Transcriptomic Modulation in Psoriatic Skin Following Envudeucitinib Treatment: A Subgroup Analysis of a Phase 2 STRIDE Trial Skin Tape Strips

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Background

- Envudeucitinib* (formerly known as ESK-001) is an oral, selective allosteric TYK2 inhibitor
- In the recent Phase 2 STRIDE study in moderate-to-severe plaque psoriasis, envudeucitinib demonstrated clinically meaningful and statistically significant dose-dependent improvements in psoriasis skin severity and quality of life (NCT05600036)
- We evaluated molecular changes in the 40 mg QD and 40 mg BID subgroups to characterize immune modulation associated with treatment efficacy

**Envudeucitinib is investigational and has not been approved by any regulatory authority*

Objectives

- Characterize molecular pathways modulated by envudeucitinib in psoriatic skin via tape strips
- Evaluate dose-dependent immune suppression molecular patterns
- Correlate molecular changes in tape stripped skin with clinical improvements

Methods

Study Design

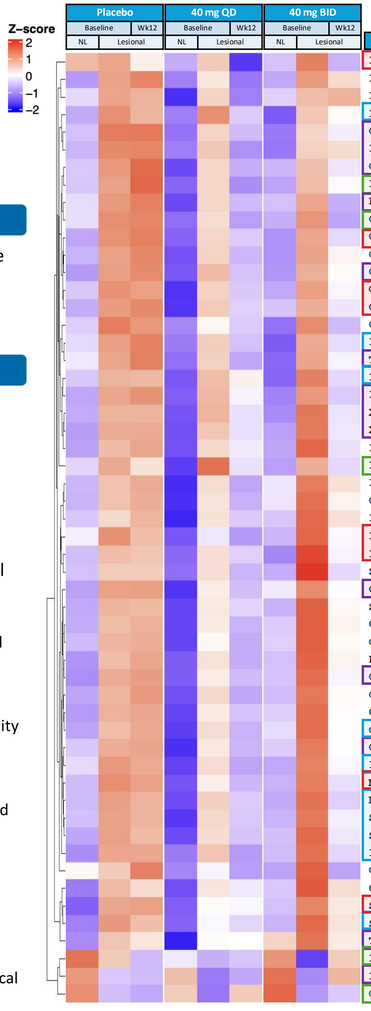
- Phase 2 randomized, placebo-controlled trial (STRIDE) Participants: Adults ages 18-75 with moderate-to-severe plaque psoriasis (≥10% BSA, PASI ≥12, sPGA ≥3) received envudeucitinib for 12 weeks at varying doses. The doses analyzed here are:
  - 40 mg BID (n = 8)
  - 40 mg QD (n = 10)
  - Placebo (n = 10)
- Sample collection: Skin tape strips obtained at baseline and Week 12 in non-lesional and lesional skin

Analyses

- Demographics and baseline clinical scores were compared across highest treatment groups and placebo with F-test and Wilcoxon-Mann-Whitney for continuous and categorical outcomes, respectively, and found to be similar across all treatment arms
- Transcriptomic: RNA-seq for differential expression and gene set variation analysis
  - FASTQ files were mapped to the GRCh38 reference genome with the STAR aligner, and quality control metrics were evaluated with FastQC and MultiQC software
  - Counts were voom transformed and expression for each gene were analyzed with mixed effects models as implemented in the R limma package
  - Contrasts of interest were evaluated with empirical Bayes with the report of unadjusted and FDR-adjusted p-values
  - Pathway activity was quantified with the GSVA Z-score method implemented in the gsva R library
  - Heatmap row order was determined by hierarchical clustering based on gene expression profile across the columns using the R package ComplexHeatmap. Only immune-related genes with significant change in expression between BID vs. Placebo or QD vs. Placebo are shown
- Spearman correlation coefficient calculated for biomarkers and post-treatment changes in clinical scores

Results

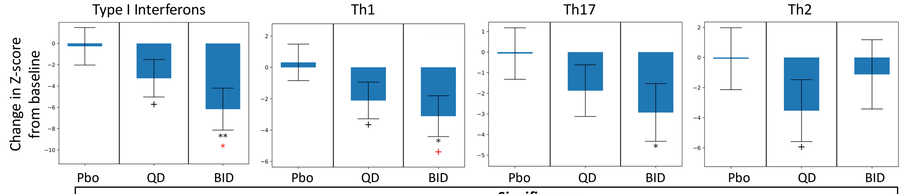
Both 40 mg QD and BID groups showed downregulation of immune gene expression, with significant decreases in Interferon-, Th1-, and Th17-related markers



Immune Genes	Week 12 vs. Baseline				
	PBO	40 mg QD	40 mg BD	40 mg QD vs. PBO	40 mg BID vs. PBO
IFNA2 ---:	-1.61	-5.50*	-3.51	-3.41	-2.17
ITGB2 ---:	1.29	-4.06*	-1.73	-5.24*	-2.23
ITGAX ---:	-1.13	-4.29*	1.08	-3.81	1.21
IL24 ----:	-1.43	-5.39*	-1.68	-3.76	-1.17
CCL19 ---:	1.03	-4.26*	-2.25	-4.38+	-2.33
IL27 ----:	1.03	-3.86*	-1.02	-3.94	-1.05
CD8A ----:	1.60	-3.92*	-2.53	-6.28*	-4.06
ITK -----:	1.74	-4.59*	-1.91	-8.00*	-3.32
LAG3 ----:	1.32	-3.76*	-6.50**	-4.96+	-8.57*
CCL13 ---:	1.12	-7.62**	-16.22***	-8.46*	-18.13**
CXCL11 --:	1.36	-4.11+	-6.28*	-5.54	-8.51+
CXCL3 ---:	1.46	-5.31*	-3.36	-7.78+	-4.92
CD80 ----:	1.29	-5.54*	-2.71	-7.21+	-3.51
OASL ----:	-1.25	-5.50*	-5.98*	-4.41	-4.79
CXCL9 ---:	1.48	-7.21+	-8.06*	-10.63	-11.96+
CCL3L1 --:	-1.29	-1.74	-6.41**	-1.35	-4.96+
IL6 -----:	1.73	-7.26*	-8.17*	-12.55*	-14.12*
TNFRSF9 -:	1.41	-4.06*	-2.75	-5.74+	-3.89
IL20 ----:	1.00	-1.87	-5.82*	-1.87	-5.78+
IFNG ----:	1.39	-4.82*	-11.55**	-6.68+	-16.11*
XCL2 ----:	-1.02	-6.11*	-11.31*	-5.94	-11.08+
XCL1 ----:	1.00	-4.82+	-11.16**	-4.82	-11.16*
IFNGR1 --:	1.12	-1.32	-2.58**	-1.47	-2.89*
IL19 ----:	-1.48	-4.11*	-2.22	-2.75	-1.49
IL1B ----:	1.42	-5.46*	-4.86+	-7.78+	-6.92+
CD69 ----:	1.39	-5.58+	-10.13**	-7.67	-14.03*
IL1A ----:	1.48	-2.25	-3.63*	-3.34	-5.39*
IRF1 ----:	-1.39	-1.83	-3.71*	-1.31	-2.66
ISG20 ---:	-1.09	-2.43+	-8.69***	-2.23	-8.00**
S100P ---:	1.02	-3.43+	-18.00***	-3.53	-18.38**
CCL4L2 --:	1.01	-3.18	-6.50*	-3.23	-6.59
S100A12 -:	-1.11	-2.95	-12.73**	-2.64	-11.47*
CCR1 ----:	1.23	-3.46	-9.19**	-4.23	-11.24*
CCRL2 ---:	1.13	-3.66	-12.30**	-4.17	-13.93*
PDE4B ---:	1.33	-3.56*	-6.15**	-4.69+	-8.17*
CCL3 ----:	1.23	-3.36	-11.31**	-4.17	-13.93*
CXCL2 ---:	1.49	-5.54+	-7.01*	-8.28+	-10.41+
CXCL1 ----:	1.19	-3.07	-8.82*	-3.66	-10.48+
CXCL8 ---:	1.44	-5.35+	-11.71**	-7.78+	-17.03*
CCL4 ----:	1.14	-3.73	-7.62*	-4.26	-8.69+
IL36A ---:	-1.29	-6.87+	-8.94*	-5.31	-6.96
MX1 -----:	-1.23	-2.46	-6.59**	-2.00	-5.31+
DEFB4A --:	-1.40	-5.06+	-24.59**	-3.61	-17.39*
S100A8 --:	-1.28	-3.48	-8.34*	-2.73	-6.50+
S100A7 --:	-1.27	-2.23	-4.99*	-1.75	-3.92
IL22 ----:	1.01	-6.28+	-8.34*	-6.32	-8.40
CD3D ----:	1.87	-2.10	-6.54**	-3.92	-12.21**
CAMP ----:	-1.65	-2.22	-7.94*	-1.35	-4.82
STAT1 ---:	1.06	-1.09	-2.20*	-1.16	-2.33
STAT3 ---:	-1.39	-1.27	-2.89*	1.10	-2.07
TNFSF10 -:	-1.33	1.01	-2.77*	1.36	-2.08
IL16 ----:	-1.77	1.05	3.23*	1.85	5.70*
IL18 ----:	-1.06	1.35	3.18*	1.43	3.39+
GATA3 ---:	-1.16	3.39*	1.29	3.89+	1.48

Type 1 IFN
Th1
Th17/Th22
Th2

Gene set variation analysis of tape strip RNA-seq revealed greater molecular suppression in the 40 mg BID group at Week 12



Black: significant difference compared to baseline
Red: significant difference compared to placebo

Significance:
+ : p<0.1 *** : p<0.05**
**** : p<0.01** ***** : p<0.001**

- These molecular findings mirror the dose-dependent clinical improvements found in the full clinical trials

Clinical improvements were strongly correlated with transcript reductions of IFNG, IL22, IL17A, and key cytokines

Correlation with BSA		
Biomarker	R	p-value
IFNG	**0.711**	**3.28E-05**
CD80	0.700	4.74E-05
TNFRSF9	0.677	1.05E-04
ITK	0.659	1.87E-04
CD3D	0.651	2.33E-04
CXCL11	0.632	4.11E-04
CD69	0.623	0.001
CD8A	0.616	0.001
CXCL8	0.605	0.001
XCL1	0.602	0.001
IL1A	0.602	0.001
LAG3	0.598	0.001
IL22	**0.597**	**0.001**
CCL3	0.581	0.001
IL17A	**0.542**	**0.003**

Correlation with PASI		
Biomarker	R	p-value
IFNG	**0.663**	**0.0001**
CD69	0.593	0.001
CXCL8	0.575	0.001
CXCL11	0.536	0.003
IL1A	0.528	0.004
CCR1	0.524	0.004
LAG3	0.520	0.005
ISG20	0.520	0.005
IL22	**0.510**	**0.006**
CD3D	0.499	0.007
CCRL2	0.495	0.007
XCL1	0.493	0.008
IL6	0.489	0.008
PDE4B	0.486	0.009
IL17A	**0.459**	**0.014**

Correlation with PNRS		
Biomarker	R	p-value
IFNG	**0.848**	**1.26E-08**
IL22	**0.745**	**5.36E-06**
IL17A	**0.724**	**1.34E-05**
XCL1	0.720	1.54E-05
XCL2	0.708	2.55E-05
ITK	0.687	5.48E-05
TNFRSF9	0.666	1.11E-04
CD3D	0.665	1.13E-04
LAG3	0.665	1.14E-04
CD8A	0.609	0.001
CD80	0.559	0.002
CXCL11	0.522	0.004
DEFB4A	0.519	0.005
CXCL9	0.470	0.012
CD69	0.469	0.012

- IFNG, IL22, and IL17A are strongly correlated with all three clinical severity scores. Top correlated immune-related genes listed

Conclusions

- Envudeucitinib at 40 mg QD and BID produces robust suppression of pathogenic Th1, Th17, and interferon-related pathways at the transcriptomic level in skin tape specimens
- Molecular modulation parallels clinical efficacy, supporting TYK2 inhibition as a potent therapeutic strategy for moderate-to-severe psoriasis

References

1. Ucpinar S, Kwan JK, Hoffman JD, Tilley MK, Douglas JA, Rubio RG, Lu R, Nunn PA, Langrish CL. Safety, tolerability, pharmacokinetics, and pharmacodynamics of the oral allosteric TYK2 inhibitor ESK-001 using a randomized, double-blind, placebo-controlled study design. Clin Transl Sci. 2024 Dec;17(12):e70094. doi: 10.1111/cts.70094. PMID: 39604226; PMCID: PMC11602527.
2. Blauvelt A, Arenberger P, Sauder MB, Couvillion M, Rubio RG, Vlahakis NE, Ucpinar S, Ma G, Hitraya E, Tilley MK, Papp KA; STRIDE Investigators. Highly selective, allosteric inhibition of TYK2 with oral ESK-001 in patients with moderate-to-severe plaque psoriasis: Results from STRIDE, a 12-week, randomized, double-blinded, placebo-controlled, dose-ranging phase 2 study. J Am Acad Dermatol. 2025 Jul 12:S0190-9622(25)02466-1. doi: 10.1016/j.jaad.2025.07.013.

Disclosures

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†Author is employed by Alumis Inc.