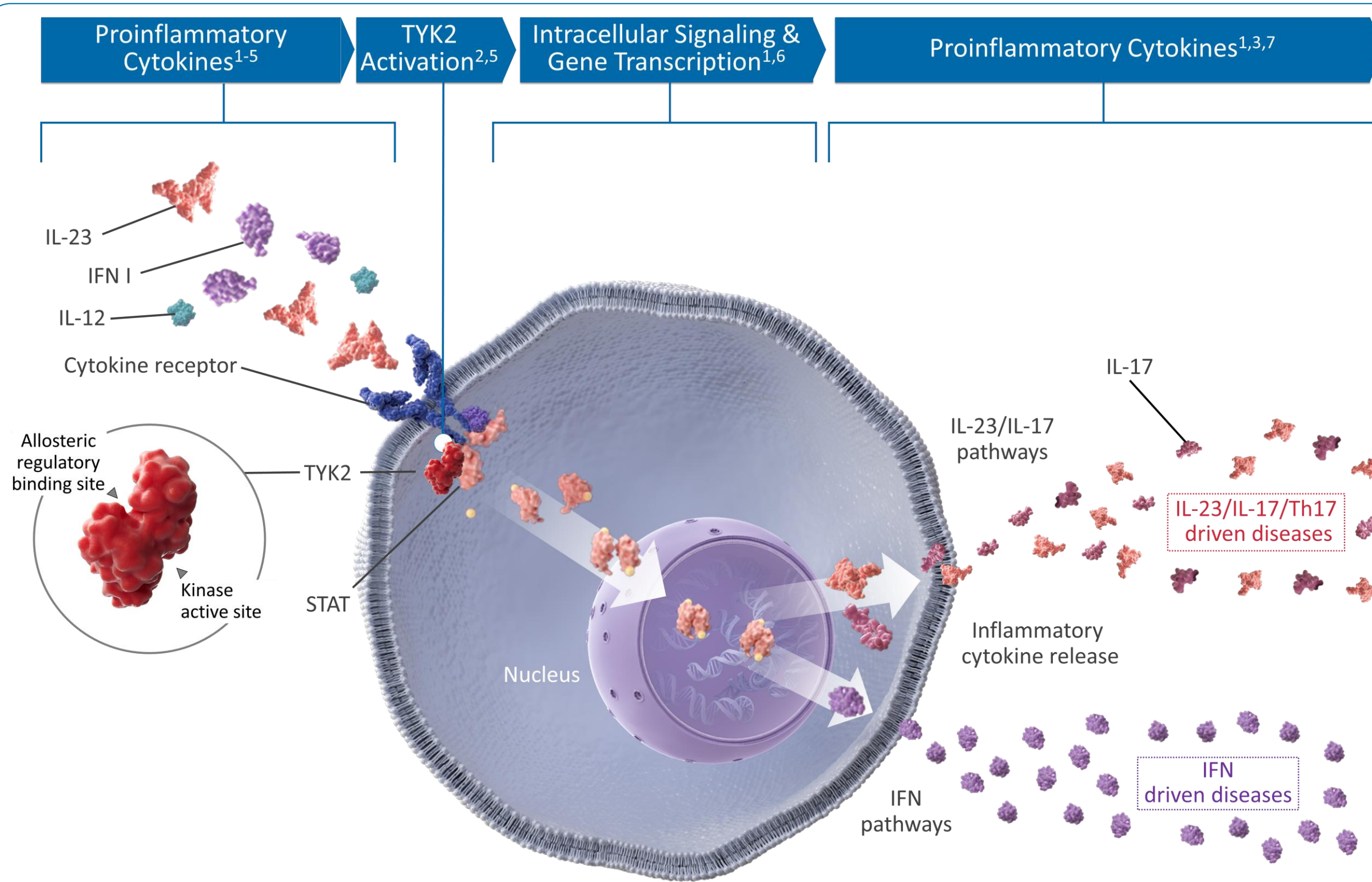


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Background



Plaque psoriasis negatively impacts quality of life in patients

- Plaque psoriasis affects 3% of adult population in US and approximately 125 million people worldwide.^{8,9}
- Substantial morbidity and often coexistent inflammatory arthritis, cardiometabolic disease, or mental health disorders negatively impact daily life.^{8,10}
- ESK-001 is an oral, next-generation tyrosine kinase 2 (TYK2) inhibitor** that delivers maximal target inhibition and reduces off-target effects to correct immune dysregulation across the spectrum of diseases driven by proinflammatory mediators, including IL-23, IL-17, and IFN I.^{1,11}
- Combining convenient oral administration with highly selective targeting, it delivers maximal inhibition while minimizing off-target binding and associated adverse effects.¹
- ESK-001 is currently being investigated for the treatment of plaque psoriasis and systemic lupus erythematosus. Potential future indications include psoriatic arthritis, IBD, and other chronic inflammatory conditions.¹²⁻¹⁴
- The **Phase 2 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.

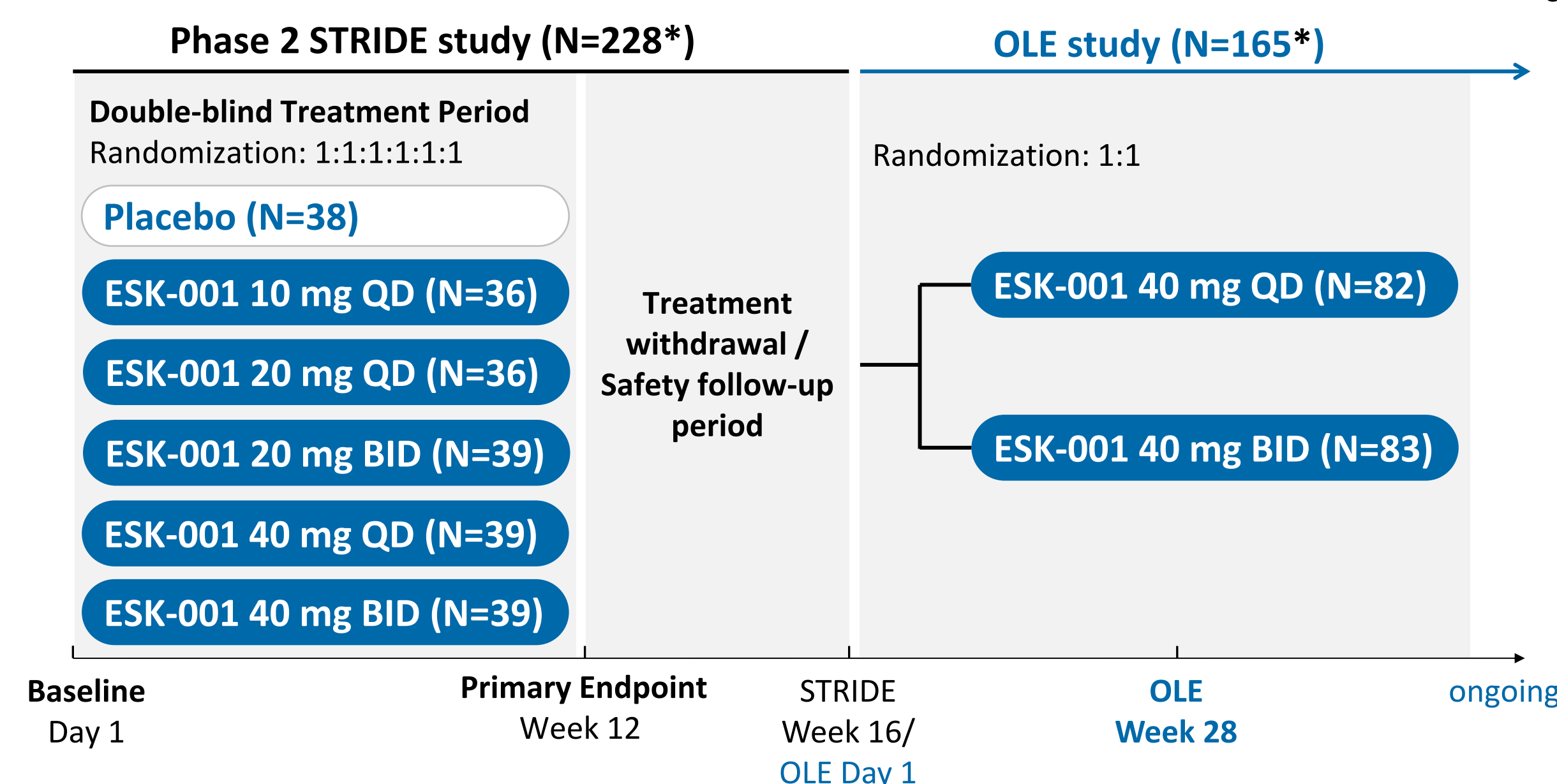
Objectives

This study aimed to evaluate changes in patient-reported outcomes (PROs), measured by Dermatology Life Quality Index (DLQI) and pruritus numerical rating scale (NRS), as well as Psoriasis Area and Severity Index (PASI) responses following treatment with ESK-001 in the Phase 2 STRIDE study and the subsequent OLE study in adults with moderate-to-severe plaque psoriasis.

Methods

Study Design

- STRIDE study** = a completed 12-week randomized, double-blinded, placebo-controlled Phase 2 study of ESK-001 in adults with moderate-to-severe plaque psoriasis (NCT05600036).
 - Adults aged 18-75 years (PASI \geq 12, sPGA \geq 3, BSA \geq 10%) with plaque psoriasis were randomized to receive 1 of the 5 doses of ESK-001 or placebo, given orally for 12 weeks.
 - Study design and eligibility criteria were presented previously.¹⁵
 - Endpoints at Week 12 with non-responder imputation (NRI).
- OLE study** = 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 28 time point of prolonged ESK-001 treatment in ongoing OLE study with modified NRI (non-responder if discontinued due to an adverse event [AE] or inadequate response).
 - Treatment with ESK-001 can be continued while development program is ongoing or until ESK-001 becomes commercially available.



Primary Endpoint (STRIDE)

- Achievement of PASI-75 at Week 12

Secondary Endpoints (STRIDE)

- PROs
 - Change from baseline in DLQI at Week 12
 - Change from baseline in NRS score at Week 12
- Achievement of PASI-90 at Week 12
- Achievement of PASI-100 at Week 12

Conclusions

In these Phase 2 studies in patients with moderate-to-severe plaque psoriasis, ESK-001 demonstrated **significant improvements in clinical response rates and important PRO measures** that support the efficacy of ESK-001 for treatment of moderate-to-severe plaque psoriasis.

- ESK-001 significantly improved PROs 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.

Longer ESK-001 treatment in OLE study resulted in substantially increased PASI and sPGA response rates, while maintaining the improved quality of life measures seen in STRIDE.

These clinical responses and PROs highlight the **positive impact of ESK-001 treatment on the lives of patients with psoriasis**.

ESK-001 was **well tolerated** across all dose arms in the STRIDE and OLE study, and no clinically important safety signals have been identified to date.

Results

ESK-001 improved patient-reported quality of life and skin outcomes in STRIDE and OLE study

	STRIDE, Week 12						
	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)	Pruritus NRS, On Average, Change from Baseline Median (IQR)	Pruritus NRS, At Worst, Change from Baseline Median (IQR)	Average Pruritus NRS \leq 3 % patients (95% CI)	Worst Pruritus NRS \leq 3 % patients (95% CI)
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 28						
40 mg QD (N=82)	67.1 (55.6, 77.3)	44.3 (33.1, 55.9)	51.3 (39.8, 62.6)	-4.0 (-6.0, -2.0)	-5.0 (-7.0, -2.0)	67.5 (56.1, 77.6)	63.8 (52.2, 74.2)
40 mg BID (N=82)	82.7 (72.7, 90.2)	63.0 (51.5, 73.4)	66.7 (55.3, 76.8)	-5.0 (-7.0, -3.0)	-5.5 (-8.0, -3.0)	81.5 (71.3, 89.2)	84.0 (74.1, 91.2)

PASI-response statistics: NRI for STRIDE Week 12 results and modified NRI for OLE Week 28 results; *p<0.05 vs placebo, **p<0.001 vs placebo, ***p<0.0001 vs placebo.
PROs statistics: Median (interquartile range) change from baseline in Pruritus NRS (scored 0-10: severity of itch, on average or at worst, within the past 24 hours).

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

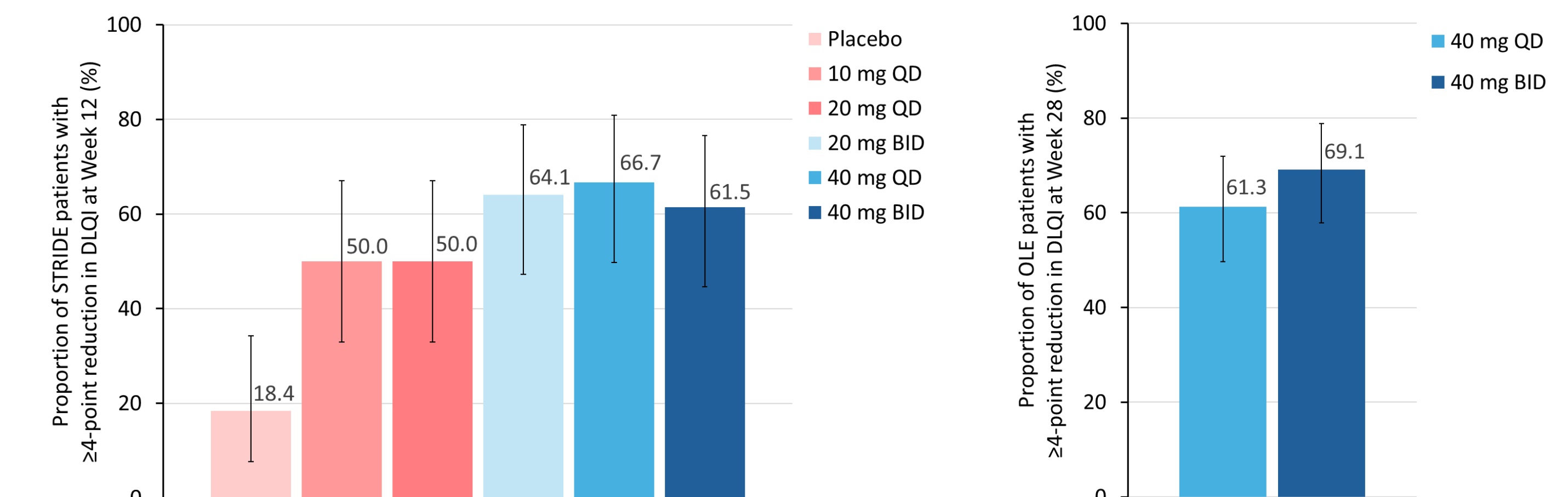
- Dose-dependent response.
- Primary (PASI-75) and key secondary (PASI-90) endpoints met at 3 highest doses (p<0.0001 vs placebo) at Week 12 in STRIDE study.
- Continued ESK-001 treatment increased efficacy by Week 28 in OLE study.
- The proportion of patients that achieved sPGA \leq 1 was largest at highest ESK-001 dose (40 mg BID) at Week 12 in STRIDE study and Week 28 in OLE study.
 - sPGA 0 = 23% (STRIDE; p<0.001 vs placebo 0%), 35% (OLE).
 - sPGA 0/1 = 59% (STRIDE; p<0.001 vs placebo 8%), 68% (OLE).

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 (\geq 4 points) in DLQI at the top 3 highest ESK-001 doses in STRIDE study.
- 64% of STRIDE patients achieved DLQI-0/1 at highest ESK-001 dose (40 mg BID; p<0.0001 vs placebo).
- This improvement in quality of life was maintained in OLE study with a reduction in DLQI of \geq 4 points in 69.1% of patients receiving highest ESK-001 dose (40 mg BID) 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 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 \leq 3 at the highest ESK-001 dose with steady improvement during OLE study**
 - Significantly more patients achieved pruritus NRS \leq 3 when treated with 3 highest ESK-001 doses compared to placebo (p<0.001 vs placebo).
 - Dose-dependent response.
 - Maximal effects were obtained following prolonged exposure to ESK-001 in OLE study.



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