Efficacy and Safety of ESK-001, a Highly Selective Oral TYK2 Inhibitor, in a Phase 2 Study (STRIDE) and OLE Study in Adults with Moderate-to-Severe Plaque Psoriasis

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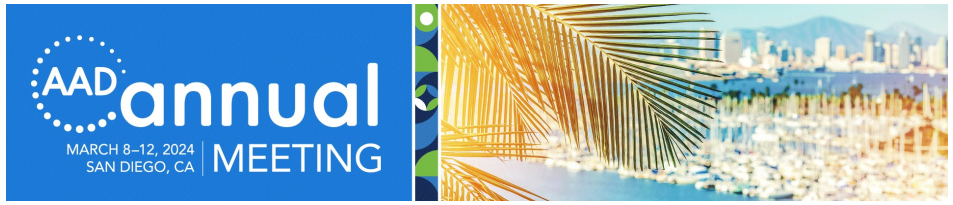
Disclosure of Relationships with Industry

Kim Papp, MD, PhD, FRCPC, FAAD

S026: Late Breaking Research: Session 1



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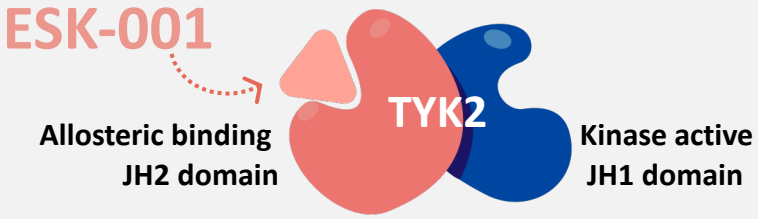
- No patient care recommendations are made

ESK-001: A Selective Oral Allosteric TYK2i Achieves Maximal TYK2 Inhibition for 24 hours at 40 mg BID dose



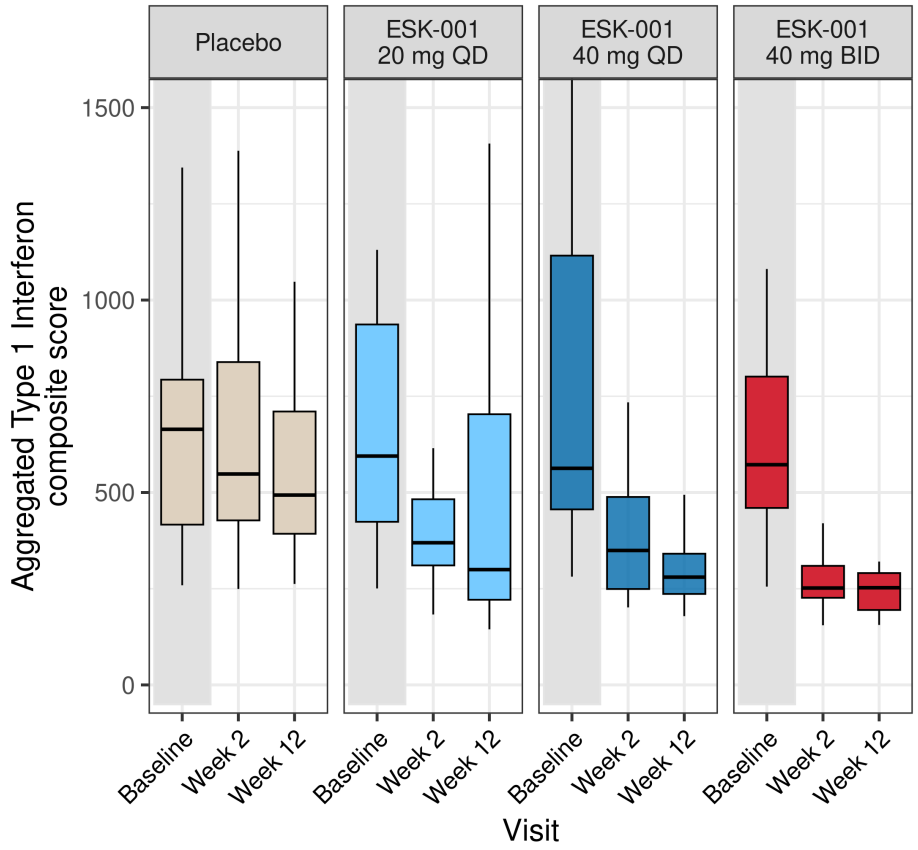
ESK-001, a highly selective allosteric TYK2 inhibitor

- High intrinsic TYK2 selectivity, avoids classic JAKi liabilities

Robust PK/PD correlation

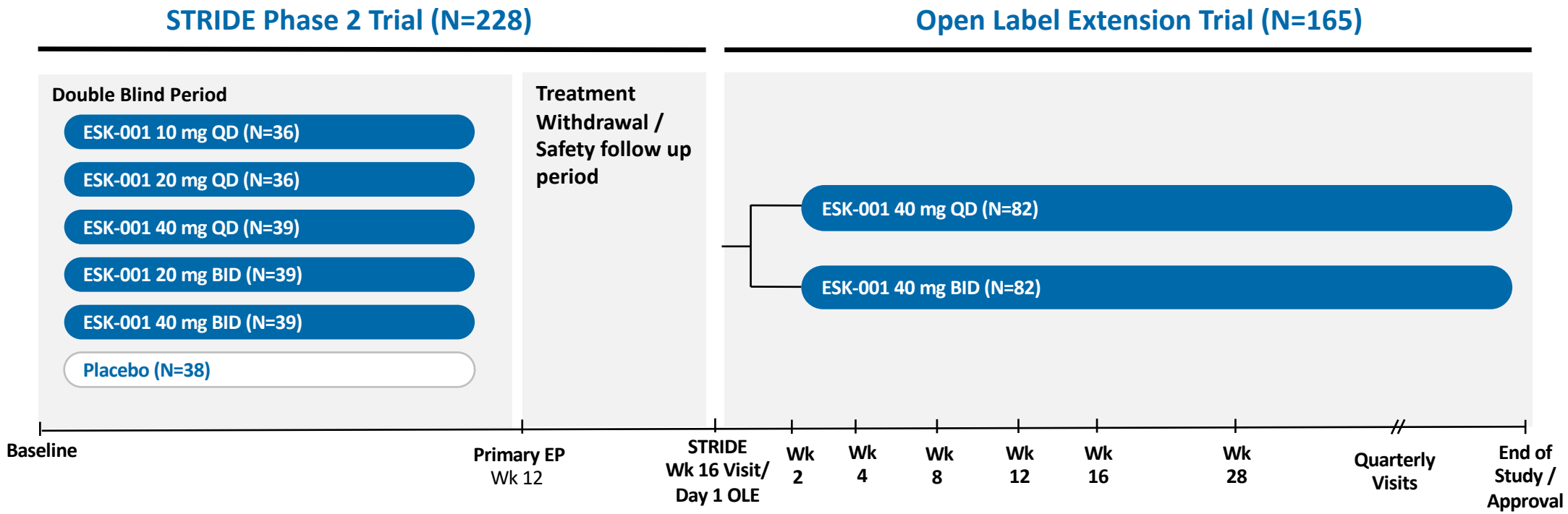
- Maximal target inhibition of Type 1 IFN gene signature achieved at highest clinical dose
- Maintained across 24 hour-dosing period
- PK/PD dose-dependence reflected in clinical outcomes
- Aligns with Phase 1 PK/PD, AAD abstract #53968

ESK-001 Inhibition of Type 1 IFN Gene Signature*



*In blood by RNA-seq from STRIDE PsO study. Blood sampled at baseline, pre-dose (trough) weeks 2 & 12

ESK-001 Phase 2 STRIDE and OLE Studies Designed to Assess both Short- and Long-Term Efficacy



Stride Phase 2 Study

- **Key Inclusion Criteria:** adults 18-75 years with plaque psoriasis
  - PASI ≥ 12, sPGA ≥ 3, BSA ≥ 10%
- **1°EP:** PASI 75 Response at Week 12
- **Key 2°EPs at Week 12**: PASI 90, PASI 100, sPGA 0/1, and sPGA 0

Open Label Extension Study

- **OLE Dose Assignment:** same or higher dose as in parent study
- **Safety EPs**: Incidence of TEAEs and SAEs over time
- **Key Efficacy EPs:** PASI-75, PASI-90 and PASI-100; sPGA 0/1 and sPGA 0

STRIDE: Demographics and Baseline Disease Characteristics were Well-Balanced Across Study Arms

	Placebo (N=38)	10 mg QD (N=36)	20 mg QD (N=36)	20 mg BID (N=40)	40 mg QD (N=39)	40 mg BID (N=39)	Overall (N=228)
Age, mean (SD)	49.1 (11.7)	48.8 (12.7)	43.9 (12.0)	47.7 (12.5)	49.5 (10.5)	47.9 (14.2)	47.8 (12.3)
Male, n (%)	31 (81.6)	24 (66.7)	24 (66.7)	23 (57.5)	26 (66.7)	26 (66.7)	154 (67.5)
Race, n (%) White Asian Black/African American Other	 27 (71.1) 4 (10.5) 3 (7.9) 4 (10.5)	 30 (83.3) 1 (2.8) 4 (11.1) 1 (2.8)	 31 (86.1) 2 (5.6) 0 3 (8.3)	 34 (85.0) 2 (5.0) 1 (2.5) 3 (7.5)	 33 (84.6) 2 (5.1) 1 (2.6) 3 (7.7)	 33 (84.6) 2 (5.1) 1 (2.6) 3 (7.7)	 188 (82.5) 13 (5.7) 10 (4.4) 17 (7.5)
BMI (kg/m^2), mean (SD)	31.9 (6.8)	30.5 (5.9)	34.9 (12.1)	31.7 (7.4)	30.4 (6.4)	31.6 (7.1)	31.8 (7.9)
Psoriasis Duration (years), mean (SD)	19.8 (11.6)	19.3 (13.4)	17.3 (8.3)	21.8 (12.2)	16.7 (12.4)	21.5 (15.5)	19.4 (12.5)
PASI score, mean (SD)	18.0 (4.5)	16.5 (3.9)	18.9 (6.6)	18.3 (6.5)	17.4 (6.5)	17.5 (4.9)	17.8 (5.6)
PGA score, n (%) 3 (moderate) 4 (marked) 5 (severe)	 22 (57.9) 15 (39.5) 1 (2.6)	 24 (66.7) 9 (25.0) 3 (8.3)	 17 (47.2) 17 (47.2) 2 (5.6)	 23 (57.5) 16 (40.0) 1 (2.5)	 25 (64.1) 14 (35.9) 0	 23 (59.0) 16 (41.0) 0	 134 (58.8) 87 (38.2) 7 (3.1)
BSA, mean	22.9 (12.1)	20.6 (12.2)	19.9 (12.6)	21.4 (15.0)	20.1 (12.9)	21.5 (15.1)	21.1 (13.3)
Bioexperienced (biologics or JAKi), n(%)	13 (34.2)	13 (36.1)	14 (38.9)	16 (40.0)	13 (33.3)	13 (33.3)	82 (36.0)

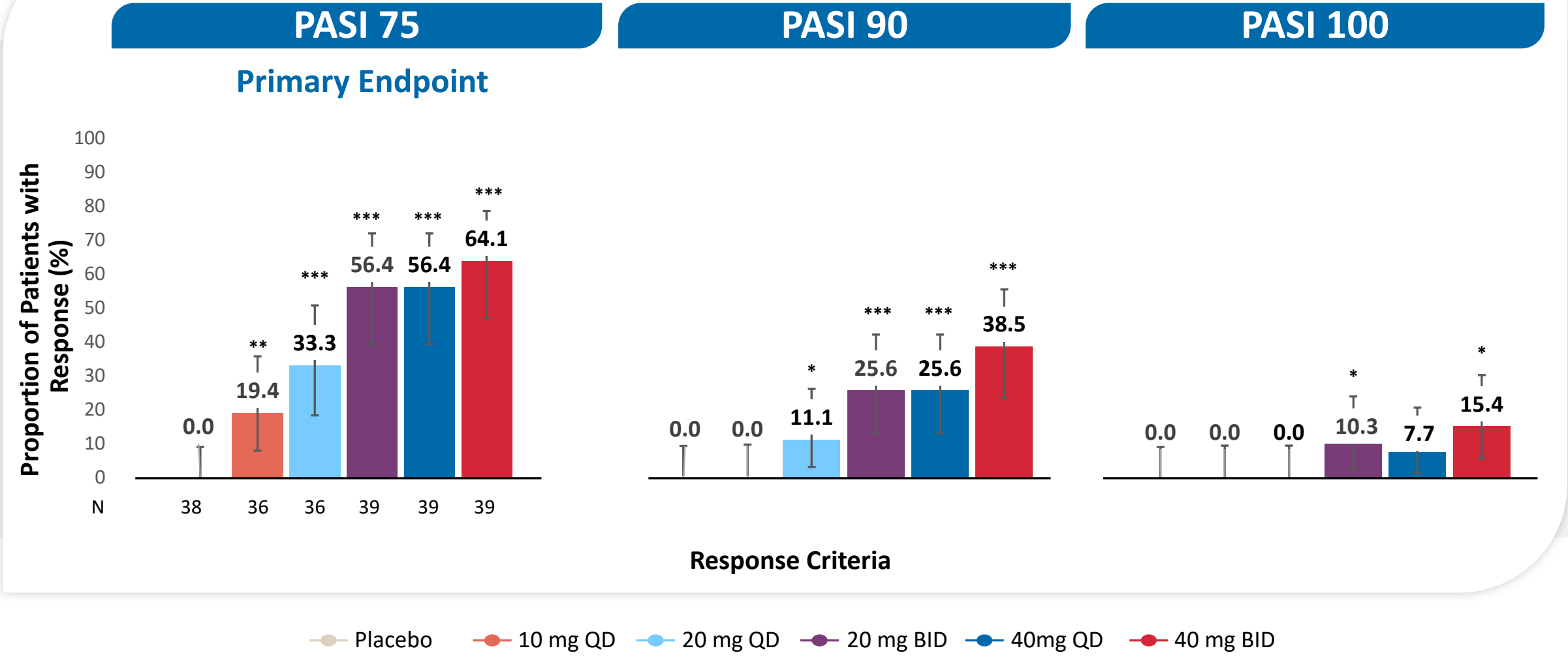
STRIDE Safety at Week 16

	Placebo (N=38)	10 mg QD (N=36)	20 mg QD (N=36)	20 mg BID (N=39)	40 mg QD (N=39)	40 mg BID (N=39)	Overall (N=227)
Subjects with ≥1 TEAE	15 (39.5)	19 (52.8)	14 (38.9)	18 (46.2)	19 (48.7)	25 (64.1)	110 (48.5)
Subjects with ≥1 SAE	0	1 (2.8)	0	3 (7.7)	1 (2.6)	0	5 (2.2)
Subjects with treatment related SAEs	0	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0
Subjects with TEAE leading to treatment discontinuation	0	0	2 (5.6)	0	2 (5.1)	1 (2.6)	5 (2.2)
Most frequent TEAEs*							
Headache	2 (5.3)	0	2 (5.6)	3 (7.7)	4 (10.3)	3 (7.7)	14 (6.2)
Upper resp. tract infection	0	2 (5.6)	2 (5.6)	1 (2.6)	2 (5.1)	3 (7.7)	10 (4.4)
Nasopharyngitis	3 (7.9)	2 (5.6)	0	1 (2.6)	1 (2.6)	3 (7.7)	10 (4.4)

Note: no MACE, serious infections, treatment related thromboses or concerning lab/ECG trends were observed.

TEAE: treatment emergent adverse event. *≥3 patients where occurrence greater in active group vs. placebo. SAEs (all unrelated): Lower limb fracture (10mg QD), tibia fracture (20mg BID), coronary artery occlusion (20mg BID), colitis and enteritis in one subject (20mg BID), dermatitis contact (40mg QD).

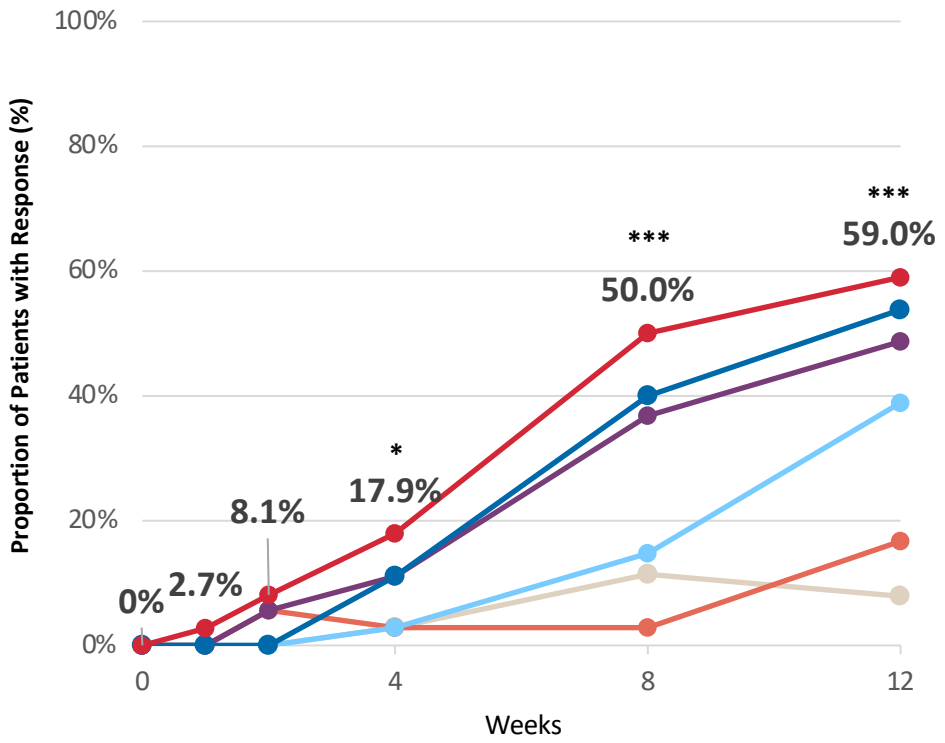
STRIDE: Primary and Secondary PASI Endpoints Achieved at Week 12 with Dose-Dependent Increase in Efficacy



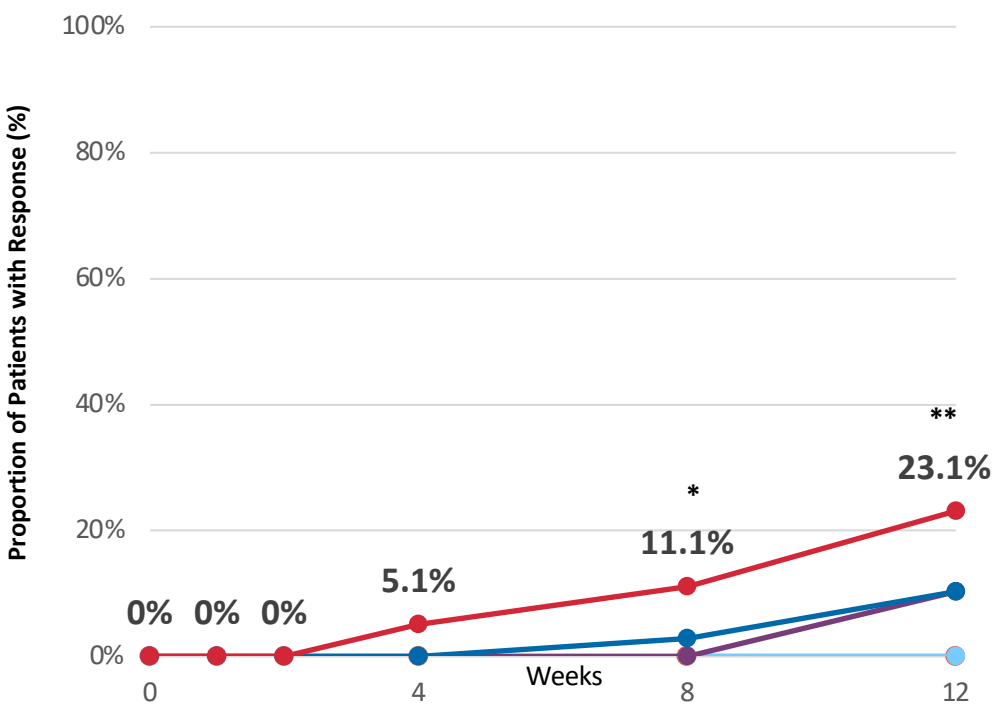
*p<0.05; **p< 0.005; ***p<0.001 . P-value is comparing proportion in each active arm vs placebo using the Cochran-Mantel-Haenszel test adjusted for stratification factors (prior use of biologics and geographic region (North American vs. ROW)). NRI imputation was applied for subjects who discontinued study.

STRIDE: Secondary sPGA Endpoints Achieved at Week 12 with Increasing Efficacy Observed over Time

sPGA 0/1



sPGA 0



Placebo | 10 mg QD | 20 mg QD | 20 mg BID | 40mg QD | 40 mg BID

*p<0.05; **p< 0.005; ***p<0.001 . P-value is comparing proportion in each active arm vs placebo using the Cochran-Mantel-Haenszel test adjusted for stratification factors (prior use of biologics and geographic region (North American vs. ROW)). NRI imputation was applied for subjects who discontinued study.

94% of Eligible STRIDE Subjects Continued in OLE Study

228
Randomized Phase 2 STRIDE Subjects

204
Subjects Completing STRIDE

165*
Eligible Subjects Entering OLE

8
Eligible for OLE but chose not to participate

31
Ineligible and not participating in OLE

27: OLE Not initiated in Czech Republic
4: Did not meet OLE inclusion criteria

Open Label Extension Trial

- ESK-001 40 mg QD (N=82)
- ESK-001 40 mg BID (N=82)

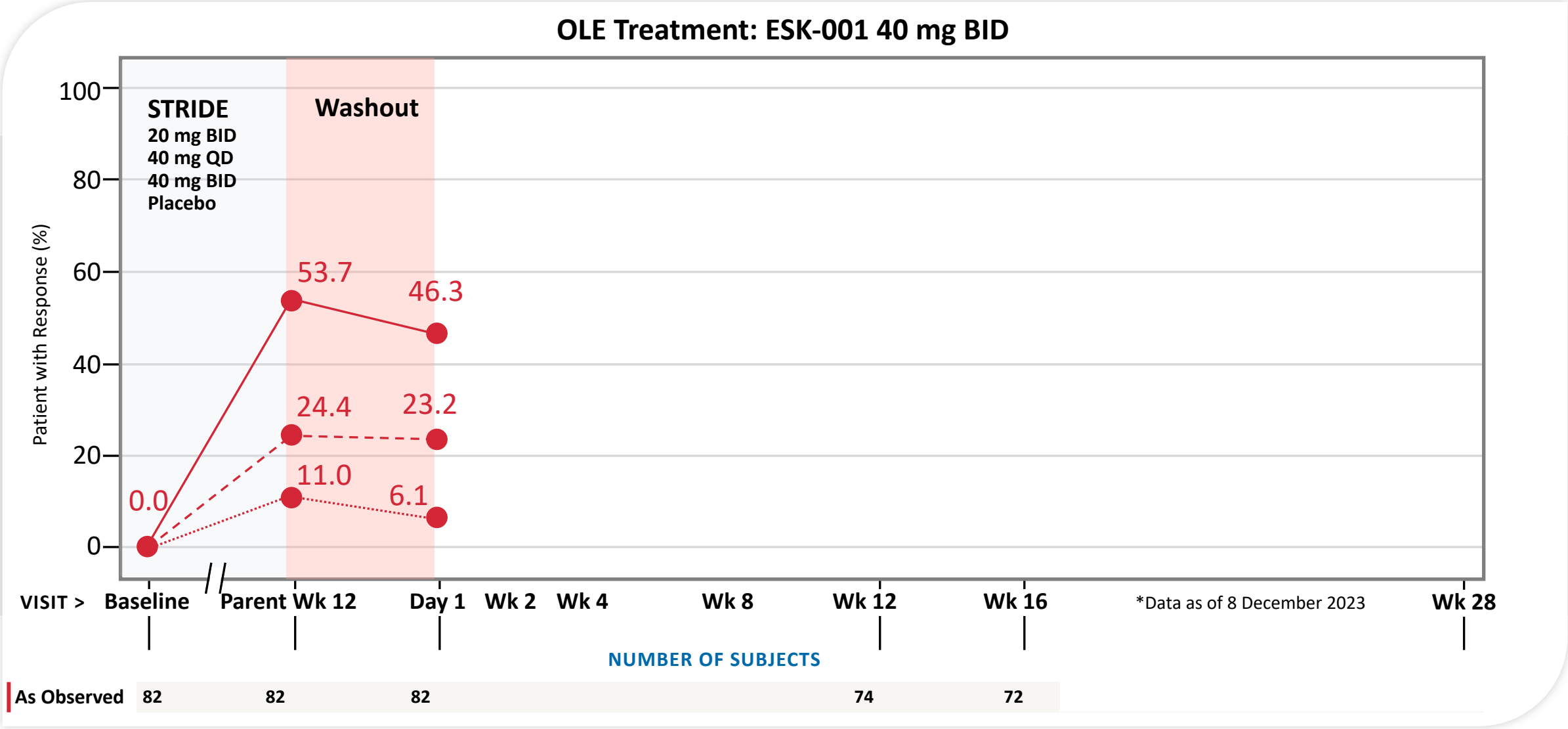
* 1 Subject randomized into OLE but not dosed and not included in mITT population analyses

OLE: Safety Summary

	ESK-001 40 mg QD (N=82)	ESK-001 40 mg BID (N=82)	Overall (N=164)
Subjects with ≥ 1 TEAE	35 (42.7)	38 (46.3)	73 (44.5)
Subjects with ≥ 1 SAE[1]	1 (1.2)	1 (1.2)	2 (1.2)
Deaths	0	0	0
Subjects with TEAE leading to treatment discontinuation[2]	0	2 (2.4)	2 (1.2)
Subjects with TEAE ≥ Grade 3[3]	0	2 (2.4)	2 (1.2)
Most frequent TEAEs[4]			
Nasopharyngitis	9 (11.0)	2 (2.4)	11 (6.7)
Upper Respiratory Tract Infection	1 (1.2)	4 (4.9)	5 (3.0)
Folliculitis	0	3 (3.7)	3 (1.8)
Urinary tract infection	0	3 (3.7)	3 (1.8)
Acne	2 (2.4)	3 (3.7)	5 (3.0)
Headache	5 (6.1)	3 (3.7)	8 (4.9)

Safety data displayed based on 8 December 2023 data cut of ongoing OLE study. [1]40mg QD arthritis (related) and 40mg BID sepsis (unrelated). [2]Dyspepsia and hypersensitivity. [3]Sepsis and chronic cardiac failure in one subject, and flank pain in one subject (all unrelated). [4]≥3 patients in any treatment group. 40mg QD dose arm includes patients from STRIDE placebo, 10mgQD, 20mg QD and 40mg QD dose arms. 40mg BID arm includes patients from STRIDE placebo, 20mg BID, 40mg QD, 40mg BID dose arms. TEAE: treatment emergent adverse event.

STRIDE and OLE Efficacy: Continued ESK-001 Exposure Achieves Significant Increases in PASI Responses



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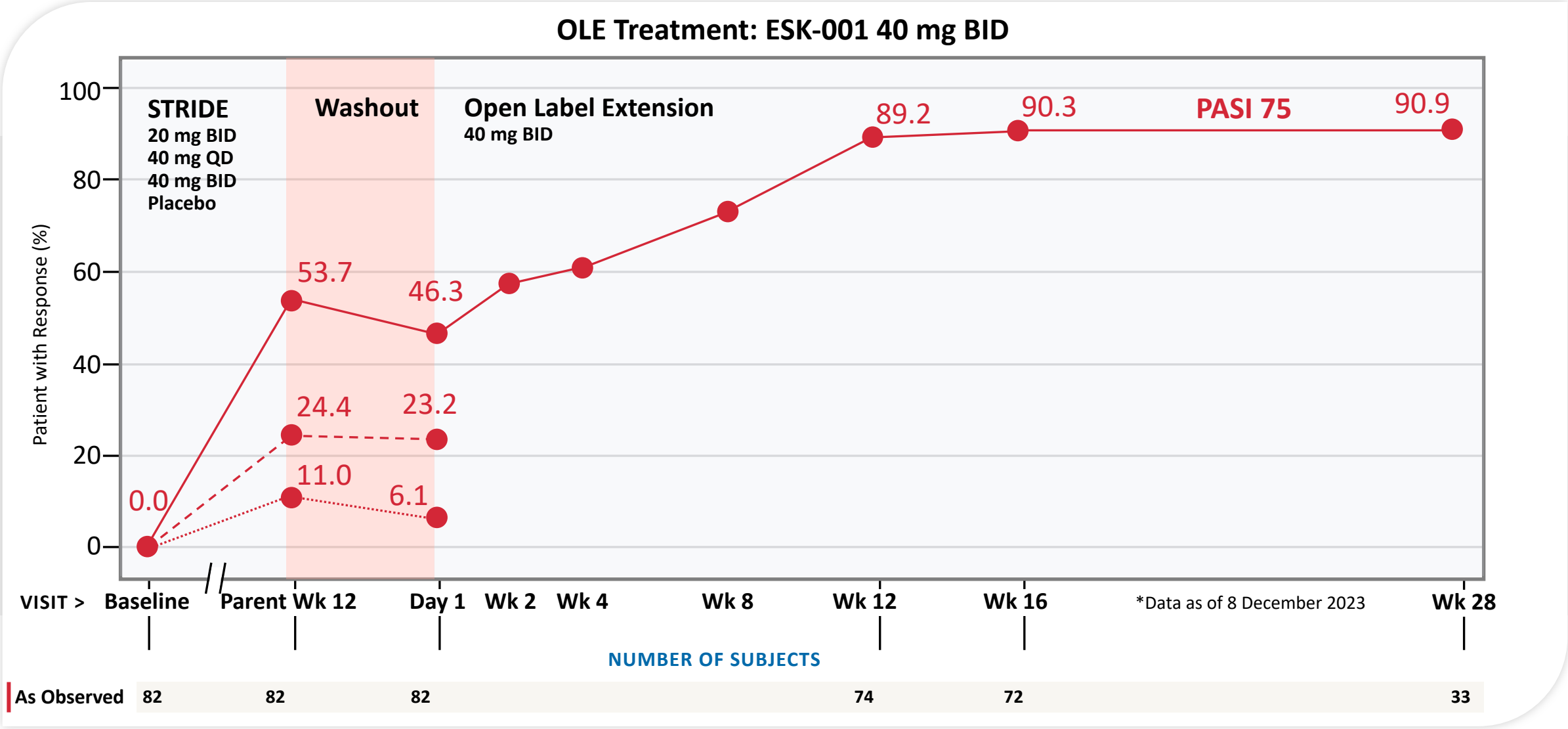

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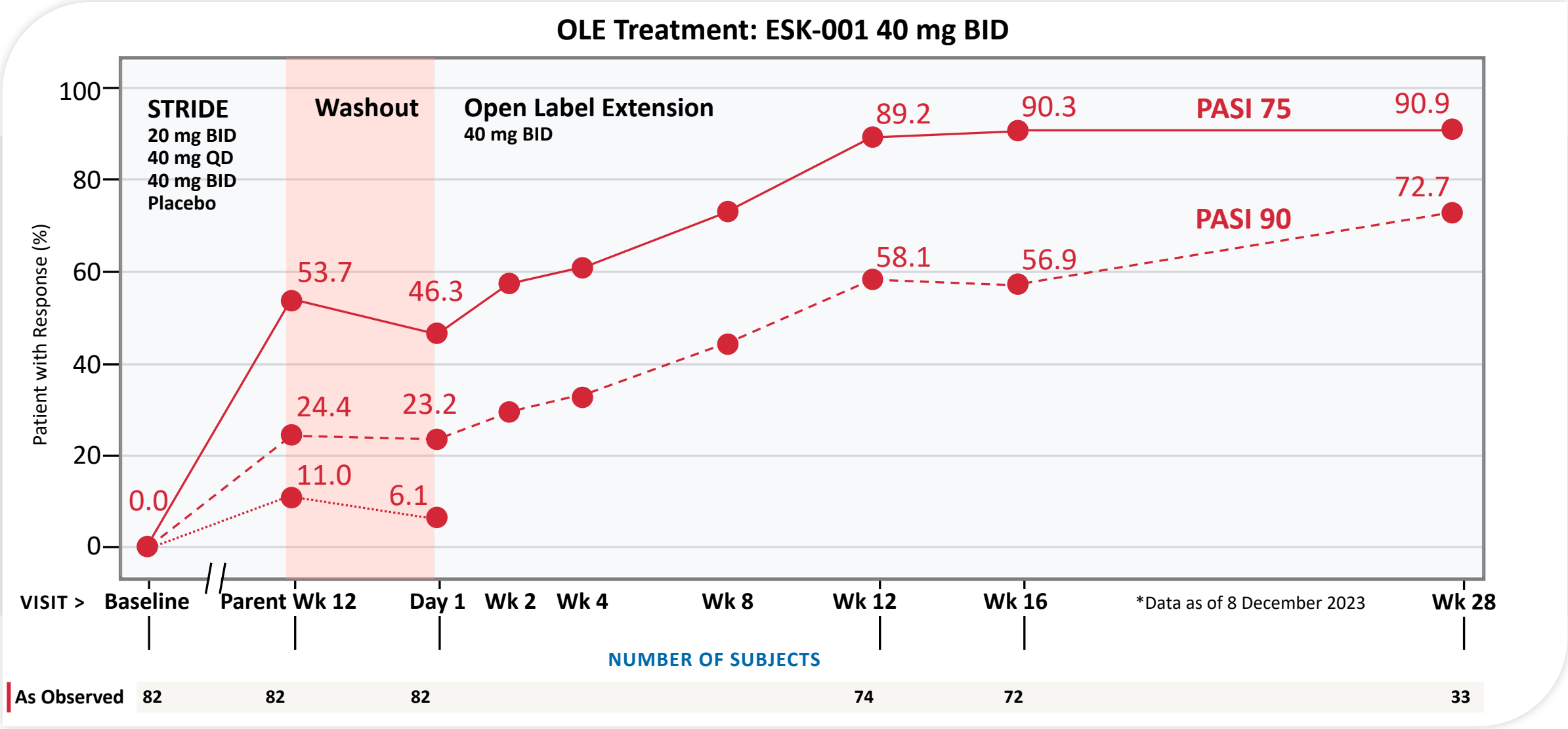

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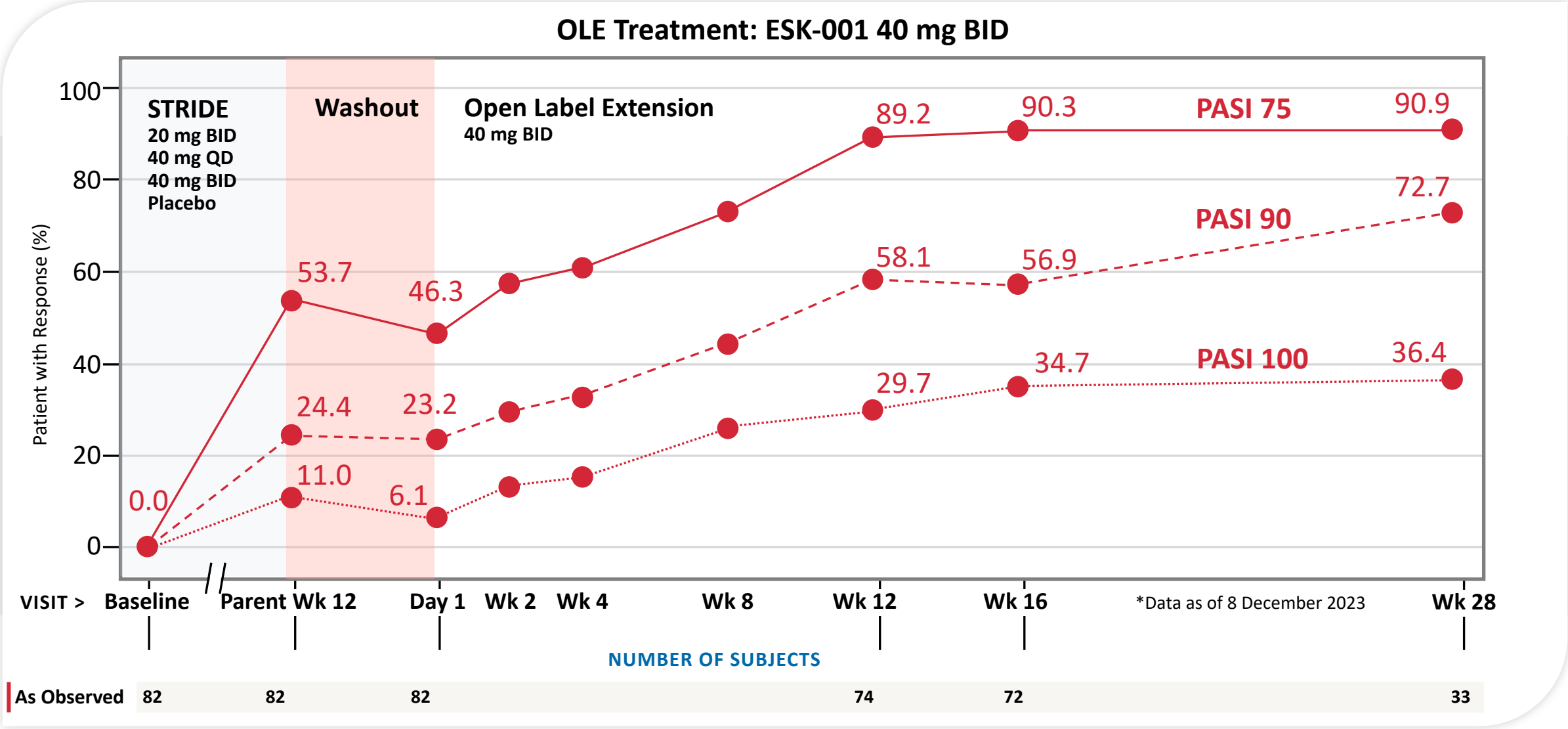

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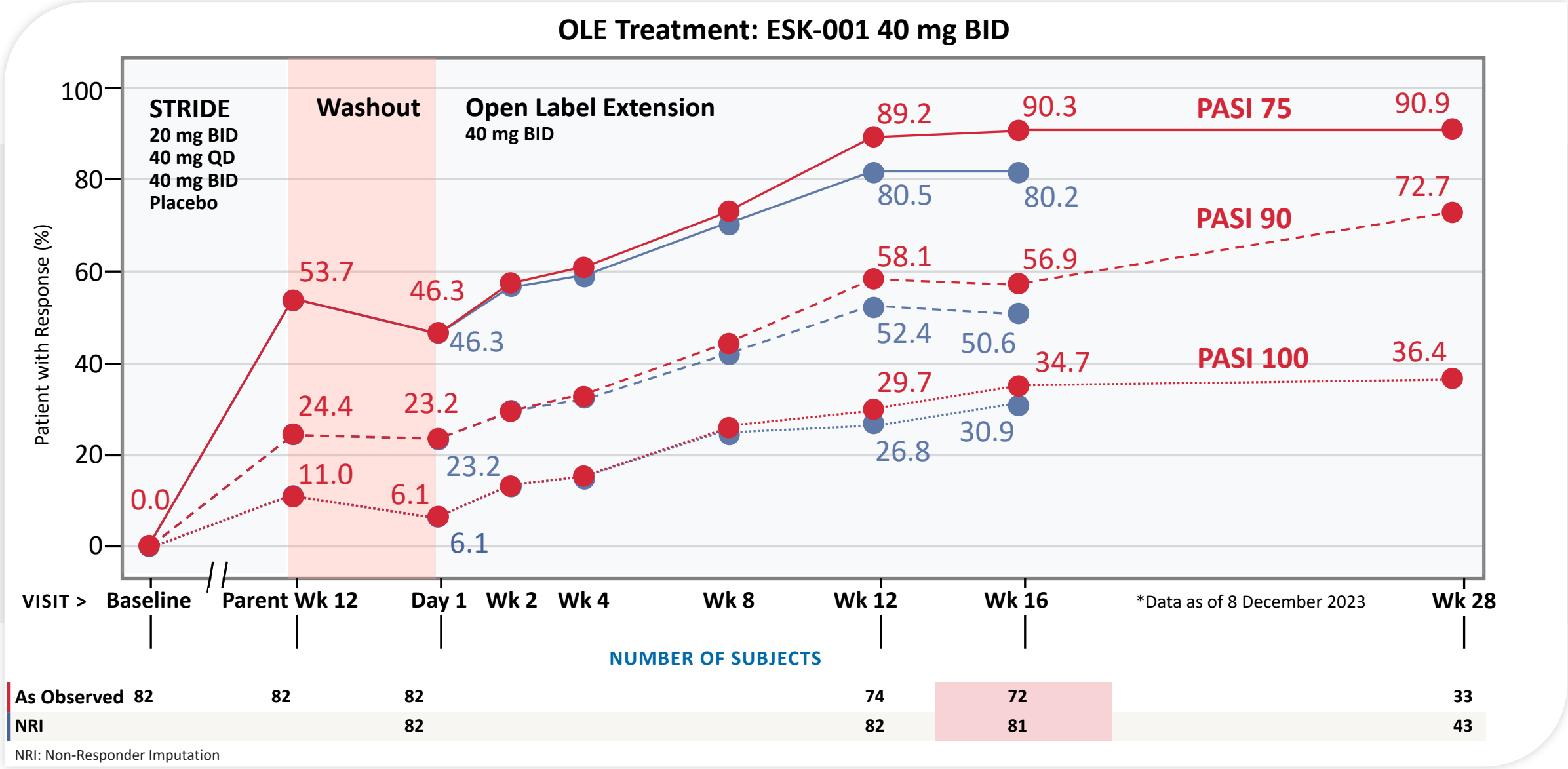

Conclusions

STRIDE and OLE studies demonstrate ESK-001 is a clinically effective and generally safe oral therapy and support continued Phase 3 development of ESK-001 in plaque psoriasis

Efficacy Summary

- Clear dose dependent efficacy demonstrated in STRIDE and OLE studies
  - Maximal TYK2 inhibition achieved at the highest 40 mg BID dose
- **STRIDE**: Significant improvement in all PASI and sPGA responses with highest doses
- **Phase 2 OLE**: Extended treatment with ESK-001 over time achieved significant efficacy at Week 16:

	PASI 75	PASI 90	PASI 100
As Observed	90%	57%	35%
NRI*	80%	51%	31%

  - Continued ESK-001 exposure has potential for greater responses in PASI-90 and PASI-100

Safety Summary

- ESK-001 was generally safe and well-tolerated across all dose levels
- The majority of TEAEs were mild-to-moderate in severity and self-limited
- Long term exposure in OLE continues to show favorable risk-benefit profile to date

*Non-Responder Imputation