ESK-001, a Highly Selective Oral TYK2 Inhibitor: 52-Week Phase 2 Study Results In Moderate-to-Severe Plaque Psoriasis

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Disclosure of relationships with industry

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Late Breaking Research: Session 1

- AbbVie: Advisory Board, Investigator
- Acelyrin: Investigator
- Almirall: Advisory Board, Investigator
- Alumis: Advisory Board, Investigator
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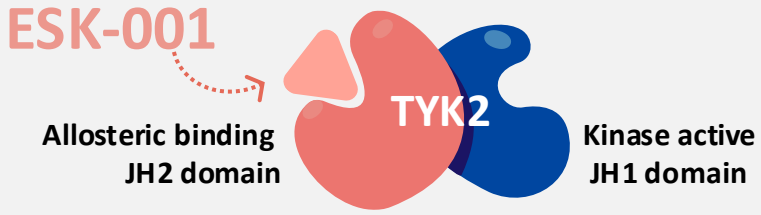
- Regeneron: Advisory Board, Investigator
- Sanofi: Advisory Board, Investigator
- Spherix Global Insights: Advisory Board
- Sun Pharmaceutical Industries: Advisory Board, Investigator
- Syncona: Advisory Board
- Takeda Pharmaceuticals: Advisory Board, Investigator
- UCB: Advisory Board, Investigator, Speaker
- Union: Advisory Board

- No patient care recommendations are made

ESK-001: a potent and selective oral allosteric TYK2 inhibitor designed to achieve durable maximal target inhibition for 24 hours



ESK-001, a highly selective allosteric TYK2 inhibitor

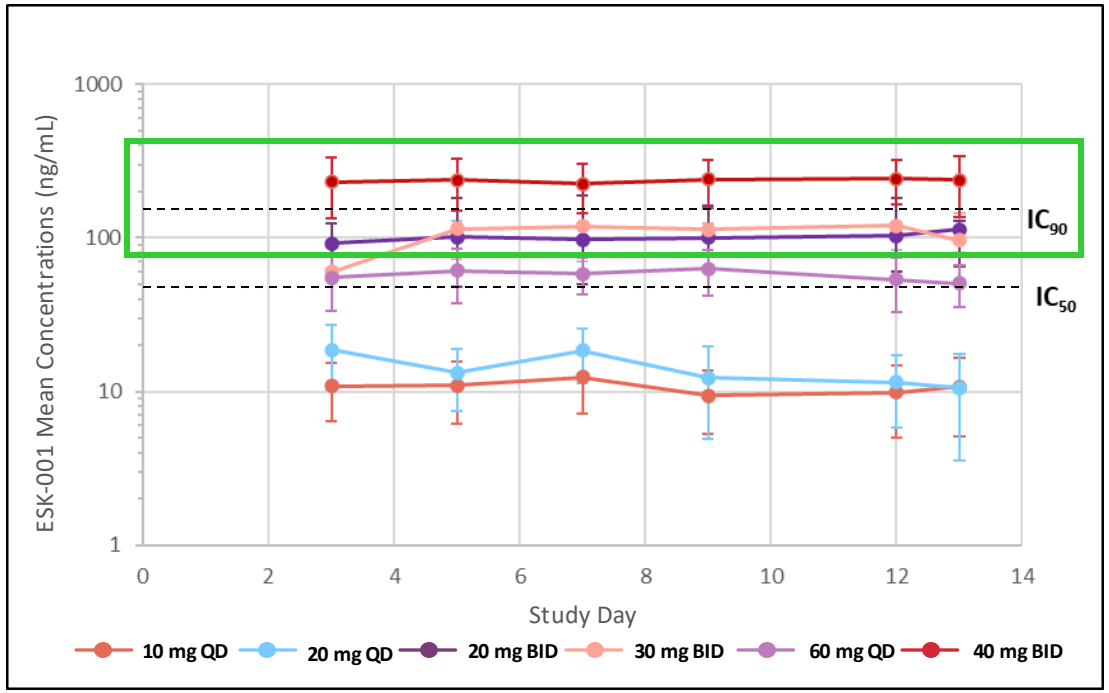
- Intrinsic TYK2 selectivity to JH2 domain allows maximal target engagement and avoids classic JAK inhibitor liabilities

Robust PK/PD relationship guided selection of Phase 2 doses

- Maximal target inhibition achieved at highest clinical dose (40 mg BID)
- Maintained across 24 hour-dosing period

No food effect nor drug-drug interactions

ESK-001 maintained IC90 coverage at trough with 40 mg BID dosing



ESK-001 Phase 1 Multidose Healthy Volunteers Study

PK measurements taken at trough (i.e., at steady state) prior to next dose

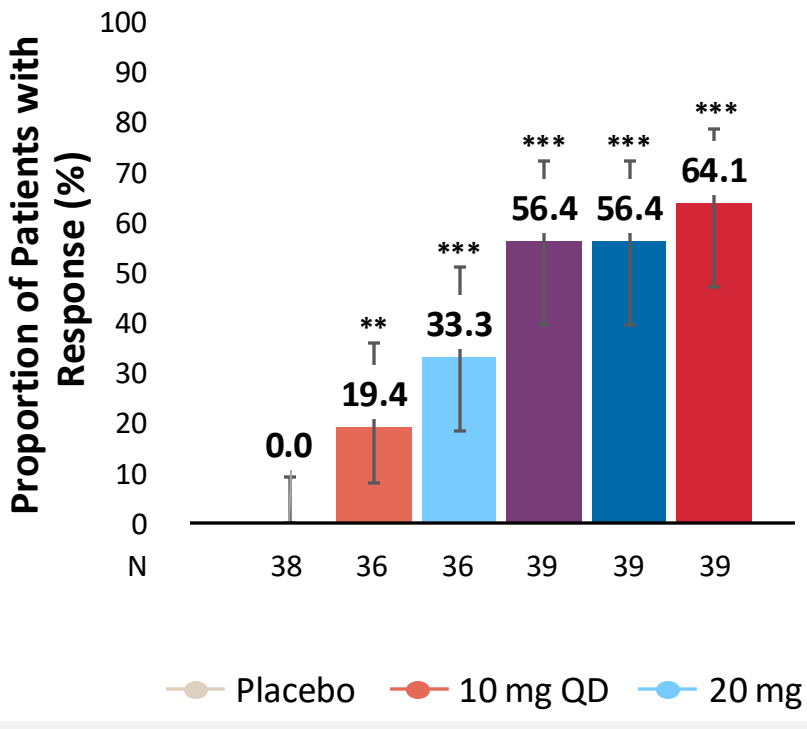
IFNα stimulated human whole blood IC50 and IC90 (dotted lines)

ESK-001 is an investigational product, and its safety and efficacy has not yet been established by any Regulatory Agency
IB Version 6.0, 23 September 2024

STRIDE Study: ESK-001 dose-dependent response, with 40 mg BID demonstrating highest response (also reflected by blood/skin biomarkers)

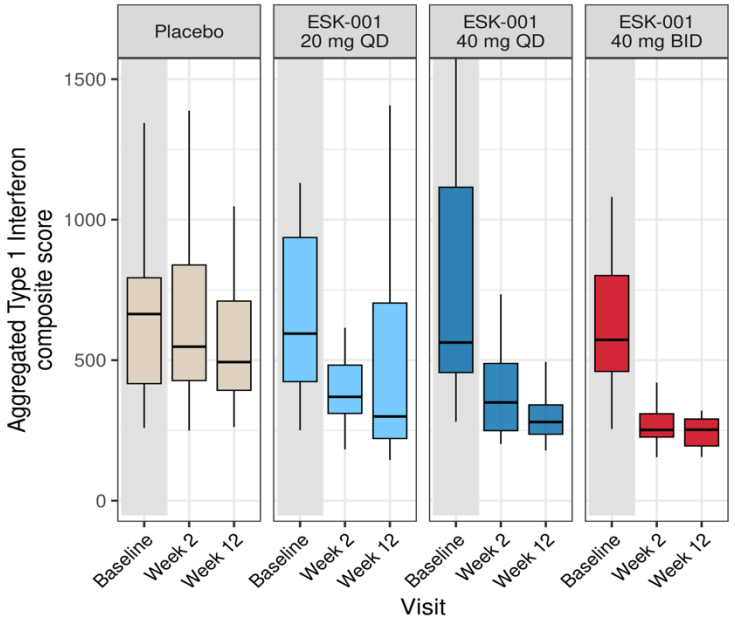
PASI-75

Primary endpoint at Week 12

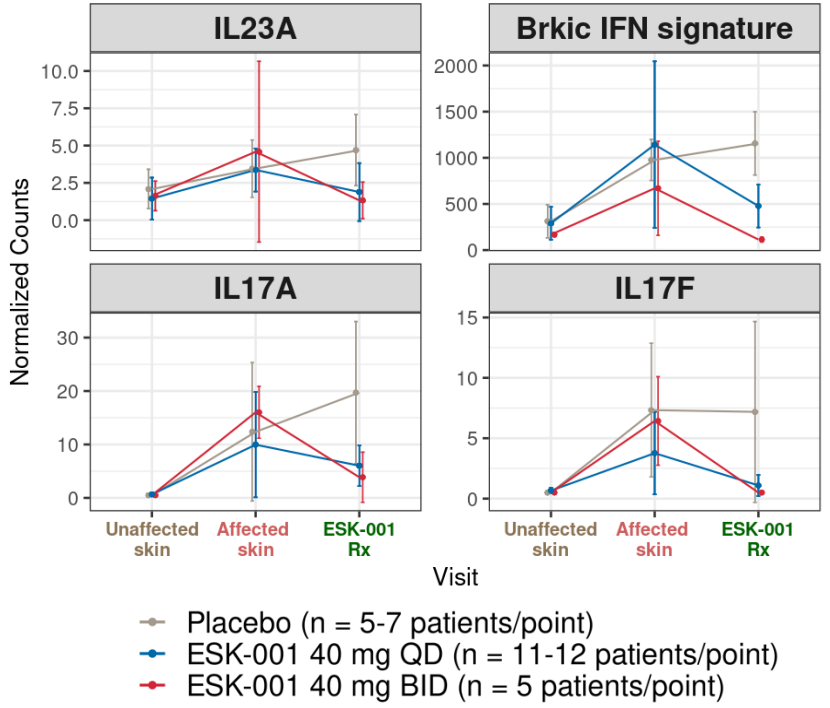


Blood and Skin Biomarkers

ESK-001 inhibition of Type 1 IFN gene signature*



ESK-001 reduced skin inflammatory markers to unaffected skin levels

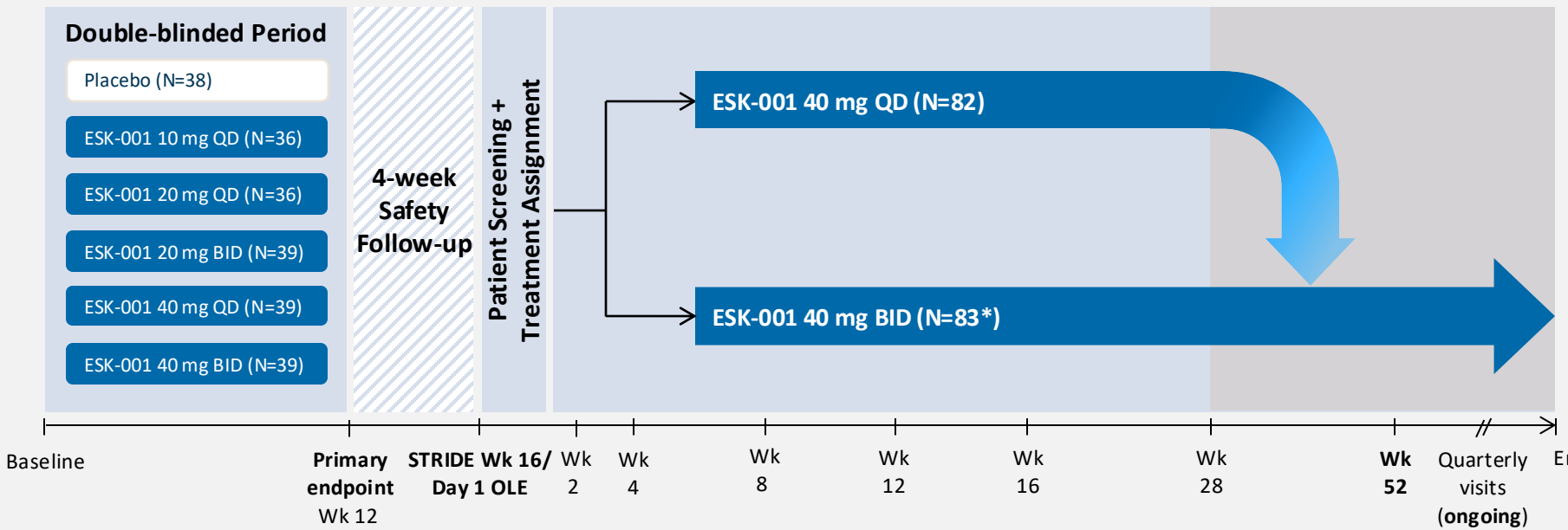


*p<0.05; **p< 0.005; ***p<0.001.
P-value: Proportion of responders of each active arm vs placebo.
Missing data was imputed based on non-responder imputation (NRI).

*In blood by RNA-seq from STRIDE psoriasis study; blood sampled at baseline and pre-dose (trough) at Weeks 2 & 12.

Timepoints:
Baseline nonlesional (Unaffected skin),
baseline lesional (Affected skin),
Week 12 lesional (ESK-001 Rx).

OLE Study: thorough dose selection to identify maximum benefit/risk for evaluation of long-term safety/efficacy of ESK-001



Dose Assignment from STRIDE to OLE

STRIDE Ph2 Dose	OLE Dose	
	40 mg QD	40mg BID
Placebo	17 (21%)	9 (11%)
10 mg QD	30 (37%)	
20 mg QD	26 (32%)	
20 mg BID		30 (36%)
40 mg QD	9 (11%)	17 (21%)
40 mg BID		27 (33%)

OLE Study - Study Design Elements

- 95% of eligible STRIDE patients rolled over to OLE study
- Two highest dose arms from STRIDE, 40 mg QD and 40 mg BID, with QD patients switching to 40 mg BID arm after Week 28**
- Primary objective: to assess the long-term safety and tolerability of ESK-001
- Secondary objectives: to evaluate long-term efficacy of ESK-001 (changes in skin and PROs), clinical response, and PK

*1 patient in the original 40 mg BID arm was not dosed.
**Upon clear identification of most beneficial dose (Week 28 cut), 40 mg QD patients switched to 40 mg BID arm between Weeks 40 and 64.

OLE demographics and baseline disease characteristics were well-balanced across study arms

	ESK-001 40 mg QD (N=82)	ESK-001 40 mg BID* (N=83**)	Overall (N=165)
Age (years), mean (SD)	47.5 (12.7)	50.8 (12.1)	49.2 (12.4)
Male, n (%)	56 (68.3)	61 (73.5)	117 (70.9)
Race, n (%)			
White	63 (76.8)	70 (84.3)	133 (80.6)
Asian	7 (8.5)	4 (4.8)	11 (6.7)
Black/African American	5 (6.1)	1 (1.2)	6 (3.6)
Other/not reported	7 (8.5)	8 (9.6)	15 (9.1)
BMI (kg/m^2), mean (SD)	33.1 (8.8)	31.7 (7.4)	32.4 (8.12)
Psoriasis duration (years), mean (SD)	17.2 (10.9)	22.3 (14.3)	19.8 (13.0)
Previously exposed to biologics or JAK inhibitors, n (%)	38 (46.3)	42 (50.6)	80 (48.5)
PASI, mean (SD)	10.2 (7.2)	6.8 (7.0)	8.5 (7.2)
sPGA score, n (%)			
3 (moderate)	39 (47.6)	23 (27.7)	62 (37.6)
4 (marked)	12 (14.6)	7 (8.4)	19 (11.5)
5 (severe)	0	0	0
BSA involvement (%), mean (SD)	12.9 (13.4)	8.7 (11.1)	10.8 (12.5)

Data are based on the intention-to-treat analysis population and present OLE baseline data.
*Based on original dose assignment at start of OLE; **1 patient in the original 40 mg BID arm was not dosed.
BMI, body mass index; PASI, Psoriasis Area and Severity Index; sPGA, static Physician's Global Assessment; BSA, body surface area.

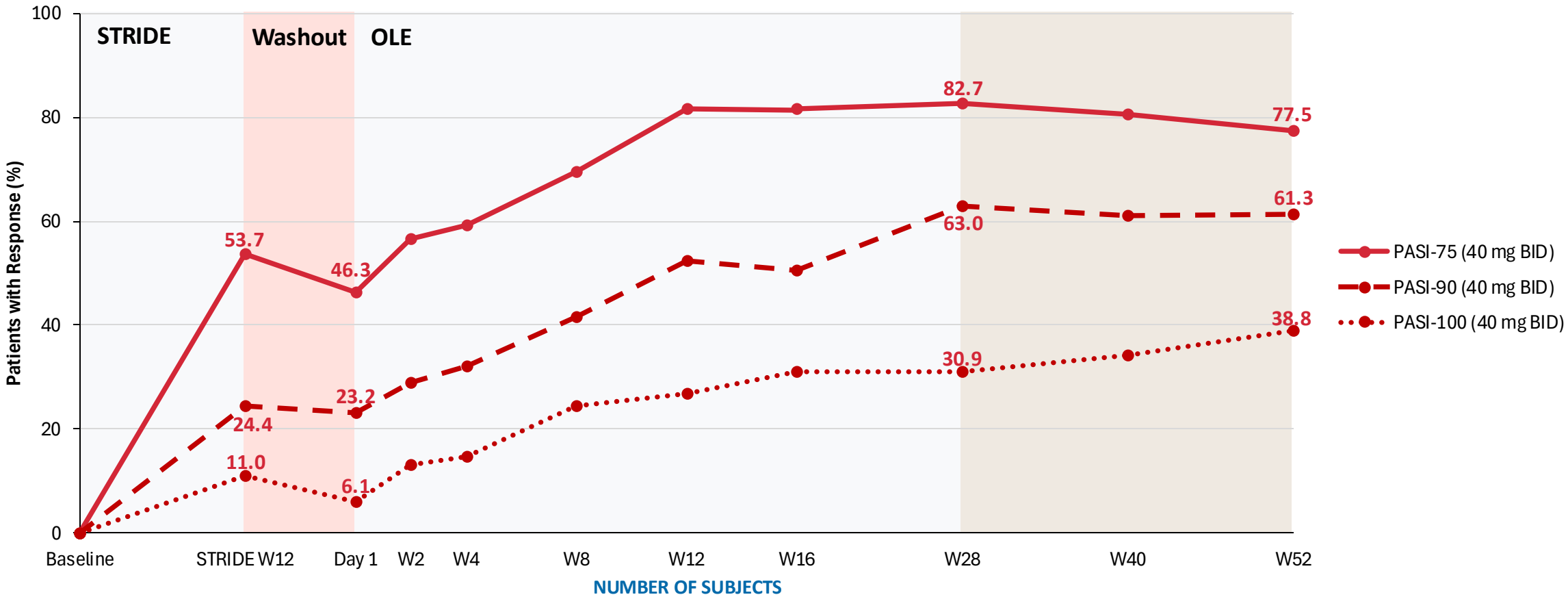
OLE Safety profile of ESK-001: no significant safety findings throughout 52 weeks

	ESK-001 40 mg QD (N=82)		ESK-001 40 mg BID* (N=147)		Overall (N=164)	
	n (%)	EAIR	n (%)	EAIR	n (%)	EAIR
Subjects with ≥ 1 TEAE	50 (61)	122.76	73 (50)	102.33	108 (66)	108.18
Subjects with ≥ 1 TE SAE[1]	2 (2)	3.10	4 (3)	3.39	6 (4)	3.29
Subjects with TEAE related to study drug	12 (15)	20.19	15 (10)	13.83	26 (16)	15.70
Subjects with SAE related to study drug	2 (2)	3.10	2 (1)	1.67	4 (2)	2.17
Subjects with TEAE leading to death	0	-	0	-	0	-
Subjects with TEAE leading to study drug discontinuation[2]	1 (1)	1.55	5 (3)	4.19	6 (4)	3.26
Subjects with TEAE ≥ Grade 3	3 (4)	4.66	6 (4)	5.12	8 (5)	4.42
Most frequent TEAEs (≥5% in any treatment group)						
Nasopharyngitis	10 (12)	16.88	6 (4)	5.15	14 (9)	8.09
Upper respiratory tract infection	3 (4)	4.71	13 (9)	11.66	16 (10)	9.20
Headache	5 (6)	8.28	5 (3)	4.28	10 (6)	5.71
COVID-19	3 (4)	4.74	8 (5)	6.88	11 (7)	6.17

Data are based on the safety analysis population (all treated patients). Safety data displayed are based on 06 SEP 2024 data cut of ongoing OLE study.
*Includes subjects who were randomized to ESK-001 40 mg BID from the start of OLE and who switched from 40 mg QD to 40 mg BID.
[1]TE SAE: inflammatory arthritis, asthma exacerbation, cellulitis, peritonsillar abscess, septic shock, sepsis, non-small cell lung carcinoma, renal cell carcinoma.
[2]40 mg QD: non-small cell lung carcinoma; 40 mg BID: dyspepsia, hypersensitivity, osteomyelitis, pruritus, renal cell carcinoma.
TEAE, treatment-emergent adverse event; SAE, serious adverse event; EAIR, exposure-adjusted incidence rate per 100 patient years.

ESK-001 response over 52 weeks of treatment: increasing PASI-90 and PASI-100 responses over time (mNRI*)

40 mg BID includes only patients originally assigned to 40 mg BID at the start of OLE



*mNRI analysis: if patient discontinued due to AE or inadequate response, then imputed as a non-responder; if discontinued for other reasons, then imputed using LOCF (i.e., last observation carried forward).

ESK-001 response over 52 weeks of treatment: increasing PASI-90 and PASI-100 responses over time (mNRI*)

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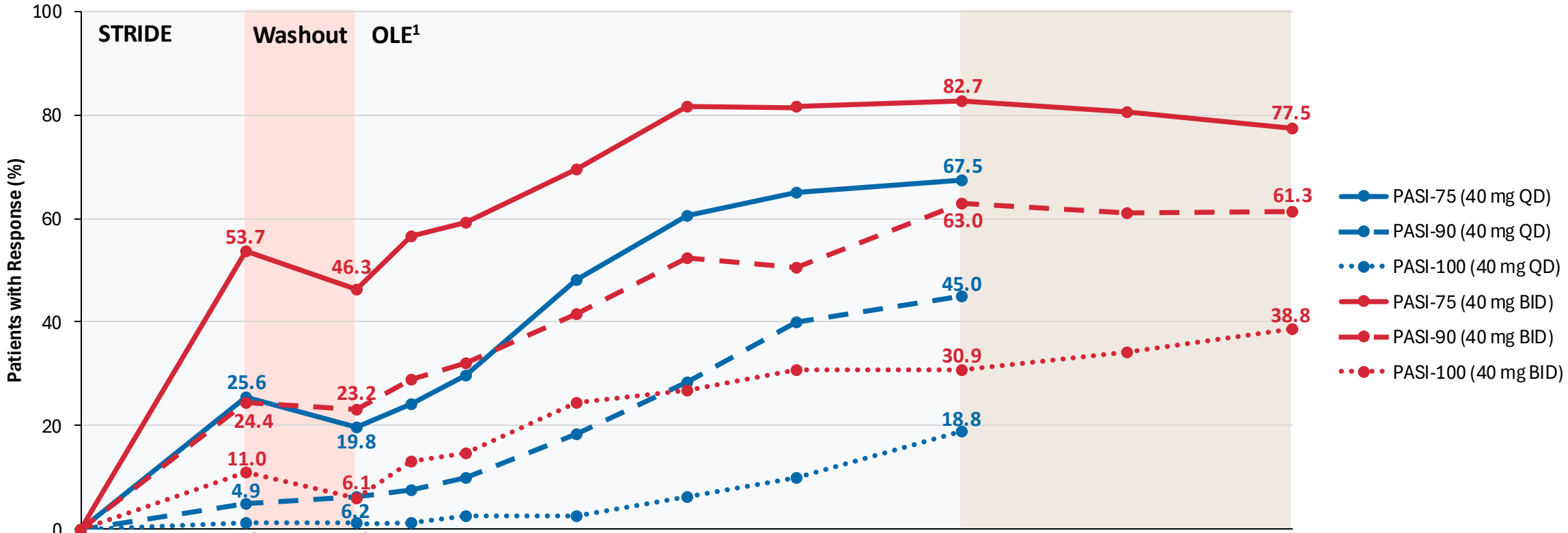


NUMBER OF SUBJECTS

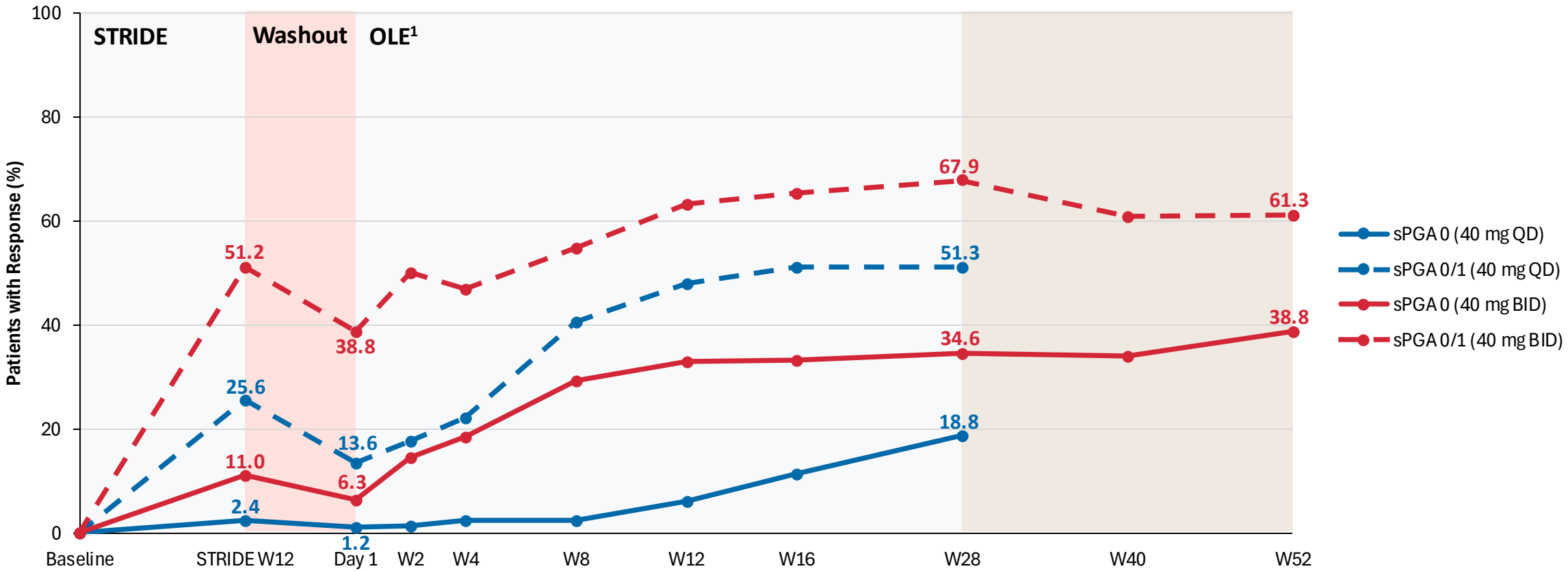
40 mg QD	82	82	81	79	81	81	81	80	80	-	-
40 mg BID	82	82	82	76	81	82	82	81	81	82	80

[1]Patients switched from 40 mg QD to BID at Week 40 and onwards. As a result, the QD series are plotted up to Week 28 only.

*mNRI analysis: if patient discontinued due to AE or inadequate response, then imputed as a non-responder; if discontinued for other reasons, then imputed using LOCF (i.e., last observation carried forward).

ESK-001 response over 52 weeks of treatment: increasing sPGA 0 and 0/1 responses over time (mNRI*)

40 mg BID includes only patients originally assigned to 40 mg BID at the start of OLE



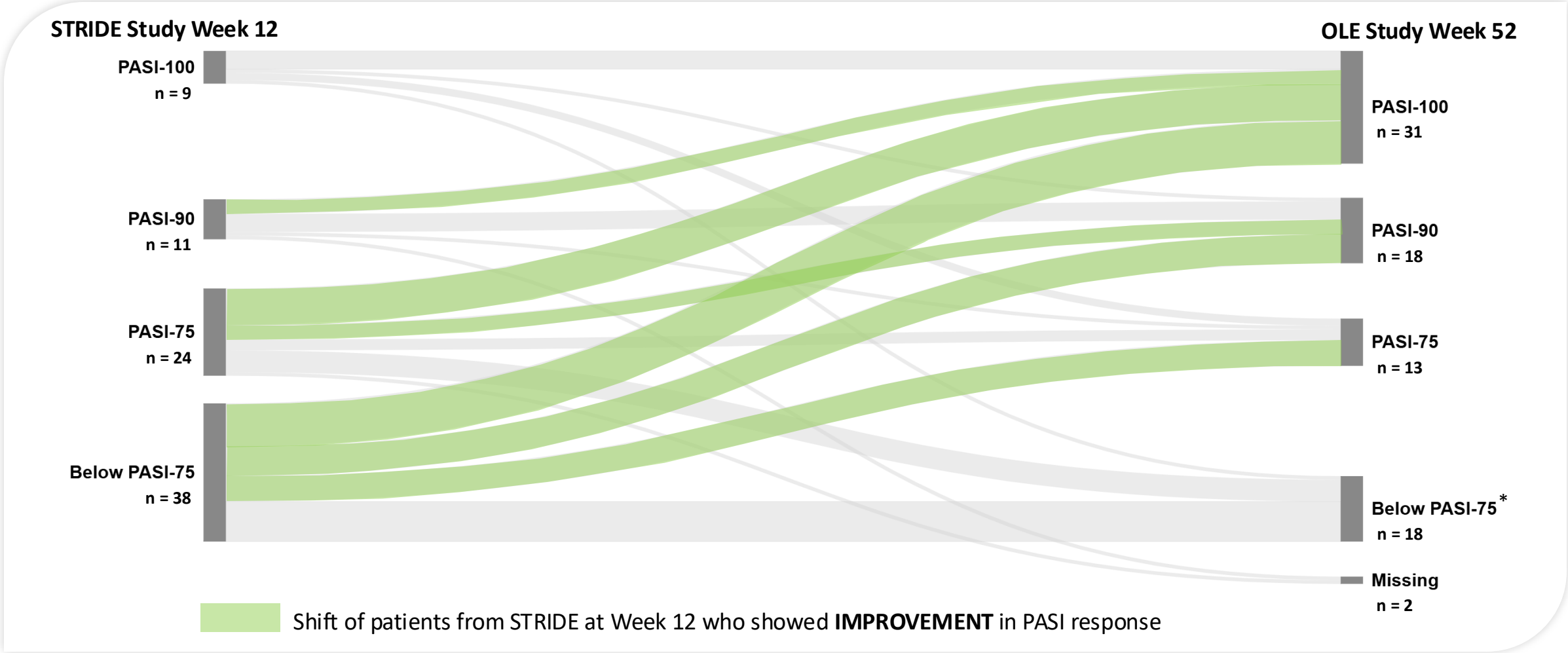
	Baseline	STRIDE W12	Day 1	W2	W4	W8	W12	W16	W28	W40	W52
NUMBER OF SUBJECTS											
40 mg QD	82	82	81	78	81	81	81	80	80	-	-
40 mg BID	82	82	80	76	81	82	82	81	81	82	80

[1]Patients switched from 40 mg QD to BID at Week 40 and onwards. As a result, the QD series are plotted up to Week 28 only.

*mNRI analysis: if patient discontinued due to AE or inadequate response, then imputed as a non-responder; if discontinued for other reasons, then imputed using LOCF (ie, last observation carried forward).

Of the original OLE 40 mg BID, 62% patients showed continued improvement in PASI response at Week 52 compared to Week 12

40 mg BID includes only patients originally assigned to 40 mg BID at the start of OLE

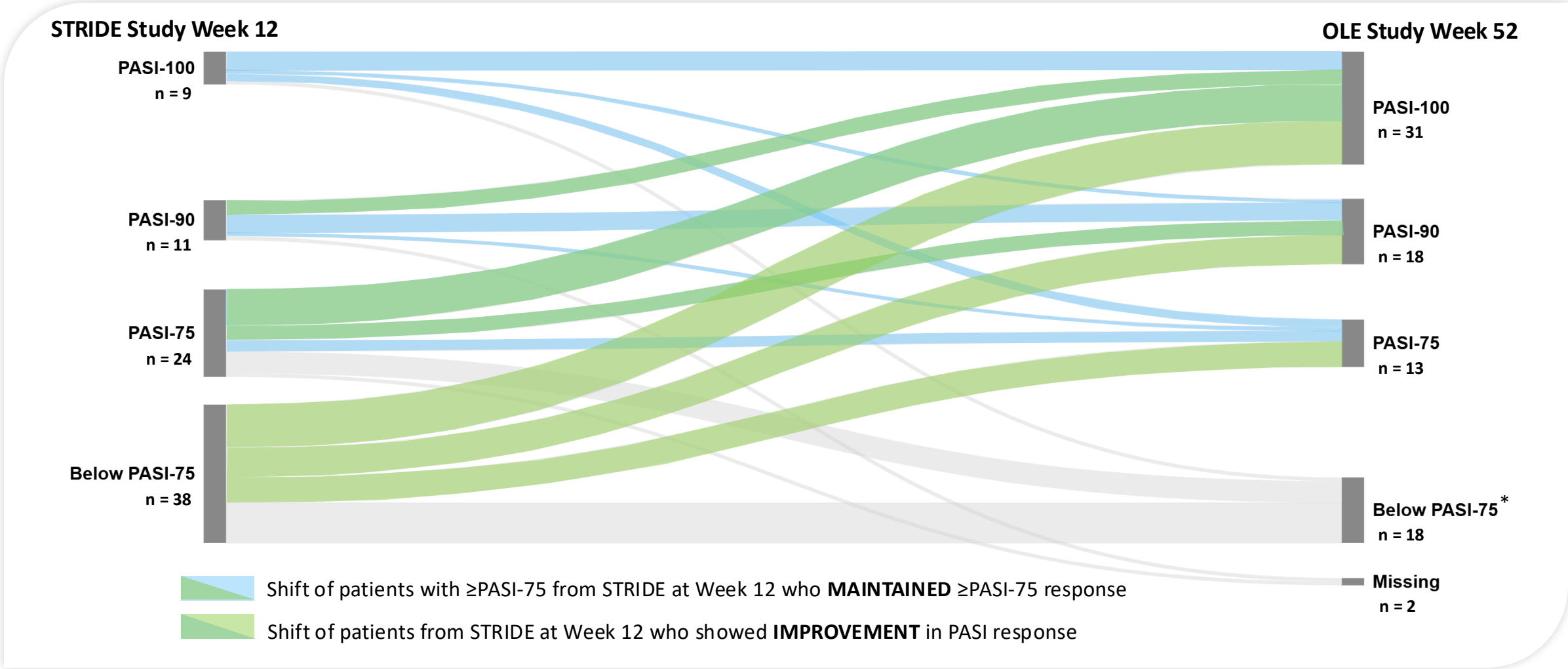


*Of the 18 non-responders at Week 52, 11 discontinued study early.

mNRI analysis: if patient discontinued due to AE or inadequate response, then imputed as a non-responder; if discontinued for other reasons, then imputed using LOCF (i.e., last observation carried forward).

Of the original OLE 40 mg BID, 80% of ≥PASI-75 responders in STRIDE maintained their ≥PASI-75 response at Week 52

40 mg BID includes only patients originally assigned to 40 mg BID at the start of OLE

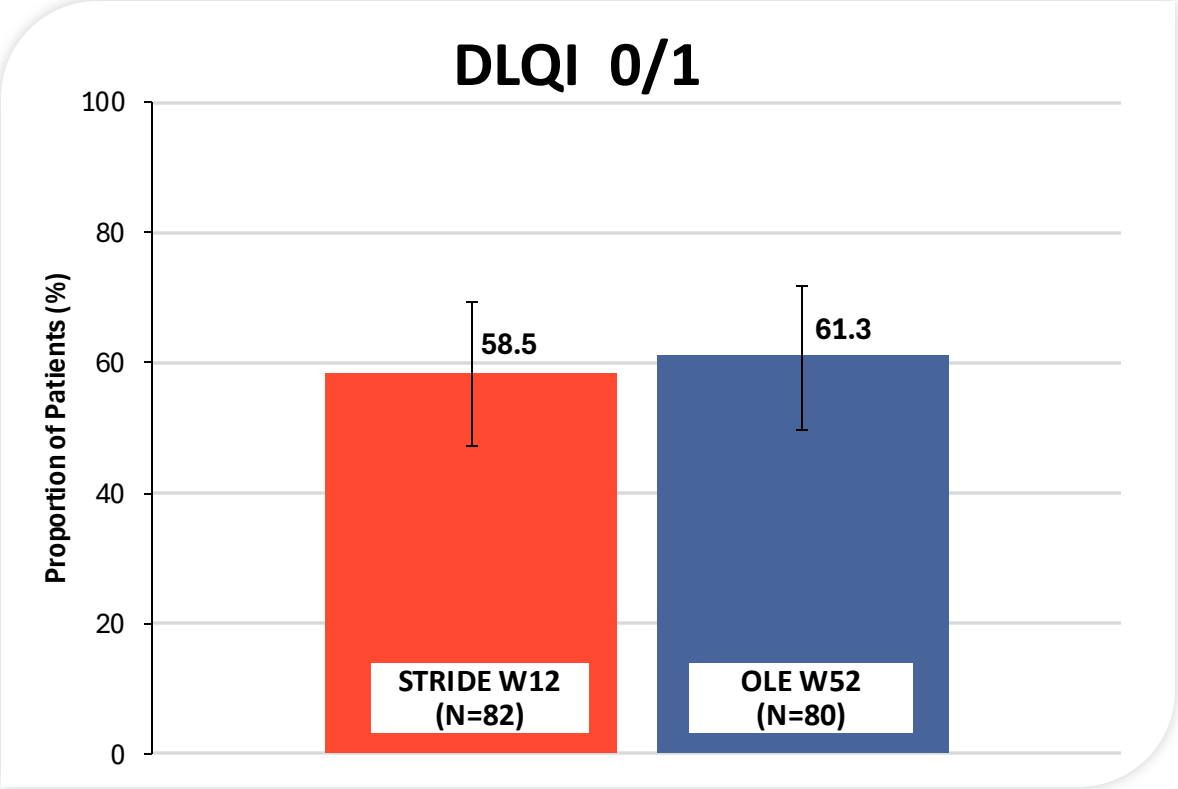


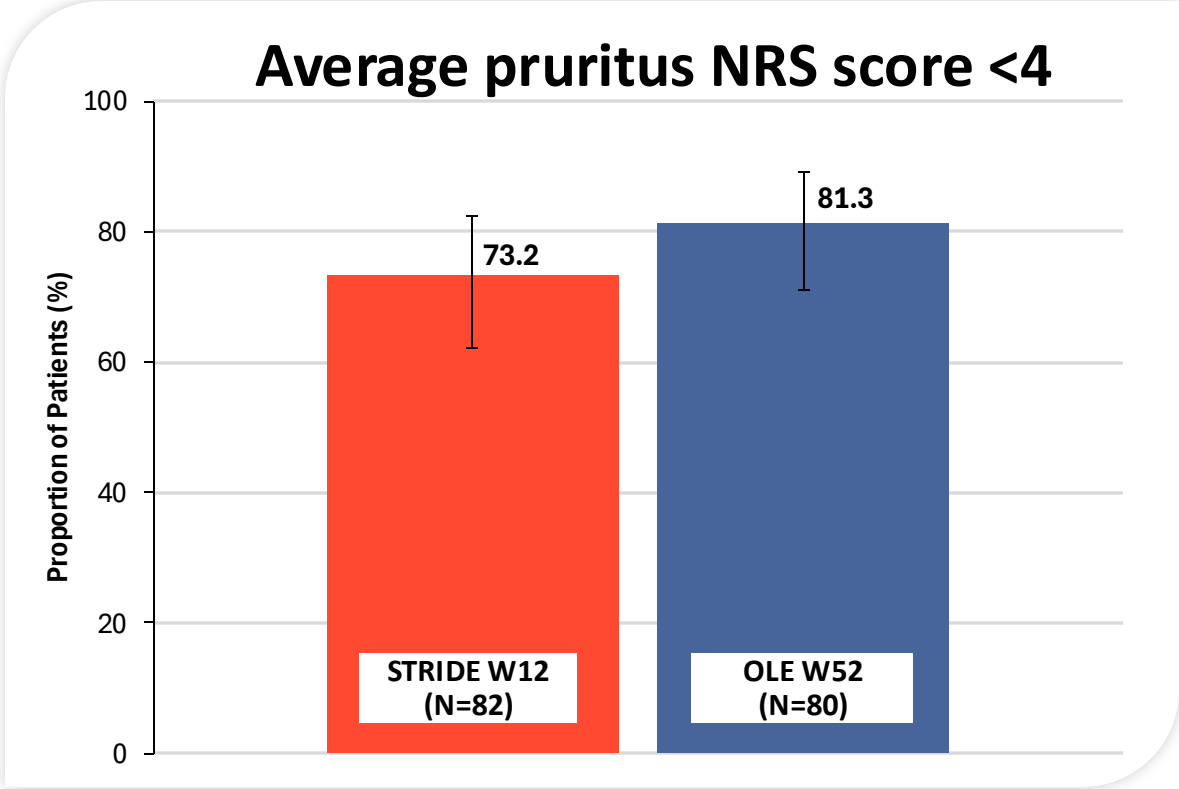
*Of the 18 non-responders at Week 52, 11 discontinued study early.

mNRI analysis: if patient discontinued due to AE or inadequate response, then imputed as a non-responder; if discontinued for other reasons, then imputed using LOCF (i.e., last observation carried forward).

Patient-reported outcomes throughout Week 52 for original 40 mg BID

Robust and rapid improvements in quality of life and control of itch maintained over time





Based on the modified intention-to-treat analysis population.
mNRI analysis: if patient discontinued due to AE or inadequate response, then imputed as a non-responder; if discontinued for other reasons, then imputed using LOCF (i.e., last observation carried forward).
DLQI, Dermatology Life Quality Index; NRS, numerical rating scale.

ESK-001 OLE: 52-week summary and conclusions

Safety summary

- ESK-001 (40 mg BID) remained generally safe and well-tolerated over 52 weeks; majority of TEAEs were mild-to-moderate in severity and self-limited; no safety signals to date

Efficacy summary

- 40 mg BID patients showed high levels of response throughout the study
- PASI-75 (77.5%), PASI-90 (61.3%) and PASI-100 (38.8%) (mNRI) scores at Week 52
- 80% of ≥PASI-75 responders at Week 12 in STRIDE maintained or improved their response at Week 52; 62% improved response over 52 weeks of treatment
- Rapid and sustained improvement in DLQI 0/1 and itch

ESK-001 pivotal program status

- ONWARD Phase 3 development program in plaque psoriasis ongoing, with over 600 patients enrolled to date
- Modified release (once daily) formulation development ongoing