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ESK-001, an allosteric TYK2 inhibitor, maximally suppresses type I interferon, a therapeutic pathway central to SLE and CLE

Poster No. 2434

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Background

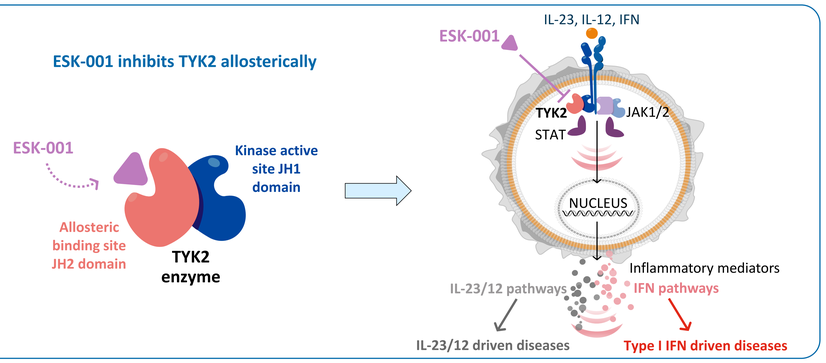
Tyrosine kinase 2 (TYK2) is central to key pathways in many immune-mediated diseases

- TYK2 mediates signaling from key proinflammatory cytokines, including **IL-23, IL-12, and type I IFN** through STAT phosphorylation.
- Human loss-of-function TYK2 genetic variants protect from immune-mediated diseases, including **systemic lupus erythematosus (SLE)**.[1]
- TYK2 is an established therapeutic target, with **TYK2 inhibitors** being recently approved for plaque psoriasis (PsO), and **trials being ongoing in SLE** and other indications.[2]

ESK-001 is a potent, highly selective, oral, allosteric small molecule inhibitor of TYK2

- ESK-001 has high intrinsic selectivity for TYK2, without observed JAK-related pharmacology.
- ESK-001 is currently under development for the treatment of immune-mediated inflammatory diseases, including PsO and **active SLE (LUMUS trial)**.
- Recent ESK-001 STRIDE trial in moderate-to-severe PsO showed a clear dose-dependent effect, with maximal therapeutic response achieved at the top 40 mg BID dose, while being generally safe and well tolerated.

ESK-001 inhibits TYK2 allosterically



Objectives

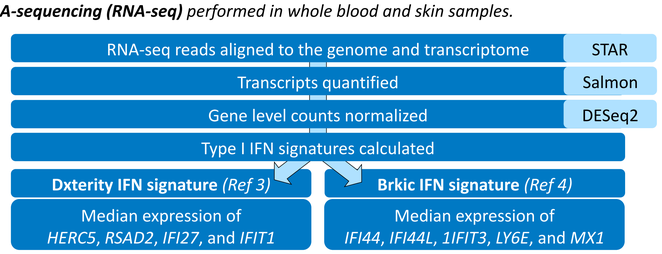
The objective of this study was to characterize the ability of ESK-001, a novel allosteric small molecule TYK2 inhibitor, to downregulate cytokine pathways such as type I interferons that signal through TYK2 and are thought to be central to SLE and cutaneous lupus erythematosus (CLE) pathogenesis.

Methods

- ***Public Expression Data:***
identify genes with elevated expression in patients with SLE or CLE

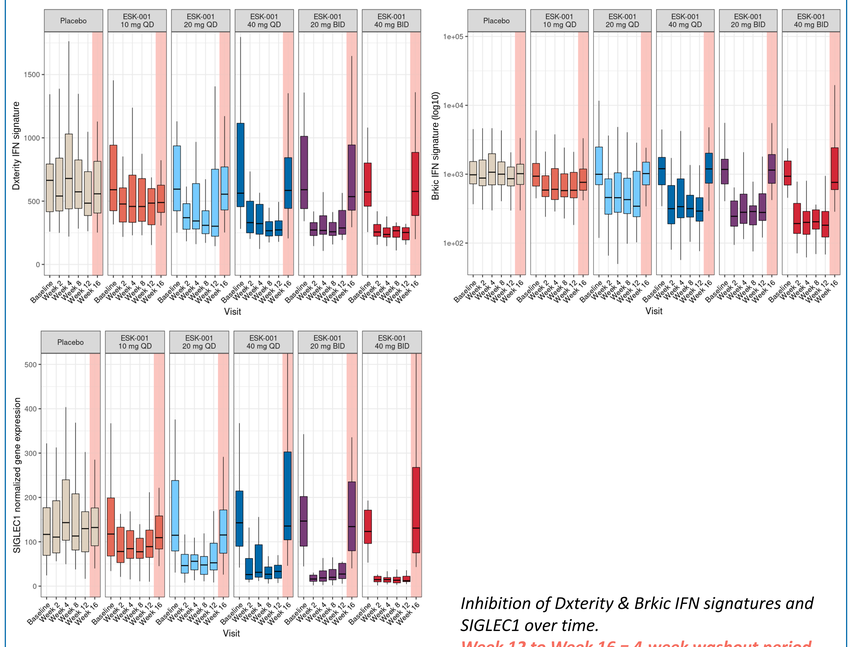
GEO accession	Study description	Analysis of
GSE110169	Total blood RNA profiling to define molecular signatures of **SLE**	normalized microarray values
GSE112087	Whole-blood RNA-sequencing in patients with **SLE**	raw RNA-seq count tables
GSE154851	Investigation of genes associated with atherosclerosis in blood of patients with **SLE**	normalized microarray values
GSE109248	Genome-wide analysis of gene expression of **CLE** skin lesions	normalized microarray values

- ***STRIDE Psoriasis Trial Data:***
explore if expression of IFN signatures is altered by ESK-001
  - ***STRIDE trial*** = a 12-week randomized, double-blinded, placebo-controlled Phase 2 trial 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.*
    - ***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 in whole blood and skin samples.*



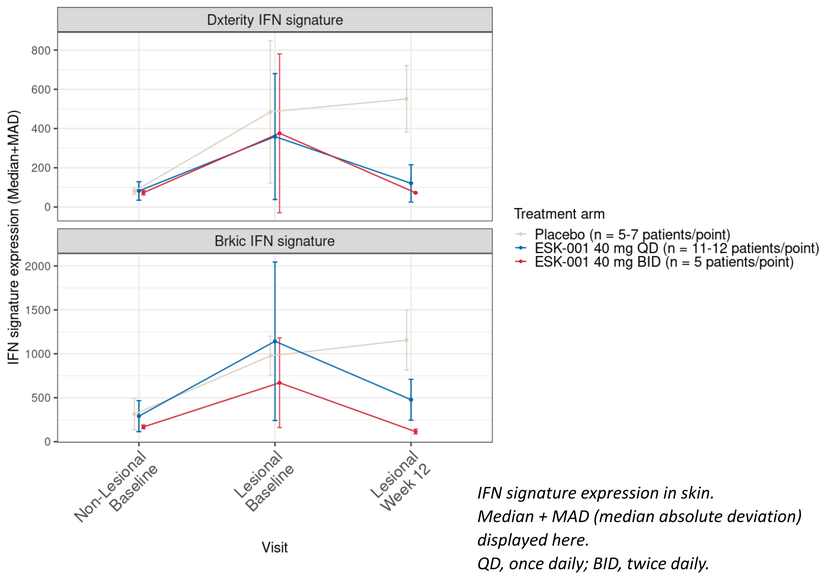
Results

STRIDE blood RNA-seq analysis shows that ESK-001 administration suppresses expression of two type I IFN signatures in a dose-dependent manner along with the novel TYK2 pharmacodynamic biomarker *SIGLEC1*



Inhibition of Dxterity & Brkic IFN signatures and SIGLEC1 over time.
Week 12 to Week 16 = 4-week washout period.
QD, once daily; BID, twice daily.

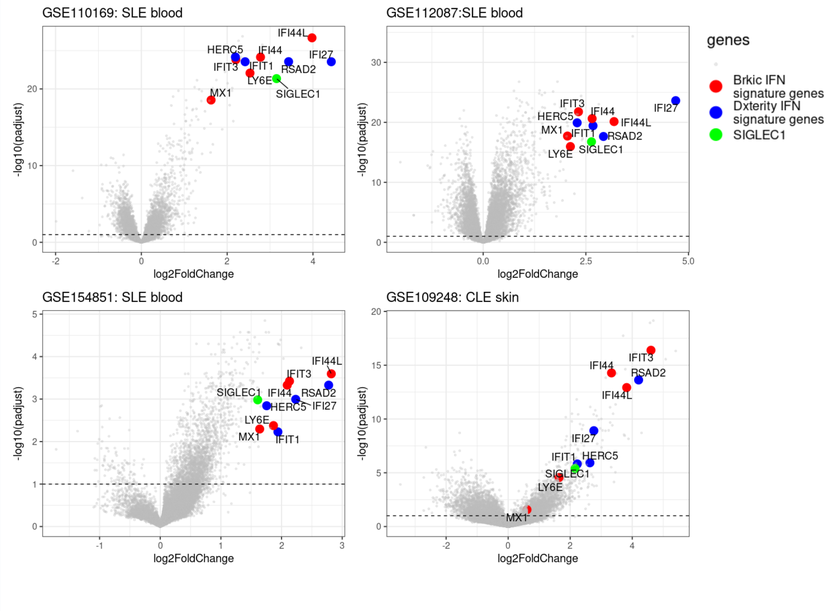
STRIDE skin RNA-seq analysis shows that ESK-001 administration suppresses expression of two type I IFN signatures in a dose-dependent manner to non-lesional baseline levels



IFN signature expression in skin.
Median + MAD (median absolute deviation) displayed here.
QD, once daily; BID, twice daily.

Results

Analysis of four public gene expression datasets of SLE blood and CLE skin shows that expression of genes in two definitions of type I IFN response and of *SIGLEC1* is highly elevated in patients versus controls



Differential expression analysis of public SLE blood and CLE skin gene expression datasets.
Genes with positive fold change are enriched in SLE or CLE.
Horizontal dashed line: -log10(padjust) = 0.1

Conclusions

- ESK-001 demonstrates **dose-dependent suppression of type I IFN, a key pathway believed to be central to SLE and CLE pathogenesis**.
  - Blood RNA-seq shows **dose-dependent inhibition of type I IFN gene expression signatures**.
  - **Type I IFN** was also **suppressed in the skin** in a dose-dependent manner.
- Analysis of public gene expression datasets of SLE blood and CLE skin shows significant enrichment of type I IFN signature genes and of our novel pharmacodynamic biomarker, *SIGLEC1*, in SLE compared to controls.
- These findings **support the full dose range in the ongoing SLE Ph2b LUMUS trial** *(NCT05966480)*, assessing maximal inhibition of type I IFN gene expression signatures believed to be central to the pathophysiology of SLE and CLE at the ESK-001 40 mg BID dose.

References

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Disclosures

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All authors are employed by Alumis.
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