# 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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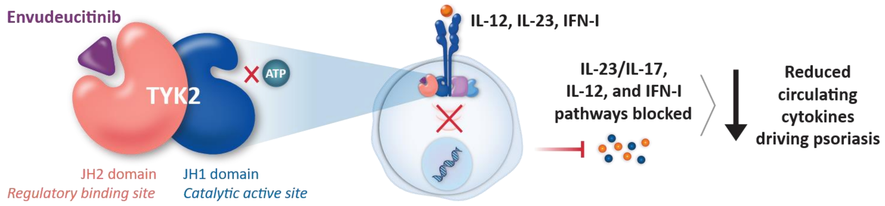
## Synopsis

- 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 decisions[1]
- 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 tolerability[5]

### Figure 1. Envudeucitinib mechanism of action




*IFN-I, interferon type I; IL-12/17/23, interleukin 12/17/23; JH1/2, Janus kinase homology 1/2.*
***Envudeucitinib is an investigational therapy not reviewed or approved by any regulatory agency.***

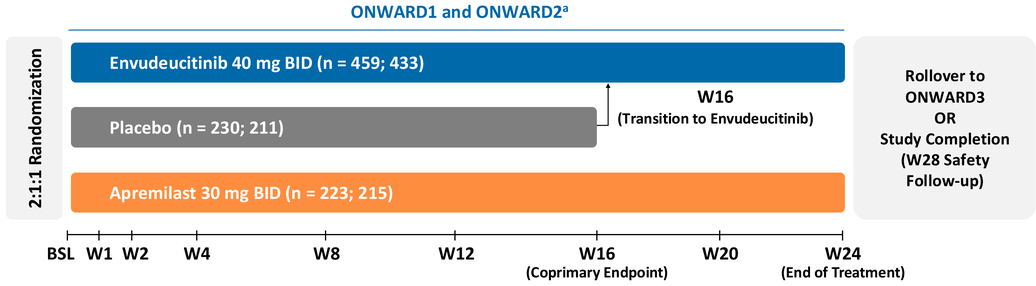
## Objective

- 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**)
- 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

### Figure 2. ONWARD1 and ONWARD2 study designs




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

## 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/m², 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) |

*[a]Includes Black or African American, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, and Other or not reported. [b]Any 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

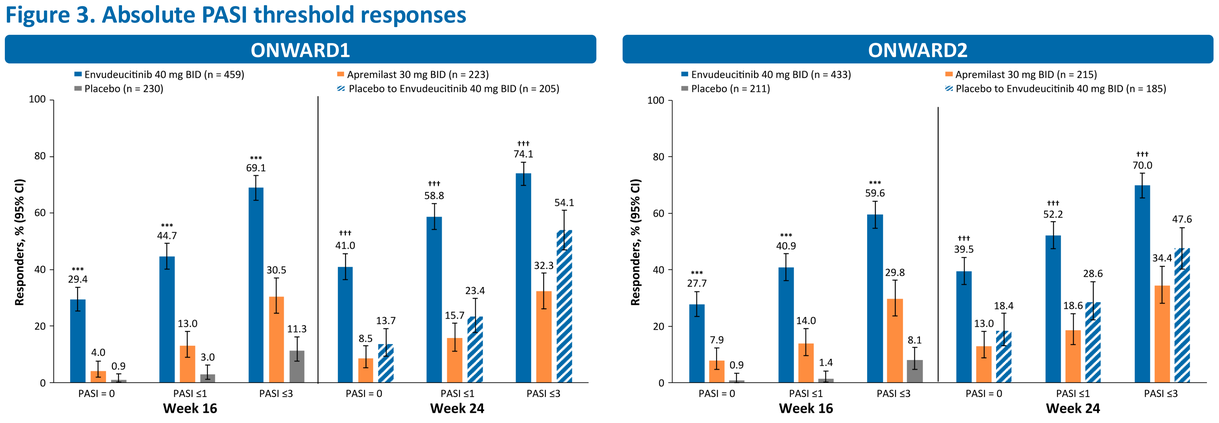
- At Week 16, significantly more patients treated with envudeucitinib achieved clinically meaningful PASI treatment targets (**Figure 3**) and BSA treatment targets (**Figure 4**) vs placebo and apremilast
  - Responses continued to improve through Week 24 for all thresholds
- Example patient photographs 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 5. Patient photographs




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

### Figure 3. Absolute PASI threshold responses

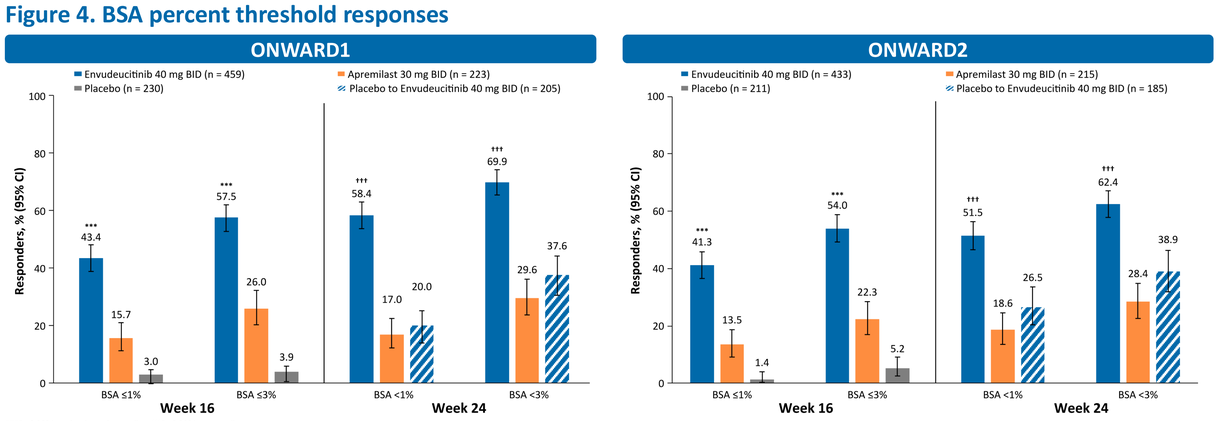






****P <0.0001 vs placebo and apremilast. †††P <0.0001 vs apremilast.*

### Figure 4. BSA percent threshold responses

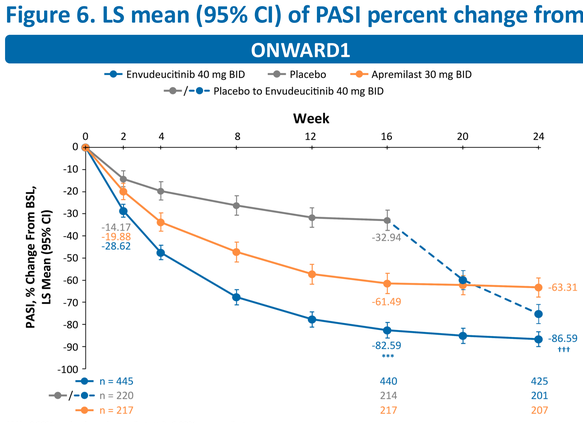


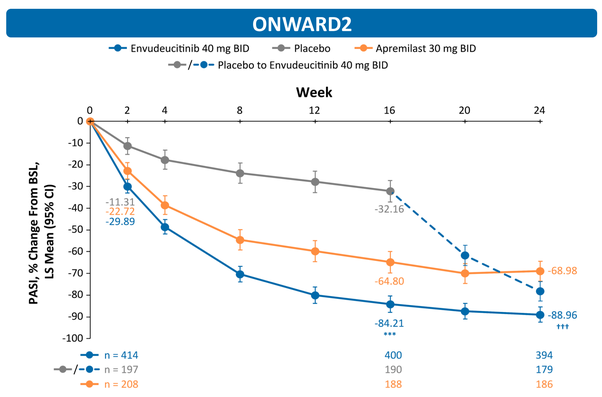




****P <0.0001 vs placebo and apremilast. †††P <0.0001 vs apremilast.*

### Figure 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 extension[6]

## References


1. Mahil SK, et al. *Br J Dermatol*. 2020;182(5):1158-66. 2. Armstrong AW, et al. *J Am Acad Dermatol*. 2017;76(2):290-8. 3. Gisondi P, et al. *Dermatol Ther (Heidelb)*. 2021;11(1):235-52. 4. Armstrong AW, et al. *Dermatol Ther (Heidelb)*. 2026;16(6):2661-73. 5. Blauvelt A, et al. Envudeucitinib (ESK-001) in moderate-to-severe plaque psoriasis: 24-week results from the randomized, double-blind, active comparator- and placebo-controlled, phase 3 ONWARD 1 and 2 studies. Presented at American Academy of Dermatology; March 27-31, 2026. 6. Papp KA, et al. *J Am Acad Dermatol*. 2026;94(1):187-95.


## Disclosures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