

Nicole R. Narayan¹, Joshua D. Hoffman¹, Claire L. Langrish¹, Pedro Corpuz Jr¹, Nicholas E. Vlahakis¹, Mera K. Tilley¹

¹ Alumis Inc., South San Francisco, CA

nnarayan@alumis.com

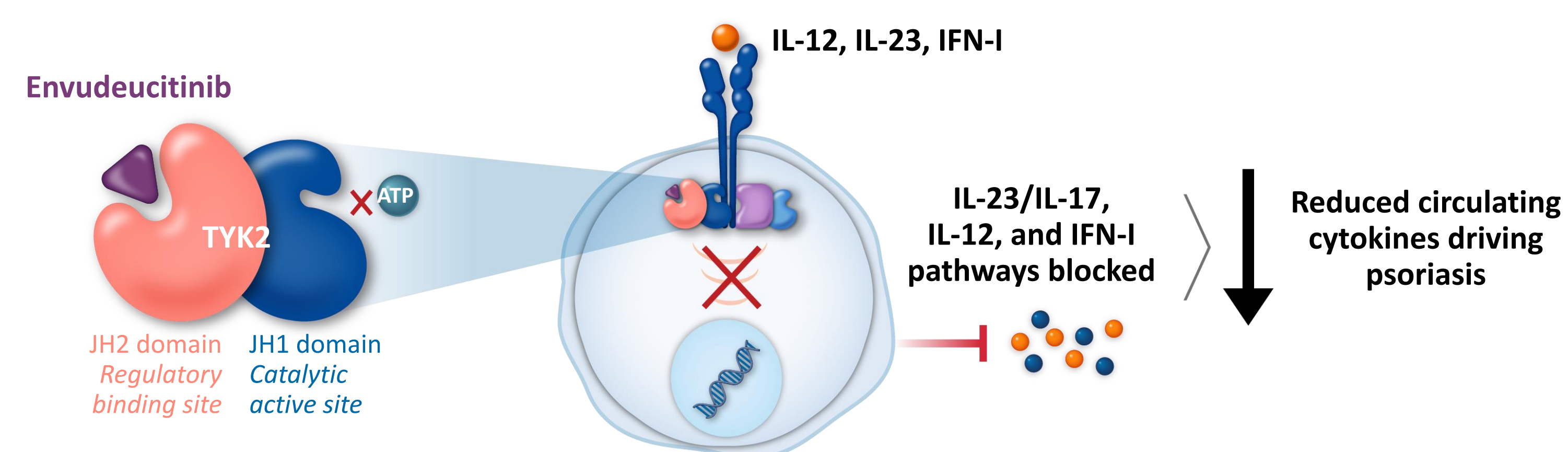
Background

Envudeucitinib (formerly known as ESK-001) is an investigational*, oral, selective small molecule allosteric inhibitor of kinase 2 (TYK2) that is designed to deliver maximal target inhibition over 24 hours while reducing off-target effects.¹⁻⁹

➤ TYK2 mediates signaling from key proinflammatory cytokines, including IL-23, IL-12, and type I IFN.

➤ Envudeucitinib is under development for the treatment of immune-mediated inflammatory diseases, including plaque psoriasis (PsO) and systemic lupus erythematosus (SLE).

➤ The STRIDE Phase 2 and its open-label extension results demonstrated the **favorable benefit/risk profile of envudeucitinib**, with **meaningful clinical efficacy** throughout 52 weeks, and **good tolerability**.^{10,11}



*Envudeucitinib is an investigational therapy not reviewed or approved by any regulatory agency.
ATP, adenosine triphosphate; IL-12/17/23, interleukin 12/17/23; IFN-I, interferon type I; JH1/2, Janus kinase homology 1/2; TYK2, tyrosine kinase 2.

Objectives

Characterize TYK2 and PsO-related biomarker changes in response to envudeucitinib treatment through spatial transcriptomic analysis of skin punch biopsies, in patients with moderate-to-severe plaque PsO in the Phase 2 STRIDE study.

Methods

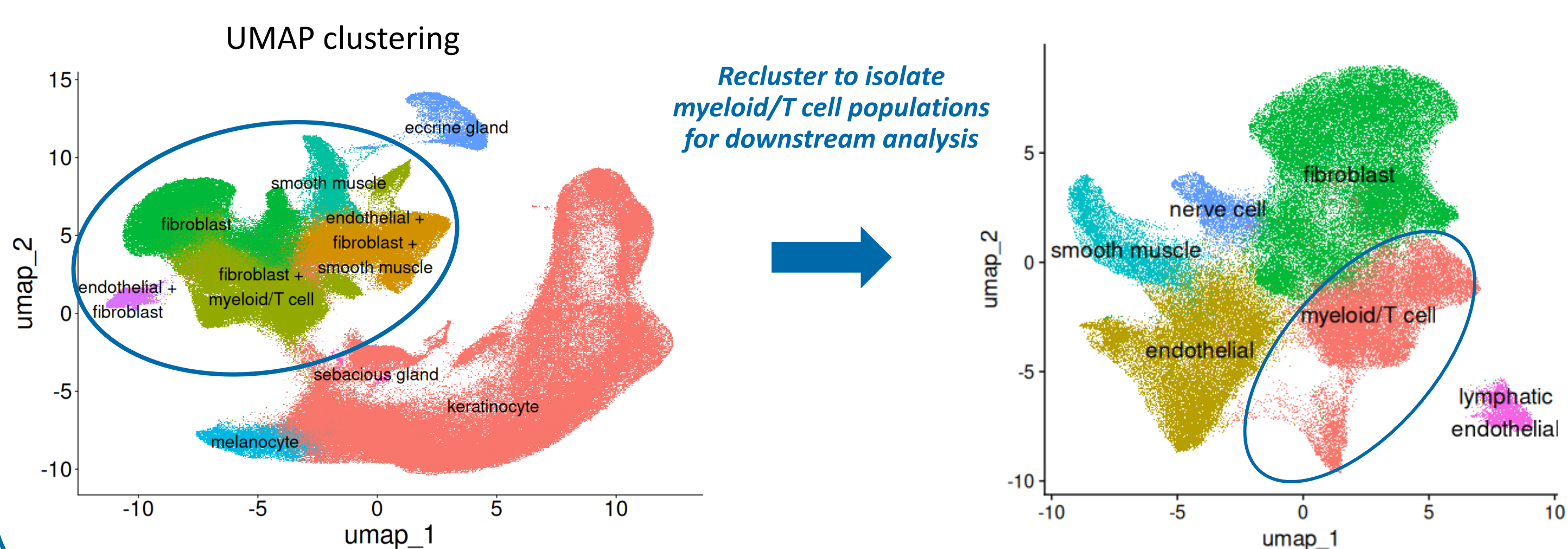
Study design

- **STRIDE study** = a 12-week randomized, double-blinded, placebo-controlled Phase 2 study of envudeucitinib in adults with moderate-to-severe plaque PsO (NCT05600036).
 - A total of 228 subjects were 1:1:1:1:1 randomized to receive 1 of the 5 doses of envudeucitinib or placebo, given orally for 12 weeks.
 - Optional lesional and non-lesional 4 mm skin punches were taken from a subset of patients at baseline and Week 12.
 - Lesional = actively inflamed psoriatic plaque, not typically ultraviolet (UV) exposed.
 - Non-lesional = non-inflamed skin, taken 5 cm away from the margin of lesional skin.
 - Subjects selected based on availability of baseline and week 12 biopsies: placebo (n=4) and envudeucitinib 40 mg twice daily (BID) (highest dose, n=5) are presented.

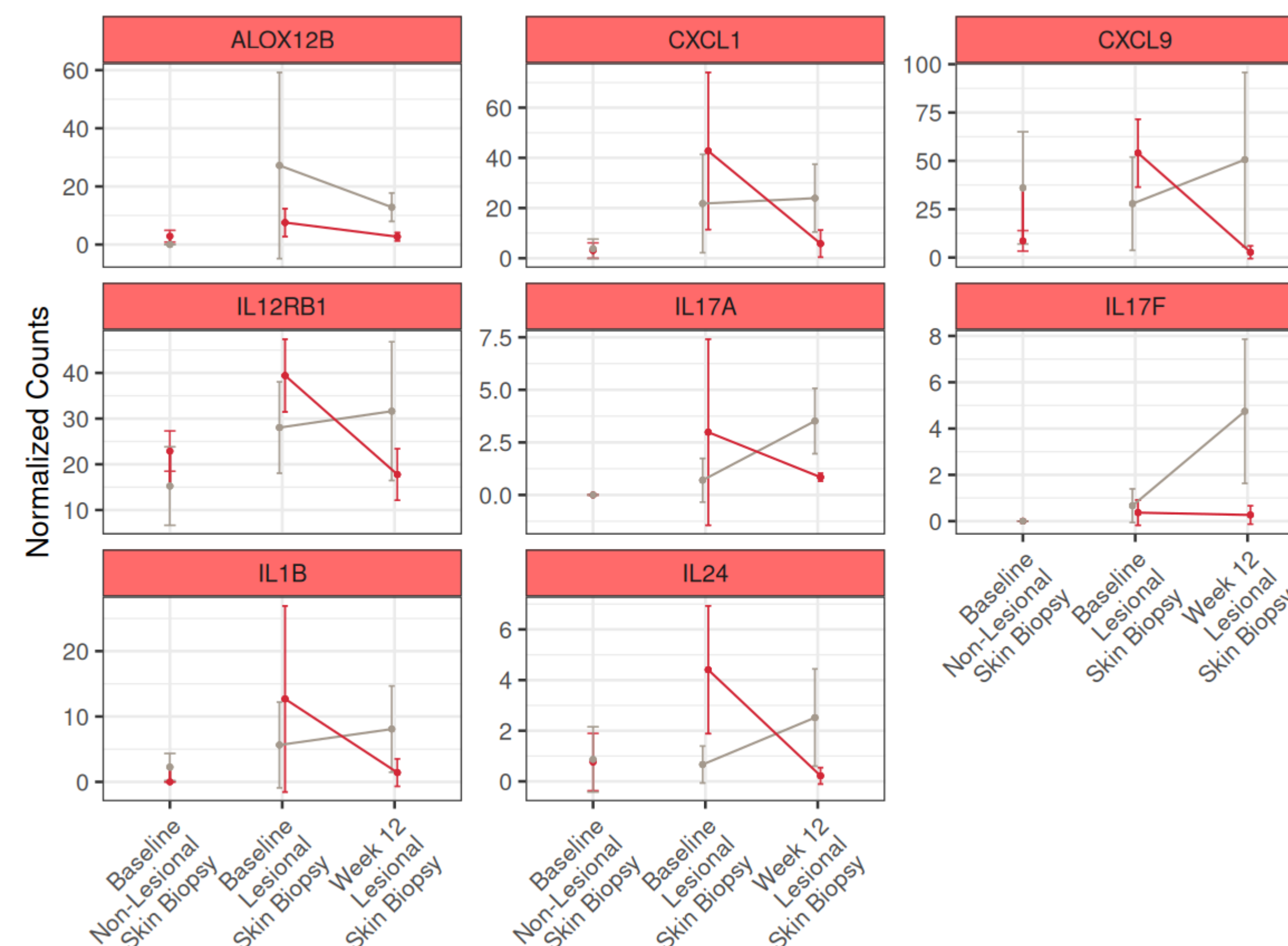
➤ Spatial transcriptomics was performed on formalin-fixed paraffin-embedded tissues using the **10X Genomics Visium HD** platform. Sequencing-reads were processed with Space Ranger 4.0 with nuclei segmentation. Analysis was performed with **Seurat** package in R. After QC and filtering, samples were normalized and harmony-based sample integration was performed.

➤ Myeloid/T-cell and keratinocyte spatial-cell clusters were identified and visualized with **UMAP** (Uniform Manifold Approximation and Projection). Clusters were manually annotated based on expression of marker genes for skin cell types established in Ma *et al.*¹²

➤ Expression of key TYK2 pathway and PsO-associated biomarkers were compared across treatment groups.



Expression of IL-23 signaling genes in myeloid/T cell subsets inhibited after envudeucitinib treatment



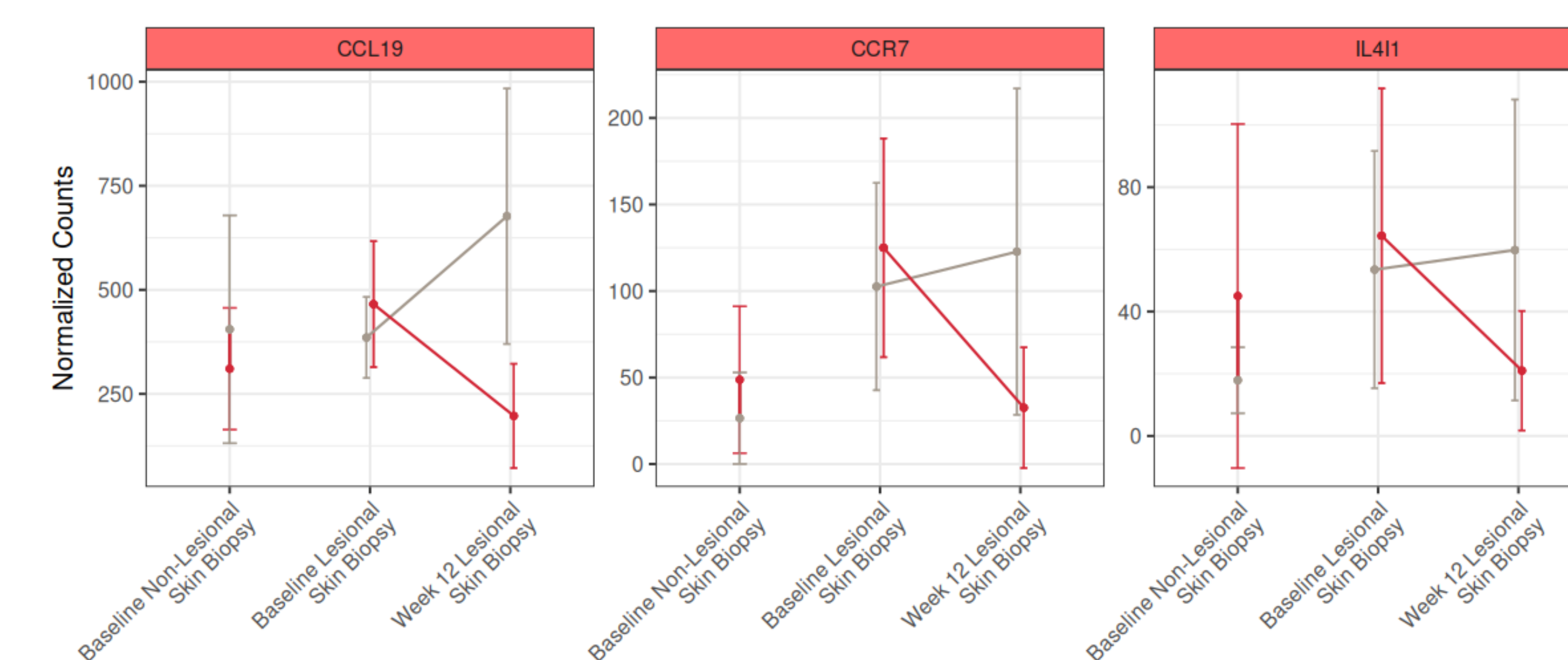
The genes plotted above are components of the Pathway Interaction Database IL-23 pathway gene set.

Treatment arm
— Placebo
— envudeucitinib 40 mg BID

Results

Expression of IL-23 producing dendritic cell markers inhibited after envudeucitinib treatment

- Expression of *CCL19*, *CCR7*, and *IL4I1* return to non-lesional levels after envudeucitinib treatment
- *CCR7+IL4I1+* dendritic cells are primary producers of IL-23 in PsO.¹³

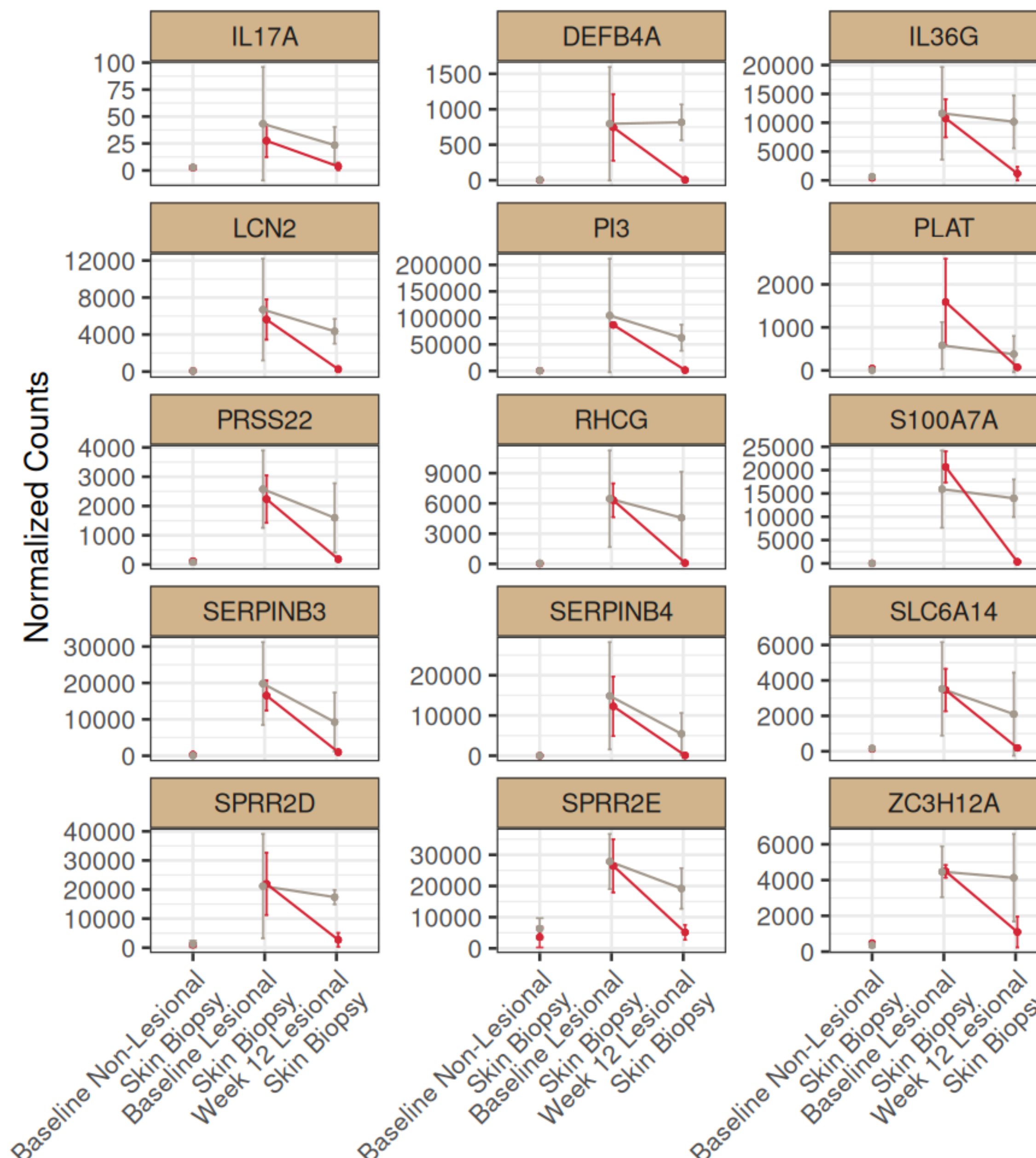


Pseudobulk analysis of spatial transcriptomics by cell type. Median \pm MAD are displayed.

BID, twice daily; MAD, median absolute deviation.

Envudeucitinib inhibited expression of IL-17A and downstream response genes in keratinocytes

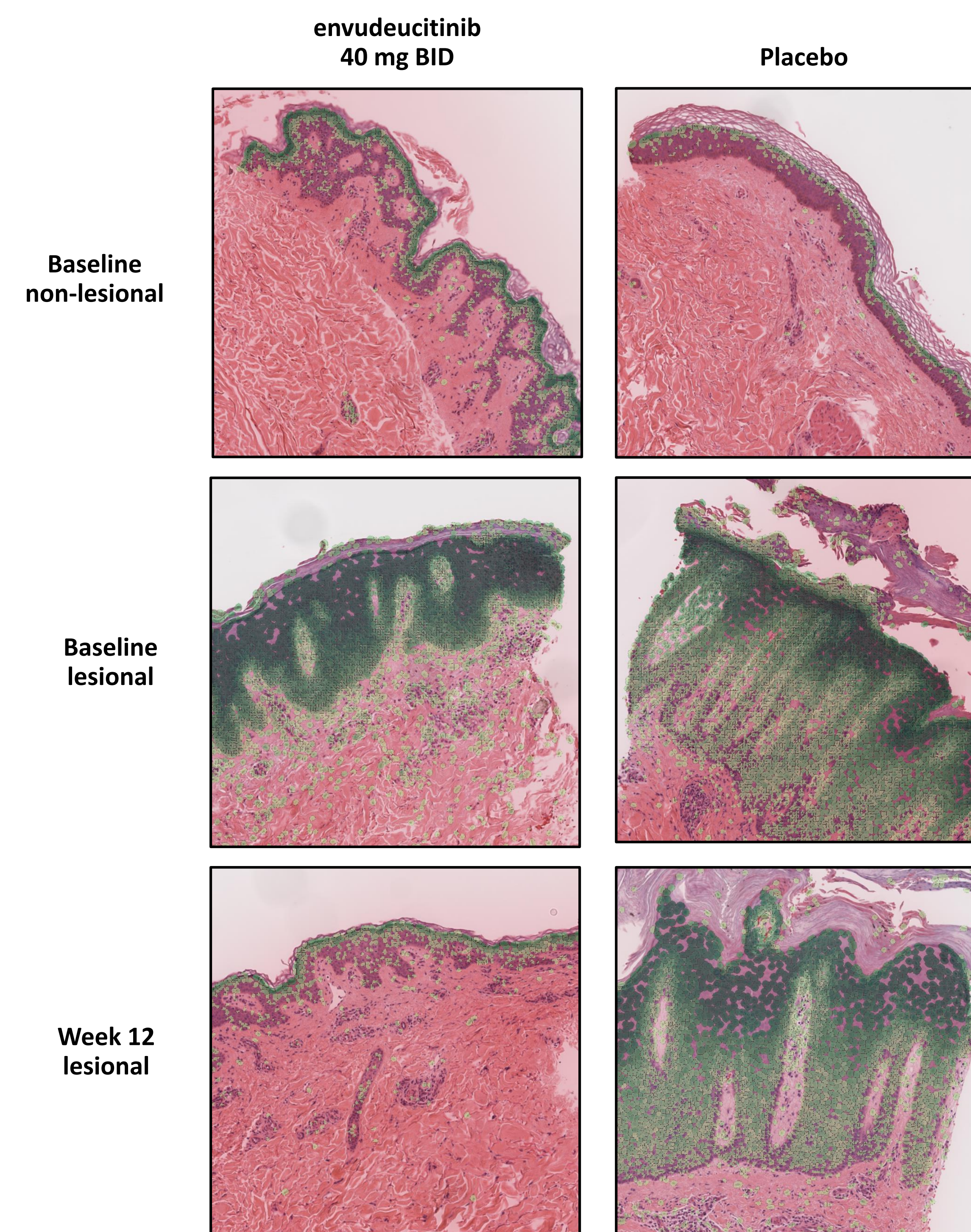
- Expression of IL-17A and downstream signaling genes¹⁴ in keratinocytes return to non-lesional levels after 12 weeks of envudeucitinib treatment



Pseudobulk analysis of spatial transcriptomics by cell type. Low expressing genes from IL-17 downstream signaling signature omitted. Median \pm MAD are displayed.

BID, twice daily; MAD, median absolute deviation.

Aggregated expression of IL-17A response genes returned to non-lesional levels after envudeucitinib treatment



Aggregated expression of IL-17A response genes¹⁴ (green) visualized using Loupe Browser. Representative samples from one patient receiving envudeucitinib 40 mg BID and one patient receiving placebo are shown above.

Conclusions

In the Phase 2 STRIDE study, spatial transcriptomic analysis demonstrated that envudeucitinib robustly inhibited pathogenic IL-23 and IL-17 pathway signaling in PsO-relevant skin cell types, including keratinocytes and myeloid/T cell subsets

References

1. Ucpinar S, et al. Clin Transl Sci. 2024. 2. Yao BB, et al. Arch Biochem Biophys. 1999.
3. Aggarwal S, et al. J Biol Chem. 2003. 4. Minegishi Y, et al. Immunity. 2006. 5. Ragimbeau J, et al. EMBO J. 2003. 6. Karaghiosoff M, et al. Immunology. 2000. 7. Chiricozzi A, et al. J Invest Dermatol. 2011. 8. Page KM, et al. J Invest Dermatol. 2020. 9. Zhou Y, et al. Front Immunol. 2022. 10. Blauvelt A, et al. J Am Acad Dermatol. 2026. 11. Papp KA, et al. J Am Acad Dermatol. 2026. 12. Ma F, et al. Nat Commun. 2023. 13. Sun Y, et al. Nat Commun. 2025.
14. Francis L, et al. Nat Commun. 2024.

Disclosures

Disclosures: Commercial support was provided by Alumis Inc. All authors are employed by Alumis Inc. The authors have no other relationships or conflicts of interest to disclose.