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Achievement of Clinically Meaningful Treat-to-Target Thresholds With Envudeucitinib in Moderate-to-Severe Plaque Psoriasis: Results From ONWARD1 and ONWARD2

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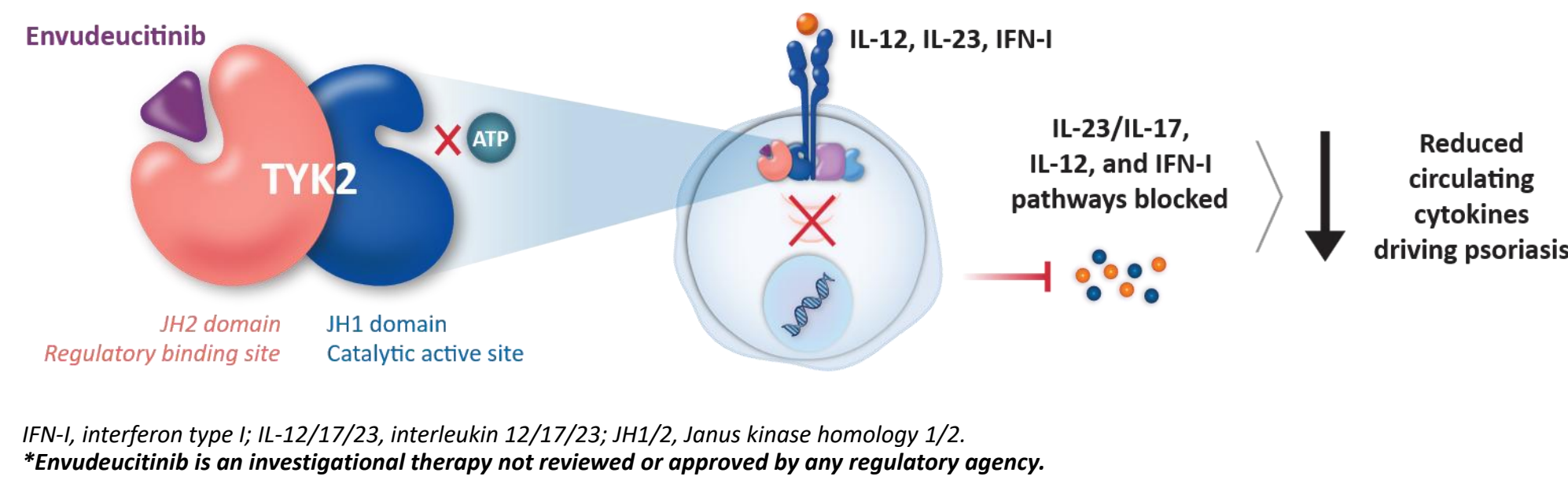
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Synopsis

- Treat-to-target approaches are becoming increasingly relevant in psoriasis clinical practice, with an emphasis on achieving defined levels of disease control to guide treatment decisions¹
- The National Psoriasis Foundation defines body surface area (BSA) ≤1% as the treatment target during maintenance therapy, while absolute Psoriasis Area and Severity Index (PASI) ≤3 has also been proposed as a clinically meaningful treatment goal^{1,3}
- **Envudeucitinib (ESK-001)* is a next-generation, oral, allosteric tyrosine kinase 2 (TYK2) inhibitor that provides maximal inhibition over a 24-hour period in patients with psoriasis (Figure 1)⁴**
- The **ONWARD1 and ONWARD2** Phase 3 trials of **envudeucitinib** met coprimary and all key secondary endpoints and maintained favorable tolerability⁵

Figure 1. Envudeucitinib mechanism of action



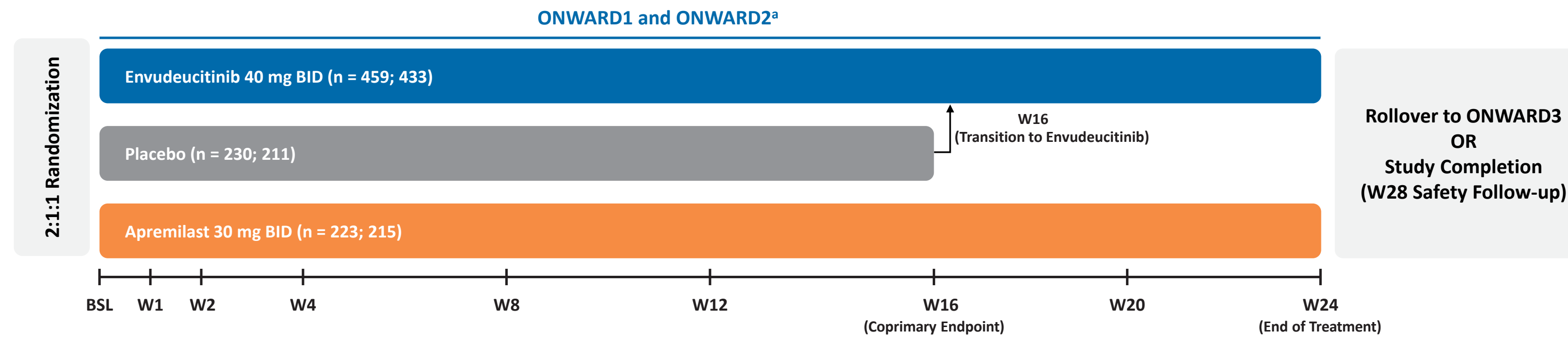
Objective

- To evaluate the achievement of clinically relevant treat-to-target thresholds for PASI and BSA in a post hoc analysis of ONWARD1 and ONWARD2

Methods

- ONWARD1 and ONWARD2 were randomized, double-blinded, placebo- and active comparator-controlled, Phase 3 trials (Figure 2)

Figure 2. ONWARD1 and ONWARD2 study designs



*Replicate design; actual enrollment is reported as ONWARD1 (NCT06586112); ONWARD2 (NCT06588738). BID, bis in die (twice daily); BSL, baseline; W, week.

- Absolute PASI thresholds (0, ≤1, and ≤3) and BSA (≤3% and ≤1%) were calculated post hoc and assessed at Week 16 (vs placebo and apremilast) and Week 24 (vs apremilast)
- The 95% confidence intervals (CIs) for each arm's proportion were obtained using Clopper–Pearson methods, and the 95% CIs and *P*-value of the treatment difference were calculated using the Cochran–Mantel–Haenszel test adjusted for stratification factors
- Patients who discontinued or had missing data were imputed as nonresponders
- Least squares (LS) means and corresponding 95% CIs for percent change from baseline in PASI total score were estimated using a mixed model with repeated measures (MMRM) with modified baseline observation carried forward (mBOCF) imputation; nominal *P*-values for treatment comparisons are presented at Weeks 16 and 24

Results

Baseline demographics and disease characteristics

- Baseline demographics and disease characteristics were balanced across treatment arms and representative of a typical moderate-to-severe population (Table 1)

Table 1. Baseline demographics and disease characteristics

	ONWARD1			ONWARD2		
	Envudeucitinib 40 mg BID N = 459	Placebo N = 230	Apremilast 30 mg BID N = 223	Envudeucitinib 40 mg BID N = 433	Placebo N = 211	Apremilast 30 mg BID N = 215
Age, years, mean (SD)	49.1 (13.4)	49.2 (13.3)	47.7 (11.8)	48.3 (13.1)	49.5 (13.3)	48.0 (12.8)
Sex, male, n (%)	300 (65.4)	156 (67.8)	152 (68.2)	283 (65.4)	135 (64.0)	135 (62.8)
Race, n (%)						
White	358 (78.0)	182 (79.1)	177 (79.4)	388 (89.6)	181 (85.8)	193 (89.8)
Asian	68 (14.8)	28 (12.2)	30 (13.5)	10 (2.3)	10 (4.7)	7 (3.3)
Other ^a	33 (7.2)	20 (8.7)	16 (7.2)	35 (8.1)	20 (9.5)	15 (7.0)
BMI, kg/m ² , mean (SD)	30.6 (7.2)	30.6 (7.2)	29.8 (6.5)	31.2 (7.8)	31.1 (7.3)	30.9 (5.9)
Duration of disease, years, mean (SD)	19.9 (13.5)	19.5 (13.3)	17.2 (11.8)	19.0 (13.5)	20.2 (14.5)	18.7 (14.5)
PASI, mean (SD)	20.4 (8.0)	19.9 (7.5)	20.3 (6.9)	20.6 (8.3)	21.8 (9.0)	20.4 (8.4)
BSA % affected, mean (SD)	25.8 (15.8)	26.2 (16.0)	25.2 (14.9)	25.2 (14.7)	27.3 (16.7)	25.8 (14.1)
DLQI, mean (SD)	10.6 (6.5)	10.1 (6.7)	10.8 (6.8)	10.8 (7.0)	10.8 (6.8)	9.7 (7.1)
Prior systemic psoriasis treatment, n (%) ^b	221 (48.1)	113 (49.1)	107 (48.0)	213 (49.2)	105 (49.8)	102 (47.4)

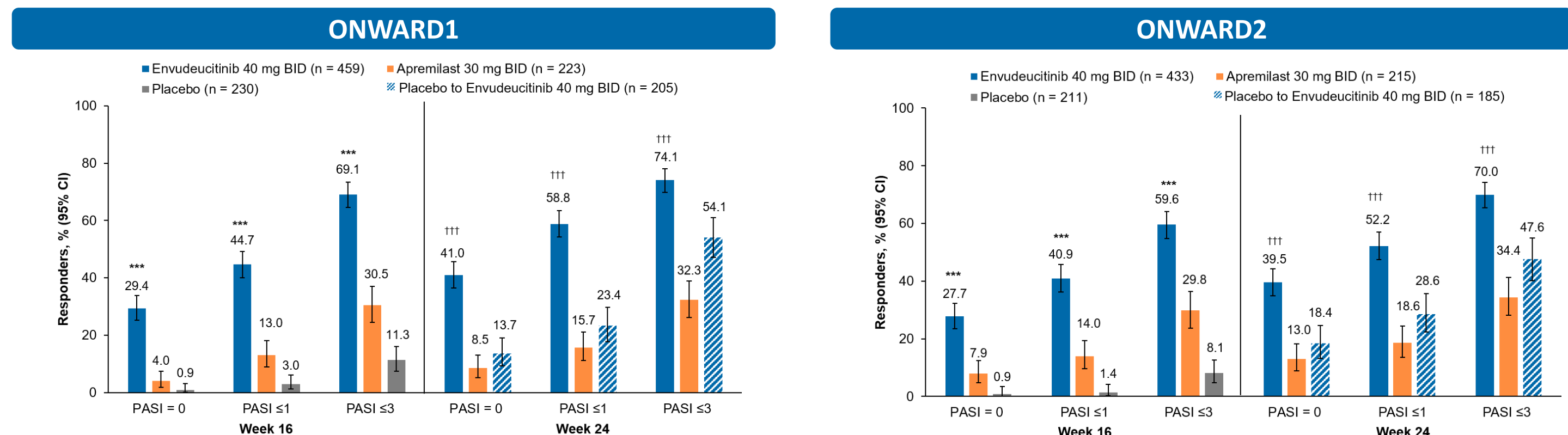
^aIncludes Black or African American, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, and Other or not reported. ^bAny prior exposure to systemic therapies for psoriasis (excluded phototherapy); all patients were required to meet protocol-defined exclusion and washout criteria prior to Study Day 1.

BMI, body mass index; DLQI, Dermatology Life Quality Index; SD, standard deviation.

PASI and BSA treatment targets achieved by Week 16, deepening through Week 24

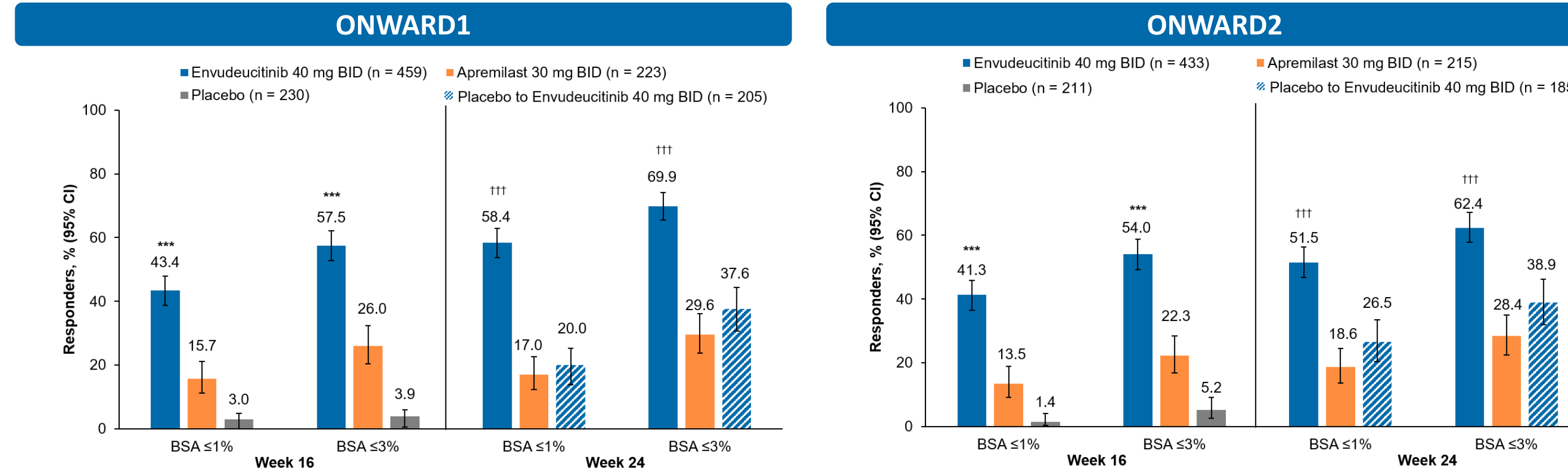
- At Week 16, significantly more patients treated with envudeucitinib achieved clinically meaningful PASI treatment targets (Figure 3) and BSA treatment targets (Figure 4) vs placebo and apremilast
- Responses continued to improve through Week 24 for all thresholds
- Example patient photographs are shown in Figure 5
- Improvement in PASI from baseline with envudeucitinib was evident at Week 2 (Figure 6)
- Responses continued to improve through Week 24

Figure 3. Absolute PASI threshold responses



****P* < 0.0001 vs placebo and apremilast. ****P* < 0.0001 vs apremilast.

Figure 4. BSA percent threshold responses



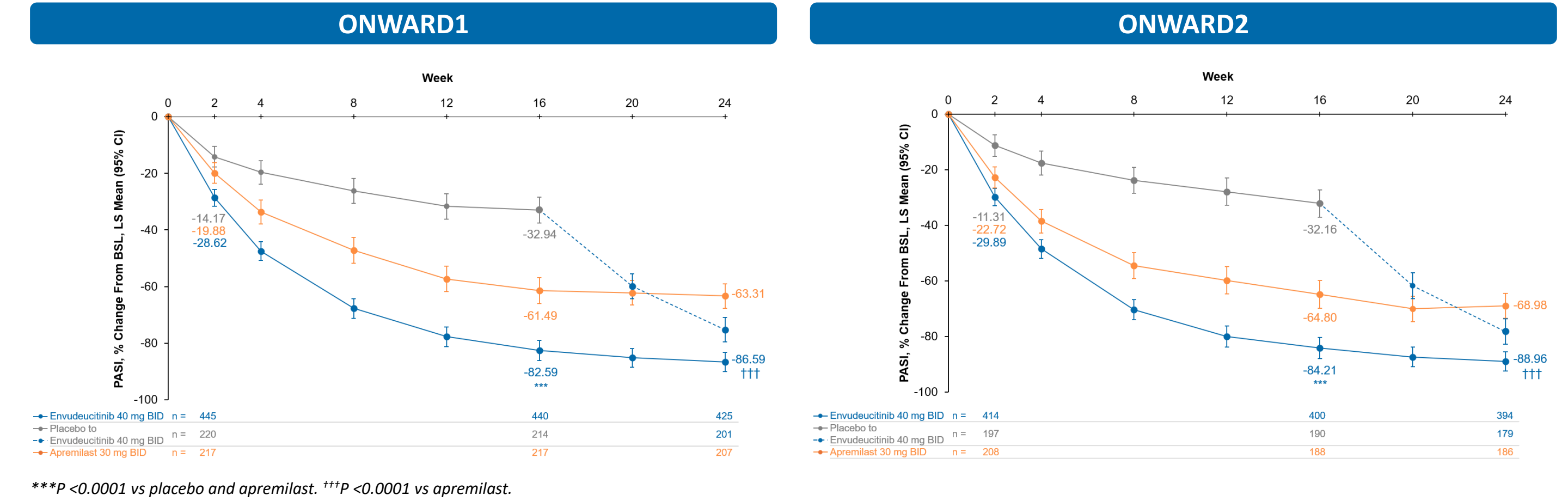
****P* < 0.0001 vs placebo and apremilast. ****P* < 0.0001 vs apremilast.

Figure 5. Patient photographs



sPGA, static Physician's Global Assessment.

Figure 6. LS mean (95% CI) of PASI percent change from baseline



****P* < 0.0001 vs placebo and apremilast. ****P* < 0.0001 vs apremilast.

Conclusion

- Patients receiving **envudeucitinib** met stringent treat-to-target thresholds associated with disease control, with response rates increasing from Weeks 16 to 24
- **Improvements** were seen as early as **Week 2** and were consistent in magnitude with Week 52 results from the Phase 2 open-label extension⁶

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