P1004

Patient-Reported Outcomes in the Randomized, Double-Blind Phase 2 Study of ESK-001, an Oral Allosteric TYK2 Inhibitor, in Adults with Moderate-to-Severe Plaque Psoriasis

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Background

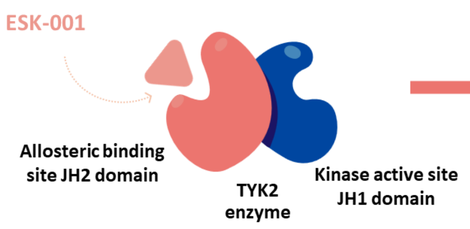
Plaque psoriasis negatively impacts quality of life in patients

- Plaque psoriasis affects 3% of adult population in US and approximately 125 million people worldwide.[1,2]
- Substantial morbidity and often coexistent inflammatory arthritis, cardiometabolic disease, or mental health disorders negatively impact daily life.[1,3]

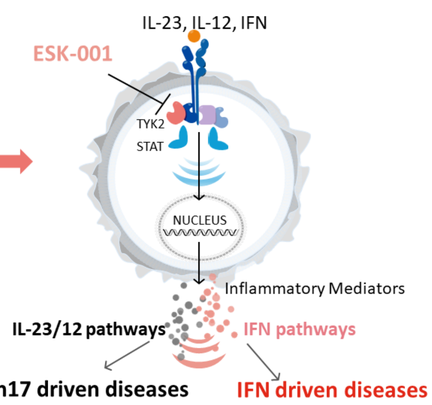
Tyrosine Kinase 2 (TYK2) has a central role in plaque psoriasis pathology

- TYK2 mediates key proinflammatory pathways in plaque psoriasis (IL-23/IL-12/IFN).
- Human TYK2 loss-of-function genetic variants protect from psoriasis development.[4]
- TYK2 is an established therapeutic target, with TYK2 inhibitors being recently approved for psoriasis.

ESK-001 inhibits TYK2 allosterically



ESK-001 maximally inhibits receptor-mediated TYK2 activation



ESK-001 is a highly selective, oral, allosteric small molecule TYK2 inhibitor under development for treatment of moderate-to-severe plaque psoriasis

- ESK-001 is potent and intrinsically selective for TYK2, without observed JAK-related pharmacology.
- ESK-001 allosterically inhibits TYK2, with maximal target inhibition maintained over 24 hours with 40 mg BID dose (both IC50 and IC90).
- The **Phase II ESK-001 program** consists of a completed **placebo-controlled dose ranging study (STRIDE)** and an **ongoing open-label extension (OLE) study** to evaluate the efficacy and safety of ESK-001 in patients with moderate-to-severe plaque psoriasis. More data on the safety, efficacy and tolerability of ESK-001 is shown on **Poster P3284,** and **Presentation at Free Communication 6, Section 5769.**

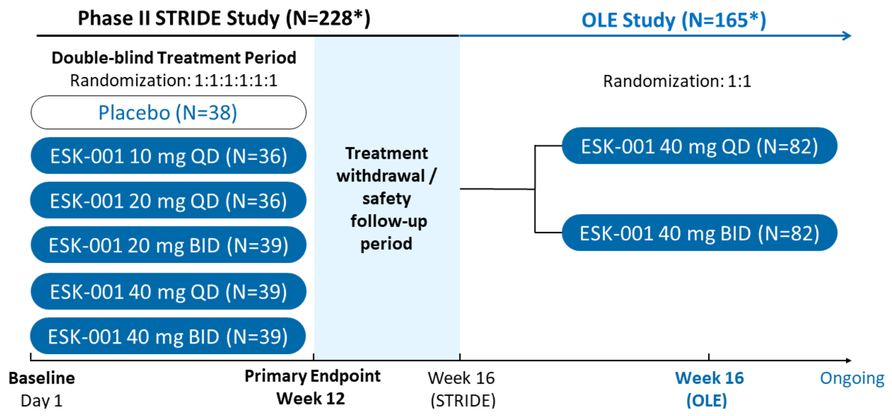
Objectives

This study aimed to evaluate changes in patient-reported outcomes (PROs) measured by Dermatology Life Quality Index (DLQI) and pruritus numerical rating scale (NRS) following treatment with ESK-001 in the Phase II STRIDE study and the subsequent OLE study in adults with moderate-to-severe plaque psoriasis.

Methods

Study Design

- ***STRIDE*** is a randomized, double-blinded, placebo-controlled Phase II study in adults with moderate-to-severe plaque psoriasis (PASI ≥12, sPGA ≥3, BSA ≥10%) *(NCT05600036).*
  - *Endpoints at Week 12 with non-responder imputation (NRI).*
- ***OLE*** is an ongoing open-label extension study in patients with plaque psoriasis who have completed STRIDE study *(NCT05739435)*.
  - *95% of eligible STRIDE patients rolled over to OLE study.*
  - *Data presented for Week 16 time point of prolonged ESK-001 treatment in ongoing OLE study with modified NRI (non-responder if discontinued due to an AE or inadequate response)*
  - *Treatment with ESK-001 can be continued until completion of ESK-001 development in plaque psoriasis.*



** One patient enrolled, but not dosed. N=24: Did not complete STRIDE, N=30: Ineligible for OLE, N=9: Chose not to participate in OLE.*

Primary Endpoint

- Achievement of PASI-75

Secondary Endpoints

- PROs
  - *DLQI*
  - *NRS*
- Achievement of PASI-90
- Achievement of sPGA 0/1

Results

ESK-001 Improved Patient-Reported Quality of Life and Skin Outcomes in STRIDE and OLE Study

	Skin Outcomes Following ESK-001 Treatment		*PROs Following ESK-001 Treatment*				
	PASI-75 % patients (95% CI)	**PASI-90** % patients (95% CI)	**DLQI 0/1** % patients (95% CI)	**Average Pruritus NRS, Change from Baseline** Median (IQR)	**Worst Pruritus NRS, Change from Baseline** Median (IQR)	**Average Pruritus NRS ≤3** % patients (95% CI)	**Worst Pruritus NRS ≤3** % patients (95% CI)
STRIDE, Week 12							
Placebo (N=38)	0.0 (0.0, 9.3)	0.0 (0.0, 9.3)	18.4 (7.7, 34.3)	0.0 (-3.0, 1.0)	-0.5 (-2.0, 1.0)	28.9 (15.4, 45.9)	26.3 (13.4, 43.1)
10 mg QD (N=36)	19.4 (8.2,36.0)**	0.0 (0.0, 9.7)	27.8 (14.2, 45.2)	-2.0 (-3.0, 0.0)*	-2.0 (-4.0, -1.0)**	47.2 (30.4, 64.5)	47.2 (30.4, 64.5)*
20 mg QD (N=36)	33.3 (18.6, 51.0)**	11.1 (3.1, 26.1)*	33.3 (18.6, 51.0)	-2.5 (-6.0, 0.0)**	-2.5 (-5.0, 1.0)**	58.3 (40.8, 74.5)*	50.0 (32.9, 67.1)*
20 mg BID (N=39)	56.4 (36.9, 72.2)***	25.6 (13.0, 42.1)**	51.3 (34.8, 67.6)*	-3.0 (-5.0, -2.0)***	-4.0 (-6.0, -1.0)***	69.2 (52.4, 83.0)**	66.7 (49.8, 80.9)**
40 mg QD (N=39)	56.4 (36.9, 72.2)***	25.6 (13.0, 42.1)**	48.7 (32.4, 65.2)*	-5.0 (-6.0, -3.0)***	-5.0 (-7.0, -3.0)***	69.2 (52.4, 83.0)**	69.2 (52.4, 83.0)**
40 mg BID (N=39)	**64.1 (47.2, 78.8)*** **	**38.5 (23.4, 55.4)*** **	**64.1 (47.2, 78.8)*** **	**-4.0 (-8.0, -3.0)*** **	**-5.0 (-7.0, -3.0)*** **	**71.8 (55.1, 85.0)** **	**74.4 (57.9, 87.0)*** **
OLE, Week 16							
40 mg QD (N=82)	65.0 (53.5, 75.3)	40.0 (29.2, 51.6)	56.8 (45.3, 67.8)	-4.0 (-6.0, -2.0)	-5.0 (-7.0, -2.0)	66.7 (55.3, 76.8)	65.4 (54.0, 75.7)
40 mg BID (N=82)	**81.5 (71.3, 89.2)**	**50.6 (39.3, 61.9)**	**64.2 (52.8, 74.6)**	**-4.0 (-7.0, -2.0)**	**-5.0 (-7.0, -3.0)**	**77.8 (67.2, 86.3)**	**79.0 (68.5, 87.3)**

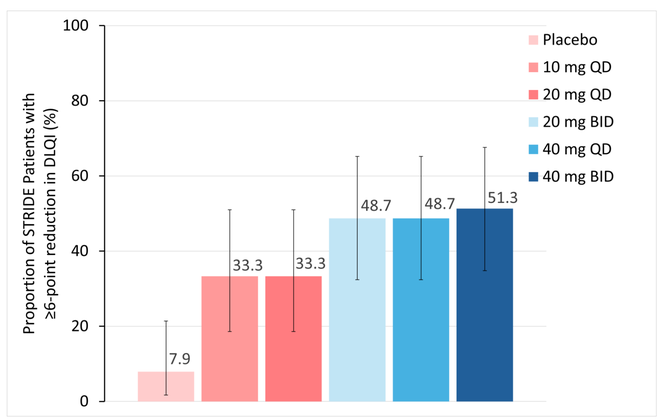
*STRIDE statistics: *p<0.05 vs placebo, **p<0.001 vs placebo, ***p<0.0001 vs placebo*

Higher doses of ESK-001 significantly improved skin outcomes (PASI, sPGA) with substantially higher responses in OLE study

- Dose-dependent response.
- Primary (PASI-75) and secondary (PASI-90) endpoints met at three highest doses (p<0.001 vs placebo) in STRIDE study.
- Continued ESK-001 treatment increased efficacy by Week 16 in OLE study.
- The proportion of patients that achieved sPGA≤1 was largest at highest ESK-001 dose (40 mg BID) at Week 12 in STRIDE study and Week 16 in OLE study.
  - *sPGA 0 = 23% (STRIDE; p<0.001 vs placebo 0%), 33% (OLE).*
  - *sPGA 0/1 = 59% (STRIDE; p<0.001 vs placebo 8%), 65% (OLE).*

ESK-001 was safe and well tolerated in STRIDE and OLE study

- The majority of TEAEs were mild-to-moderate and self-limited, irrespective of dose/exposure time.
- Upper respiratory tract infections, nasopharyngitis and headache were most common.



ESK-001 treatment led to clinically meaningful reductions in DLQI-scores and higher DLQI-0/1 responses in STRIDE and OLE study

- Dose-dependent response with improvement in all dose arms of STRIDE study.
- Largest clinically meaningful reductions in DLQI at highest ESK-001 dose (40 mg BID) in STRIDE study.
  - *62% had ≥4 point reduction, 54% had ≥5 point reduction, 51% had ≥6 point reduction.*
- 64% of STRIDE patients achieved DLQI 0/1 at highest ESK-001 dose (40 mg BID; p<0.0001 vs placebo).
- This improvement in QoL was maintained in OLE study with a reduction in DLQI of 4, 5, and 6 points in 67%, 53% and 47% of patients, respectively, and achievement of DLQI 0/1 similar to STRIDE study.

Higher doses of ESK-001 significantly reduced pruritus severity in STRIDE and OLE study

- Maximal reduction in both average and at worst pruritus severity at highest doses in STRIDE study.
- Dose-dependent response for both average and worst pruritus NRS.
- Continued treatment with ESK-001 in OLE study maintained benefit.

Over 70% of patients in STRIDE study achieved pruritus score ≤3 at the highest ESK-001 dose with steady improvement during OLE study

- Significantly more patients achieved pruritus NRS ≤3 when treated with three highest ESK-001 doses compared to placebo (p<0.001 vs placebo).
- Dose-dependent response was observed.
- Maximal effects were obtained following prolonged exposure to ESK-001 in OLE study.

Conclusions

Phase II studies with **ESK-001 in patients with moderate-to-severe plaque psoriasis** show that ESK-001 **positively impacted the life of patients** by inducing clinically meaningful **improvements** in important **PRO measures (DLQI and psoriasis-associated pruritus)** that support the efficacy of ESK-001 for treatment of moderate-to-severe plaque psoriasis.

- ESK-001 significantly improved patient-reported quality of life (DLQI & pruritus NRS) in a **dose-dependent manner** in patients who carry a high disease and quality of life burden.
- Improved DLQI & pruritus NRS scores were consistent with improved skin outcomes.
- Improvements in PROs were maintained in the OLE study.
- ESK-001 was **well tolerated** across all dose arms in STRIDE and in OLE studies, and no clinically important safety signals have been identified to date.

References

[1] National Psoriasis Foundation, 2022
[2] Armstrong et al. *JAMA Dermatol,* 2021
[3] Bu et al. *Front Immunol*, 2022
[4] Dendrou et al. *Sci Transl Med*, 2016

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