EA DV CONGRESS
AMSTERDAM 25-28 SEPTEMBER 2024
EUROPEAN ACADEMY OF DERMATOLOGY & VENEREOLOGY

Abstract N°: 8009

Efficacy and safety of ESK-001, a highly selective oral TYK2 inhibitor, in moderate-to-severe plaque psoriasis: Phase 2 results through week 28

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Introduction & Objectives: ESK-001 is an oral, highly selective allosteric TYK2 inhibitor being developed for patients with moderate-to-severe plaque psoriasis. The Phase 2 ESK-001 program consists of a completed randomized, placebo-controlled, dose-ranging study (STRIDE, NCT05600036) and an ongoing open-label extension study (OLE, NCT05739435) in patients completing STRIDE. Herein, efficacy and safety results of ESK-001 through Week 28 in the OLE are reported.

Materials & Methods: STRIDE was a randomized, double-blinded, placebo-controlled, 12-week study in patients with moderate-to-severe psoriasis, evaluating five ESK-001 dose groups, from 10 mg QD to 40 mg BID compared to placebo. The OLE study is ongoing and evaluating long-term safety and efficacy in patients from all dose groups completing STRIDE, with patients allocated 1:1 to receive long term ESK-001 40 mg QD or 40 mg BID. The primary endpoint was safety and efficacy endpoints included PASI 75/90/100 and sPGA 0/1. All clinical data through Week 28 were analyzed, with response rates reported using as observed (AO) and modified non-responder imputation (mNRI) methods.

Results: The primary and key secondary endpoints in STRIDE were met ($p<0.0001$) at Week 12 for the top dose levels with clear dose-dependent effects. Clinical efficacy was mirrored by decreased expression of pathogenic cytokines within lesions, including IL-23 and IL-17A, which returned to non-lesional levels at Week 12. In the OLE, efficacy increased substantially in a dose-dependent manner through Week 28 (**Table**). In the 40 mg BID group, 83% (mNRI)/93% (AO) of patients achieved PASI 75 and 63% (mNRI)/72% (AO) achieved PASI 90. sPGA 0/1 responses increased from 59% at Week 12 to 68% (mNRI)/76% (AO) at Week 28 in the 40 mg BID group. Median % changes in PASI from baseline to Week 28 were 95% (40 mg BID) and 89% (40 mg QD). Patients within each OLE dose arm achieved similar levels of efficacy by Week 28 regardless of their initial dose in STRIDE including placebo. ESK-001 was generally safe and well-tolerated in STRIDE, with a similar safety profile in the OLE. TEAE frequency and severity were similar across study arms, with the majority being mild-to-moderate and self-limited. No deaths, treatment-related AEs associated with classic JAK inhibitor labeling, or clinically significant laboratory or ECG trends were observed. In both STRIDE and the ongoing OLE, the most common TEAEs were URTIs, nasopharyngitis, and headache.

Table: Increased Efficacy Responses with Longer Exposure to ESK-001

	40 mg BID	40 mg QD
	STRIDE **Week 12**	**OLE** **Week 28**
	NRI (N=39)	AO (N=71)
PASI 75 (%)	64	93
PASI 90 (%)	39	72
PASI 100 (%)	15	35
sPGA 0/1 (%)	59	76

Conclusion: In STRIDE and OLE, Phase 2 studies in patients with moderate-to-severe plaque psoriasis, the oral selective TYK2 inhibitor ESK-001 demonstrated clear dose-dependent efficacy. At the highest dose, 40 mg BID, maximal clinical responses were safely achieved at Week 28. Indirect comparisons of historical data suggest that ESK-001 has the potential for best-in-class efficacy, with efficacy in the range reported for many biologic therapies for psoriasis.