AAD Annual Meeting 2025
Orlando, Florida
March 7-11, 2025

ESK-001, an allosteric TYK2 inhibitor, modulates disease and TYK2-related pathway transcriptomic and proteomic biomarkers in Psoriasis STRIDE trial patients

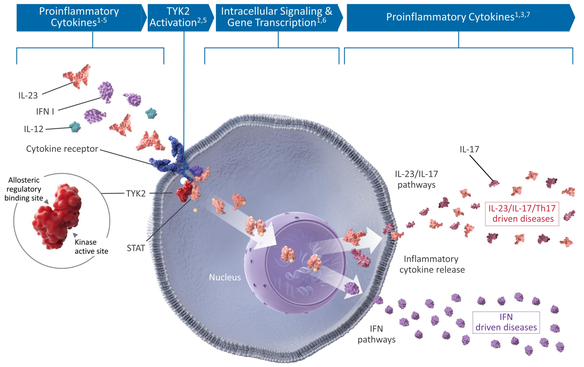
Nicole R. Narayan, Joshua D. Hoffman, Pedro Corpuz, Sibel Ucpinar, Roman Rubio, Nicholas E. Vlahakis, Claire L. Langrish, Mera K. Tilley

Poster No. 62905

nnarayan@alumis.com

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

Background



IL, interleukin; IFN I, type 1 interferon; STAT, signal transducer and activator of transcription; Th17, T helper 17 cell; TYK2, tyrosine kinase 2.

- **ESK-001 is an oral, next-generation tyrosine kinase 2 (TYK2) inhibitor** that delivers maximal target inhibition and reduces off-target effects to correct immune dysregulation across the spectrum of diseases driven by proinflammatory mediators, including IL-23, IL-17, and type 1 IFN.[1,8]
- Combining convenient oral administration with highly selective targeting, ESK-001 delivers maximal inhibition while minimizing off-target binding and associated adverse effects.[1]
- ESK-001 is currently being investigated for the treatment of plaque psoriasis (PsO) and systemic lupus erythematosus. Potential future indications include psoriatic arthritis, inflammatory bowel disease, and other chronic inflammatory conditions.[9-11]

Objectives

To characterize the ability of ESK-001, a next-generation allosteric TYK2 inhibitor, to alter IL-23/IL-17-related biomarker expression by performing proteomic and transcriptomic analysis on blood and skin of patients with moderate-to-severe plaque PsO in the STRIDE study.

Methods

Study Design

- ***STRIDE study*** = a 12-week randomized, double-blinded, placebo-controlled Phase 2 study of ESK-001 in adults with moderate-to-severe plaque PsO *(NCT05600036)*.
  - A total of 228 subjects were 1:1:1:1:1:1 randomized to receive 1 of the 5 doses of ESK-001 or placebo, given orally for 12 weeks.

Proteomic analysis

- **Plasma** collected at baseline and Week 12.
- **Single Molecule Array (SIMOA)** performed on plasma of patients treated with ESK-001 40 mg once daily (QD), ESK-001 40 mg twice daily (BID), and placebo for detection of various disease-relevant cytokines, such as IL-17A and IL-23.

Transcriptomic analysis

- **Whole blood** collected at baseline, Weeks 2, 4, 8, and 12, and after a 4-week washout period (Week 16).
- **Skin punch biopsies** collected at baseline and Week 12.
- **RNA-sequencing (RNA-seq)** performed on whole blood and skin samples of patients treated with ESK-001 40 mg QD, ESK-001 40 mg BID, and placebo.

Machine learning on blood RNA expression

- Machine learning is a tool in which computers learn from data and choose the most relevant features from a dataset, such as what features are associated with an outcome (e.g., PASI75 response). Many machine learning algorithms take advantage of multiple data simulations to determine the association of features (e.g., pathway level gene expression) in a robust manner.
- To associate baseline pathway expression with PASI75 response (≥75% reduction from baseline in Psoriasis Area and Severity Index) at Week 12 in ESK-001 40 mg BID dose group:
  1. **Gene Set Variation Analysis (GSVA)** to calculate sample-wise gene set enrichment scores based on Reactome cytokine signaling and customized gene sets relevant to ESK-001 and PsO.
  2. **Subset the level of baseline pathway gene expression** for downstream machine learning.
  3. **Boruta**, a feature selection method, to assess feature importance of baseline pathway gene expression based on PASI75 response at Week 12.

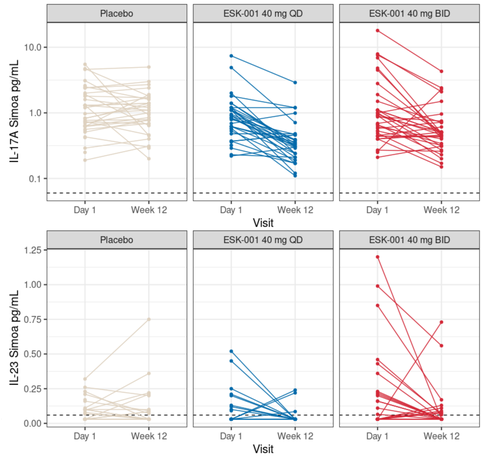
References

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.** Rusiñol L, Puig L. Int J Mol Sci. 2023. **9.** NCT05966480. **10.** NCT06588738. **11.** NCT05953688.

Results

Proteomic analysis showed reduced expression of blood biomarkers IL-23 and IL-17A after 12 weeks of ESK-001 treatment.

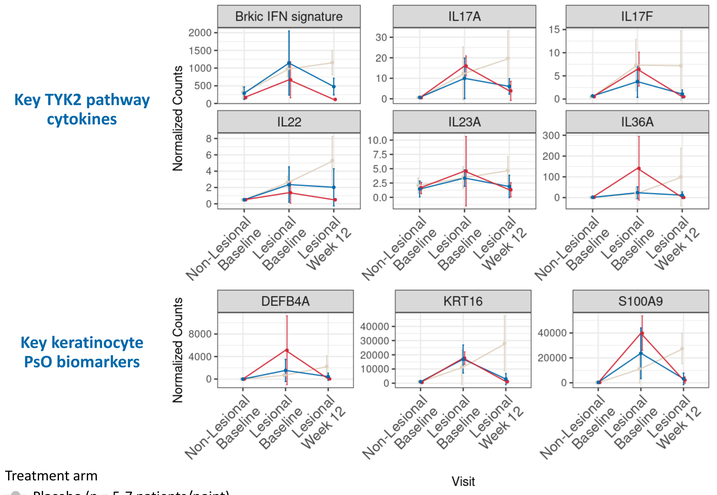
- ESK-001 40 mg QD and 40 mg BID reduced circulating IL-23 protein plasma levels by a median of nearly 100%.
- ESK-001 40 mg QD and 40 mg BID reduced circulating IL-22 levels by 0.99 and 2.1 log2 foldchange, respectively.



Placebo: n = 32, ESK-001 40 mg QD: n = 30, and ESK-001 40 mg BID: n = 31. QD, once daily; BID, twice daily.

Transcriptomic analysis showed that gene expression of lesional skin levels of key cytokines and PsO-relevant biomarkers returned to non-lesional levels after 12 weeks of ESK-001 treatment.

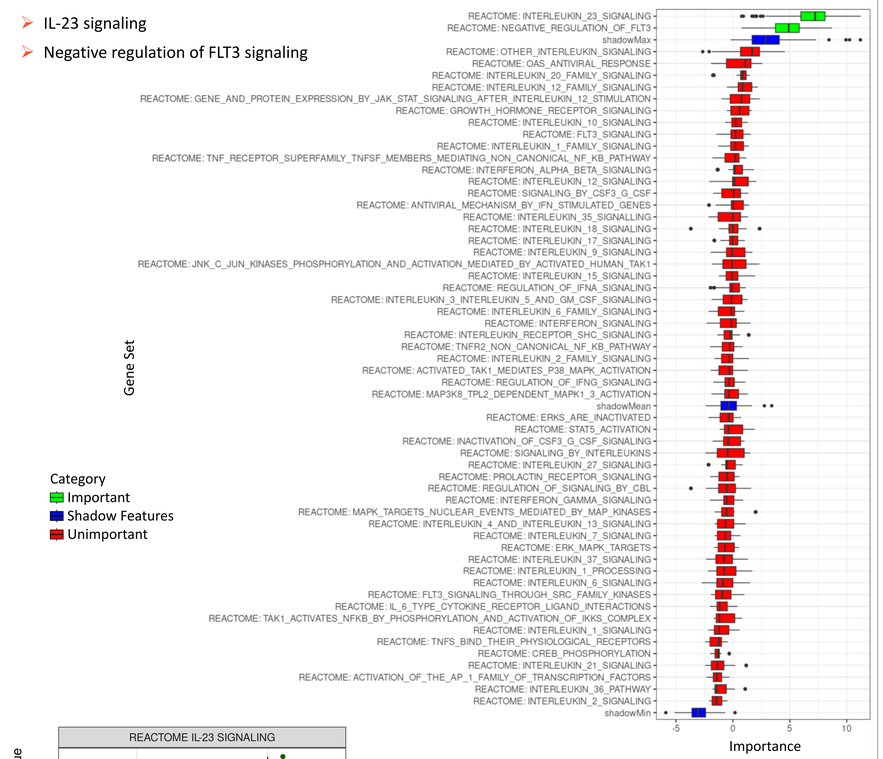
- RNA-seq data in lesional tissue **confirmed maximal inhibition with ESK-001**.

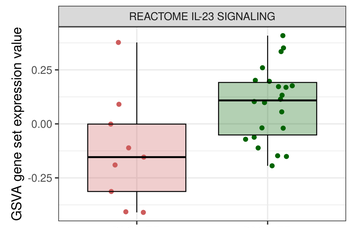


Skin biopsies collected in subset of patients. All available skin biopsy samples with valid RNAseq data were included in the analysis. Median ±MAD (median absolute deviation) are displayed. QD, once daily; BID, twice daily.

Feature selection using PASI75 at week 12 in 40 mg BID baseline gene expression yielded 2 relevant gene signatures.

- IL-23 signaling
- Negative regulation of FLT3 signaling





- **GSVA** as part of machine learning showed that **STRIDE responders** based on PASI75 at Week 12 have **higher baseline IL-23 signaling expression** compared to non-responders in the 40 mg BID dose group.

IL-23 signaling gene set based on Reactome gene set: IL-12B, IL-12RB1, IL-23A, IL-23R, JAK2, P4HB, STAT3, STAT4, and TYK2.

Conclusions

- **ESK-001 significantly impacted blood and skin biomarkers** downstream of the IL-23/IL-17 pathway on both proteomic and transcriptomic levels.
- PsO-relevant transcriptomic analysis in skin indicated a **return of key PsO biomarkers to non-lesional baseline levels** after 12 weeks of ESK-001 treatment.
- **Patients with high intrinsic IL-23 pathway expression** were most likely to **achieve high and rapid PASI75 response** in the dose group with maximal target engagement (ESK-001 40 mg BID).