

Envudeucitinib Attenuates Inflammatory Biomarkers in Plaque Psoriasis at Both a Proteomic and Transcriptomic Level: A Subgroup Analysis of Tape Strip Biomarkers from the STRIDE Phase 2 Clinical Trial

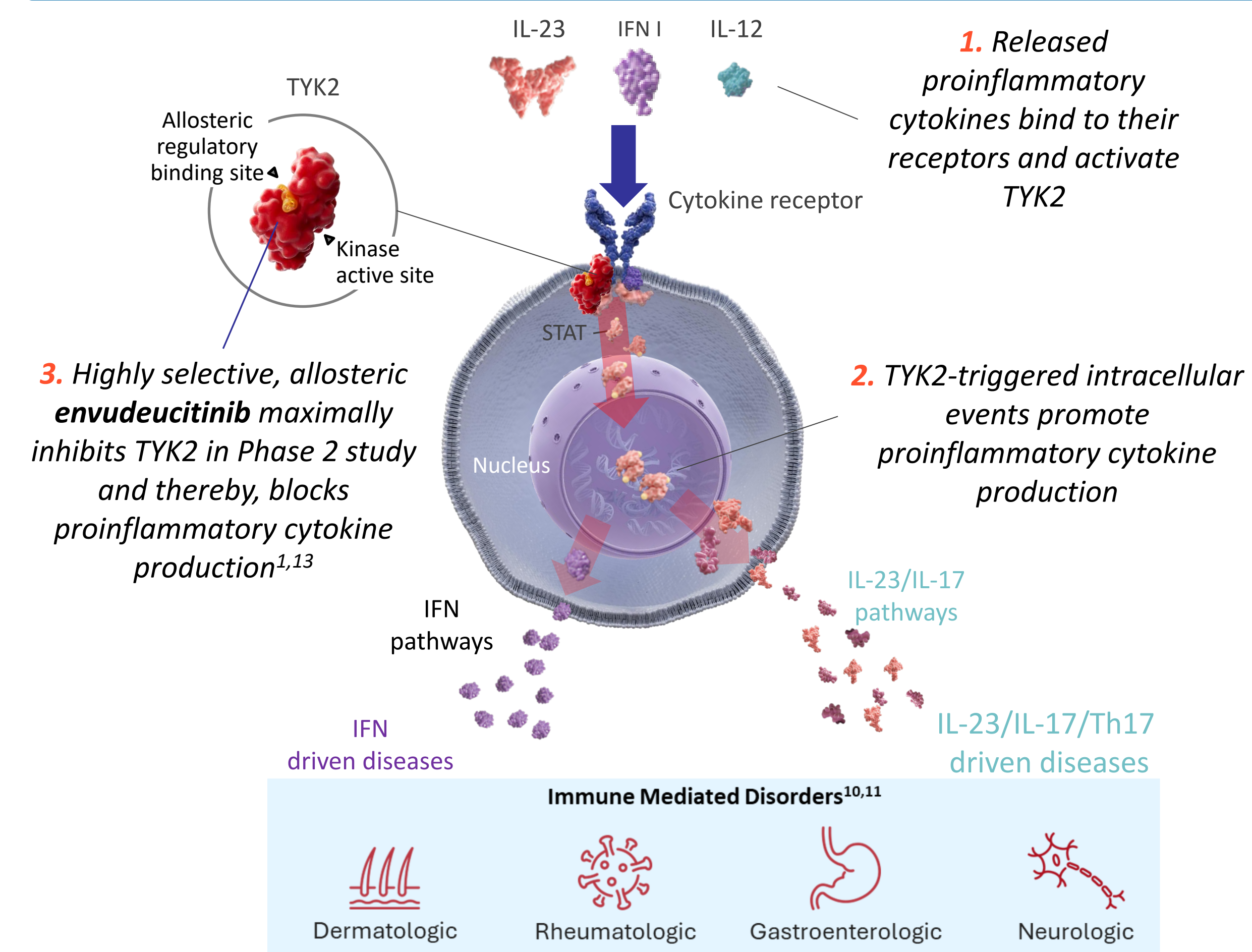
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Background



Envudeucitinib (formerly known as ESK-001) is an investigational*, oral, selective small molecule allosteric inhibitor of tyrosine 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).

*Envudeucitinib is investigational and has not been approved by any regulatory authority. IL, interleukin; IFN I, type I interferon; STAT, signal transducer and activator of transcription; Th17, T helper 17 cell; TYK2, tyrosine kinase 2.

Objectives

To assess TYK2 target engagement and characterize disease-related biomarker changes in response to envudeucitinib through transcriptomic and proteomic analysis of skin tape strips, as well as 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 skin tape strips and 4 mm skin punches from patients at baseline and Week 12.
 - Lesional = actively inflamed psoriatic plaque, not typically UV exposed.
 - Non-lesional = non-inflamed skin, taken 5 cm away from the margin of lesional skin.
 - Locations are noted in requisition form and in source documents for Week 12 reference.

Transcriptomic and proteomic analysis of skin tape strips

- Placebo (N=10), envudeucitinib 40 mg once daily (QD) (N=10), and envudeucitinib 40 mg twice daily (BID) (N=8)
- Bulk RNA-sequencing (RNAseq):** reads were aligned to the genome and transcriptome using STAR. Transcripts were quantified with Salmon.
- Olink proteomics:** protein biomarkers were quantified using the Proximity Extension Assay (PEA), with data reported as Normalized Protein eXpression (NPX) values.

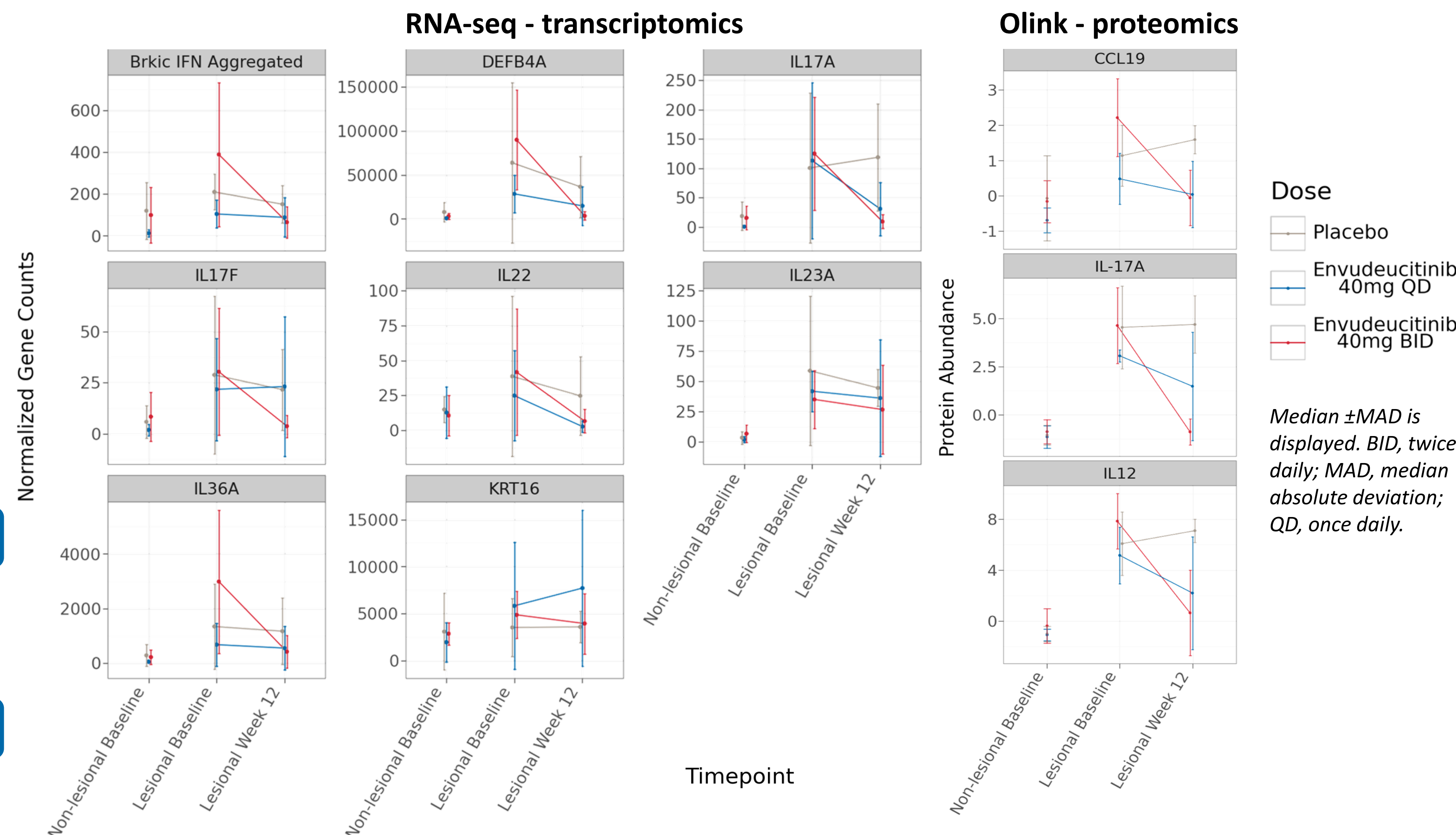
Spatial transcriptomic analysis of skin punch biopsies

- Placebo (N=4), envudeucitinib 40 mg QD (N=4), and envudeucitinib 40 mg BID (N=5)
- Spatial transcriptomic analysis performed on formalin-fixed paraffin-embedded tissues using the **10X Genomics Visium HD** platform, a high resolution spatial transcriptomic assay capable of single cell-scale spatial resolution. → After 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.
- Spatial 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 → Cells identified as **keratinocytes** were subset, re-clustered, and visualized with UMAP. Clusters were manually annotated for differentiation state based on expression of marker genes.

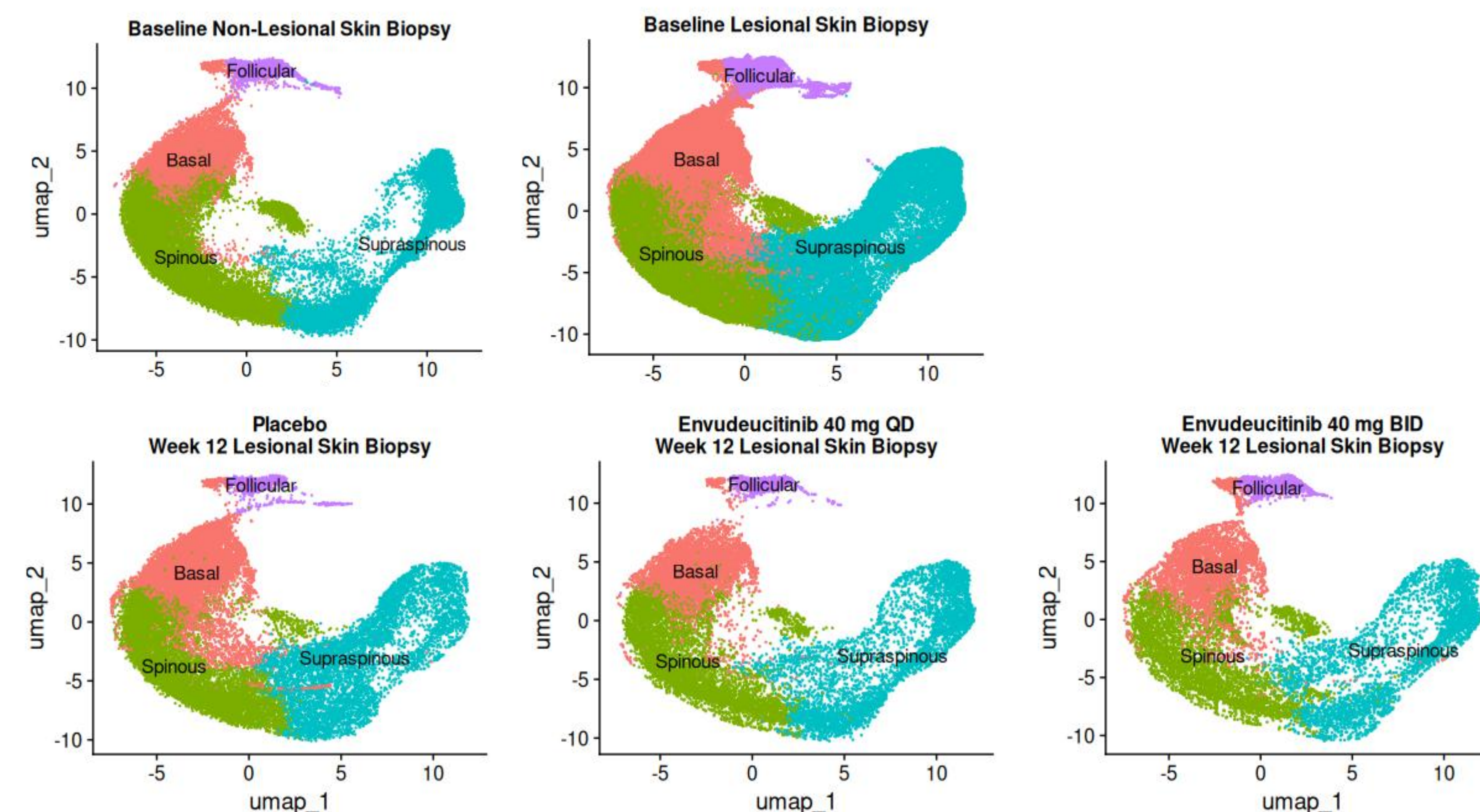
Results

Skin tape stripping data demonstrated downregulation of genes and proteins in key immune pathways, including IL-23, IL-17, and type I IFN signatures, after envudeucitinib treatment

- All available samples with valid RNAseq and/or protein data were included in the analysis.
- Greatest molecular suppression was observed in the envudeucitinib 40 mg BID group, paralleling dose-dependent improvements in clinical scores.¹³
- These results are consistent with the skin punch biopsy results.



Keratinocyte profile of skin punch biopsies of patients after envudeucitinib treatment resembled the non-lesional baseline profile



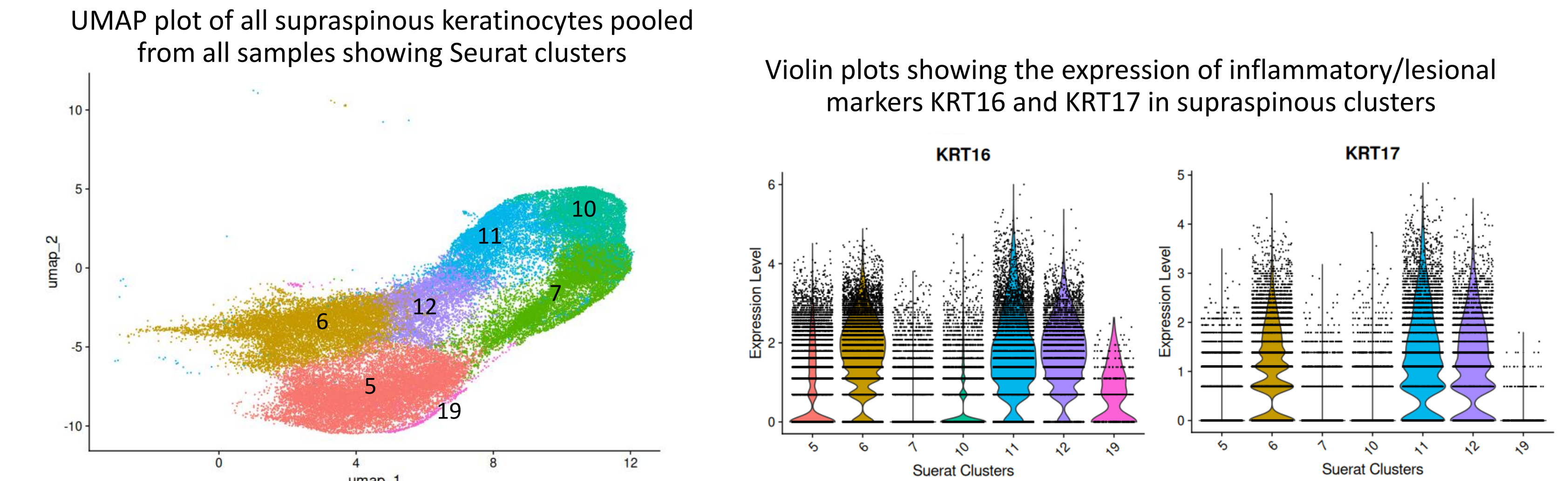
UMAP plots showing all keratinocytes pooled from all samples:

- Subtypes of keratinocytes were identified based on the differential gene expression profile.
- Supraspinous keratinocytes (blue)** showed the largest effect after envudeucitinib treatment, in which the profile resembled the non-lesional baseline profile.

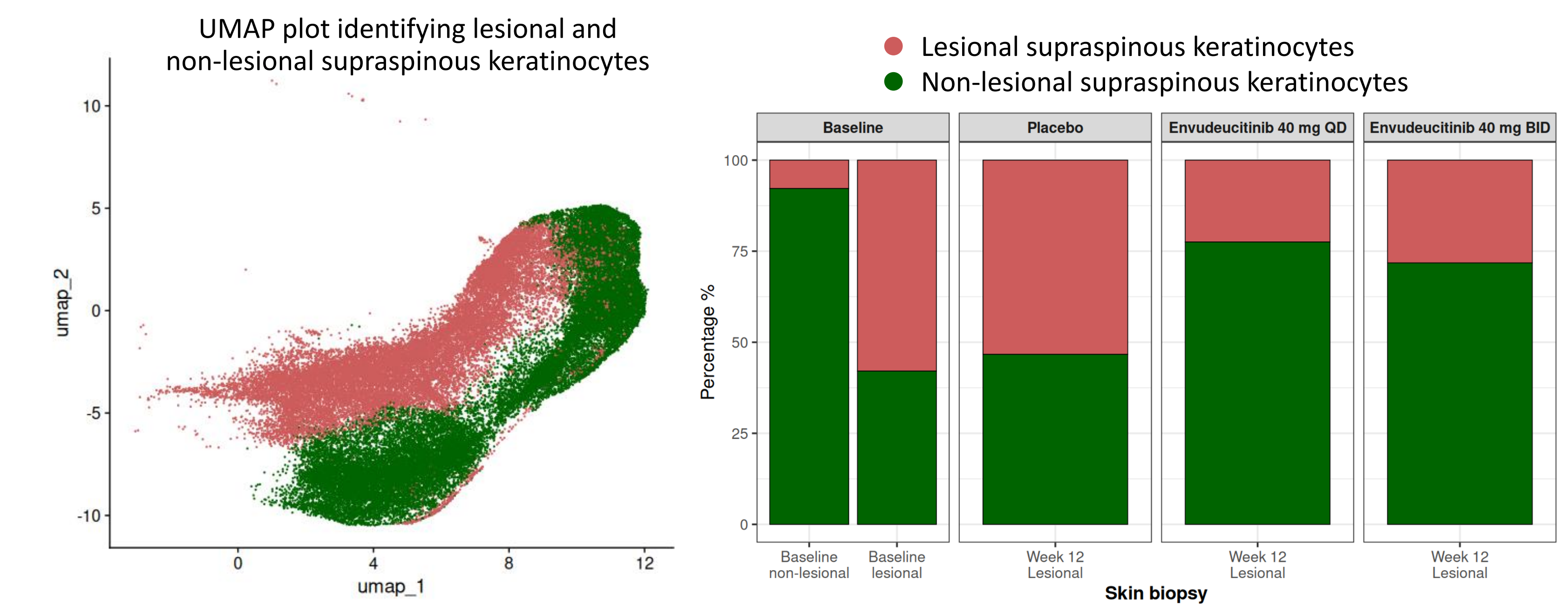
References

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. Immunity. 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. Kim J, et al. Nature Neurosci. 2024. 11. Yuan S, et al. EBioMedicine. 2023. 12. Ma F, et al. Nat Commun. 2023. 13. Blauvelt A, et al. J Am Acad Dermatol. 2026. 14. Narayan NR, et al. SID. 2025.

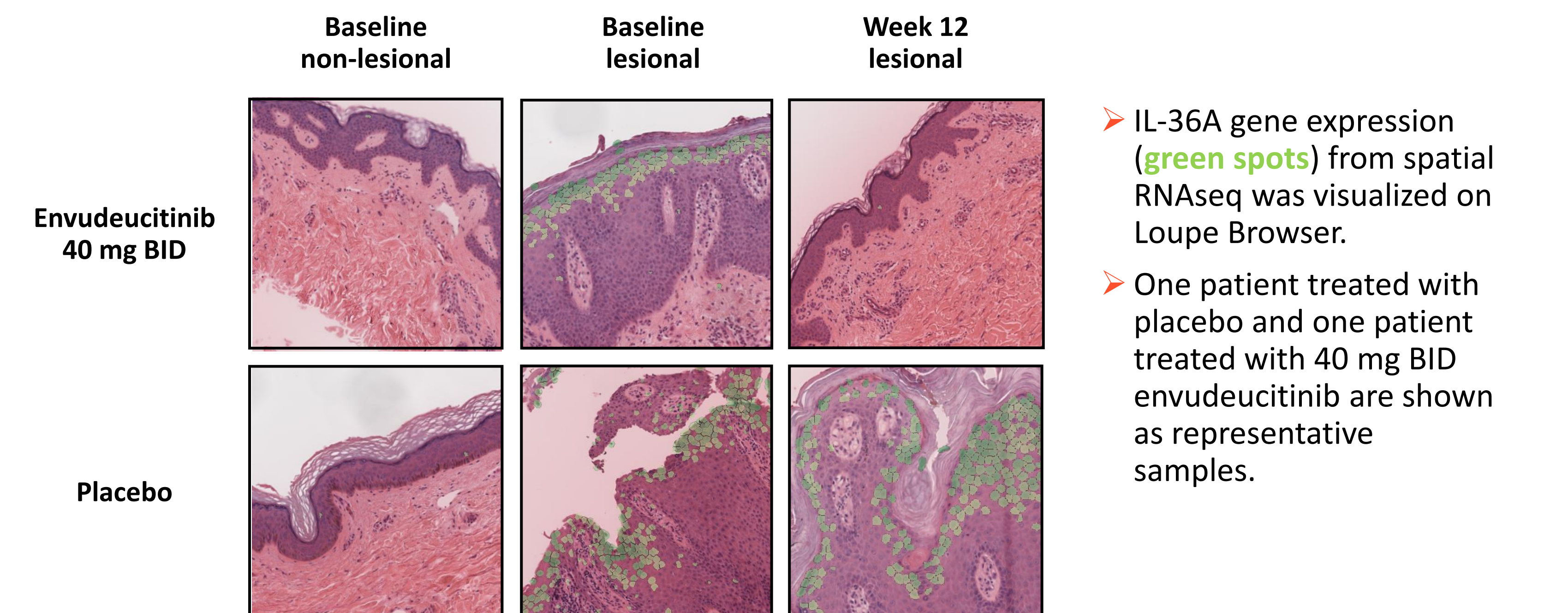
Decrease in inflammatory supraspinous keratinocytes in skin punch biopsies of patients after envudeucitinib treatment approached non-lesional levels



Clusters 6, 11, 12, and 19 express inflammatory keratinocyte genes



IL-36A expression was inhibited to non-lesional levels in skin punch biopsies of patients after envudeucitinib treatment, primarily in supraspinous keratinocyte layer



Conclusions

- In moderate-to-severe plaque PsO, envudeucitinib achieved robust suppression of pathogenic IL-23 and IFN-related pathways at transcriptomic and proteomic levels, underscoring its potential as an effective therapeutic strategy.
- The non-invasive tape-strip biomarker collection demonstrated concordance with the skin punch biopsies (previously presented)¹⁴, supporting its use for monitoring in clinical settings.

Disclosures

Disclosures: Commercial support was provided by Alumis Inc. ^{*}Employed by Alumis Inc. and have no other relationships or conflicts of interest to disclose. ^{**}Received honoraria as scientific speaker, received research grants and funding for multiple Pharma companies, and is a Principal Investigator for multiple Pharma studies.