Guttman-Yassky E, et al. Poster presentation at AAD VMX 2021; **5.** Guttman-Yassky E, et al. Late-breaking presentation at AAD VMX 2021.

Disclosures

Thomas Bieber is an advisor/speaker/researcher for AbbVie, Allmiral, AnaptysBio, Arena, Asana Biosciences, Astellas, Bayer, BioVersys, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Dermavant/Roivant, Dermtreat, Domain Therapeutics, DS Biopharma, RAPT Therapeutics (FLX Bio), Galapagos/MorphoSys, Galderma, Glenmark, GlaxoSmithKline, Incyte, Kymab, LEO Pharma, Lilly, L'Oréal, Menlo Therapeutics, Novartis, Pfizer, Pierre Fabre, Sanofi/Regeneron, and UCB. **Lisa A Beck** is an investigator and consultant for Abbvie, Astra-Zeneca, LEO Pharma, Pfizer, Regeneron and Sanofi, and reports consulting fees and/or honoraria from Benevolent AIBio, Dermtech, Incyte, Janssen, Lilly, Novartis, Principia Biopharma, Rapt Therapeutics, Regeneron, Sanofi/Genzyme and Sanofi-Aventis. She is an investigator for Kiniksa. **Andrew Pink** reports personal fees and nonfinancial support from LEO Pharma, Novartis, and UCB; and personal fees from AbbVie, Almirall, Janssen, La Roche Posay Lilly, and Sanofi. **Hidehisa Saeki** is an advisor to LEO Pharma. **Lawrence Eichenfeld** has served as an advisor/speaker/researcher for AbbVie; Almirall, Arcutis, Arena, Dermira, Forte, Galderma Glenmark/Ichnos,,Incyte, LEO Pharma, Lilly, Novartis, Pfizer, Ortho Dermatology Regeneron,and Sanofi Genzyme. **Thomas Werfel** has received lecture or consultancy fees from AbbVie, Almirall, Astellas, Galderma, Janssen/Johnson & Johnson, LEO Pharma, Lilly, Novartis, Pfizer, and Regeneron/Sanofi. **Anders Rosholm** was an employee of LEO Pharma. **Mads Repke** is an employee of LEO Pharma. **Amy Paller** has served as an investigator for AbbVie, Anaptysbio, Incyte, Janssen, LEO Pharma, Lilly, Lēnus, Novartis, Regeneron, and UCB and received honorarium for consultancy from AbbVie, Abeona, Almirall, Asana Biosciences, Boehringer Ingelheim, Bridgebio, Dermavant, Dermira, Exicure, Forté Pharma, Galderma, Incyte, InMed, Janssen, LEO Pharma, Lilly, LifeMax, Novartis, Pfizer, RAPT Therapeutics, Regeneron, Sanofi Genzyme, Sol-Gel, and UCB

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