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

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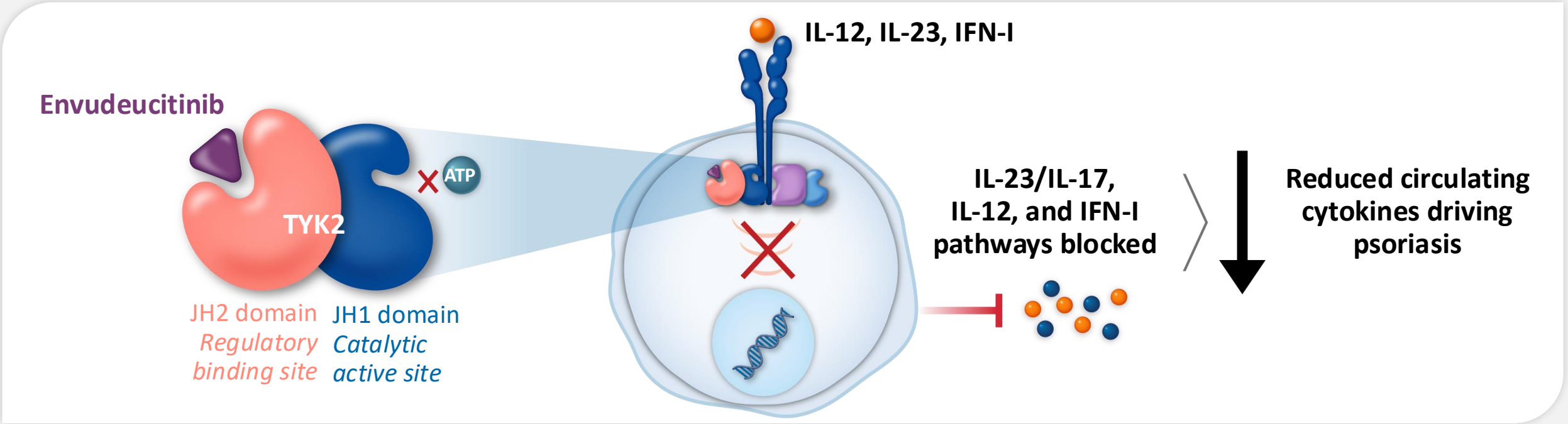
Disclosures

- **Presenting author: AB** has served as a speaker for and received honoraria from Almirall, Eli Lilly, LEO Pharma, Sanofi, and UCB; has served as a scientific adviser for and received honoraria from AbbVie, Almirall, Alumis Inc., Amgen, AnaptysBio, Apogee Therapeutics, Arcutis Biotherapeutics, Eli Lilly, Incyte, Janssen, LEO Pharma, Novartis, Oruka Therapeutics, Pfizer, Regeneron Pharmaceuticals, Sanofi, Sun Pharma, Takeda, and UCB; and owns stock in Lipidio Pharma and Oruka Therapeutics
- **Coauthors (relevant to study): HS** has nothing to report. **AA** has served as a research investigator, scientific adviser, or speaker for Alumis Inc. **BE** has received fees/honoraria/royalties as an advisory board member, contributor, and/or consultant for Alumis Inc., and received institutional funding as an investigator for Alumis Inc. **JS** has served as an investigator for Alumis Inc. **MSA** and **DR** have nothing relevant to disclose. **JW** has served as an investigator for Alumis Inc. **DV**, **GM**, and **EM** are employees and shareholders of Alumis Inc.
- All authors met the ICMJE authorship criteria and had full access to relevant data
- The ONWARD program is currently ongoing, and these studies were sponsored by Alumis Inc.
- **Envudeucitinib is an investigational therapy not reviewed or approved by any regulatory agency**

ICMJE, International Committee of Medical Journal Editors.

Envudeucitinib: A Next-Generation TYK2i for Moderate-to-Severe Psoriasis

- **Envudeucitinib**, a **next-generation**, oral, **allosteric** TYK2i, provides **maximal inhibition** over a 24-hour period in patients with psoriasis[1,2]
- STRIDE Phase 2 and its open-label extension results demonstrated the **favorable benefit/risk profile** of **envudeucitinib**, with **meaningful clinical efficacy** throughout 52 weeks, and **good tolerability**[2,3]



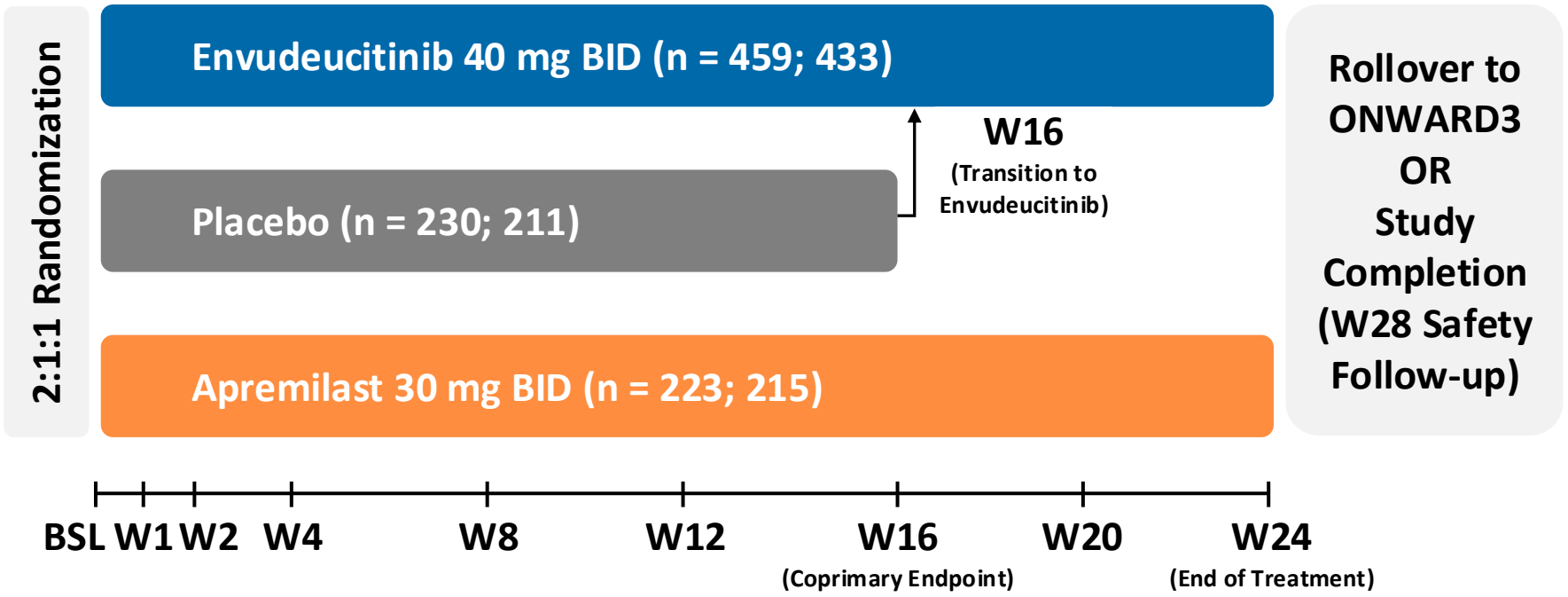
IL-12/17/23, interleukin 12/17/23; IFN-I, interferon type I; JH1/2, Janus kinase homology 1/2; TYK2, tyrosine kinase 2; TYK2i, TYK2 inhibitor.

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. 3. Papp KA, et al. *J Am Acad Dermatol*. 2026;94(1):187-95.

Envudeucitinib is investigational; not yet reviewed by regulatory agencies

ONWARD1 and ONWARD2: Study Designs and Endpoints

ONWARD1 and ONWARD2[a]



Rollover to ONWARD3 OR Study Completion (W28 Safety Follow-up)

Coprimary Endpoints (vs Placebo)

- PASI 75
- 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)
- DLQI-0/1 (baseline ≥2)

Safety Endpoints

Key Inclusion Criteria

- Age ≥18 years; weight >40 kg
- Plaque psoriasis ≥6 months
- BSA ≥10%; PASI ≥12; sPGA ≥3
- Phototherapy- or systemic therapy-eligible

Key Exclusion Criteria

- Nonplaque psoriasis or other inflammatory skin conditions
- Immune-mediated conditions commonly associated with psoriasis

[a]Replicate design; actual enrollment is reported as ONWARD1 (NCT06586112); ONWARD2 (NCT06588738).

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.

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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, 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)
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, kg, mean (SD)	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, 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)
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)

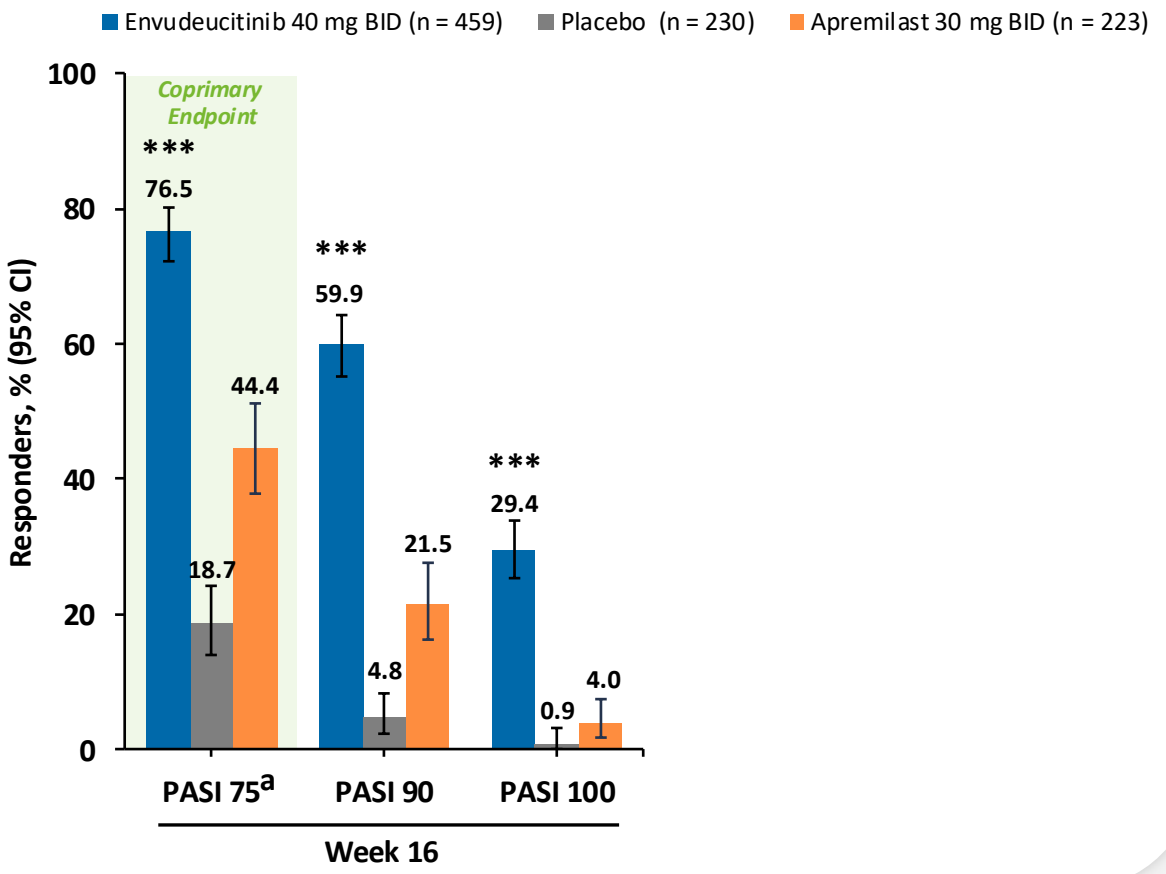
[a]Includes Black or African American, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, and Other or not reported. [b]Any prior exposure to systemic therapies for psoriasis (excluded phototherapy); all patients were required to meet protocol-defined exclusion and washout criteria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

BID, *bis in die* (twice daily); BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; NRS, numeric rating scale; PASI, Psoriasis Area and Severity Index; SD, standard deviation; sPGA, static Physician's Global Assessment.

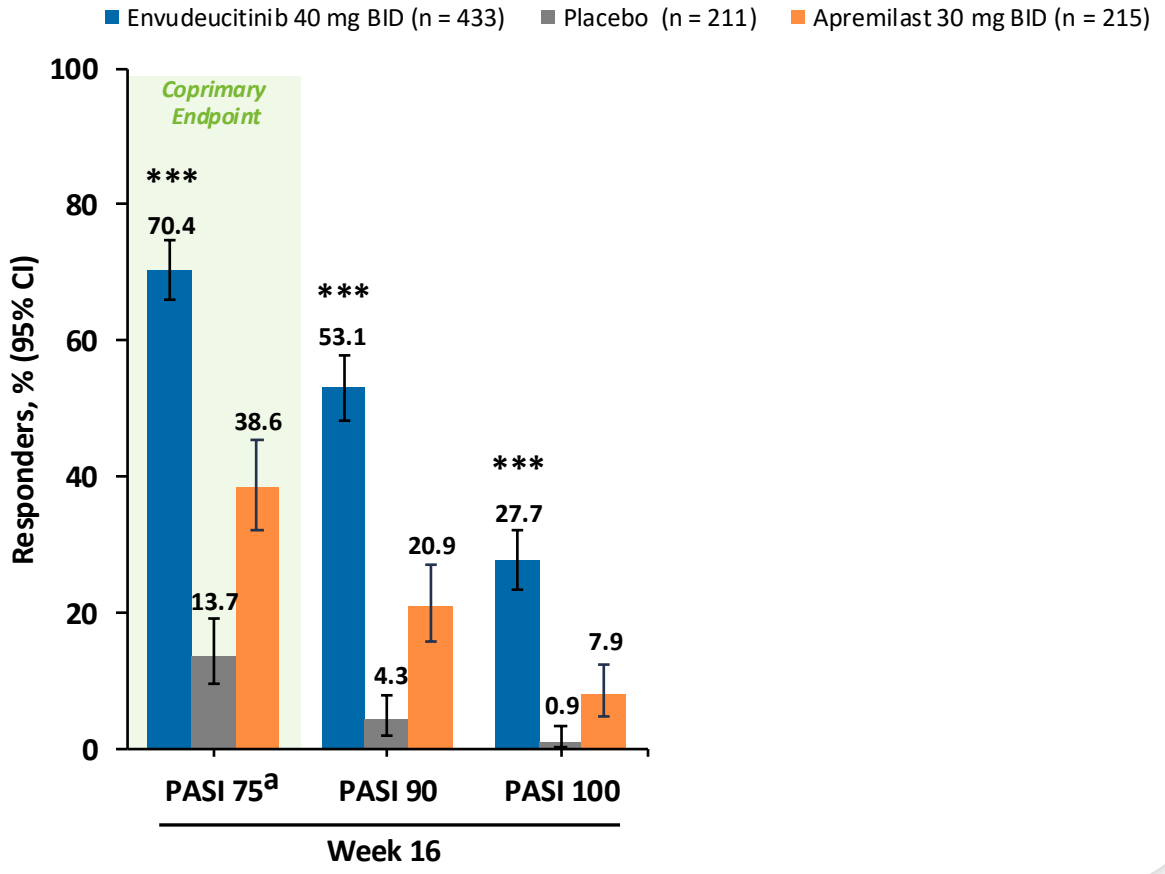
Robust and Statistically Significant PASI Response Rates at Week 16

Almost 30% of patients receiving envudeucitinib achieved PASI 100 at Week 16

ONWARD1



ONWARD2



Intention-to-treat population. The 95% CIs and *P*-values of the treatment differences were based on the Cochran-Mantel-Haenszel test adjusted for stratification factors. Nonresponder imputation was applied for missing data. [a]Coprimary endpoint: PASI 75 at Week 16 vs placebo. ***P <0.0001 vs placebo and apremilast.

BID, *bis in die* (twice daily); CI, confidence interval; PASI, Psoriasis Area and Severity Index; PASI 75/90/100, ≥75%/≥90%/100% improvement in PASI.

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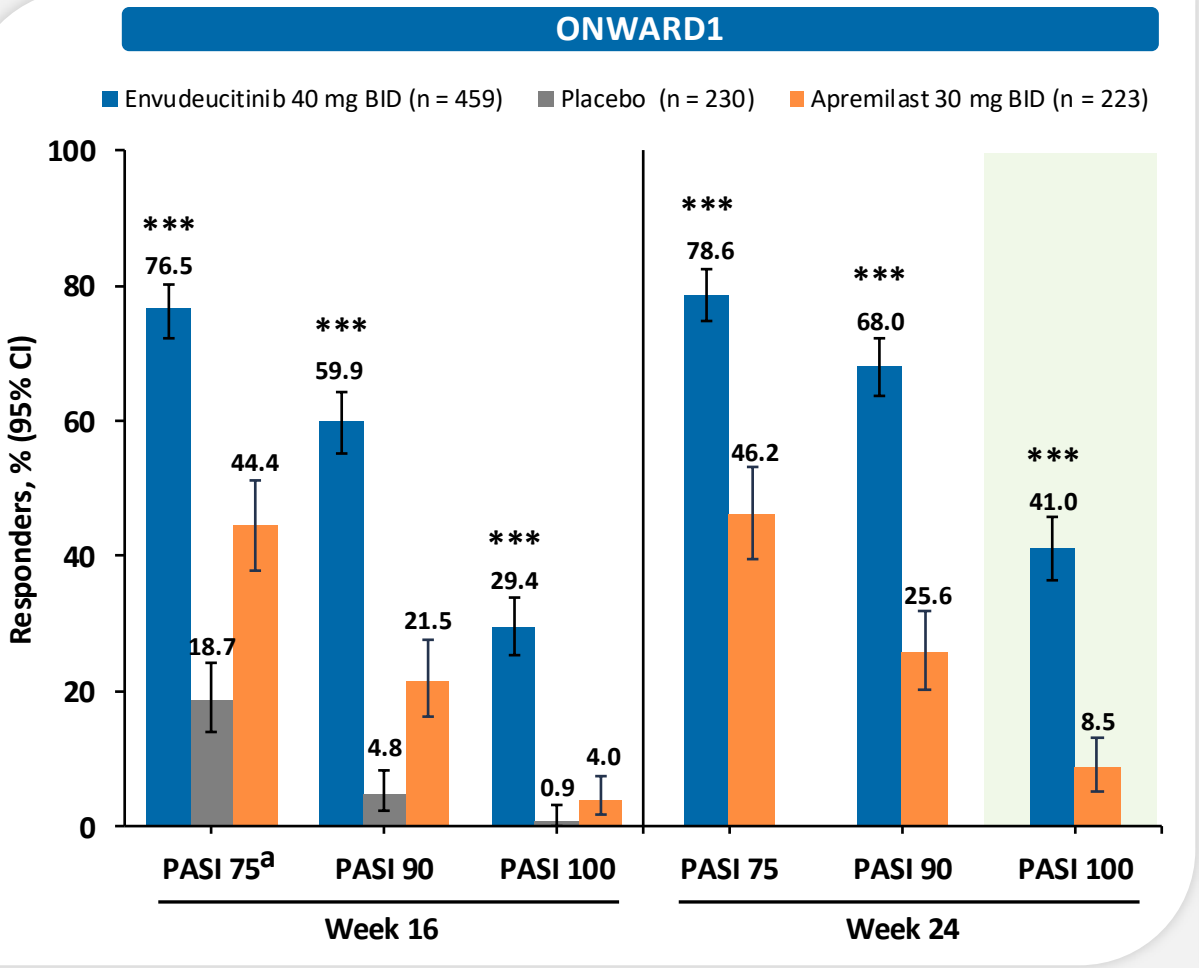
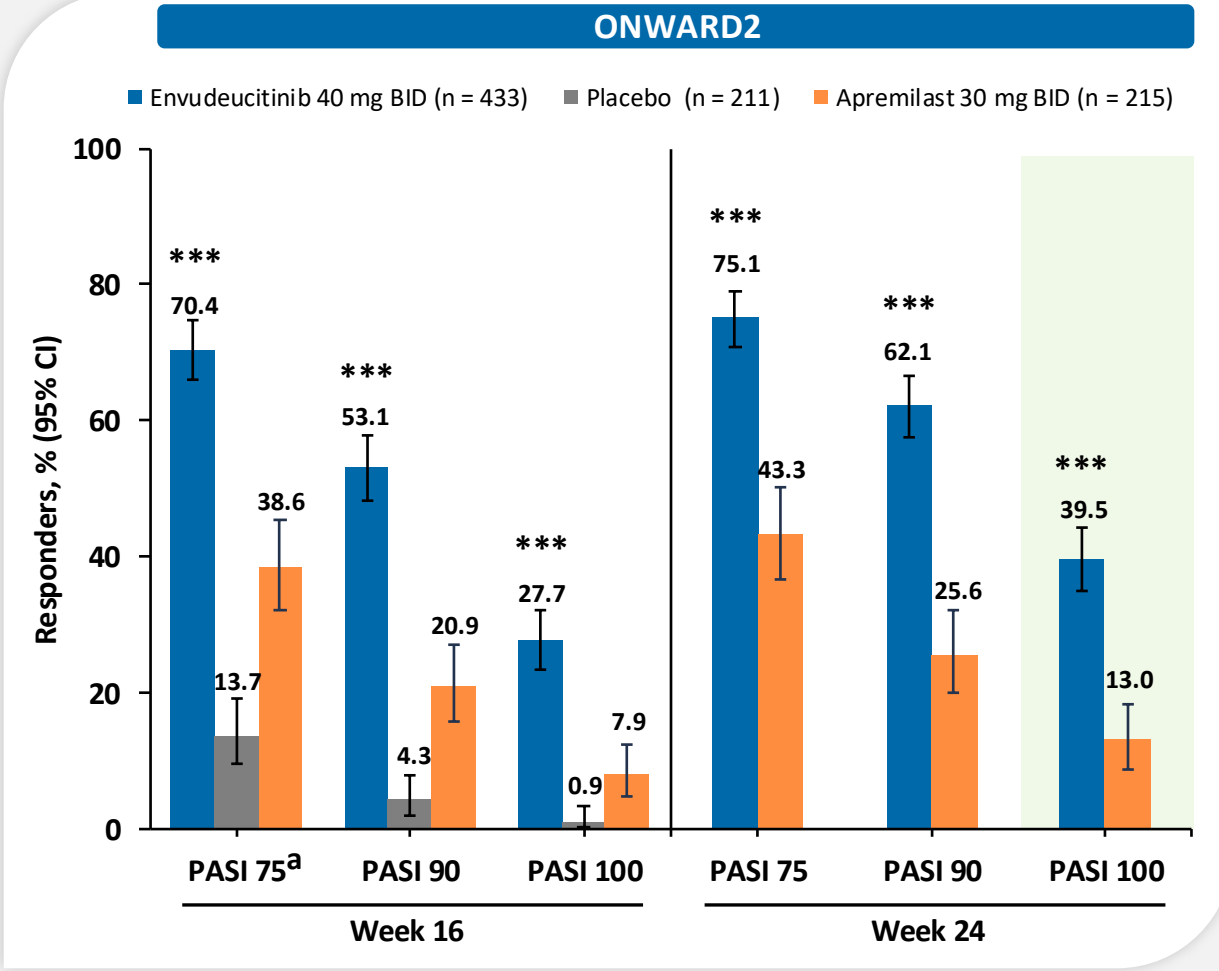
Sustained and Continued PASI Response Rates Through Week 24

Approximately 65% and 40% of patients achieved PASI 90 and PASI 100 with envudeucitinib at Week 24





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BID, *bis in die* (twice daily); CI, confidence interval; PASI, Psoriasis Area and Severity Index; PASI 75/90/100, ≥75%/≥90%/100% improvement in PASI.

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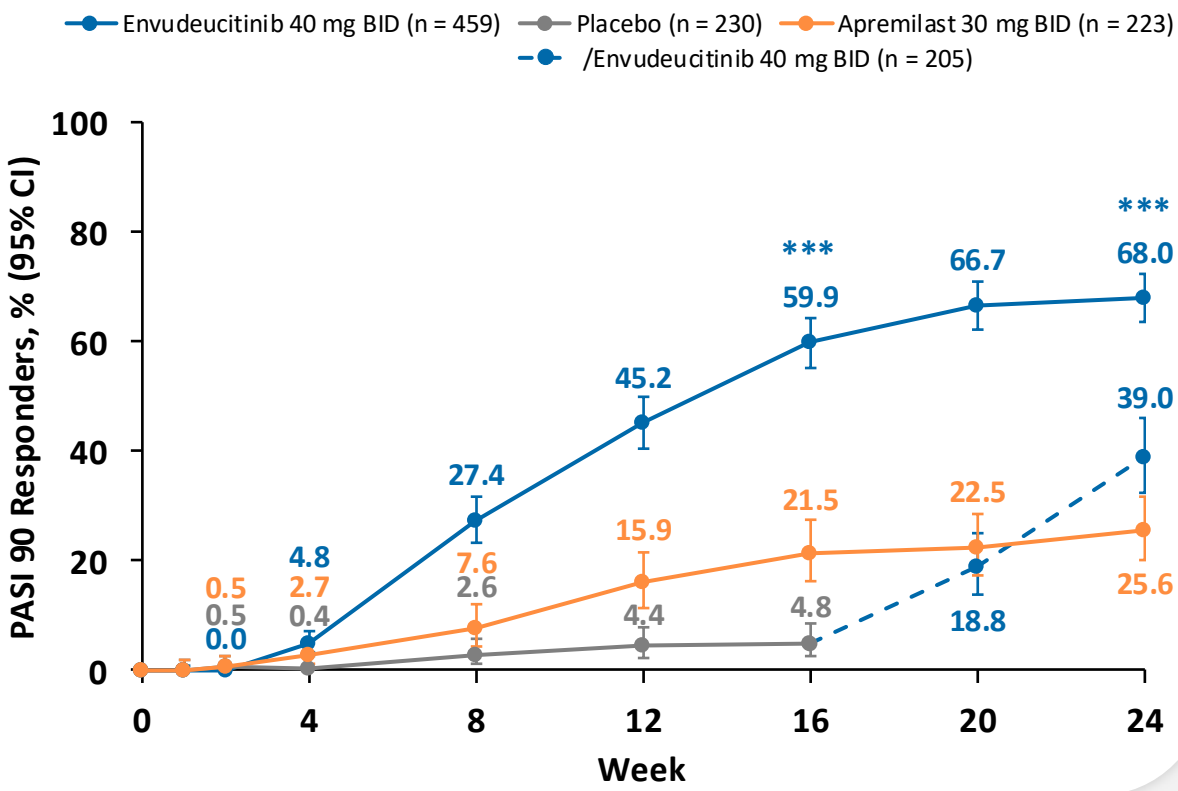
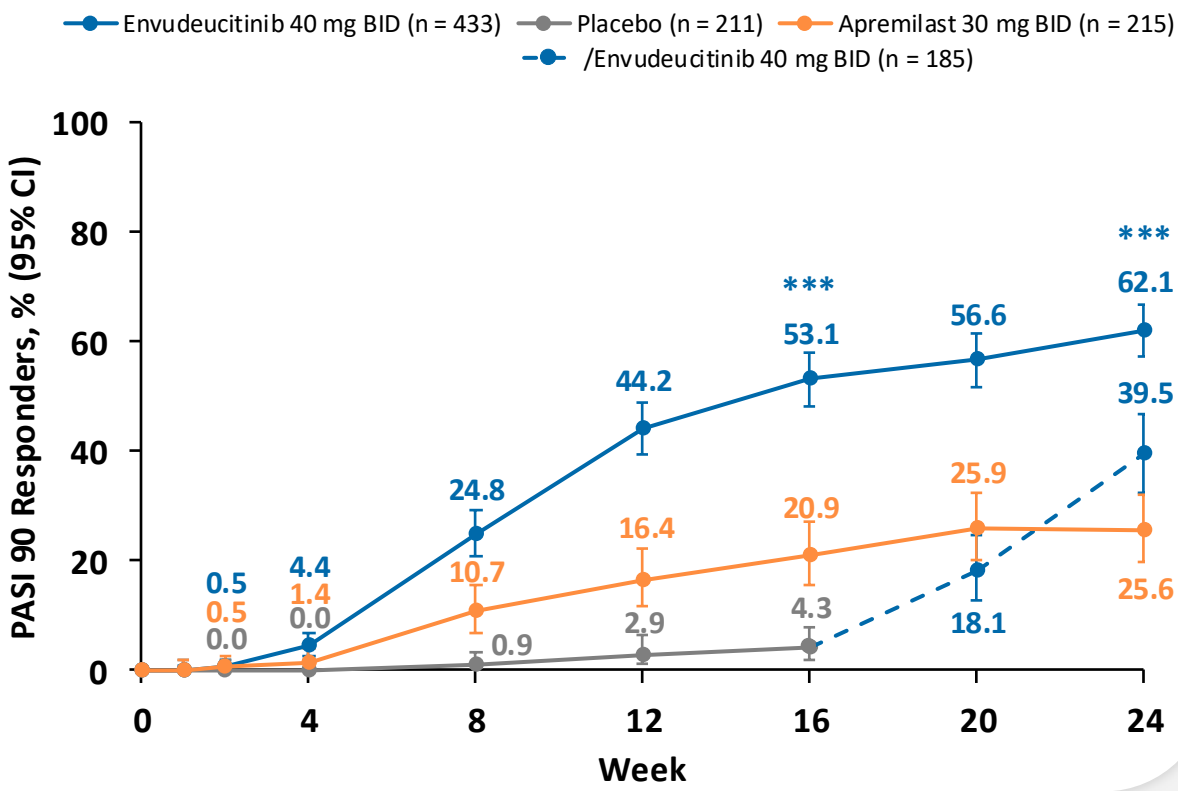
Envudeucitinib Resulted in Rapidly Increasing, Statistically Significant PASI 90 Response Rates vs Placebo and Apremilast

Early onset of action: Separation vs placebo observed at Week 4

ONWARD1



ONWARD2



Intention-to-treat population. The 95% CIs and *P*-values of the treatment differences were based on the Cochran-Mantel-Haenszel test adjusted for stratification factors. Nonresponder imputation was applied for missing data. ****P* <0.0001 vs placebo and apremilast.

BID, *bis in die* (twice daily); CI, confidence interval; PASI 90, ≥90% improvement in Psoriasis Area and Severity Index.

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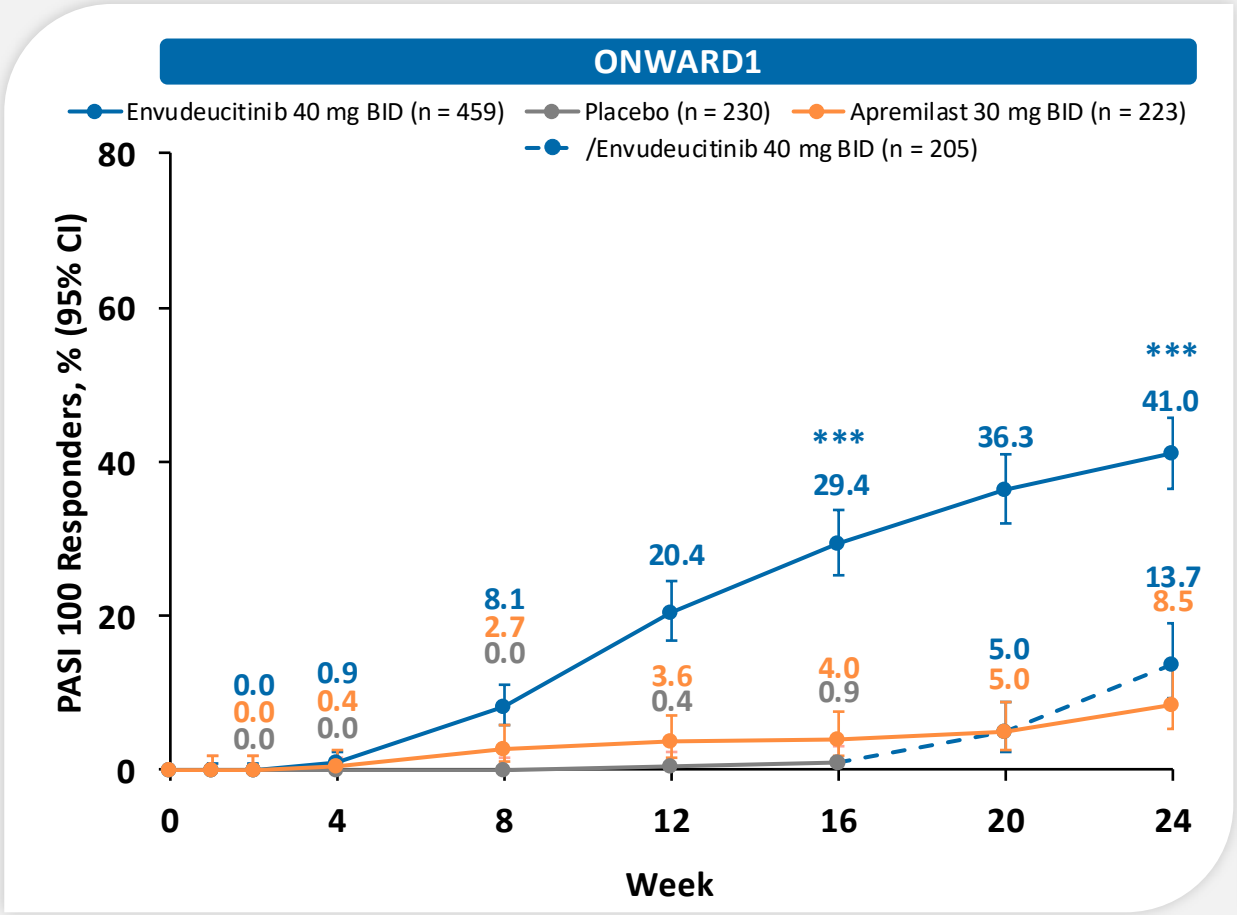
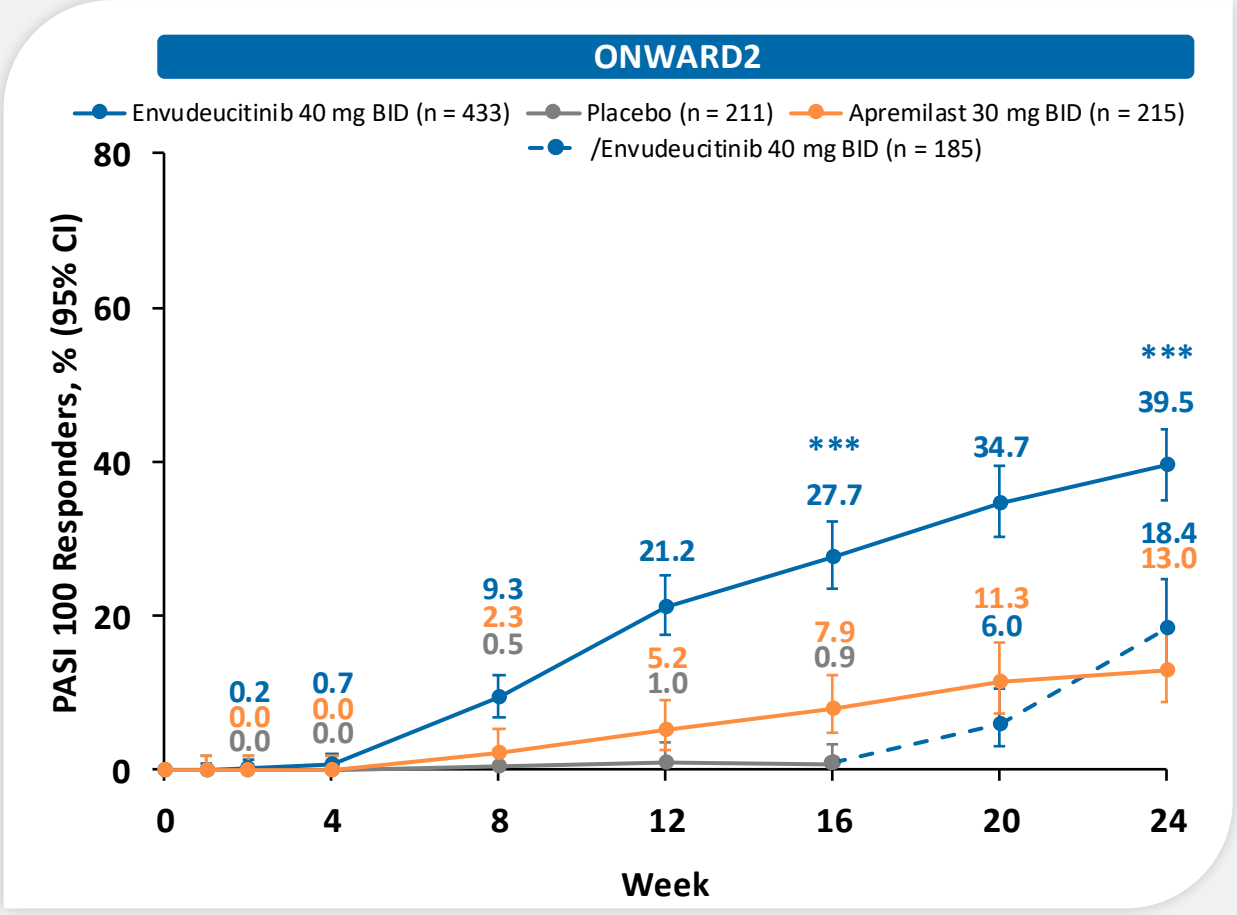
Envudeucitinib Demonstrated Robust and Progressive Improvement in PASI 100 Response Rates Over Time

Approximately 40% complete skin clearance at Week 24 without evidence of plateau





Intention-to-treat population. The 95% CIs and *P*-values of the treatment differences were based on the Cochran-Mantel-Haenszel test adjusted for stratification factors. Nonresponder imputation was applied for missing data. ****P* <0.0001 vs placebo and apremilast.

BID, *bis in die* (twice daily); CI, confidence interval; PASI 100, 100% improvement in Psoriasis Area and Severity Index.

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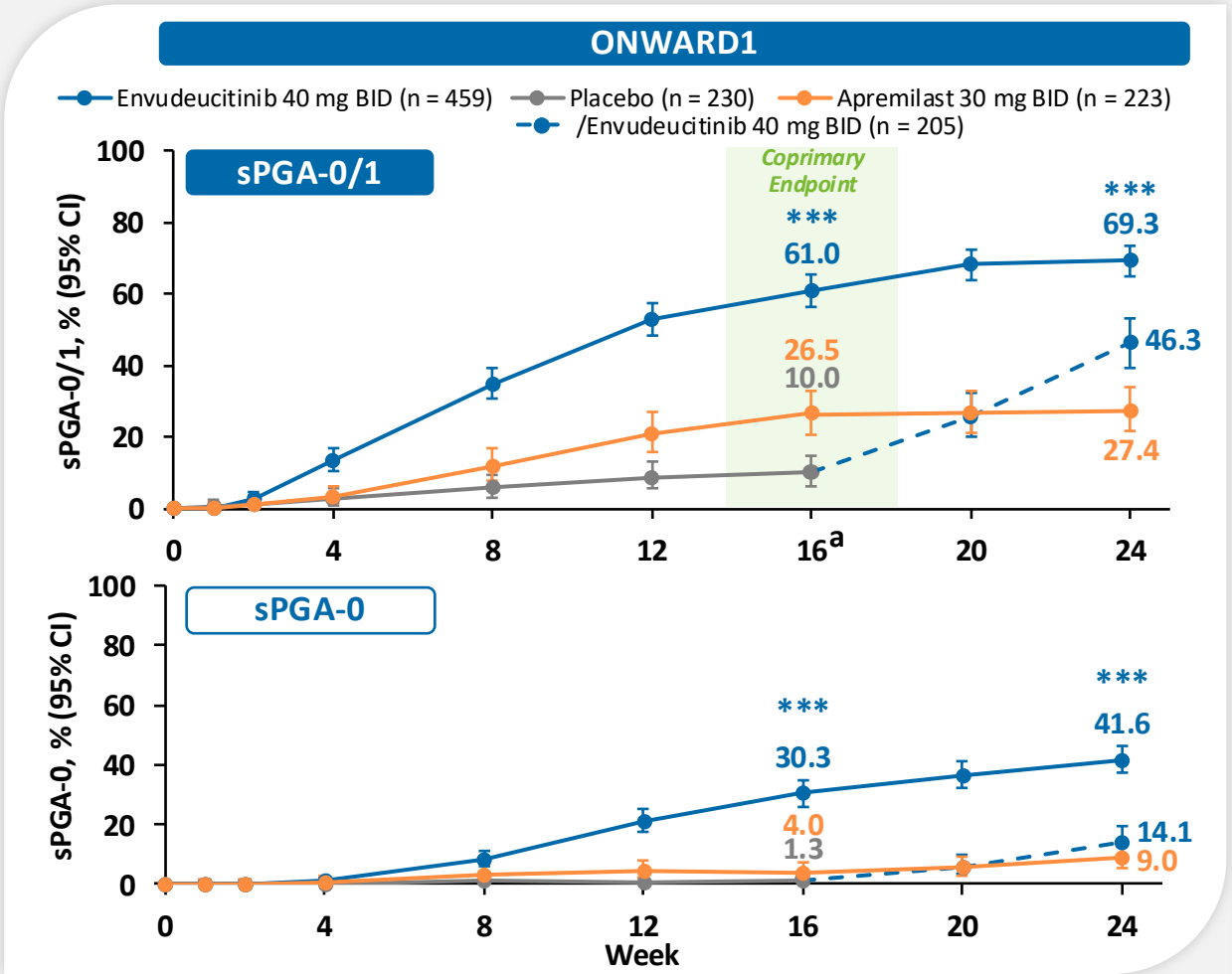
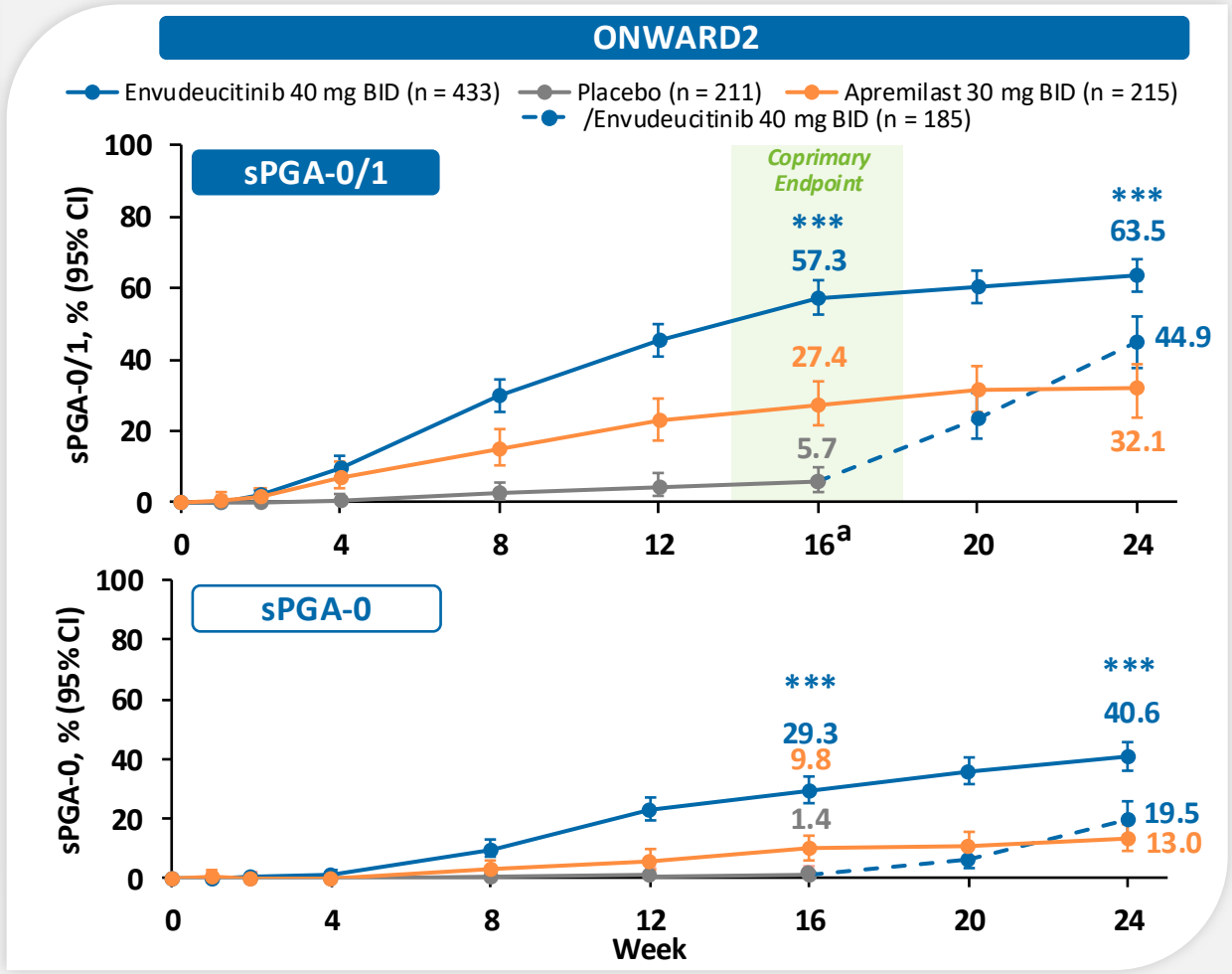
Envudeucitinib Demonstrated Significant sPGA-0/1 and sPGA-0 Responses

Approximately 60% and 30% of patients receiving envudeucitinib achieved sPGA-0/1 and sPGA-0 at Week 16, and responses continued to improve through Week 24





Intention-to-treat population. The 95% CIs and *P*-values of the treatment differences were based on the Cochran-Mantel-Haenszel test adjusted for stratification factors. Nonresponder imputation was applied for missing data. [a]Coprimary endpoint: sPGA-0/1 at Week 16 vs placebo. ***P <0.0001 vs placebo and apremilast.

BID, *bis in die* (twice daily); CI, confidence interval; sPGA, static Physician's Global Assessment; sPGA-0, sPGA 0 (clear); sPGA-0/1, sPGA 0 (clear) or 1 (almost clear).

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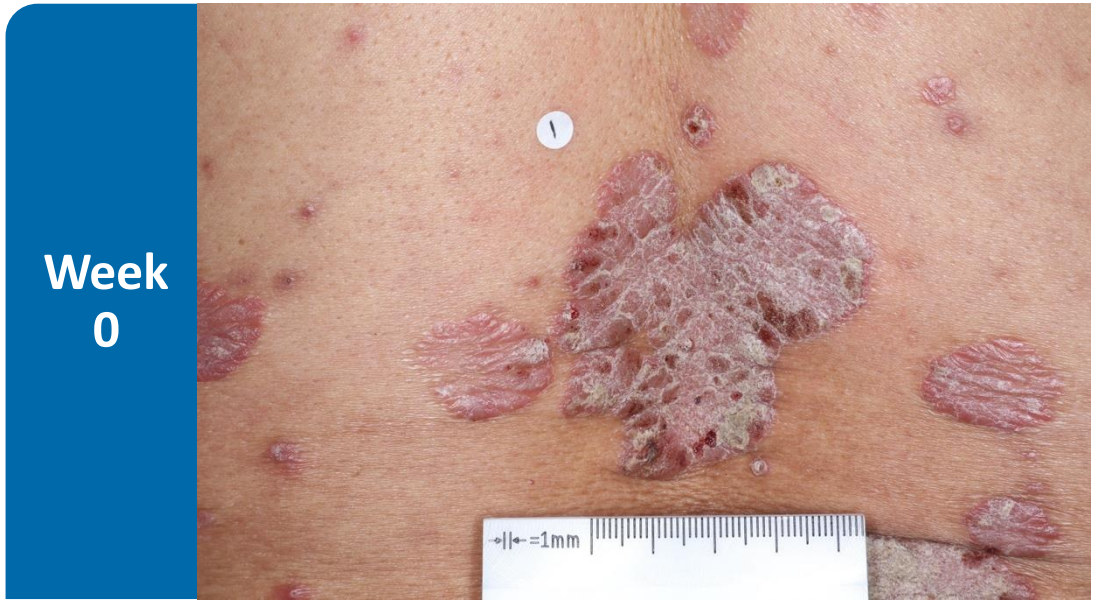
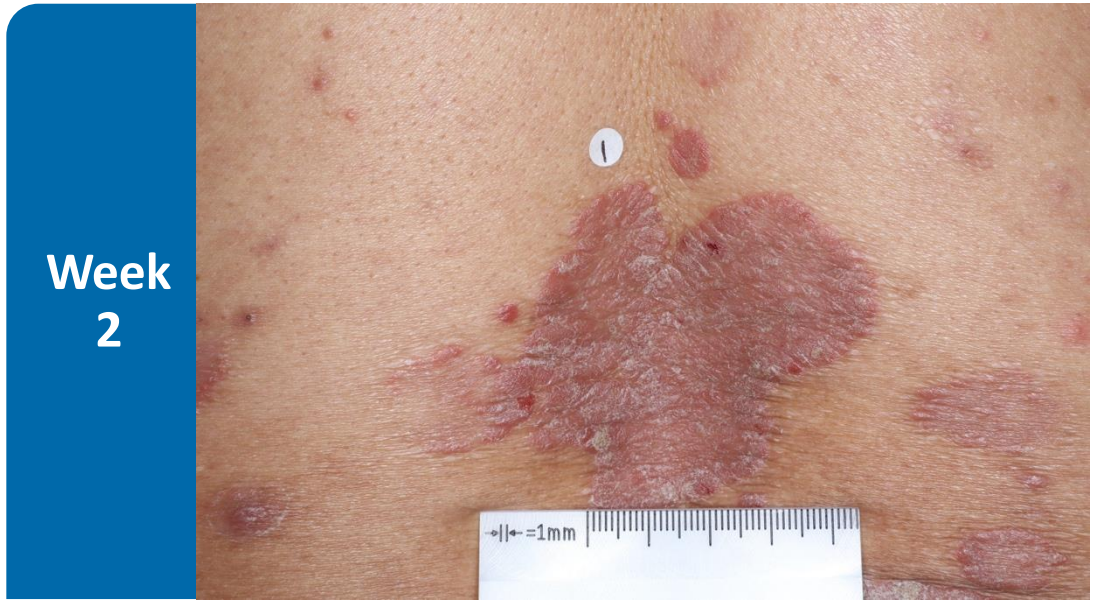
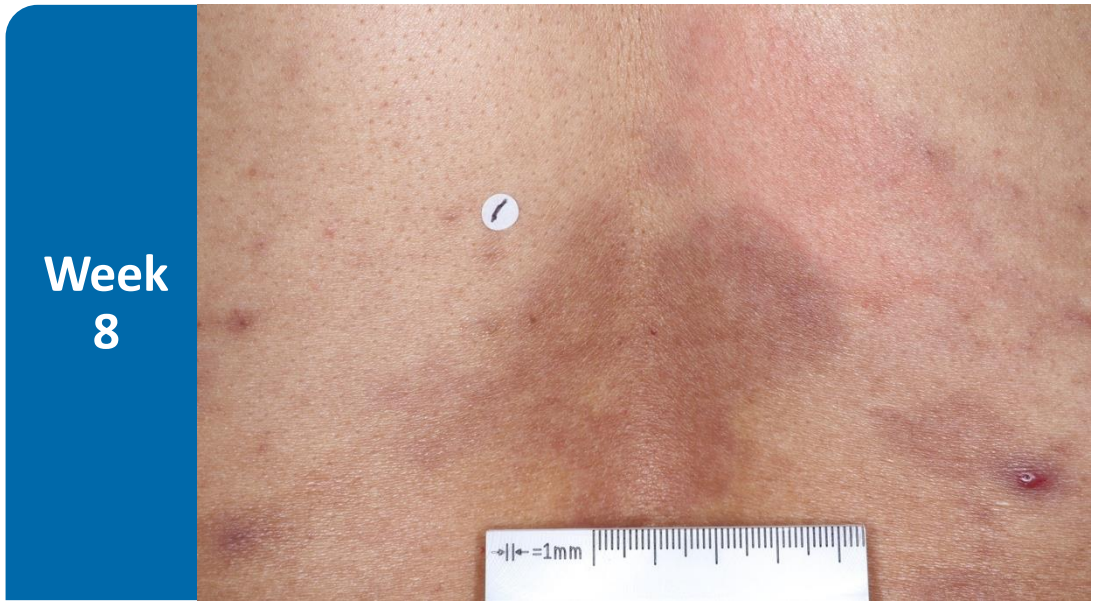
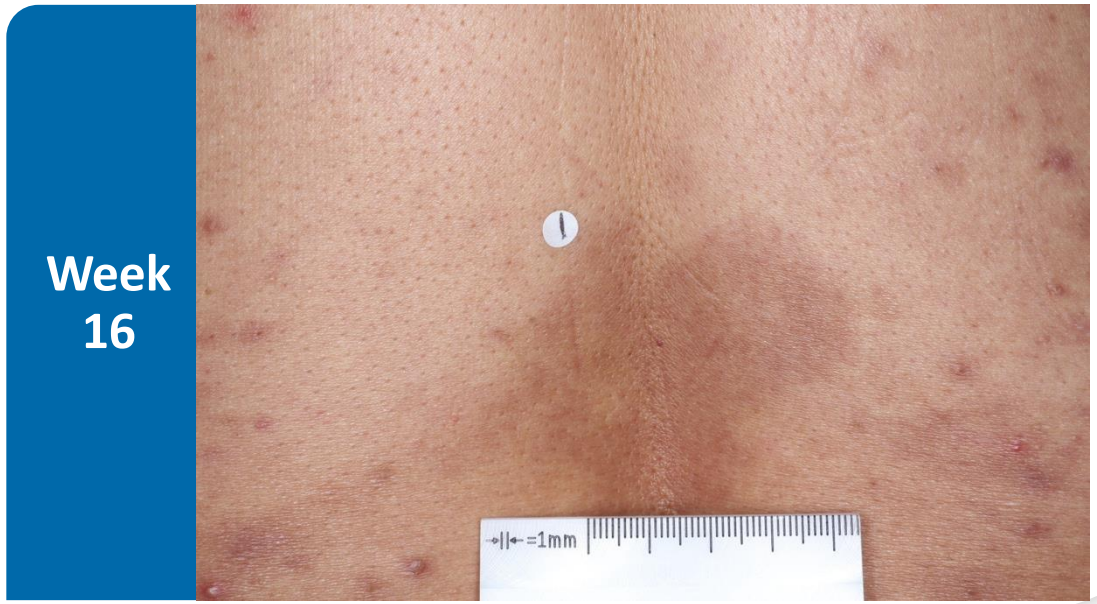
Visible Skin Improvement by Week 2 With Envudeucitinib









Patient with severe disease (PASI, 22.3; sPGA, 4) at baseline. PASI, Psoriasis Area and Severity Index; sPGA, static Physician's Global Assessment.

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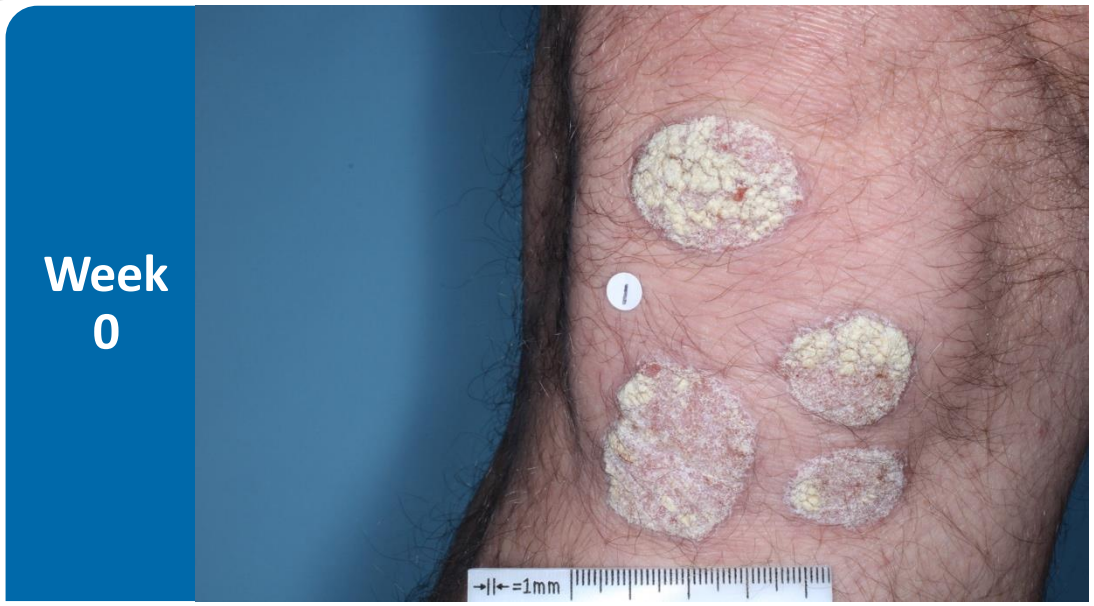
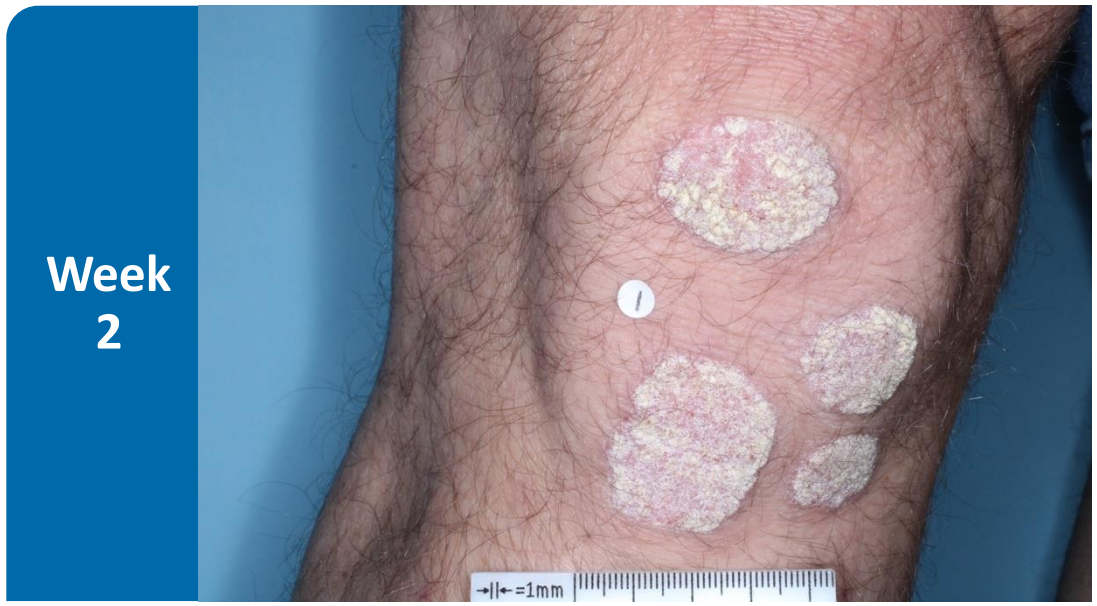
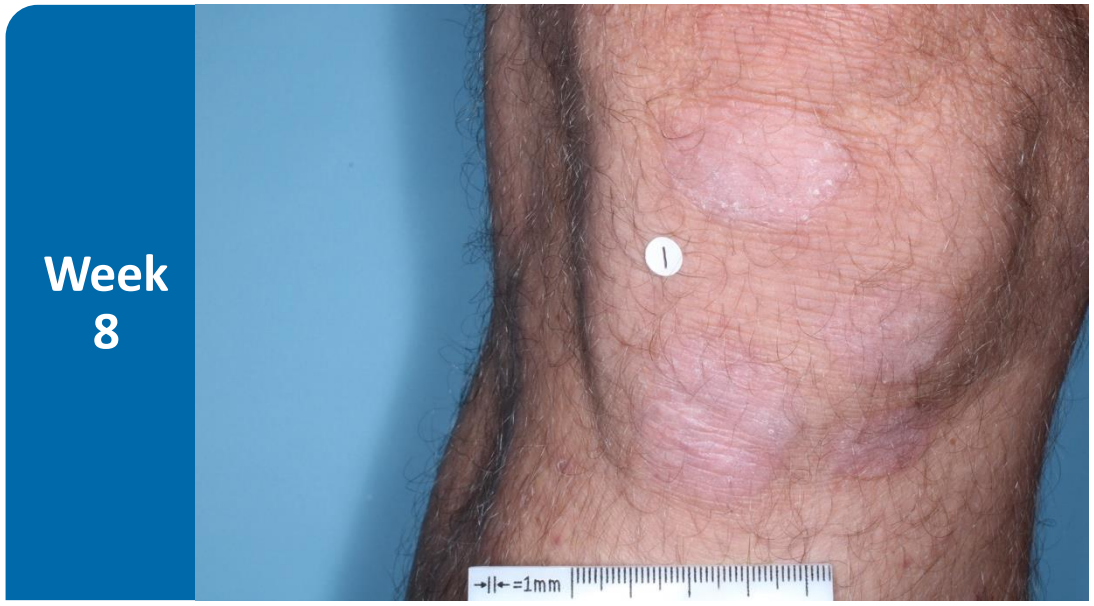
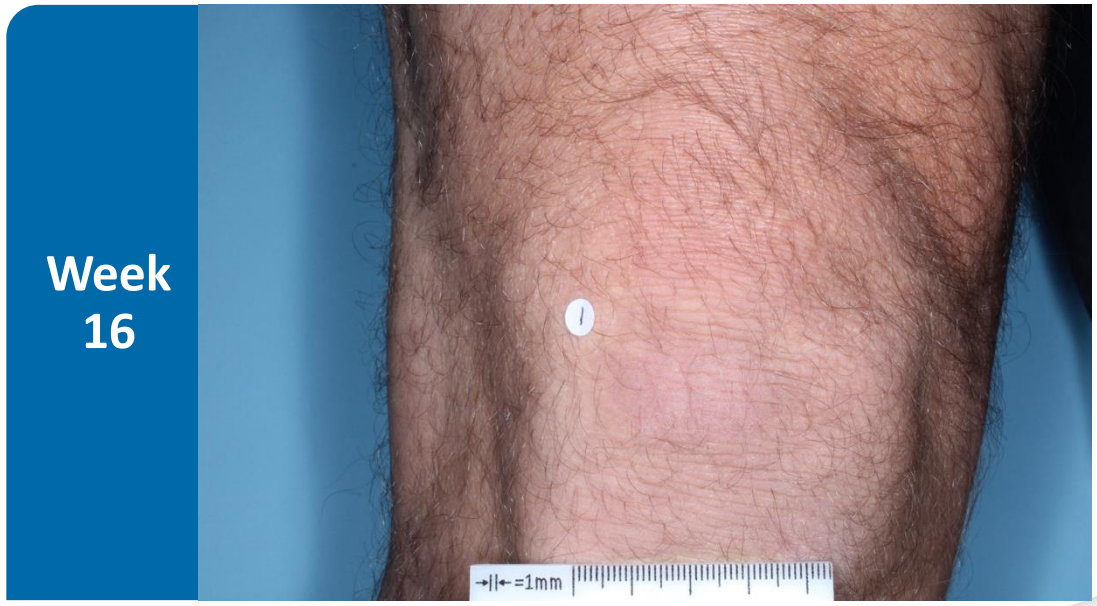
Envudeucitinib Resulted in Rapid and Significant Skin Improvement









Patient with moderate disease (PASI, 12.4; sPGA, 3) at baseline. PASI, Psoriasis Area and Severity Index; sPGA, static Physician's Global Assessment.

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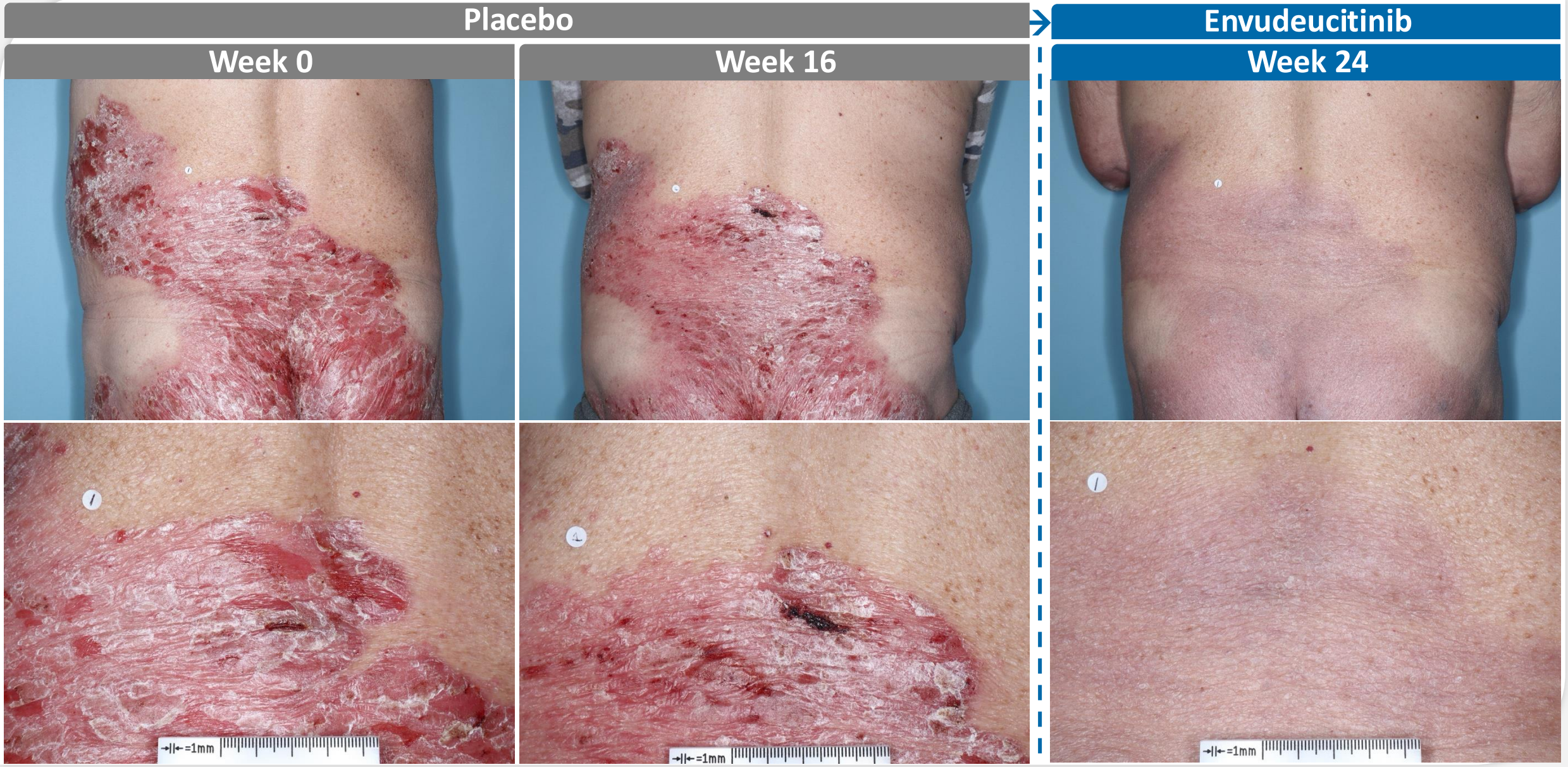
Substantial Skin Improvement Achieved After Switching to Envudeucitinib in 8 Weeks



Patient with severe disease at baseline (PASI, 31.8; sPGA, 4) who crossed over from placebo to envudeucitinib at Week 16. PASI, Psoriasis Area and Severity Index; sPGA, static Physician's Global Assessment.

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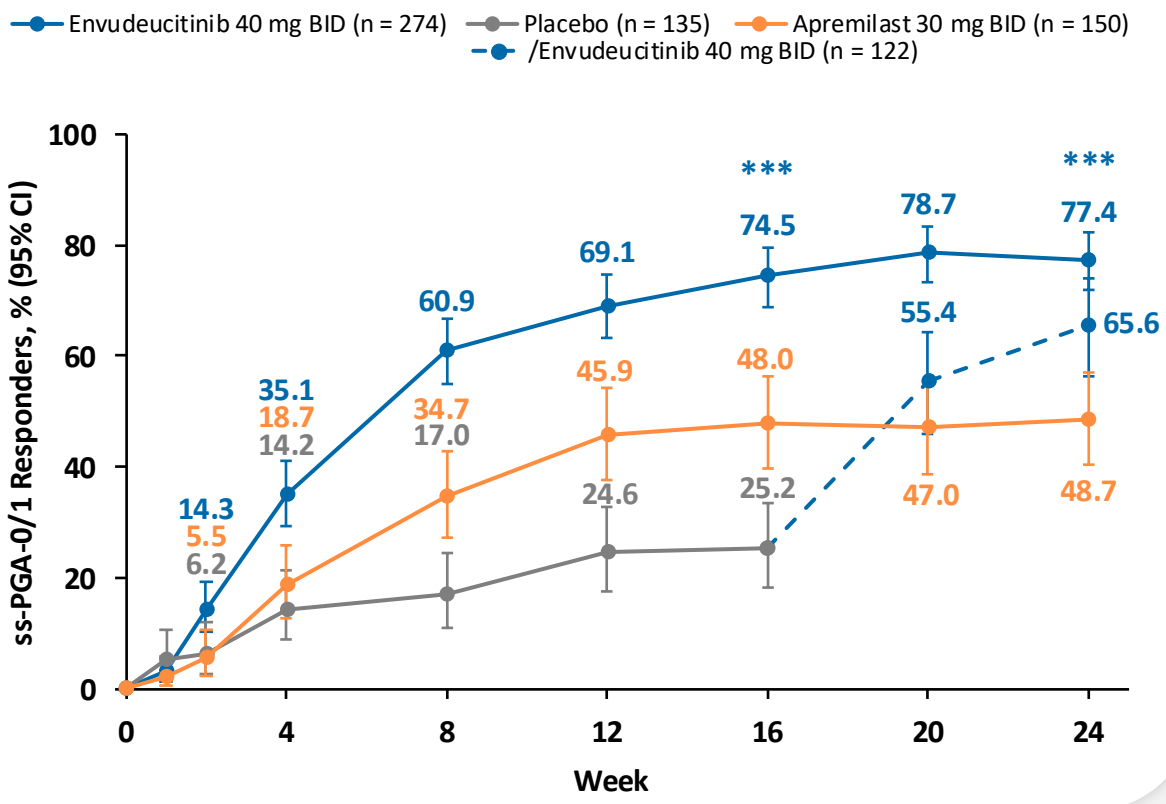
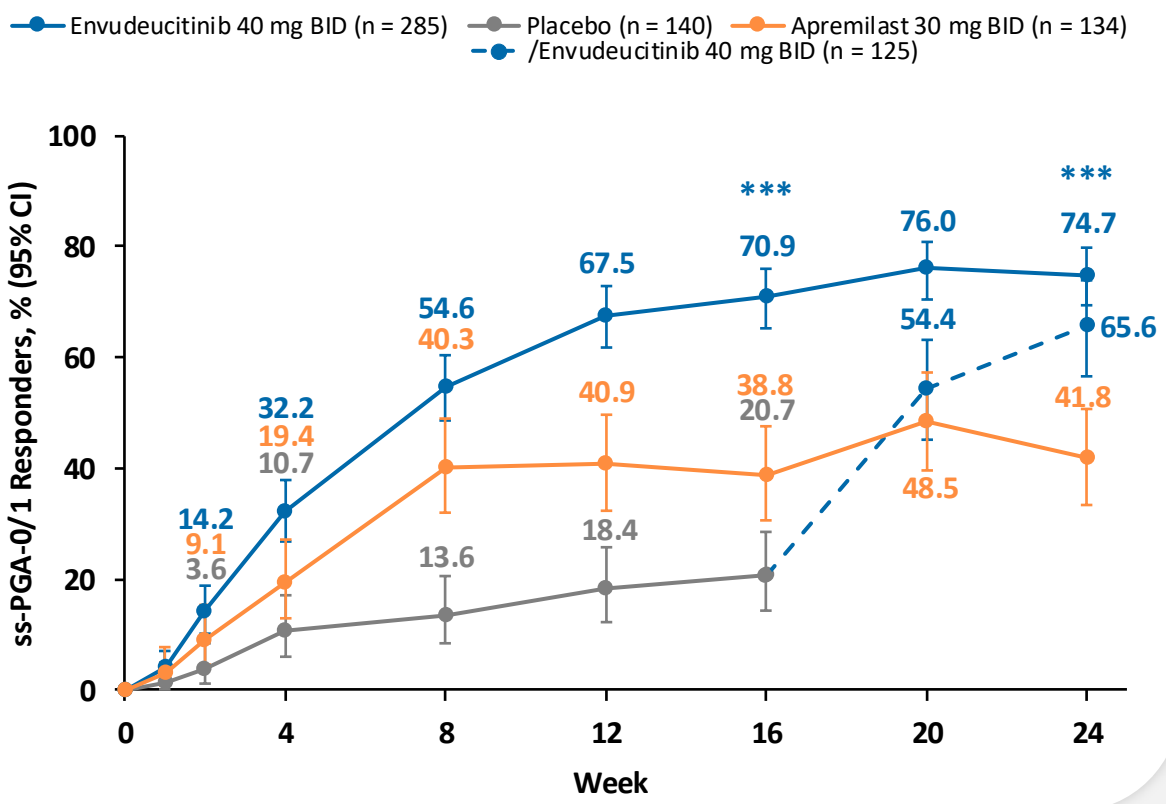
Rapid, Significant, and Sustained Scalp Psoriasis Improvement With Envudeucitinib

Approximately 3 in 4 patients receiving envudeucitinib achieved ss-PGA-0/1[a] at Week 24, with over 30% response as early as Week 4

ONWARD1



ONWARD2



Intention-to-treat population. The 95% CIs and *P*-values of the treatment differences were based on the Cochran-Mantel-Haenszel test adjusted for stratification factors. Nonresponder imputation was applied for missing data. [a]In patients with baseline ss-PGA ≥3. ***P <0.0001 vs placebo at Week 16 and apremilast at Week 24.
BID, *bis in die* (twice daily); CI, confidence interval; ss-PGA-0/1, scalp-specific Physician's Global Assessment 0 (clear) or 1 (almost clear).

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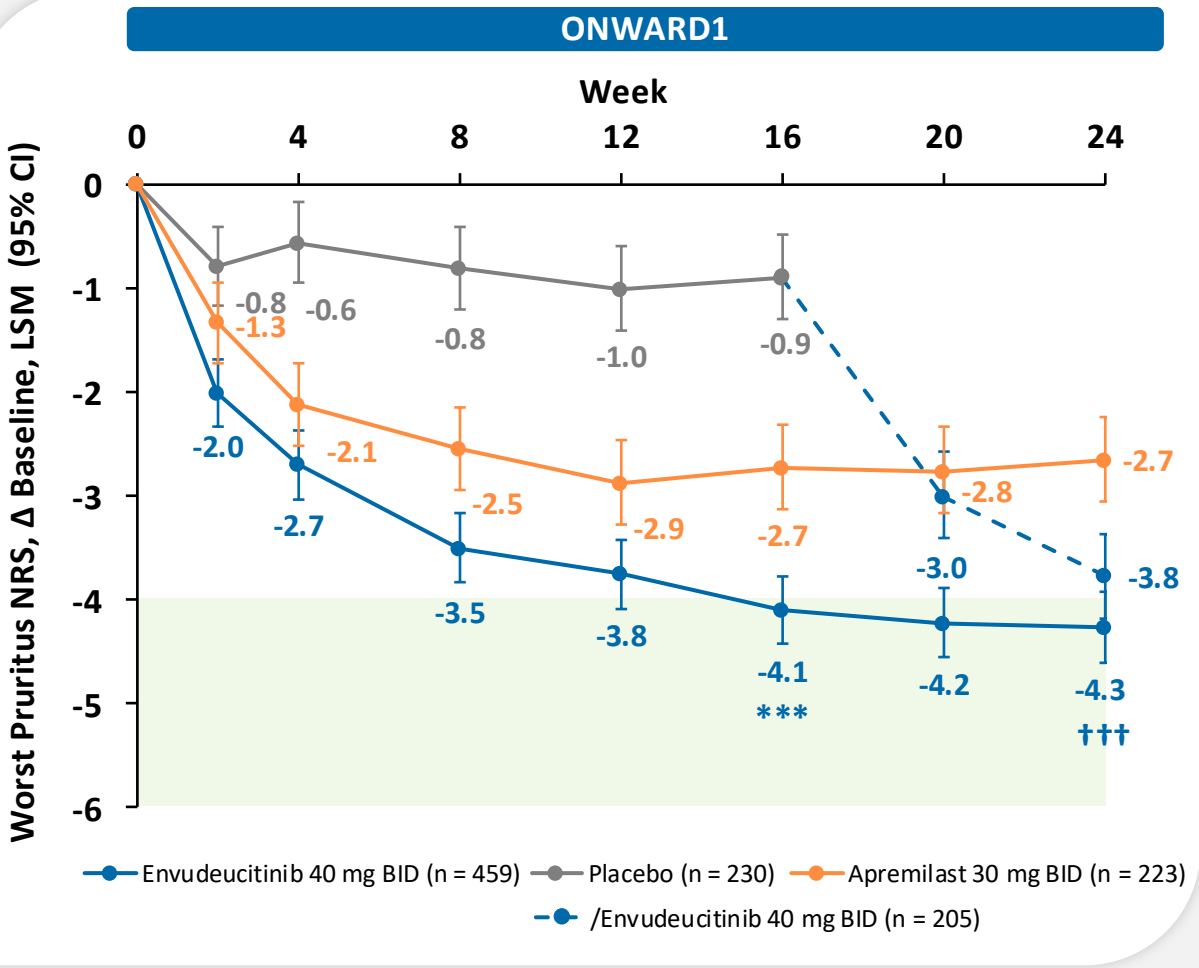
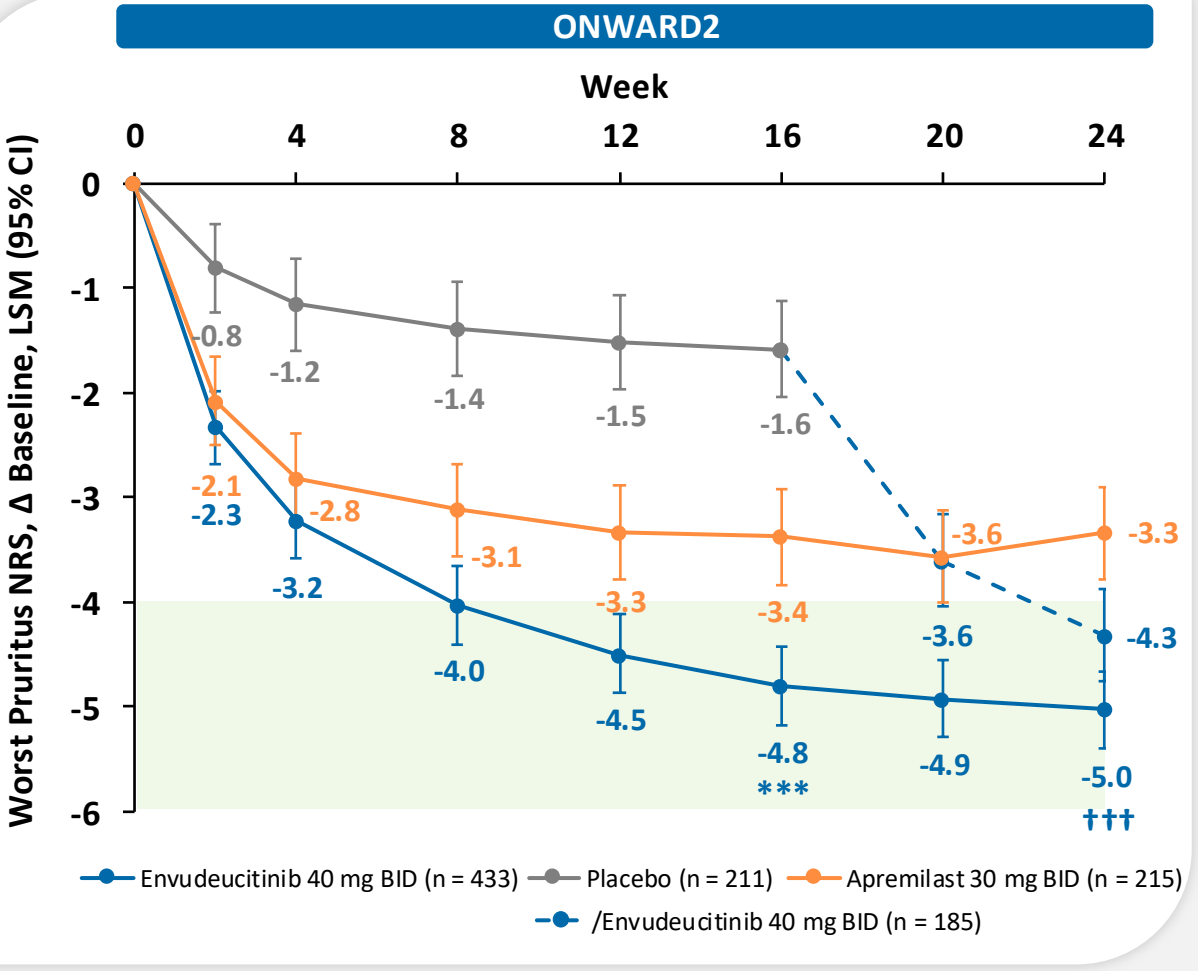
Envudeucitinib Rapidly Reduced Itch With Deepening Response Over Time

On average >4-point mean decrease from baseline in worst pruritus NRS by Week 12, with continued symptom improvement over time





Intention-to-treat 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).

BID, *bis in die* (twice daily); CI, confidence interval; LSM, least squares mean; MMRM, mixed model for repeated measures; NRS, numeric rating scale.

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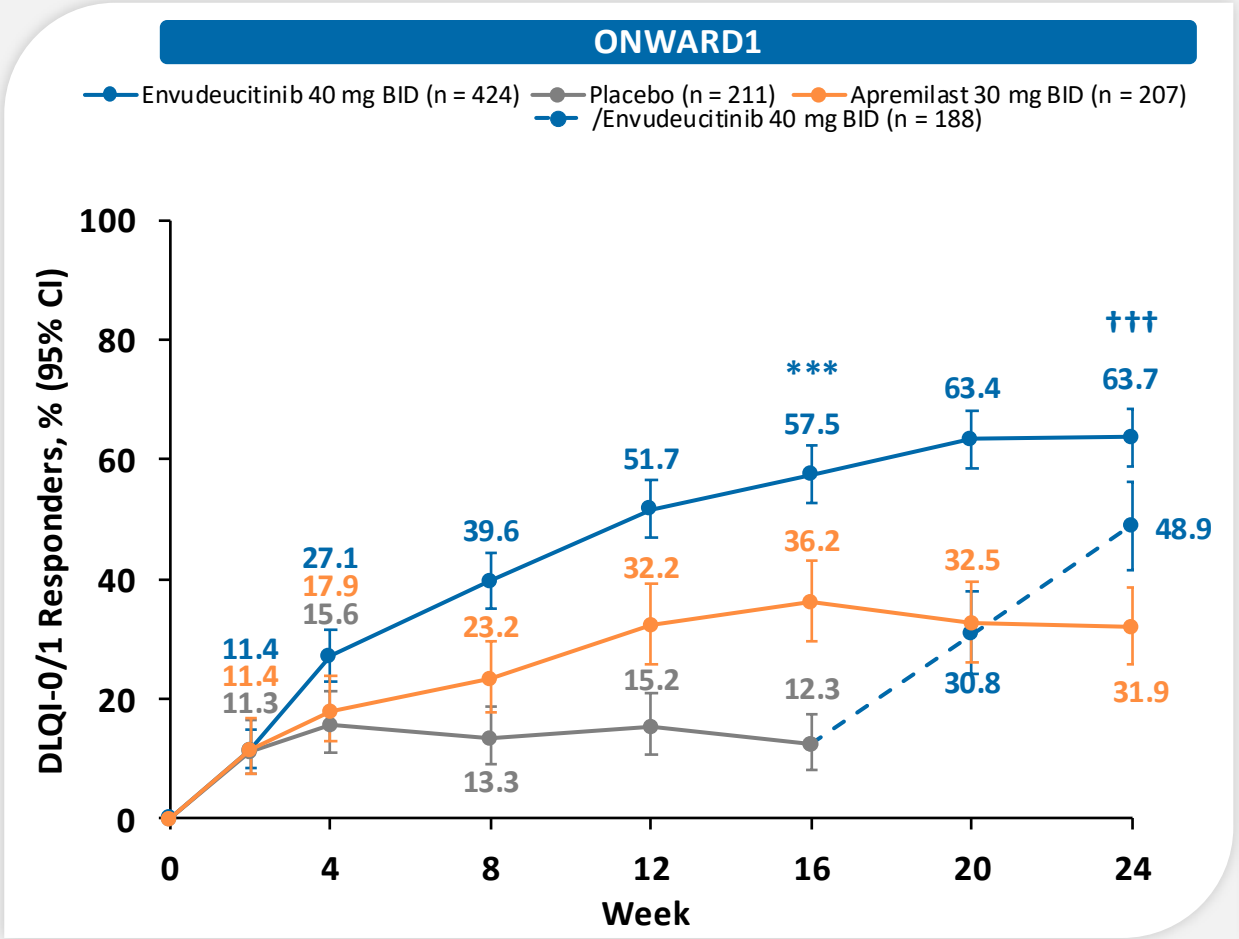
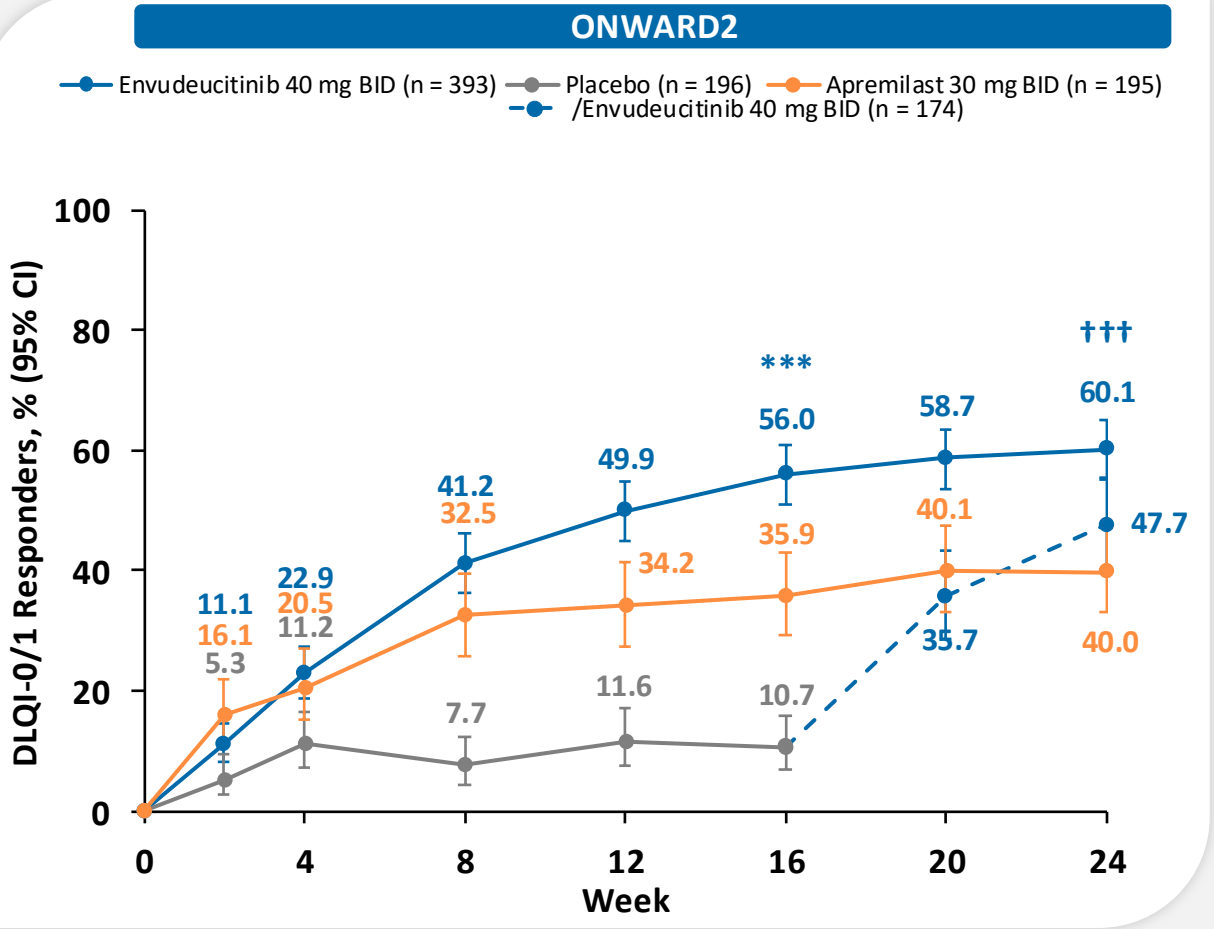
Envudeucitinib Treatment Significantly Improved Patient Quality of Life

Approximately 50% of patients receiving envudeucitinib reported DLQI-0/1[a] by Week 12, with continued improvement through Week 24



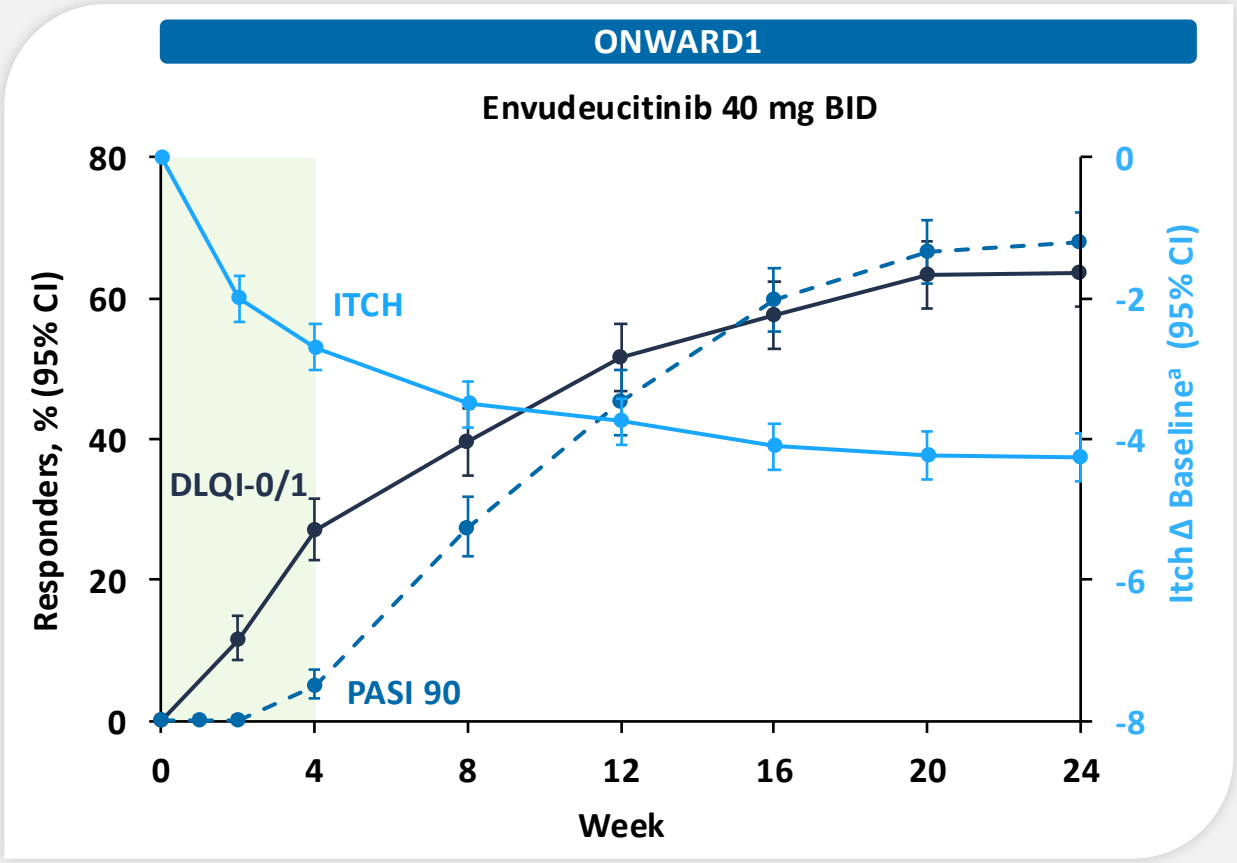


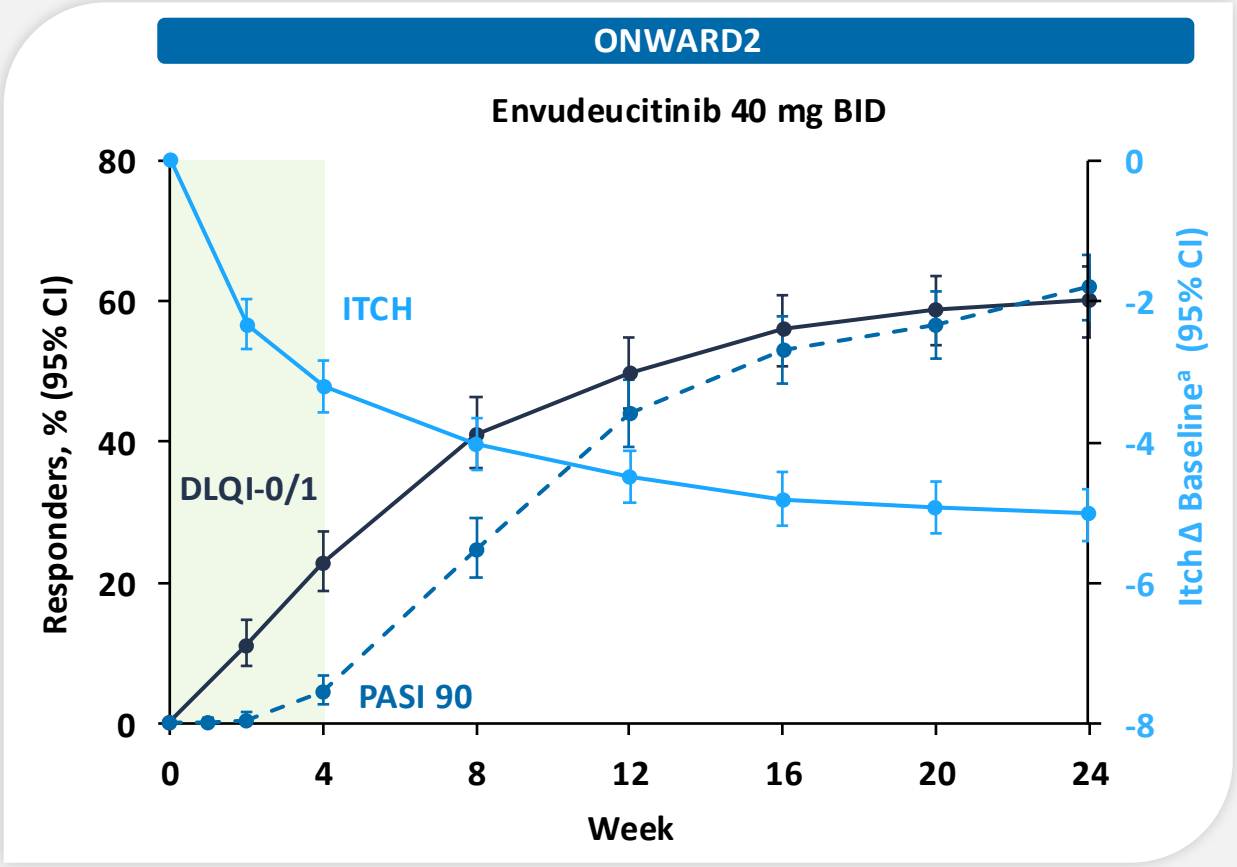
Intention-to-treat population. The 95% CIs and *P*-values of the treatment differences were based on the Cochran-Mantel-Haenszel test adjusted for stratification factors. Nonresponder imputation was applied for missing data. [a]In patients with baseline DLQI ≥2. ***P <0.0001 vs placebo. †††P <0.0001 vs apremilast (nominal).

BID, *bis in die* (twice daily); CI, confidence interval; DLQI-0/1, Dermatology Life Quality Index 0 (no impact) or 1 (minimal impact).

Benefits in Itch Reduction and Quality of Life Visible Before Skin Clearance

Patients receiving envudeucitinib showed robust, early improvements in DLQI and itch that preceded PASI 90 responses





Intention-to-treat population. For DLQI and PASI 90, the 95% CIs and *P*-values of the treatment differences were based on the Cochran-Mantel-Haenszel test adjusted for stratification factors. Nonresponder imputation was applied for missing data. For itch, LSMs, CIs, and *P*-values are based on MMRM. [a]LSM change from baseline in worst pruritus NRS.

BID, *bis in die* (twice daily); CI, confidence interval; DLQI, Dermatology Life Quality Index; DLQI-0/1, DLQI 0 or 1; LSM, least-squares mean; MMRM, mixed model for repeated measures; NRS, numeric rating scale; PASI 90, ≥90% improvement in Psoriasis Area and Severity Index.

Envudeucitinib is investigational; not yet reviewed by regulatory agencies

ONWARD1 and ONWARD2 Pooled Safety Through Week 16

n (%)	Through Week 16		
	Envudeucitinib 40 mg BID n = 890	Placebo n = 441	Apremilast 30 mg BID n = 438
≥1 TEAE	524 (58.9)	166 (37.6)	223 (50.9)
≥1 SAE	19 (2.1)	5 (1.1)	5 (1.1)
TEAE leading to treatment discontinuation	30 (3.4)	7 (1.6)	9 (2.1)
TEAE grade ≥3	42 (4.7)	14 (3.2)	18 (4.1)
Most-frequent TEAEs (≥5%)[a]			
Nasopharyngitis	64 (7.2)	21 (4.8)	16 (3.7)
Headache	92 (10.3)	11 (2.5)	40 (9.1)
Upper respiratory tract infection	43 (4.8)	7 (1.6)	16 (3.7)
Acne	53 (6.0)	3 (0.7)	3 (0.7)
Nausea	20 (2.2)	4 (0.9)	23 (5.3)
Diarrhea	14 (1.6)	11 (2.5)	36 (8.2)

- Envudeucitinib showed low rates of SAEs and AEs leading to discontinuation, with no clusters of events
  - No deaths; no MACE or cytopenia signals; no TB reactivation[b]
- No clinically significant laboratory abnormalities were observed across lipid, hematologic, or chemistry panels, with comparable variability across treatment arms up to Week 16

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; BID, *bis in die* (twice daily); MACE, major adverse cardiovascular event; SAE, serious AE; TB, tuberculosis; TEAE, treatment-emergent AE.

ONWARD1 and ONWARD2 Pooled Safety Through Weeks 16 and 24

n (%)	Through Week 16			Through Week 24			
	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]							
Nasopharyngitis	64 (7.2)	21 (4.8)	16 (3.7)	92 (10.3)	18 (4.6)	110 (8.6)	26 (5.9)
Headache	92 (10.3)	11 (2.5)	40 (9.1)	97 (10.9)	11 (2.8)	108 (8.4)	42 (9.6)
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)
Acne	53 (6.0)	3 (0.7)	3 (0.7)	60 (6.7)	17 (4.4)	77 (6.0)	3 (0.7)
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)

- Envudeucitinib showed low rates of SAEs and AEs leading to discontinuation, with no clusters of events
  - 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

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; BID, *bis in die* (twice daily); MACE, major adverse cardiovascular event; SAE, serious AE; TB, tuberculosis; TEAE, treatment-emergent AE.

Envudeucitinib, a next-generation TYK2i, delivered early and progressively deepening skin clearance, with meaningful improvements in patient-reported outcomes in ONWARD1 and 2

- All primary and secondary efficacy **endpoints met**, with approximately **65% and 40%** of patients receiving envudeucitinib achieving **PASI 90 and PASI 100 at Week 24**
- **Rapid and significant** improvement in moderate-to-severe **scalp psoriasis, itch,** and **quality of life**
- Envudeucitinib treatment was generally well tolerated, with **no new signals** and a safety profile consistent with the previous long-term Phase 2 studies
- **One year, Phase 3 long-term** data will be available in the second half of 2026
- **Once-daily** formulation and **pediatric** plan under development

Envudeucitinib is investigational; not yet reviewed by regulatory agencies
PASI 90/100, ≥90%/100% improvement in Psoriasis Area and Severity Index; TYK2i, tyrosine kinase 2 inhibitor.

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