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

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Introduction & Objectives:

TYK2 is a validated therapeutic target with potential applications in many immune-mediated indications. Variants within the *TYK2* gene, such as P1104A, lead to loss of TYK2 kinase function, and protects for an array of diseases, including psoriatic arthritis, systemic lupus erythematosus, IBD, and multiple sclerosis. P1104A homozygotes are conferred a greater magnitude of protection against disease than heterozygotes, suggesting that complete blockage of TYK2 kinase activity is important for maximal therapeutic benefit.

ESK-001 is an oral, highly selective small molecule allosteric inhibitor of TYK2. In the ESK-001 STRIDE trial, a phase 2 placebo-controlled dose ranging study in moderate-to-severe plaque psoriasis, the primary and secondary endpoints were all met at the highest doses with clear dose dependent improvement in efficacy. We undertook extensive transcriptomic analysis of disease-related pathways in both blood and skin of patients in order to define dose response, maximum target inhibition, and optimal dosing for subsequent trials.

Materials & Methods:

RNA-sequencing (RNA-seq) of both blood and skin punch biopsy samples was conducted at multiple time points in the STRIDE PsO trial for transcriptomic analysis. Whole blood was collected for RNA-seq from participants at baseline, week 2, week 4, week 8, week 12, and week 16 (post 4-week washout). Skin punch biopsies were collected from a subset of patients, consisting of paired lesional and non-lesional samples at baseline, and a lesional sample at week 12. Paired-end stranded libraries were generated and sequenced with a target depth of 100 million paired-end reads. Reads were aligned to the genome and transcriptome using STAR, and transcripts were quantified with Salmon. Gene level counts were aggregated in R and normalized with the DESeq2 package.

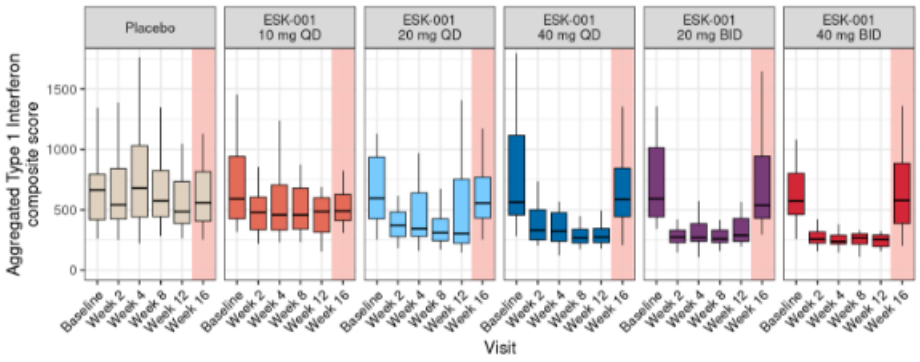
Results:

Blood RNA-seq confirmed ESK-001 dose-dependent inhibition of TYK2. Transcriptomic analysis confirmed ESK-001 maximal target engagement at the 40 mg BID dose via both type 1 interferon gene signature (Figure 1) and a novel pharmacodynamic biomarker. RNA-seq in skin shows return to baseline non-lesional levels of several key disease biomarkers, such as IL23, IL17's, and β-defensins after 12 weeks of ESK-001 treatment.

Conclusion:

RNA-Seq of blood and skin biopsies demonstrated that ESK-001 inhibited its target in a dose dependent fashion, with maximum inhibition of disease and TYK2 relevant pathways at the 40 mg BID dose. Disease-relevant transcriptomic analyses indicate a return of key psoriasis biomarkers to non-lesional baseline levels. These effects are in line with biomarker data previously reported by high-efficacy biologics such as secukinumab. Our RNA-seq results indicate a compelling relationship between maximal target engagement and markers of disease activity, further supporting the selection of 40 mg BID as the dose for the Phase 3 pivotal trial.

Figure 1



Blood samples collected at trough. All patients on study with available samples included in analysis.
Week 16 is 4 weeks post-dose (wash-out)