Envudeucitinib (ESK-001) in Moderate-to-Severe Plaque Psoriasis: 24-Week Results From the Randomized, Double-Blind, Active Comparator- and Placebo-Controlled, Phase 3 ONWARD1 and ONWARD2 Studies

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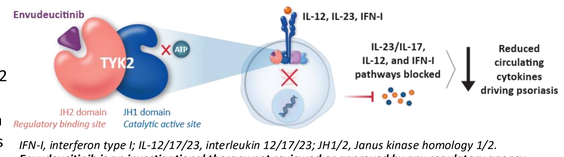
Background

- **Envudeucitinib (ESK-001), a next-generation**, oral, **allosteric** tyrosine kinase 2 (TYK2) inhibitor, provides **maximal inhibition** over a 24-hour period in patients with psoriasis[1,2]

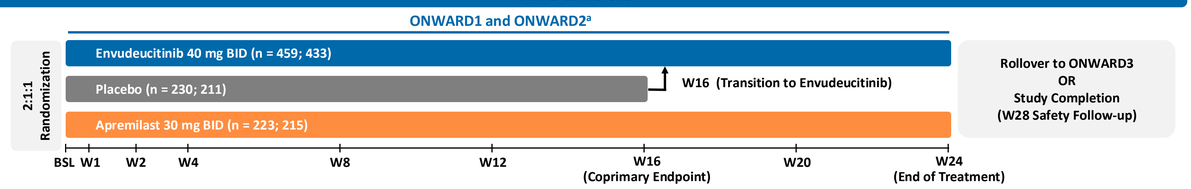


IFN-I, interferon type I; IL-12/17/23, interleukin 12/17/23; JH1/2, Janus kinase homology 1/2.
Envudeucitinib is an investigational therapy not reviewed or approved by any regulatory agency.

Objective

- To evaluate the efficacy, safety, onset of action, and patient-reported outcomes of envudeucitinib vs placebo and apremilast in adults with moderate-to-severe plaque psoriasis through Week 24

Methods



[a]Replicate design; actual enrollment is reported as ONWARD1 (NCT06586112); ONWARD2 (NCT06588738). Coprimary endpoints (vs placebo; PASI 75 and sPGA-0/1), key secondary endpoints (vs placebo or apremilast; PASI 75/90/100, sPGA-0/1, change from baseline in itch [NRS], ss-PGA-0/1 [baseline ≥3], and DLQI-0/1 [baseline ≥2]), and safety endpoints were assessed. Adult patients had moderate-to-severe plaque psoriasis (plaque psoriasis ≥6 months; BSA ≥10%; PASI ≥12; sPGA ≥3; phototherapy- or systemic therapy–eligible; no nonplaque psoriasis or other inflammatory skin conditions; no immune-mediated conditions commonly associated with psoriasis).
BID, bis in die (twice daily); BSA, body surface area; BSL, baseline; DLQI-0/1, Dermatology Life Quality Index 0 or 1; NRS, numeric rating scale; PASI, Psoriasis Area and Severity Index; PASI 75/90/100, ≥75%/≥90%/100% improvement in PASI; PGA, Physician's Global Assessment; sPGA, static PGA; sPGA-0/1, sPGA 0 (clear) or 1 (almost clear); ss-PGA-0/1, scalp-specific PGA 0 (clear) or 1 (almost clear); W, week.

Conclusions

- ✓ **Rapid onset**
  - PASI 90 separation by Week 4
- ✓ **High efficacy**
  - Progressive PASI 90/100 improvement through Week 24
  - Superior to placebo and apremilast
- ✓ **Meaningful patient benefit**
  - Rapid itch relief
  - Improved DLQI
  - Significant scalp clearance
- ✓ **Favorable safety**
  - Well tolerated, with no new safety signals

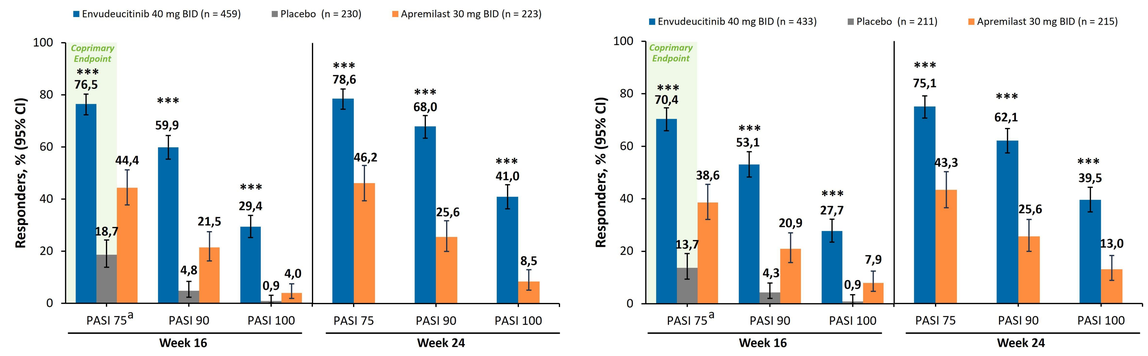
Results

Baseline demographics and disease characteristics were balanced across arms and representative of a typical moderate-to-severe population

	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, mean (SD), years	49.1 (13.4)	49.2 (13.3)	47.7 (11.8)	48.3 (13.1)	49.5 (13.3)	48.0 (12.8)
Age group, ≥65 years, n (%)	61 (13.3)	27 (11.7)	15 (6.7)	51 (11.8)	28 (13.3)	20 (9.3)
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)
Weight, mean (SD), kg	90.4 (24.0)	91.0 (24.3)	88.9 (21.0)	92.3 (23.8)	91.1 (23.1)	90.8 (19.9)
BMI, mean (SD), kg/m²	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, mean (SD), years	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)
sPGA of 4, n (%)	129 (28.1)	57 (24.8)	61 (27.4)	131 (30.3)	70 (33.2)	53 (24.7)
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)
Worst pruritus NRS, mean (SD)	6.1 (2.7)	6.0 (2.7)	6.3 (2.6)	6.4 (2.6)	6.4 (2.4)	6.0 (2.7)
Prior systemic psoriasis treatment, n (%)[b]	221 (48.1)	113 (49.1)	107 (48.0)	213 (49.2)	105 (49.8)	102 (47.4)

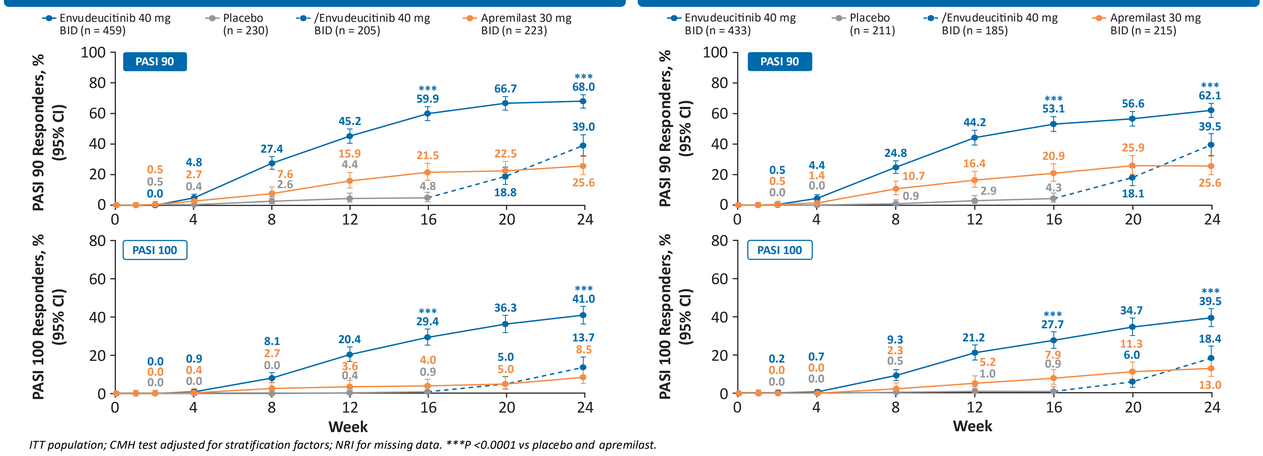
[a]Includes Black or African American, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, and Other or not reported. [b]Any prior exposure to systemic therapies for psoriasis (excluded phototherapy); all patients were required to meet protocol-defined exclusion and washout criteria prior to Study Day 1. BMI, body mass index; SD, standard deviation.

Robust and statistically significant PASI response rates at Week 16, and sustained PASI response rates through Week 24



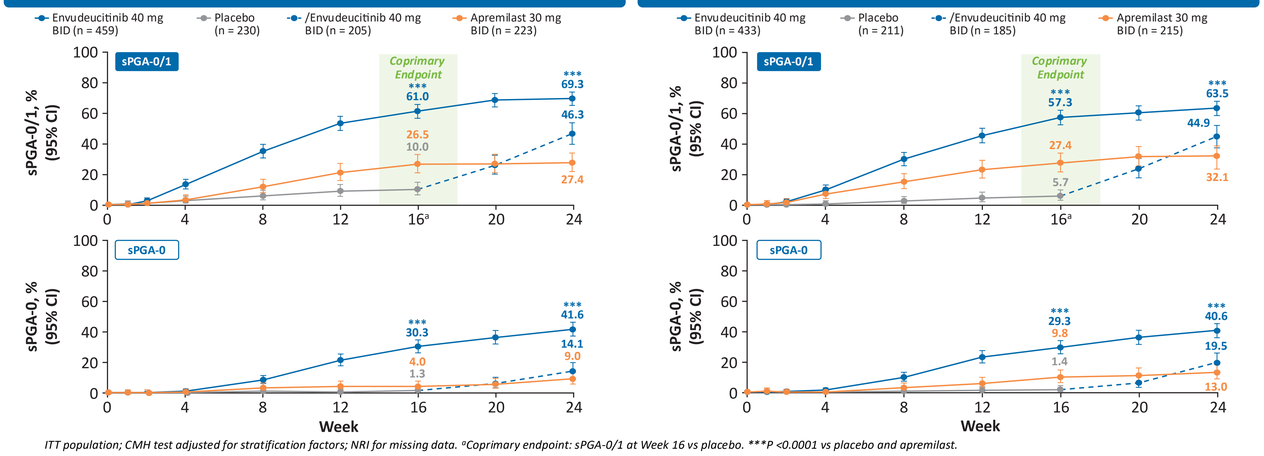
*ITT population; CMH test adjusted for stratification factors; NRI for missing data. [a]Coprimary endpoint: PASI 75 at Week 16 vs placebo. ***P <0.0001 vs placebo and apremilast. CI, confidence interval; CMH, Cochran-Mantel-Haenszel; ITT, intention-to-treat; NRI, nonresponder imputation.*

Envudeucitinib resulted in rapidly increasing PASI 90 and 100 responses vs placebo and apremilast



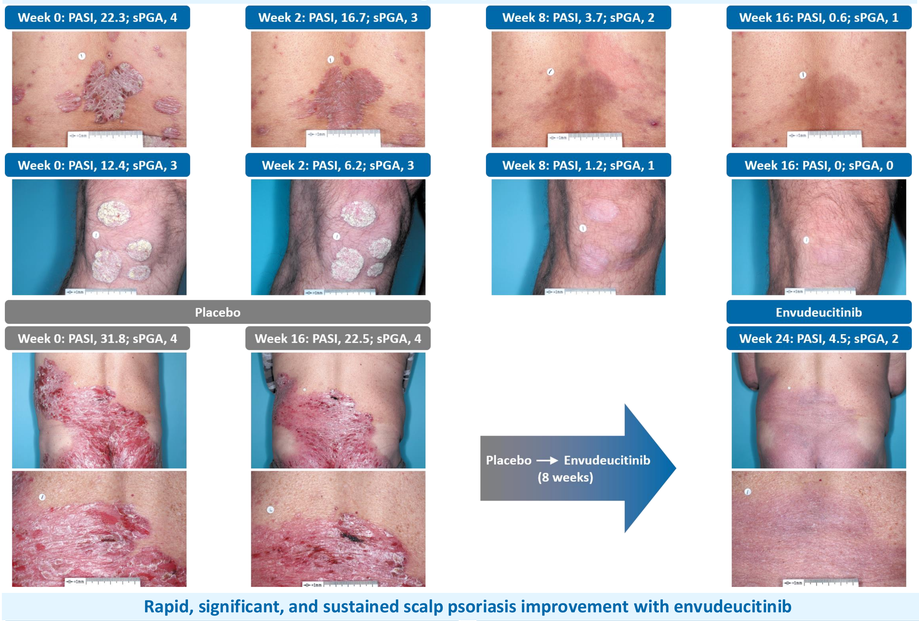
*ITT population; CMH test adjusted for stratification factors; NRI for missing data. ***P <0.0001 vs placebo and apremilast.*

Envudeucitinib demonstrated significant sPGA-0/1 and sPGA-0 responses

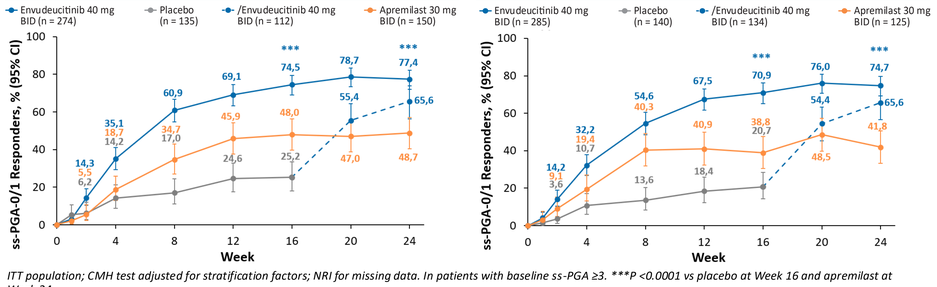


*ITT population; CMH test adjusted for stratification factors; NRI for missing data. [a]Coprimary endpoint: sPGA-0/1 at Week 16 vs placebo. ***P <0.0001 vs placebo and apremilast.*

Visible skin improvement evident as early as Week 2 and substantial changes after 8 weeks of treatment

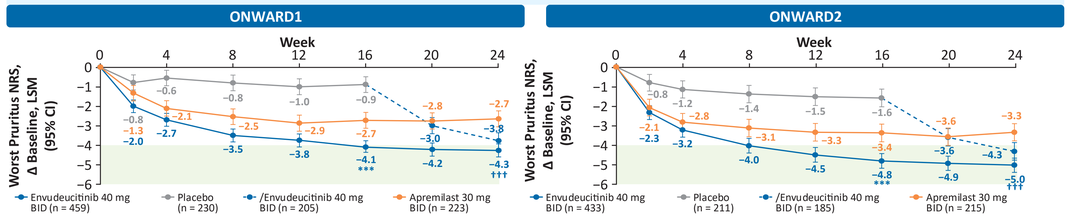


Rapid, significant, and sustained scalp psoriasis improvement with envudeucitinib



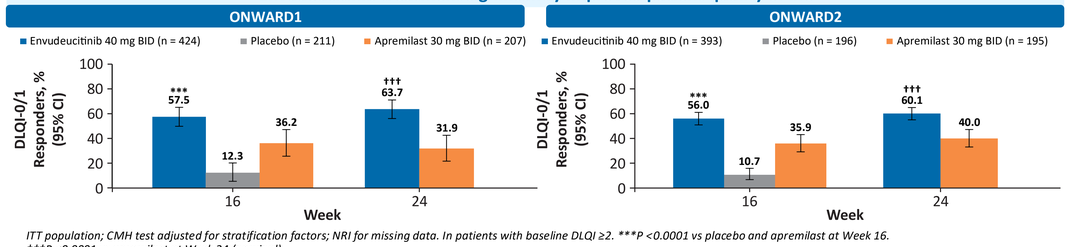
*ITT population; CMH test adjusted for stratification factors; NRI for missing data. In patients with baseline ss-PGA ≥3. ***P <0.0001 vs placebo at Week 16 and apremilast at Week 24.*

Envudeucitinib rapidly reduced itch with deepening response over time



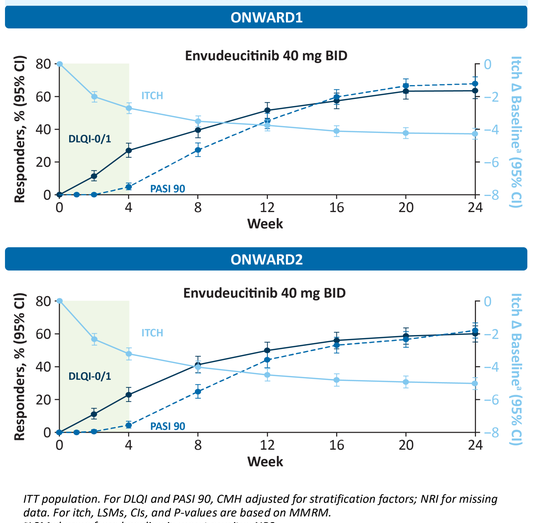
*ITT population; LSMs, CIs, and P-values are based on MMRM. ***P <0.0001 vs placebo and apremilast at Week 16. †††P <0.0001 vs apremilast at Week 24 (nominal). LSM, least squares mean; MMRM, mixed model for repeated measures.*

Envudeucitinib treatment significantly improved patient quality of life



*ITT population; CMH test adjusted for stratification factors; NRI for missing data. In patients with baseline DLQI ≥2. ***P <0.0001 vs placebo and apremilast at Week 16. †††P <0.0001 vs apremilast at Week 24 (nominal).*

Benefits in itch reduction and quality of life were visible before skin clearance



ITT population. For DLQI and PASI 90, CMH adjusted for stratification factors; NRI for missing data. For itch, LSMs, CIs, and P-values are based on MMRM. [a]LSM change from baseline in worst pruritus NRS.

ONWARD1 and ONWARD2 pooled safety through Weeks 16 and 24

	Through Week 16			Through Week 24			
n (%)	Envudeucitinib 40 mg BID n = 890	Placebo n = 441	Apremilast 30 mg BID n = 438	Envudeucitinib 40 mg BID only n = 890	Placebo to Envudeucitinib 40 mg BID n = 390	Overall Envudeucitinib 40 mg BID n = 1280	Apremilast 30 mg BID n = 438
≥1 TEAE	524 (58.9)	166 (37.6)	223 (50.9)	563 (63.3)	130 (33.3)	693 (54.1)	248 (56.6)
≥1 SAE	19 (2.1)	5 (1.1)	5 (1.1)	24 (2.7)	1 (0.3)	25 (2.0)	6 (1.4)
TEAE leading to treatment discontinuation	30 (3.4)	7 (1.6)	9 (2.1)	31 (3.5)	4 (1.0)	35 (2.7)	12 (2.7)
TEAE grade ≥3	42 (4.7)	14 (3.2)	18 (4.1)	48 (5.4)	7 (1.8)	55 (4.3)	23 (5.3)
Most-frequent TEAEs (≥5%)[a]							
Headache	92 (10.3)	11 (2.5)	40 (9.1)	97 (10.9)	11 (2.8)	108 (8.4)	42 (9.6)
Nasopharyngitis	64 (7.2)	21 (4.8)	16 (3.7)	92 (10.3)	18 (4.6)	110 (8.6)	26 (5.9)
Acne	53 (6.0)	3 (0.7)	3 (0.7)	60 (6.7)	17 (4.4)	77 (6.0)	3 (0.7)
Upper respiratory tract infection	43 (4.8)	7 (1.6)	16 (3.7)	57 (6.4)	2 (0.5)	59 (4.6)	21 (4.8)
Nausea	20 (2.2)	4 (0.9)	23 (5.3)	20 (2.2)	0	20 (1.6)	23 (5.3)
Diarrhea	14 (1.6)	11 (2.5)	36 (8.2)	16 (1.8)	1 (0.3)	17 (1.3)	36 (8.2)

Safety analysis population; pooled ONWARD1 and ONWARD2 data. [a]TEAEs occurring in ≥5% of patients in any treatment arm through either Week 16 or Week 24. [b]Thirty-nine patients with latent or treated TB were enrolled. AE, adverse event; MACE, major adverse cardiovascular event; SAE, serious AE; TB, tuberculosis; TEAE, treatment-emergent AE.

- Envudeucitinib showed low rates of SAEs and AEs leading to discontinuation
  - No deaths; no MACE or cytopenia signals; no TB reactivation[b]
- No clinically significant laboratory abnormalities were observed across lipid, hematologic, and chemistry panels, with comparable variability across treatment arms throughout the study
- At Week 24, low incidence of serious infections (0.7%) and malignancies (0.2%) observed in patients treated with envudeucitinib

References

1. Ucpinar S, et al. *Clin Transl Sci*. 2024;17(12):e70094.
2. Blauvelt A, et al. *J Am Acad Dermatol*. 2026;94(1):57-65.

Disclosures

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