

Long-term treatment with tralokinumab normalizes the molecular gene signature of atopic dermatitis

Emma Guttman-Yassky,¹ Ana Pavel,¹ Kenji Kabashima,² Delphine Staumont-Salle,³ Kilian Eyerich,⁴ Walter Nahm,⁵ Sylvia Pauser,⁶ Joel Correa Da Rosa,⁷ Mads Roepke,⁸ Petra Amoudruz,⁸ Shannon Schneider,⁹ Andrew Blauvelt,¹⁰ Kristian Reich¹¹

¹Department of Dermatology and the Immunology Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA; ²Department of Dermatology, Graduate School of Medicine, Kyoto University; ³Department of Dermatology, University Hospital of Lille, INFINITE (Institute for Translational Research in Inflammation) U1286 Inserm, University of Lille, Lille, France; ⁴Department of Dermatology and Allergy, Technical University of Munich, Munich, Germany; ⁵University Clinical Trials, San Diego, California, USA; ⁶Klinische Forschung Osnabrück, Osnabrück, Germany; ⁷Mount Sinai Laboratory of Inflammatory Skin Diseases, Icahn School of Medicine at Mount Sinai, New York, New York, USA; ⁸LEO Pharma A/S, Ballerup, Denmark; ⁹LEO Pharma, Madison, New Jersey, USA; ¹⁰Oregon Medical Research Center, Portland, Oregon, USA; ¹¹Translational Research in Inflammatory Skin Diseases, Institute for Health Services Research in Dermatology and Nursing, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Introduction. Interleukin (IL)-13 is a key driver of skin inflammation and barrier abnormalities in atopic dermatitis (AD). Tralokinumab is a high-affinity, monoclonal antibody that specifically neutralizes IL-13. Tralokinumab demonstrated efficacy and safety for AD treatment in pivotal phase 3 trials at Week 16, and high levels of EASI-75 and IGA 0/1 response were sustained through 2 years of continued treatment [Wollenberg A, et al. *Br J Dermatol.* 2021;184:437-449; Silverberg JI, et al. *Br J Dermatol.* 2021;184:450-463]. Examination of key biomarkers in skin lesions following 16 weeks of tralokinumab treatment showed shifts in inflammatory mediators and skin barrier markers towards that of uninvolved (“non-lesional”) skin. The impact of long-term treatment on the molecular phenotype of AD skin has not been assessed previously. We investigated the long-term impact of IL-13 neutralization on skin biomarkers following 2 years of tralokinumab treatment in patients with moderate-to-severe AD in the Phase 3 ECZTRA 1 trial (NCT03131648) and the long-term extension trial ECZTEND (NCT03587805).

Methods. Skin biopsies (n=13) were collected from lesional (baseline, Week 16, and Week 104) and non-lesional skin (baseline and Week 104). Gene expression levels of biomarkers related to inflammation and skin barrier integrity were assessed by RNA sequencing and validated by quantitative polymerase chain reaction. Treatment differences were estimated by linear mixed effect models with treatment and time as fixed effects and random effects for each patient.

Results. Two years of tralokinumab treatment shifted the transcriptomic profile of lesional skin towards that of non-lesional skin; this shift was larger than that seen at Week 16. These shifts included genes related to the Th2, Th17, and Th22 pathways, as well as epidermal barrier. A strong shift was also observed in atherosclerosis-signaling pathway genes. At 2 years, tralokinumab treatment also modified the transcriptomic

profile of the non-lesional skin, improving the subclinical disease seen at baseline in normal-appearing skin.

Conclusion. These shifts in the cutaneous biomarker profile highlight the role of IL-13 as a key driver of the AD molecular signature, and support the role of targeted biologic therapy for long-term AD management.