Efficacy and Safety of ESK-001, a Highly Selective Oral TYK2 Inhibitor, in Moderate-to-Severe Plaque Psoriasis: Phase 2 results through Week 28

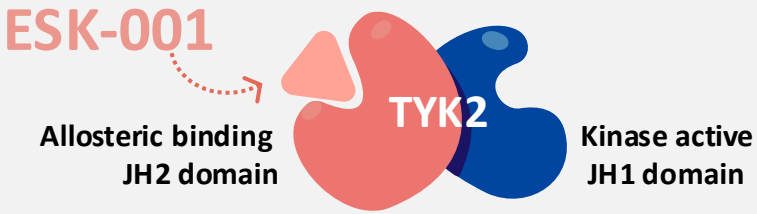
Andrew Blauvelt,[1] Steven Kempers,[2] Elena Hitraya,[3] Michelle Bettinger,[3] Roman G. Rubio,[3] Nicholas E. Vlahakis,[3] Grace Ma,[3] and Kim A. Papp[4]

[1]Blauvelt Consulting, LLC, Portland, Oregon, USA; [2]Minnesota Clinical Study Center; [3]Alumis Inc., South San Francisco, CA, USA; [4]Probity Medical Research, Waterloo, ON, Canada

Conflicts of Interest

Dr. Blauvelt has served as a speaker (received honoraria) for Eli Lilly and Company and UCB, has served as a scientific adviser (received honoraria) for AbbVie, Abcentra, Aclaris, Affibody, Aligos, Almirall, Alumis, Amgen, Anaptysbio, Apogee, Arcutis, Arena, Aslan, Athenex, Bluefin Biomedicine, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Celldex, Celltrion, CTI BioPharma, Dermavant, EcoR1, Eli Lilly and Company, Escient, Evelo, Evommune, Forte, Galderma, GlaxoSmithKline, HighlightII Pharma, Incyte, InnoventBio, Janssen, Landos, Leo, Lipidio, Microbion, Merck, Monte Rosa Therapeutics, Nektar, Novartis, Oruka, Overtone Therapeutics, Paragon, Pfizer, Q32 Bio, Rani, Rapt, Regeneron, Sanofi Genzyme, Spherix Global Insights, Sun Pharma, Takeda, TLL Pharmaceutical, TrialSpark, UCB Pharma, Union, Ventyx, Vibliome, and Xencor, has acted as a clinical study investigator (institution has received clinical study funds) for AbbVie, Acelyrin, Allakos, Almirall, Alumis, Amgen, Arcutis, Athenex, Boehringer Ingelheim, Bristol-Myers Squibb, Concert, Dermavant, DermBiont, Eli Lilly and Company, Evelo, Evommune, Galderma, Incyte, Janssen, Leo, Merck, Novartis, Pfizer, Regeneron, Sanofi, Sun Pharma, Takeda, UCB Pharma, and Ventyx, and owns stock in Lipidio and Oruka.

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



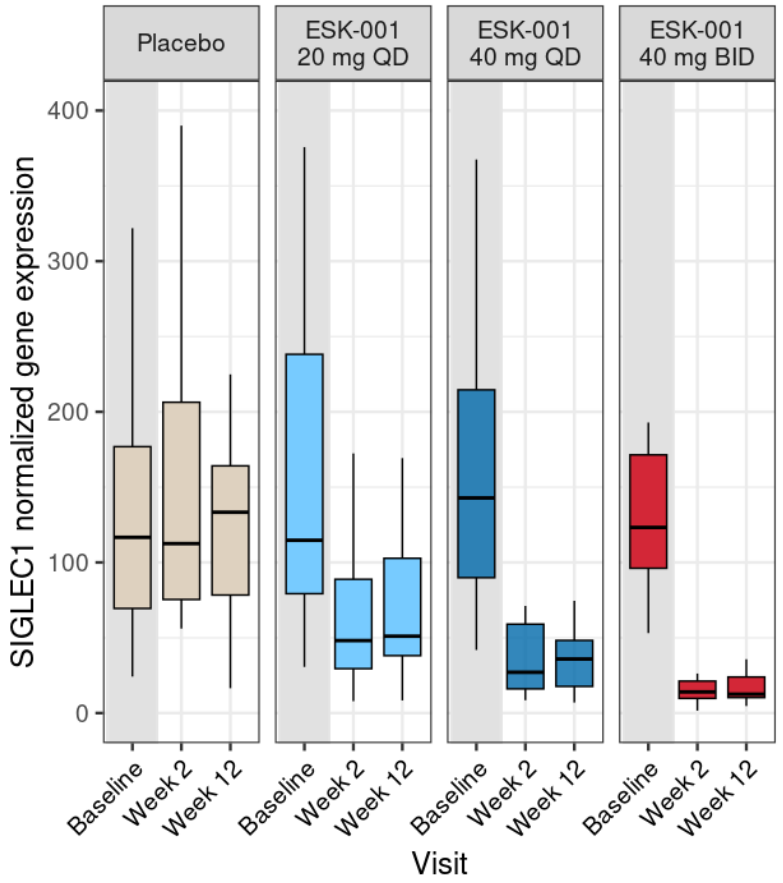
ESK-001, a highly selective allosteric TYK2 inhibitor

- High intrinsic TYK2 selectivity, avoids classic JAK liabilities

Robust PK/PD correlation

- Maximal target inhibition 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)

Inhibition of SIGLEC1, novel TYK2 PD biomarker*



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

ESK-001: Potent and Highly Selective Allosteric TYK2 Inhibitor Designed to Achieve Maximal Target Inhibition

Designed to Deliver Potentially Best-in-class Pharmacokinetic Properties

- Dose-dependent exposure with very low variability
- Excellent penetration into relevant tissues
- Robust PK/PD achieves maximal target inhibition

No Clinically Limiting Findings

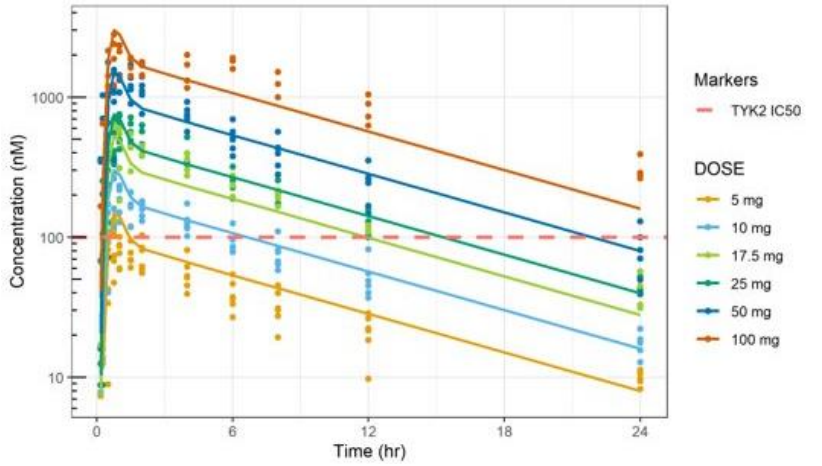
- Highly selective for TYK2 with no off-target JAK pharmacology
- Enabling clinical pharmacology profile including no drug-drug interactions

Only TYK2i to Safely Achieve Maximal Target Inhibition

		Steady State Time Above (hr)	
Drug	**Dose**	**IC50**	**IC90**
ESK-001	40 mg QD	19	7
	40 mg BID	>24	>24
Deucravacitinib	6 mg QD	9	0
Zasocitinib	30 mg QD	>24	5

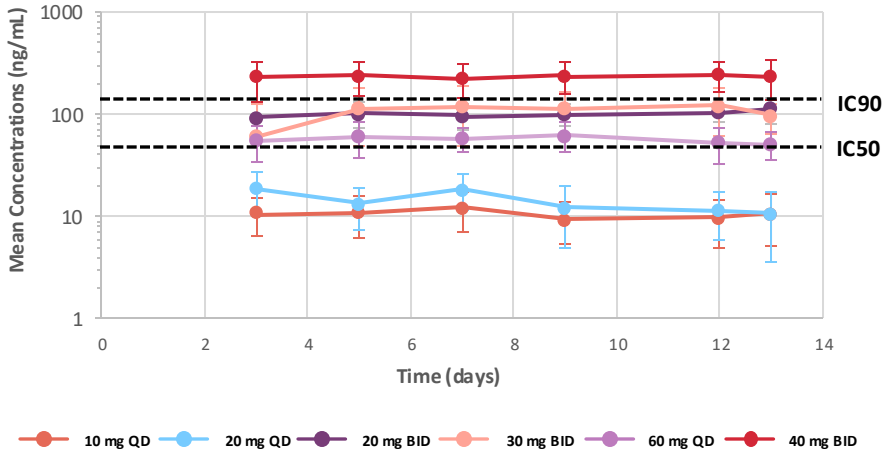
Dose-dependent Exposure, Very Low Variability

ESK-001 Phase 1 SAD PK



Coverage of IC90 at Trough with 40 mg BID Dose

ESK-001 Phase 1 Multidose, Trough PK



STRIDE: Demographics and Baseline Disease Characteristics

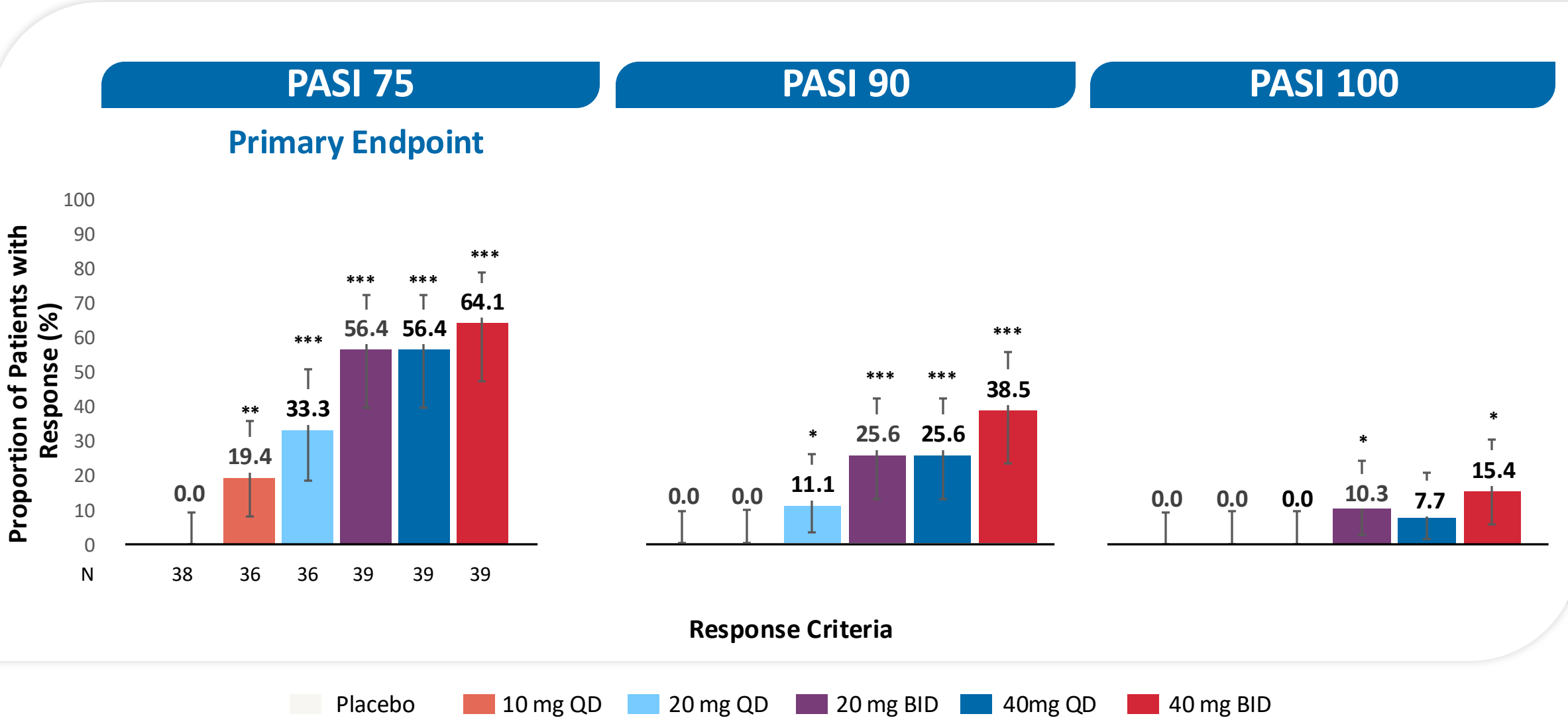
ESK-001

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, 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)

All randomized patients presented.

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

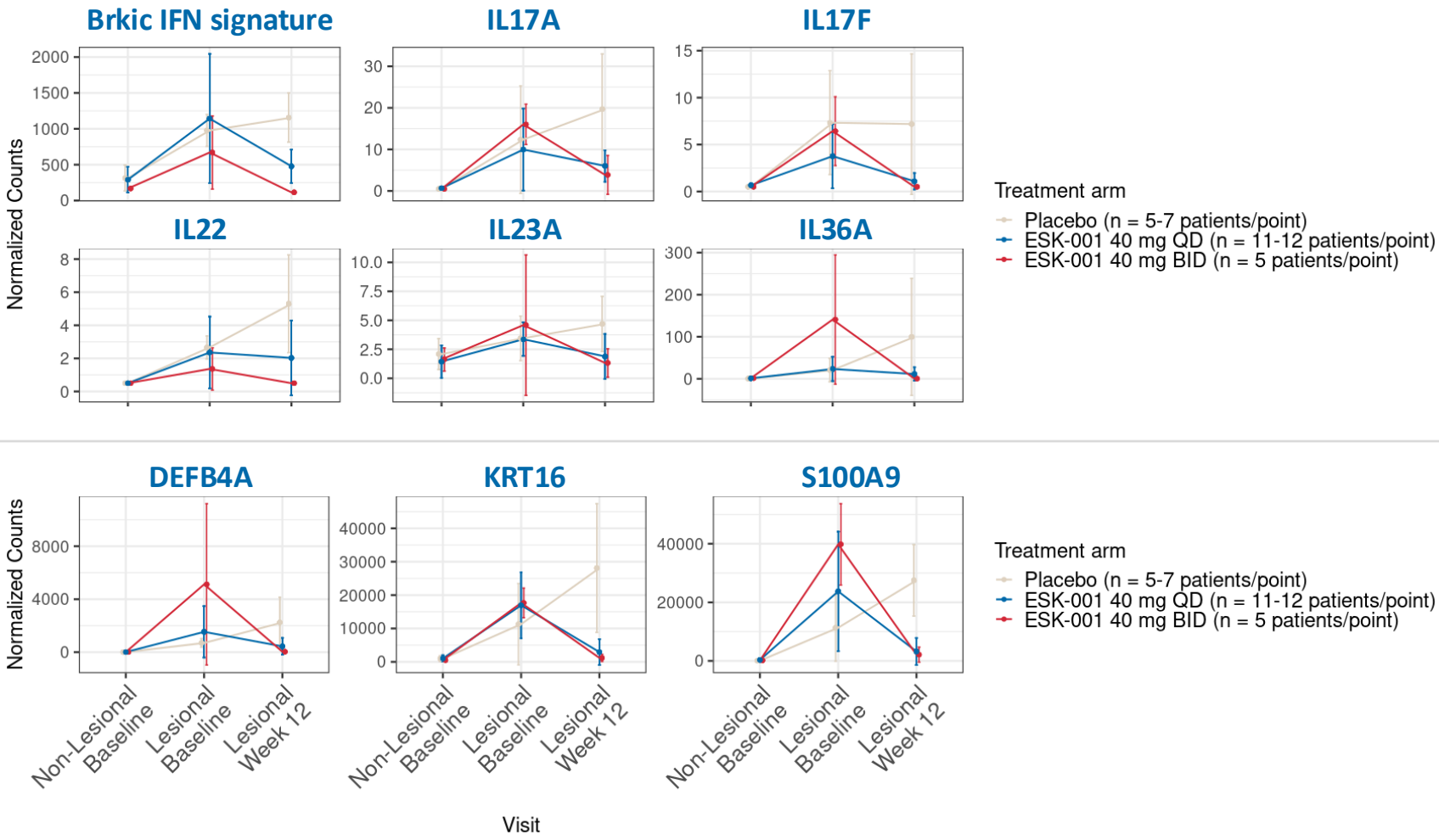


*p<0.05; **p< 0.005; ***p<0.001 . P-value is comparing proportion in each active arm vs placebo using the Cochran-Mantel-Haenszel test adjusted for stratification factors (prior use of biologics and geographic region (North American vs. ROW)). Based on mITT analysis set. NRI imputation was applied for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

RNA-seq Data in Lesional Tissue Confirm Maximal Inhibition

Lesional Skin Levels of Key Cytokines & Disease Related Biomarkers Return to Non-lesional Levels

Key TYK2 Pathway Cytokines



Key Keratinocyte Disease Biomarkers

ESK-001 Psoriasis Phase 2 Skin biopsy RNA-seq, 12/05/2023 dataset.
Skin biopsies collected in subset of patients, all available skin biopsy samples with valid RNAseq data included in analysis.

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)

No concerning lab/ECG trends, MACE, serious infections or treatment-related thromboses observed.

Based on the Safety Analysis Population (all treated patients) TEAE: treatment emergent adverse event. * ≥3 patients where occurrence greater in active group vs. placebo.

95% of Eligible STRIDE Subjects Continued in OLE Study

228 Randomized Phase 2 STRIDE Subjects

204 Subjects Completing STRIDE

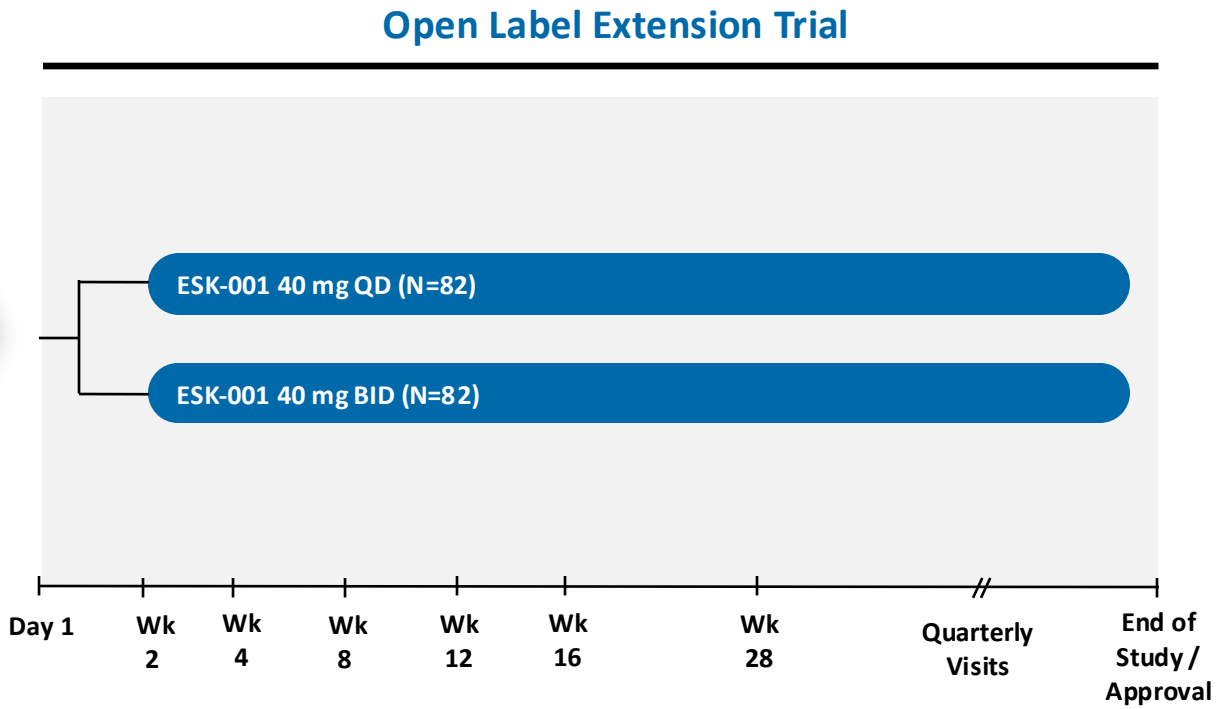
165* Eligible Subjects Entering OLE

9 Eligible for OLE but chose not to participate

30 Ineligible and not participating in OLE

25: OLE Not initiated in Czech Republic

5: Did not meet OLE inclusion criteria



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

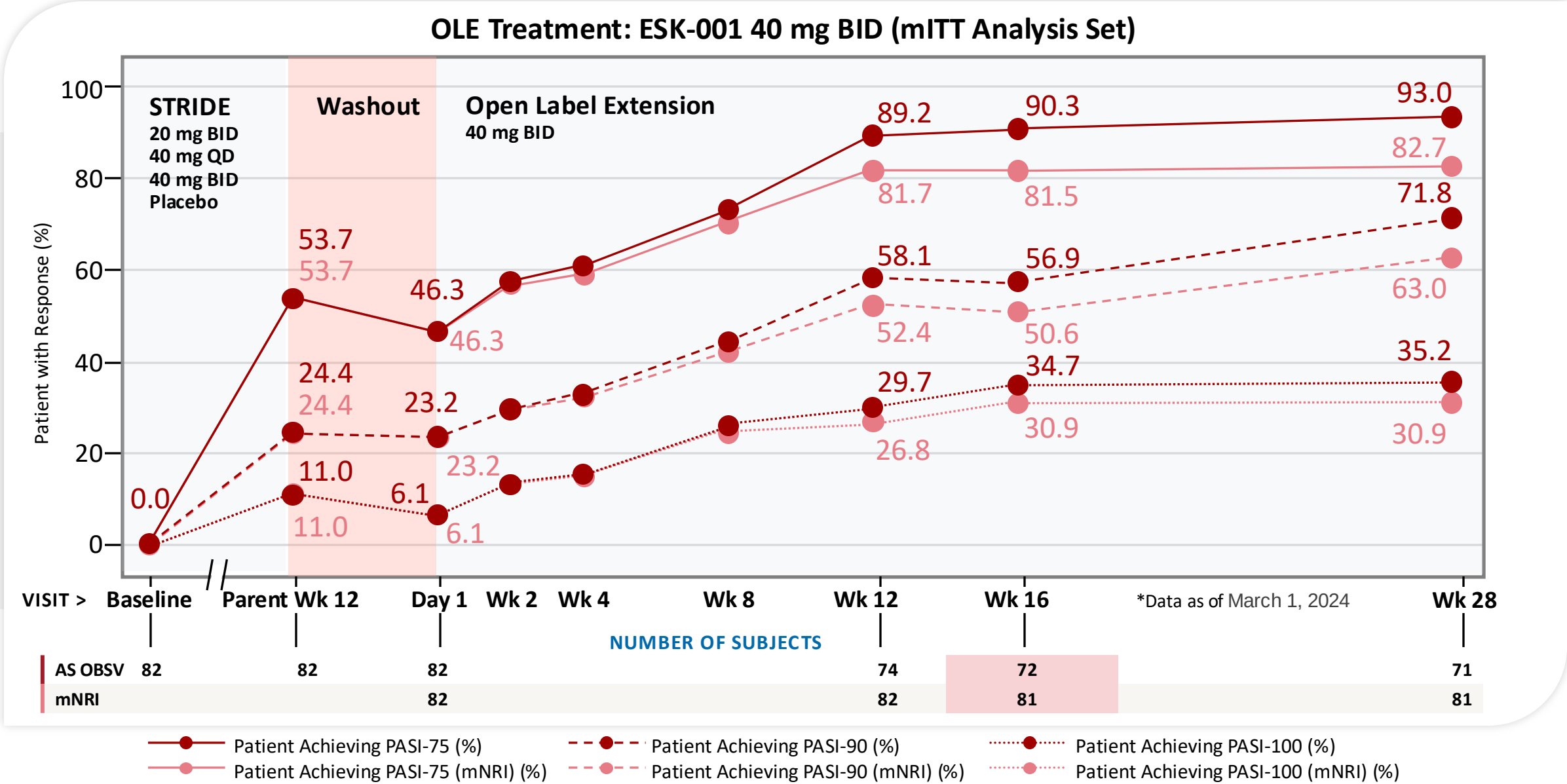
OLE Safety Summary at Week 28

	ESK-001 40 mg QD (N=82)	ESK-001 40 mg BID (N=82)	Overall (N=164)
Subjects with ≥ 1 TEAE	41 (50.0)	45 (54.9)	86 (52.4)
Subjects with ≥ 1 TE SAE	1 (1.2)	3 (3.7)	4 (2.4)
Deaths	0	0	0
Subjects with TEAE leading to treatment discontinuation	0	4 (4.9)	4 (2.4)
Subjects with TEAE ≥ Grade 3	1 (1.2)	4 (4.9)	5 (3.0)
Most frequent TEAEs (≥5%)			
Nasopharyngitis	10 (12.2)	3 (3.7)	13 (7.9)
Upper Respiratory Tract Infection	2 (2.4)	9 (11.0)	11 (6.7)
Headache	5 (6.1)	3 (3.7)	8 (4.9)

Based on the Safety Analysis Population (all treated patients). Safety data displayed based on 1 March 2024 data cut of ongoing OLE study.
TEAE: treatment emergent adverse event.

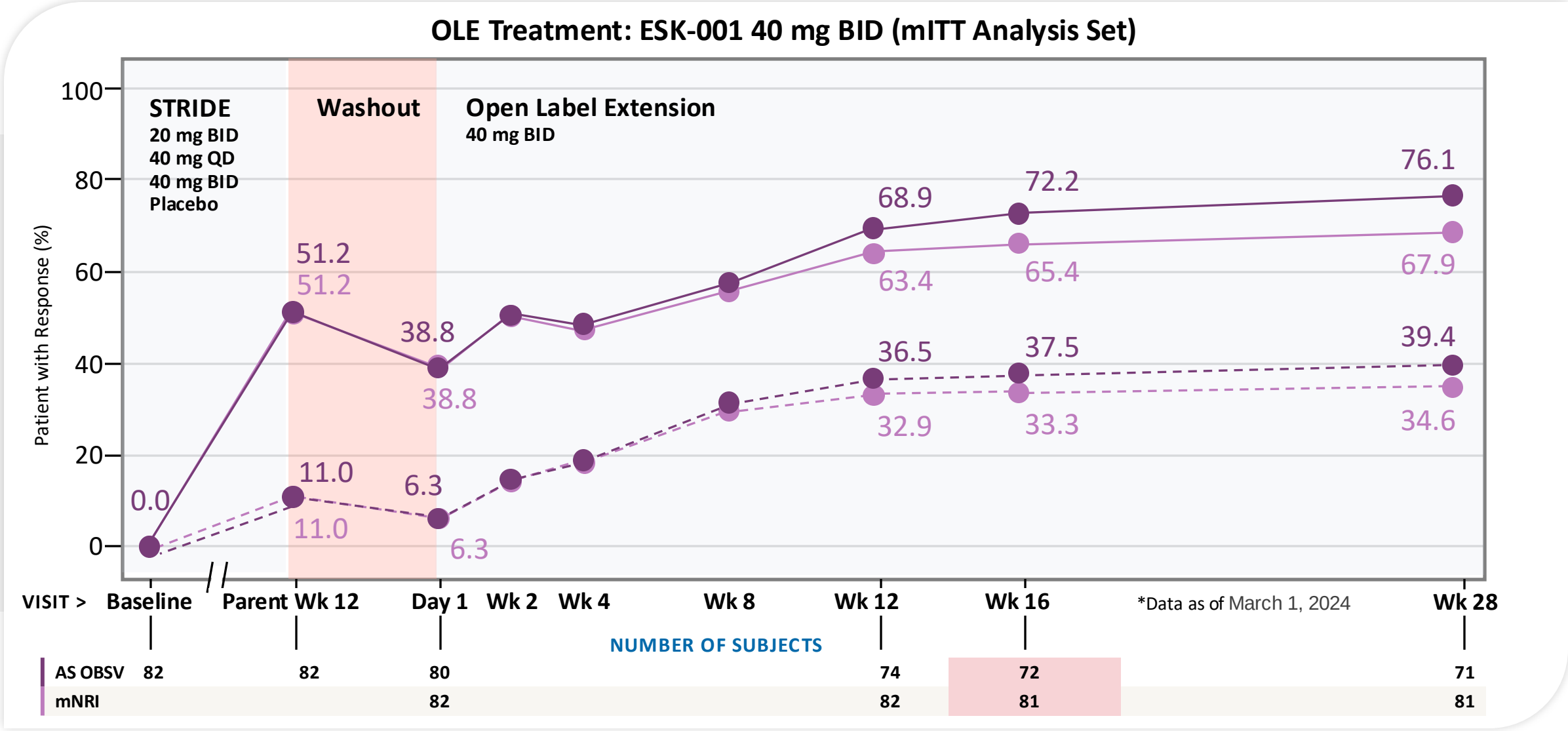
As of May 31, 2024, there were 6 SAEs reported: 40mg QD - [Arthritis, NSCLC, dyspnea]; 40mg BID - [Peritonsillar abscess, sepsis, renal cell carcinoma]. The NSCLC occurred outside of the treatment emergent period and not included in table above.

Stride and OLE Efficacy: Continued Exposure with ESK-001 40mg BID Achieves Significant Increases in PASI Responses



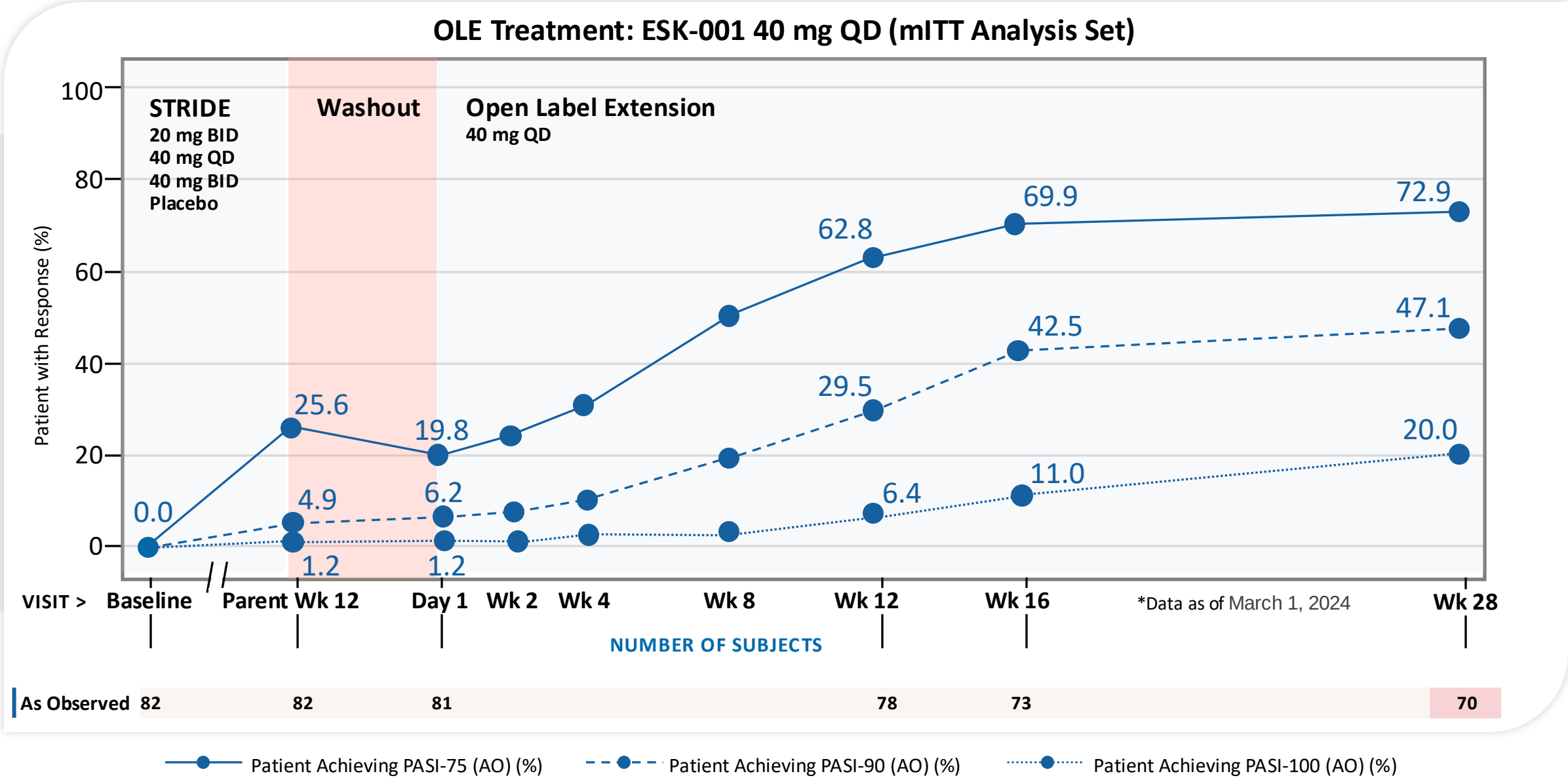
mNRI analysis: if patient discontinued due to AE or inadequate response then imputed as a non-responder; if discontinued for other reasons then imputed using LOCF

Stride and OLE Efficacy: Continued Exposure with ESK-001 40mg BID Achieves Significant Increases in sPGA Responses



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

Continued Exposure with ESK-001 40mg QD Results in Substantially Lower PASI Responses Compared to 40mg BID



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

Conclusions

STRIDE and OLE studies demonstrate ESK-001 is a clinically effective and generally safe oral therapy for the treatment of patients with moderate-to-severe plaque psoriasis

Efficacy Summary

- Maximal TYK2 inhibition achieved across entire dosing period with highest 40 mg BID dose
- STRIDE: Significant improvement in PASI-75, PASI-90, PASI-100 and sPGA-0/1 and sPGA-0 responses achieved at both 40 mg QD and 40 mg BID doses
- Phase 2 OLE: Extended treatment with ESK-001 resulted in clinically meaningful increases in efficacy over time
  - **PASI-75, PASI-90, and PASI-100 responses (mNRI) with 40 mg BID at Week 28 of 83%, 63%, and 31%, respectively**
  - sPGA 0/1 and 0 responses (mNRI) with 40 mg BID at Week 28 of 68% and 35%, respectively

Safety Summary

- ESK-001 was generally safe and well tolerated across all dose levels in both the Phase 2 and OLE studies
- 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

ONWARD Phase 3 development program with ESK-001 in plaque psoriasis ongoing.