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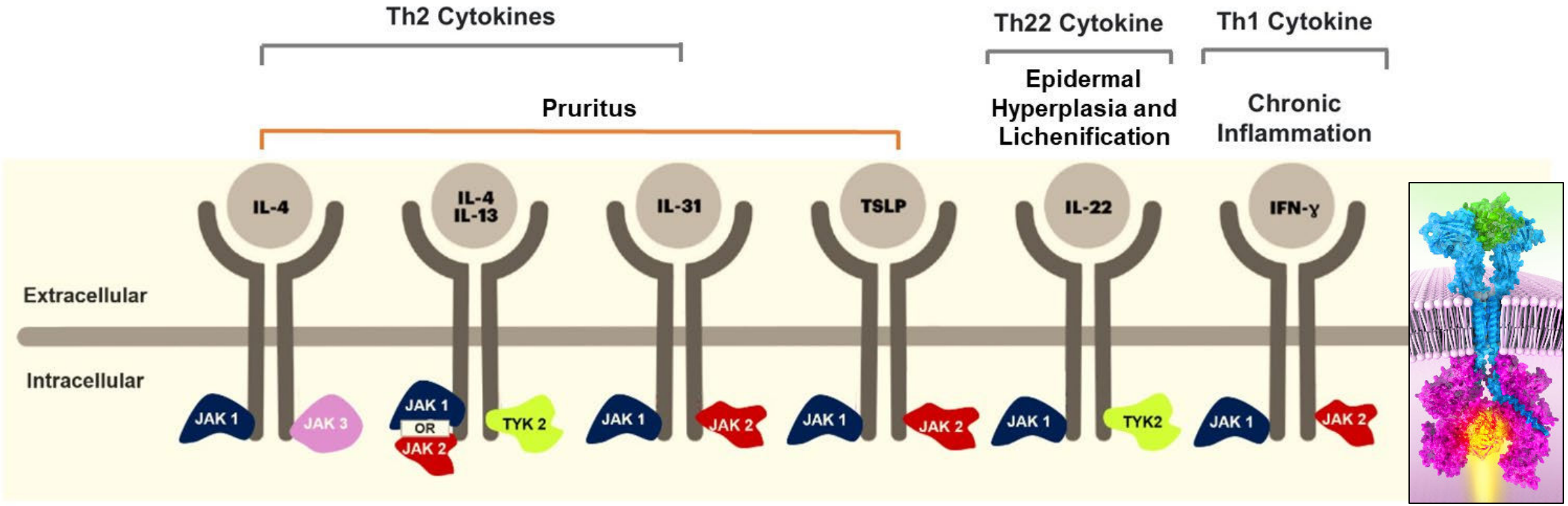
JAK Inhibitors in Atopic Dermatitis (Part 2)

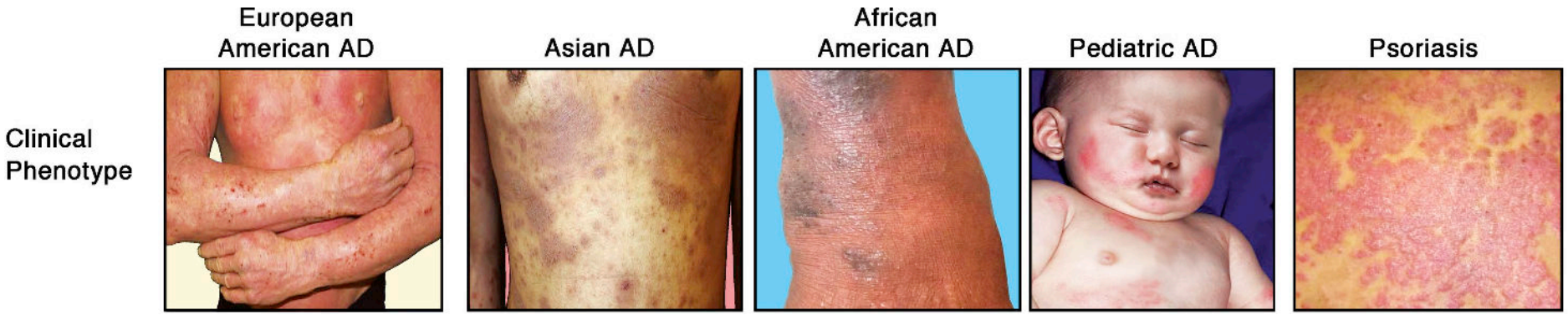


Christopher G. Bunick, MD, PhD

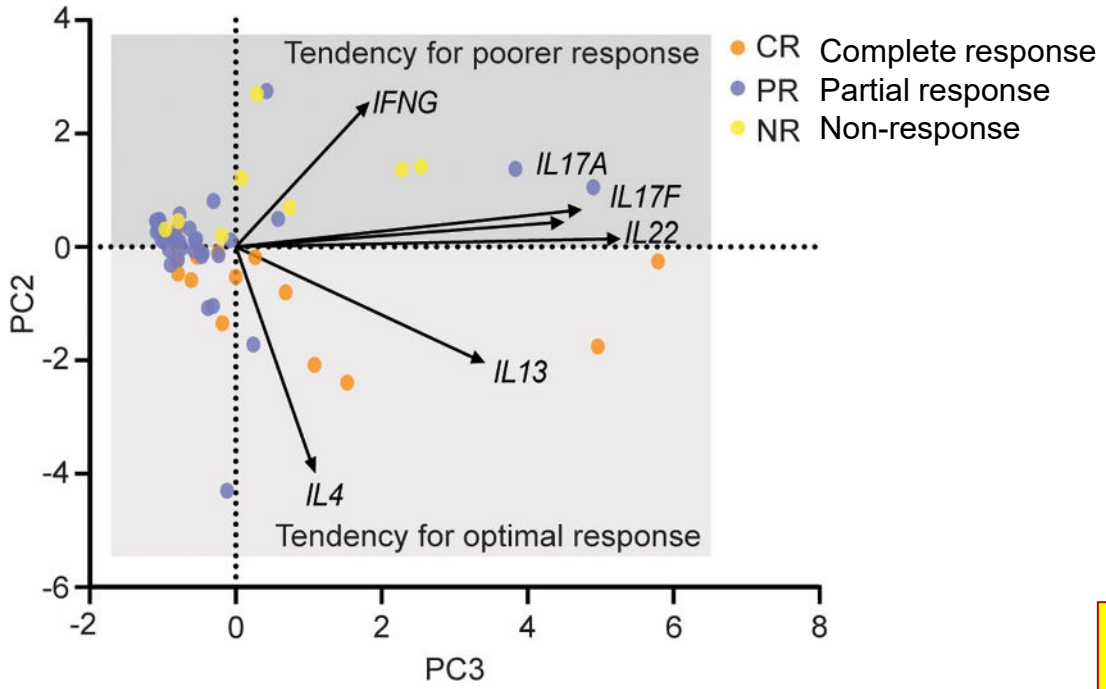
Associate Professor of Dermatology & Program in Translational Biomedicine

Yale School of Medicine

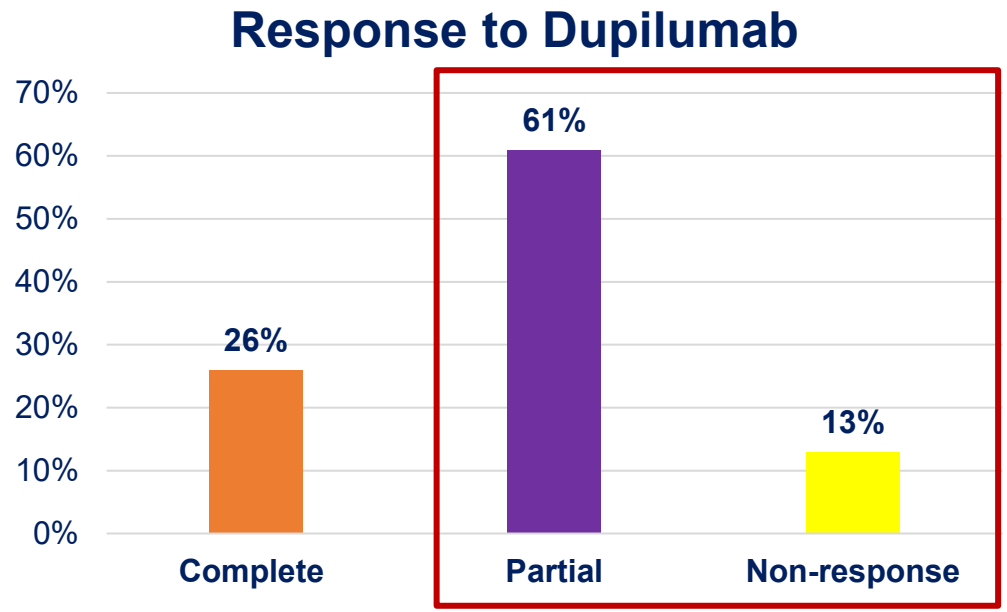
AD is a Heterogenous Disease: Inadequate or Non-Response to Dupilumab is Correlated with Upregulation of IL-17, IL-22, and IFN-γ Cytokines



Czarnowicki T, He H, Krueger JG, Guttman-Yassky E. Atopic dermatitis endotypes and implications for targeted therapeutics. Journal of Allergy and Clinical Immunology. 2019 Jan 1;143(1):1-1.



Atopic Dermatitis Endotypes: Principal components analysis of cytokine staining



74% of the AD cohort demonstrated upregulation of TH1, TH17 and TH22 cytokines

Singh K, Valido K, Swallow M, et al. Baseline skin cytokine profiles determined by RNA in situ hybridization correlate with response to dupilumab in patients with eczematous dermatitis. *J Am Acad Dermatol*. 2023;88(5):1094-1100.

Patient Selection: *When is enough time on biologics?*

Steady-state levels are achieved by Week 16

12.3 Pharmacokinetics

The pharmacokinetics of dupilumab is similar in subjects with AD, asthma, CRSwNP, EoE and PN.

Absorption

Following an initial subcutaneous (SC) dose of 600 mg, 400 mg, or 300 mg, dupilumab reached peak mean ± SD concentrations (C_{max}) of 70.1±24.1 mcg/mL, 41.8±12.4 mcg/mL, or 30.5±9.39 mcg/mL, respectively, by approximately 1 week post dose. Steady-state concentrations were achieved by Week 16 following the administration of 600 mg starting dose and 300 mg dose either weekly or Q2W, or 400 mg starting dose and 200 mg dose Q2W, or 300 mg Q2W without a loading dose. Across clinical trials, the mean ± SD steady-state trough concentrations ranged from 60.3±35.1 mcg/mL to 80.2±35.3 mcg/mL for 300 mg administered Q2W, from 173±75.9 mcg/mL to 195±71.7 mcg/mL for 300 mg administered weekly, and from 29.2±18.7 to 36.5±22.2 mg/L for 200 mg administered Q2W.

12.3 Pharmacokinetics

The mean (SD) steady-state trough concentration of tralokinumab-ldrm ranged from 98.0 (41.1) mcg/mL to 101.4 (42.7) mcg/mL following administration of ADBRY at 300 mg every other week. Tralokinumab-ldrm exposure increased proportionally over a dosage range up to 2100 mg for a 70 kg subject (30 mg/kg IV) (3.5 times the maximum approved recommended dosage). Steady-state tralokinumab-ldrm concentrations were achieved by week 16 following a 600 mg starting dose and 300 mg every other week.

If your patient is uncontrolled, inadequately controlled, or has sub-optimal response on biologic after 3-6 months, then consider JAK inhibitors.

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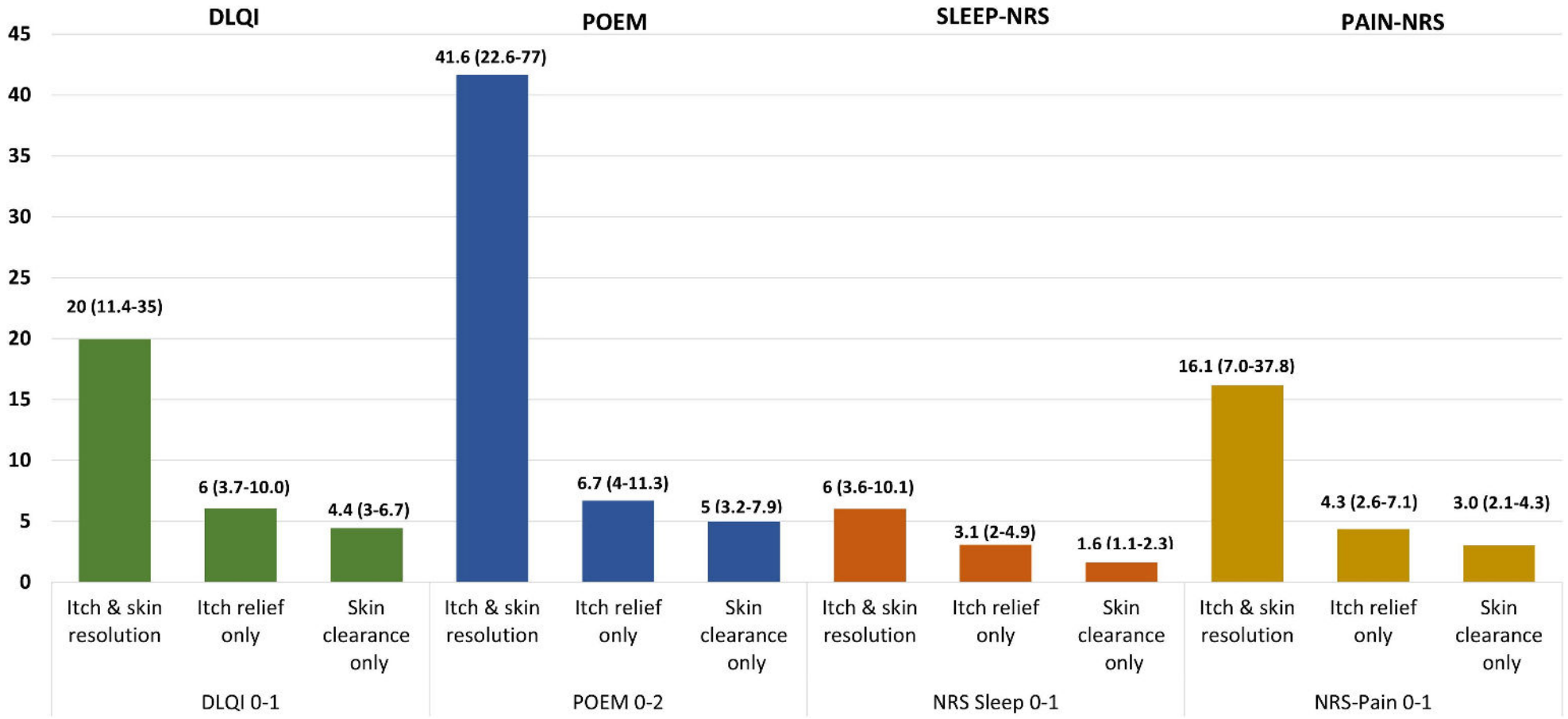
Adjusted odds ratios (95% confidence interval) of achieving improved PROs (DLQI 0–1, POEM 0–2, Sleep-NRS 0-1, and Pain-NRS 0-1) based on skin clearance and itch resolution status compared to participants with neither



The terms "Itch & skin resolution", "Itch relief only", and "Skin clearance only" are defined as WI-NRS 0/1 and IGA 0/1, WI-NRS 0/1, and IGA 0/1, respectively.

Silverberg JI, Calimlim BM, Grada A, Bunick CG, Gooderham MJ, Shi VY, Obi C, Knapp KD, Munoz B, Crawford JM, Paller AS. Real-world evidence on the benefits of optimal itch relief and skin clearance in atopic dermatitis management: a study from the TARGET-DERM AD registry. J Dermatolog Treat. 2024 Dec;35(1):2428729. doi: 10.1080/09546634.2024.2428729. Epub 2024 Dec 11. PMID: 39662888.

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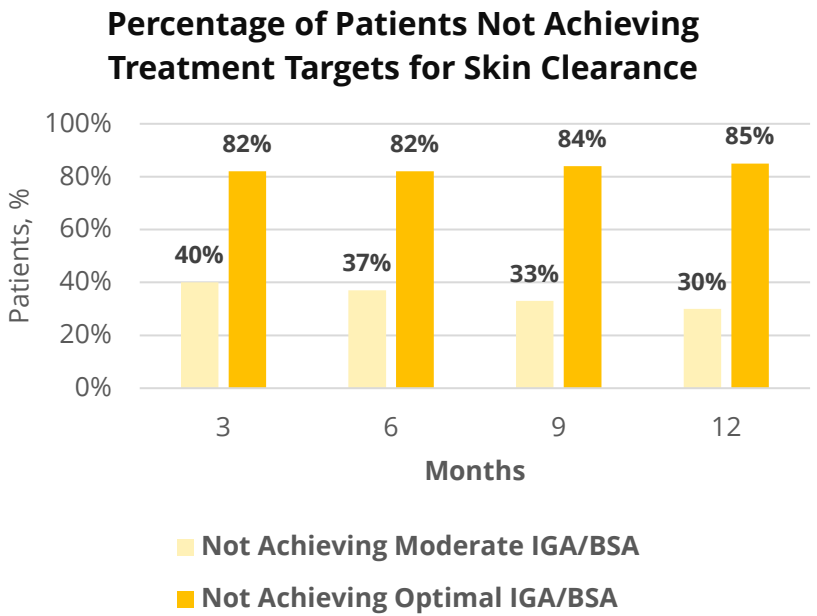
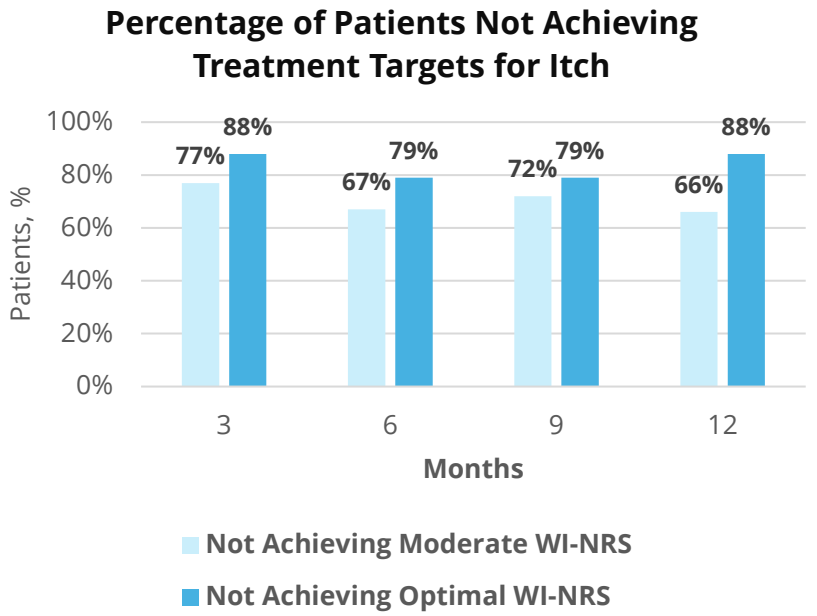
TARGET-DERM Registry: Long-Term Systemic Therapy in Moderate-to-Severe Atopic Dermatitis

Inadequate Response among Moderate-to-Severe AD Patients: % who **DO NOT Achieve Moderate or Optimal Treatment Targets (Skin Clearance or Itch Relief)** as Defined by AHEAD Recommendations





Outcome measure	Moderate target	Optimal target
Skin Clearance: IGA and BSA	**IGA ≤2 and 50% BSA improvement**	**IGA 0/1 and BSA ≤2%**
Itch Relief: Worst-Itch	**≥4-point improvement (reduction)**	**WI-NRS 0/1**

AD, atopic dermatitis; AHEAD, Aiming High in Eczema/Atopic Dermatitis; IGA, Investigator Global Assessment; BSA, body surface area; WI-NRS, Worst Itch Numeric Rating Scale; WP-NRS, Worst Pruritus Numerical Rating Scale

Eichenfield LF, JI. *British Journal of Dermatology*. 2024;190(Supplement_2):ii60-1.

Selective JAK-1 Inhibitors Approved for Atopic Dermatitis

	Abrocitinib	Upadacitinib
AD indication	Refractory, moderate to severe atopic dermatitis not adequately controlled with systemic drug products or when use of those therapies is inadvisable	
JAK selectivity	JAK-1	JAK-1
Age of approval	12 years +	12 years +
Approved strengths	100mg or 200mg daily	15mg or 30mg daily
Starting dose • **Escalation guidelines**	Initiate at 100mg • Escalate to 200mg if adequate response not achieved with 100mg	Initiate at 15mg • Escalate to 30mg if adequate response is not achieved with 15mg (≦65 years)
Laboratory guidance (per label)	Baseline labs CBC and lipids week 4	Baseline labs Lipids at week 12
Metabolism	2 active metabolites	No active metabolites

AD, atopic dermatitis; JAK, Janus kinase; CBC, complete blood count

Upadacitinib. Prescribing information. 2019. Accessed September 30, 2024.
Abrocitinib. Prescribing information.2022. Accessed September 30, 2024.

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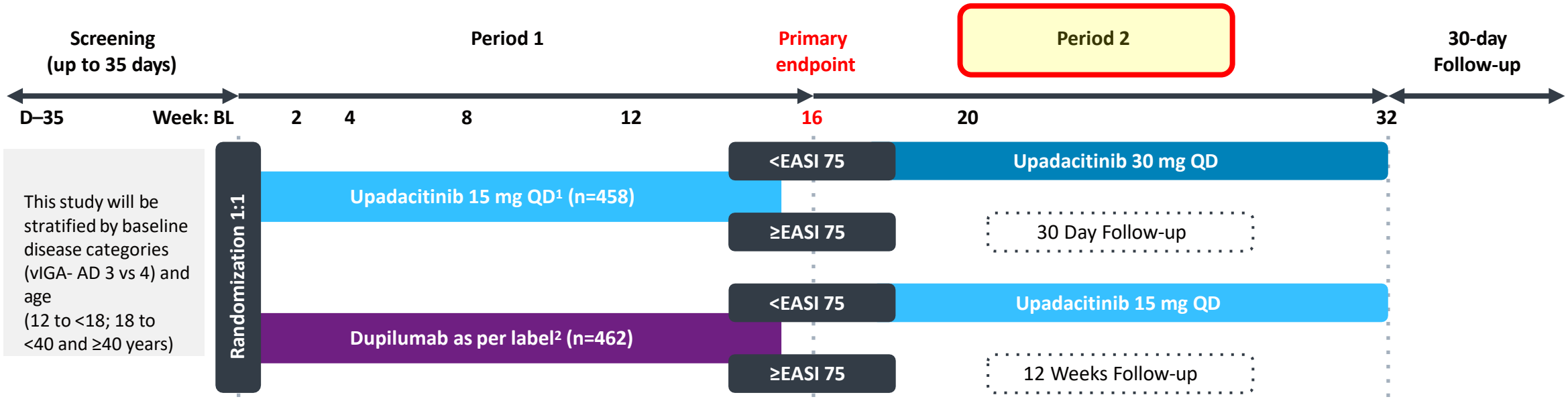
LEVEL UP: Study Design of Head-to-Head Comparison of Upadacitinib vs. Dupilumab in Moderate-to-Severe Atopic Dermatitis



[1]During Period 1, subjects randomized to upadacitinib 15 mg QD will have their dose increased to 30 mg QD if any of the following parameters are met: starting at Week 4, subject has a
<EASI 50 response; starting at Week 4, subject has a <4-point improvement in WP-NRS; starting at Week 8, subject has a < EASI 75 response

[2]Dupilumab dosing as per label:

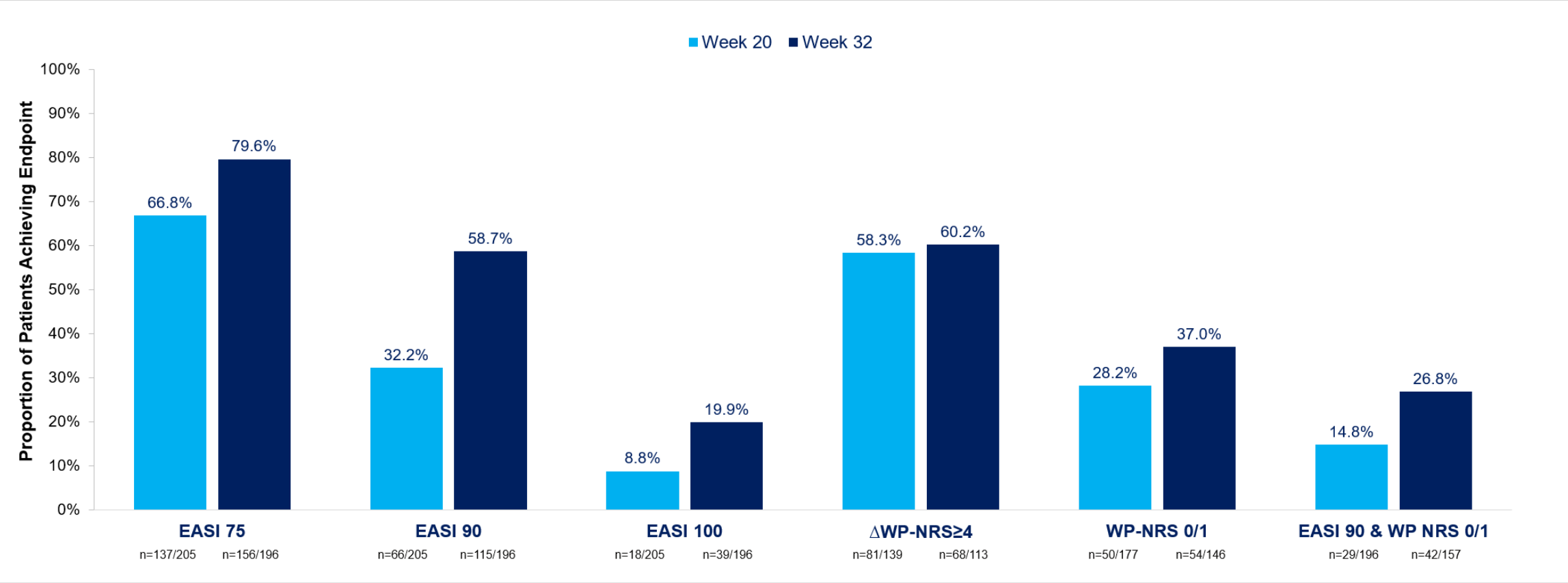
- Adults: Dupilumab 600 mg (2 x 300 mg dupilumab SC injection) at Baseline, followed by dupilumab 300 mg SC injection EOW until Week 16
- Adolescents 12 to 17 years and ≥40 kg:
  1. 40 to <60 kg: Initial dose dupilumab 400 mg (two 200 mg injections; subsequent doses (EOW) 200 mg
  2. ≥60 kg: Initial dose dupilumab 600 mg (two 300 mg injections); subsequent doses (EOW) 300 mg

QD, daily; EASI, Eczema Area and Severity Index; WP-NRS, Worst Pruritus Numerical Rating Scale; SC, subcutaneous; EOW, every other week

Silverberg JI et al. *British Journal of Dermatology*. 2024;191(Supplement_2):ljae266-107.

LEVEL UP: Period 2 SWITCH Outcomes of Dupilumab Non-Responders to Daily Upadacitinib 15 mg

Efficacy outcomes for patients at Week 20 and Week 32 who switched from DUPI to UPA at Week 16



Patients receiving topical rescue were imputed as non-responders. WP-NRS 0/1 is assessed among patients with WP-NRS>1 at baseline, WP-NRS reduction (improvement) ≥ 4 (ΔWP-NRS≥4) is assessed among patients with Baseline WP-NRS ≥ 4.

DUP, dupilumab; UPA, upadacitinib; EASI, Eczema Area and Severity Index; WP-NRS, Worst Pruritus Numerical Rating Scale.

Bunick et al. Fall Clinical Dermatology Conference, Las Vegas, NV, October 24-27, 2024

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LEVEL UP: Treatment-Emergent Adverse Events

There were no new safety signals identified for upadacitinib and dupilumab through week 16

Patients with any treatment-emergent adverse events	Upadacitinib (n=458), n (%)	Dupilumab (n=461), n (%)
Adverse event	299 (65.3)	243 (52.7)
Serious adverse event	4 (0.9)	4 (0.9)
Adverse event leading to discontinuation of study treatment	9 (2.0)	6 (1.3)
Adverse event with reasonable possibility of being related to study treatment	159 (34.7)	99 (21.5)
Severe Adverse event (CTCAE toxicity Grade ≥3)	16 (3.5)	12 (2.6)
All deaths	0	0
Treatment-emergent adverse event reported by ≥5% of patients	**Upadacitinib (n=458), n (%)**	**Dupilumab (n=461), n (%)**
Nasopharyngitis	58 (12.7)	34 (7.4)
Acne	55 (12.0)	7 (1.5)
Headache	27 (5.9)	16 (3.5)
Upper respiratory tract infection	27 (5.9)	21 (4.6)
Dermatitis atopic	24 (5.2)	15 (3.3)

CTCAE, Common Terminology Criteria for Adverse Events

1. Silverberg JI, et al. Revolutionizing Alopecia Areata, Vitiligo, and Eczema (RAVE) Conference 2024, Chicago, IL, USA, June 8–10, 2024. Poster 734; 2. Silverberg JI, et al. *Br J Dermatol*. 2024;191(2):ljae266.107.

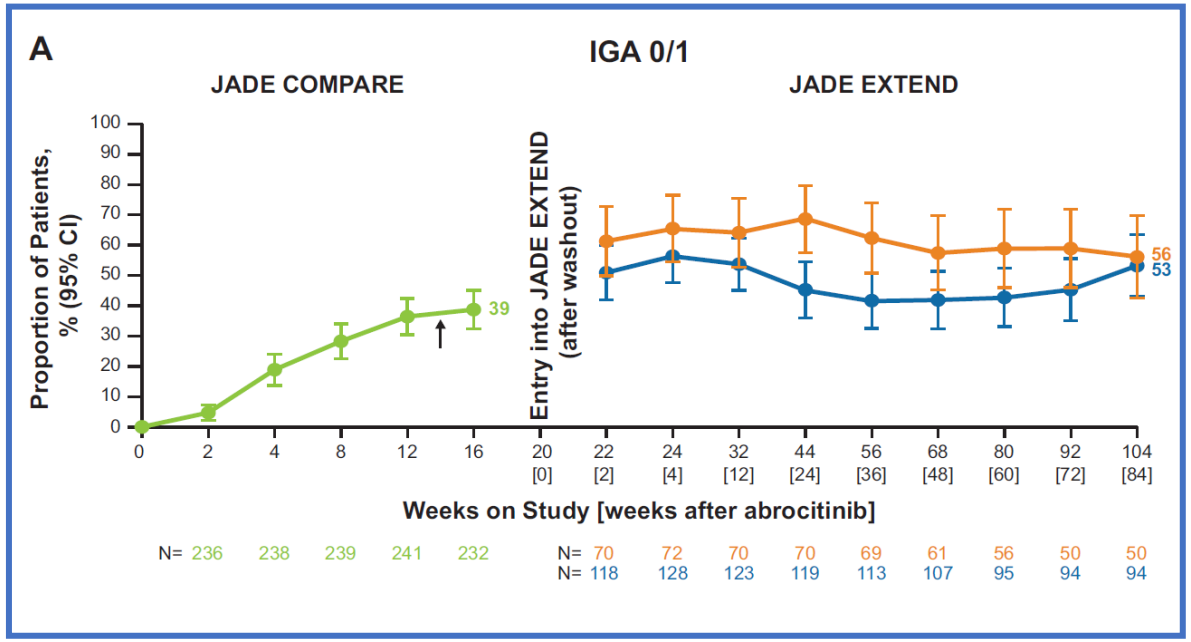
LEVEL UP: Treatment-Emergent Adverse Events of Special Interest

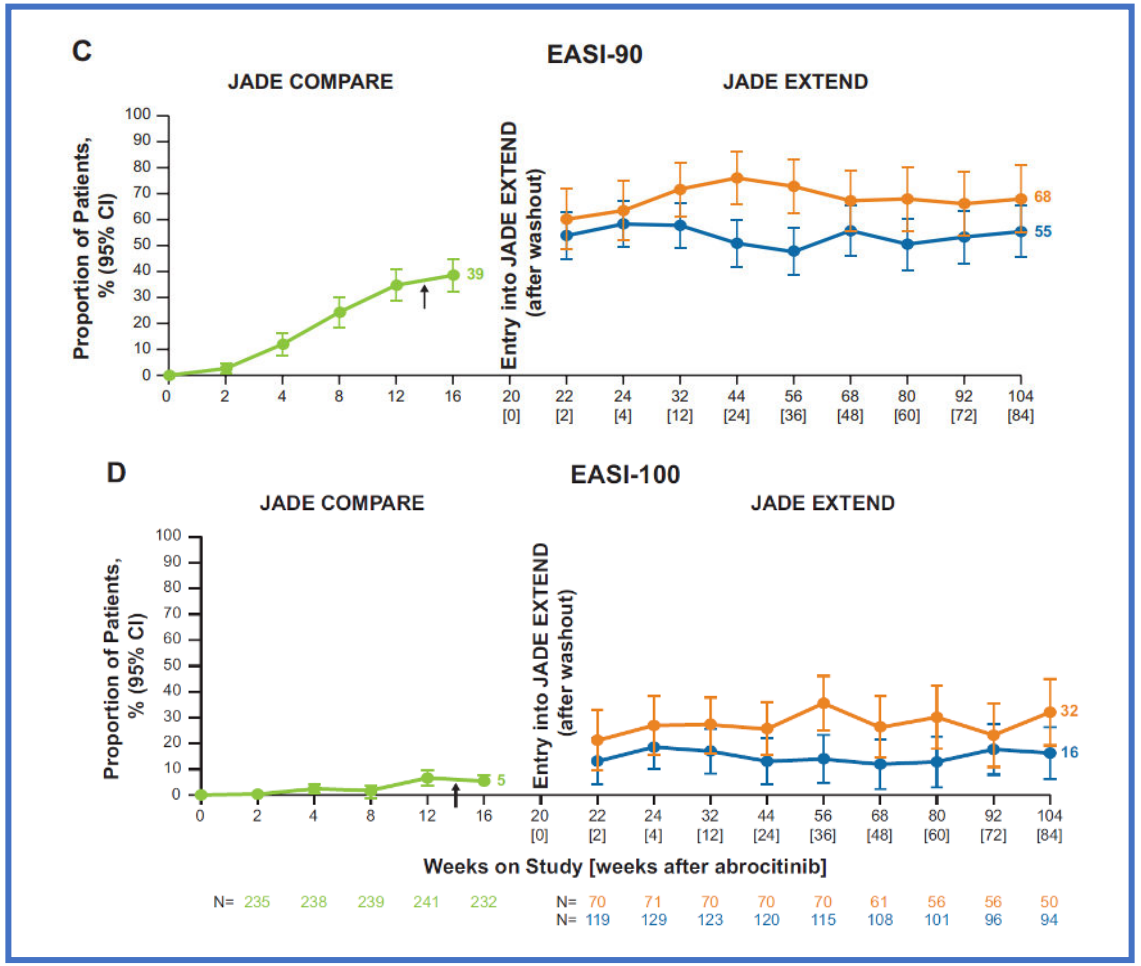
Patients with any treatment-emergent AESI	Upadacitinib (n=458), n (%)[1,2]	Dupilumab (n=461), n (%)[1,2]
Serious infections	0	1 (0.2)
Opportunistic infection[a]	5 (1.1)	0
Herpes zoster	8 (1.7)	2 (0.4)
Active tuberculosis	0	0
Malignancy	0	0
GI perforations[b]	0	0
MACE[b]	0	0
VTE[b]	0	0
Anemia	4 (0.9)	0
Neutropenia	4 (0.9)	1 (0.2)
Lymphopenia	1 (0.2)	0
Renal dysfunction	0	0
Hepatic disorder	9 (2.0)	4 (0.9)
Elevated CPK	17 (3.7)	3 (0.7)
Bone fracture	0	2 (0.4)
Retinal detachment	0	1 (0.2)
Serious hypersensitivity reactions	0	0

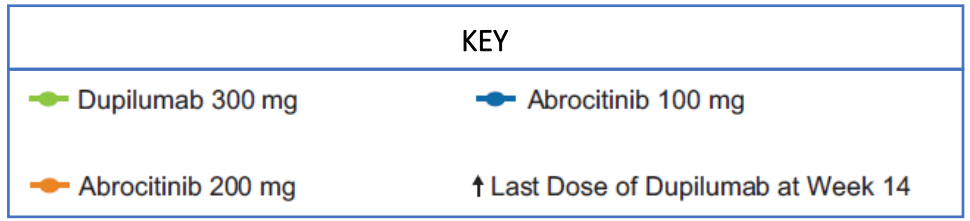
CTCAE, Common Terminology Criteria for Adverse Events

1. Silverberg JI, et al. Revolutionizing Alopecia Areata, Vitiligo, and Eczema (RAVE) Conference 2024, Chicago, IL, USA, June 8–10, 2024. Poster 734; 2. Silverberg JI, et al. *Br J Dermatol*. 2024;191(2):ljae266.107.

JADE EXTEND: Skin Clearance Response in Patients Receiving Abrocitinib Post-Dupilumab Through 104 Weeks







EASI, Eczema Area and Severity Index;.

Gooderham M, et al. Fall Clinical Dermatology Conference, Las Vegas, NV, October 24-27, 2024

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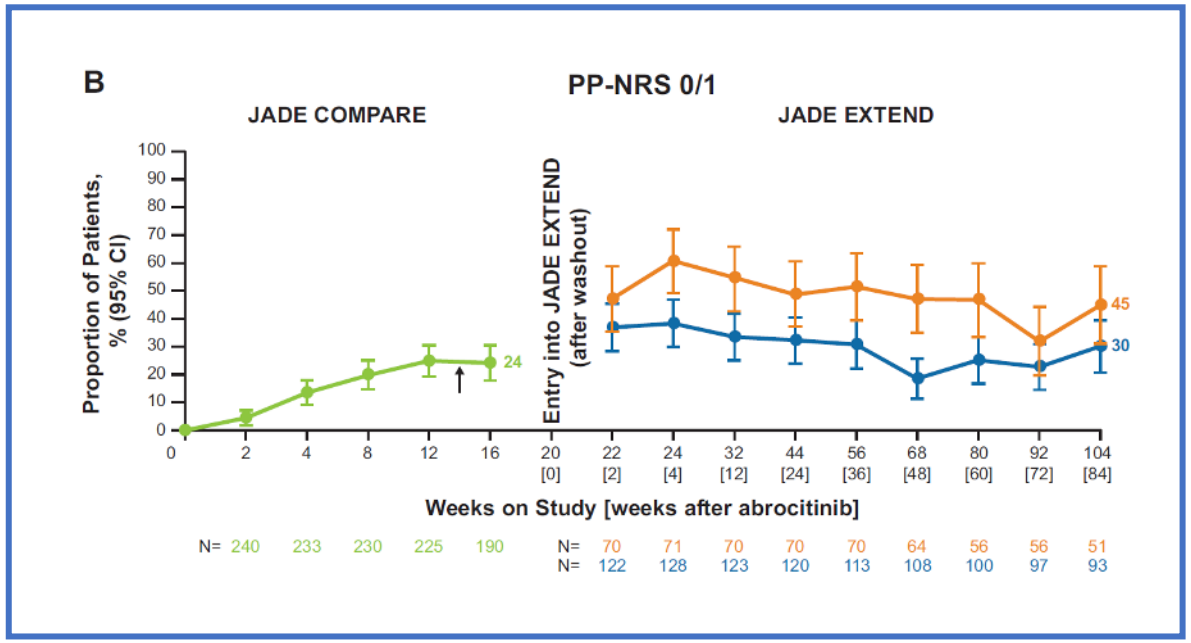
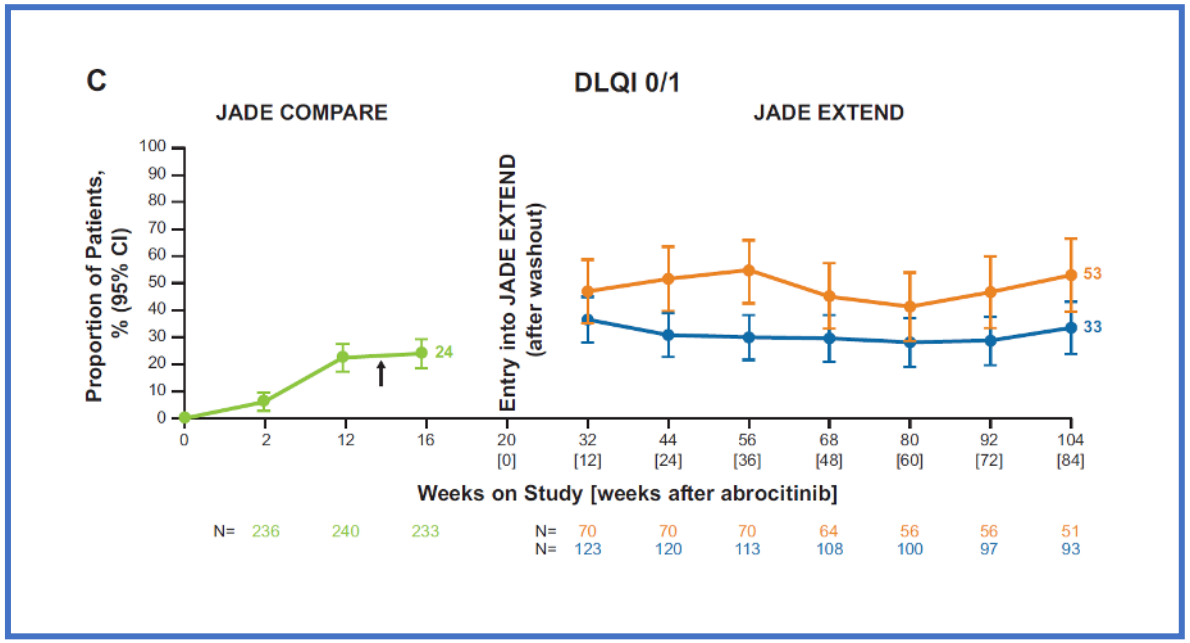
JADE EXTEND: Itch and Quality of Life in Patients Receiving Abrocitinib Post-Dupilumab Through 104 Weeks





KEY

- Dupilumab 300 mg
- Abrocitinib 100 mg
- Abrocitinib 200 mg
- Last Dose of Dupilumab at Week 14

EASI, Eczema Area and Severity Index;

Gooderham M, et al. Fall Clinical Dermatology Conference, Las Vegas, NV, October 24-27, 2024

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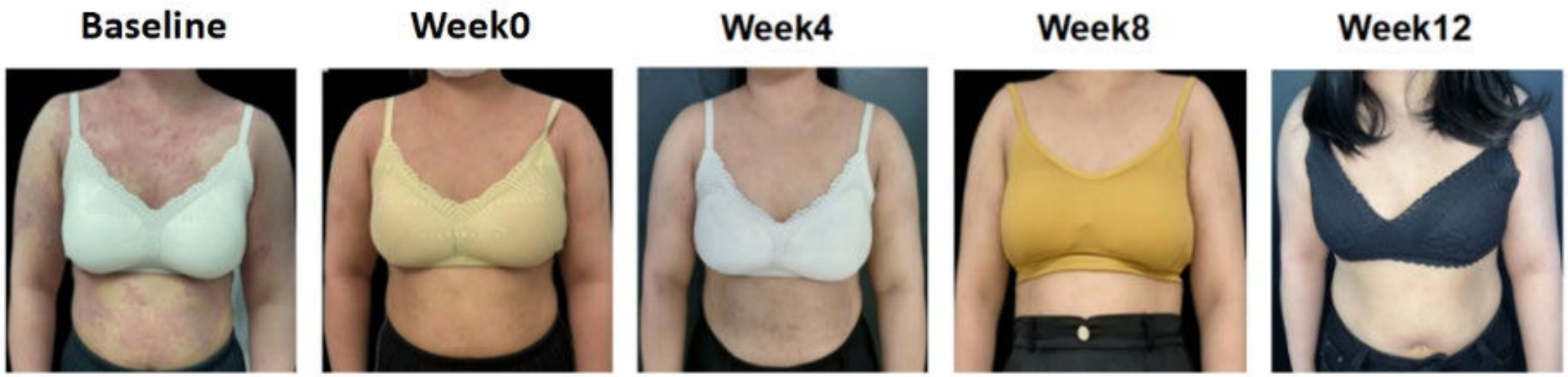
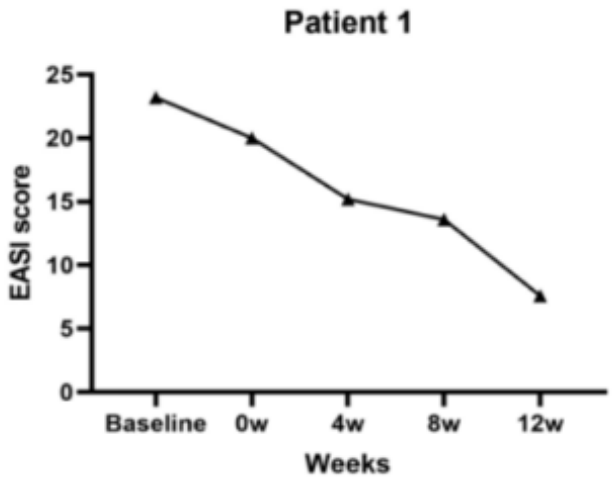
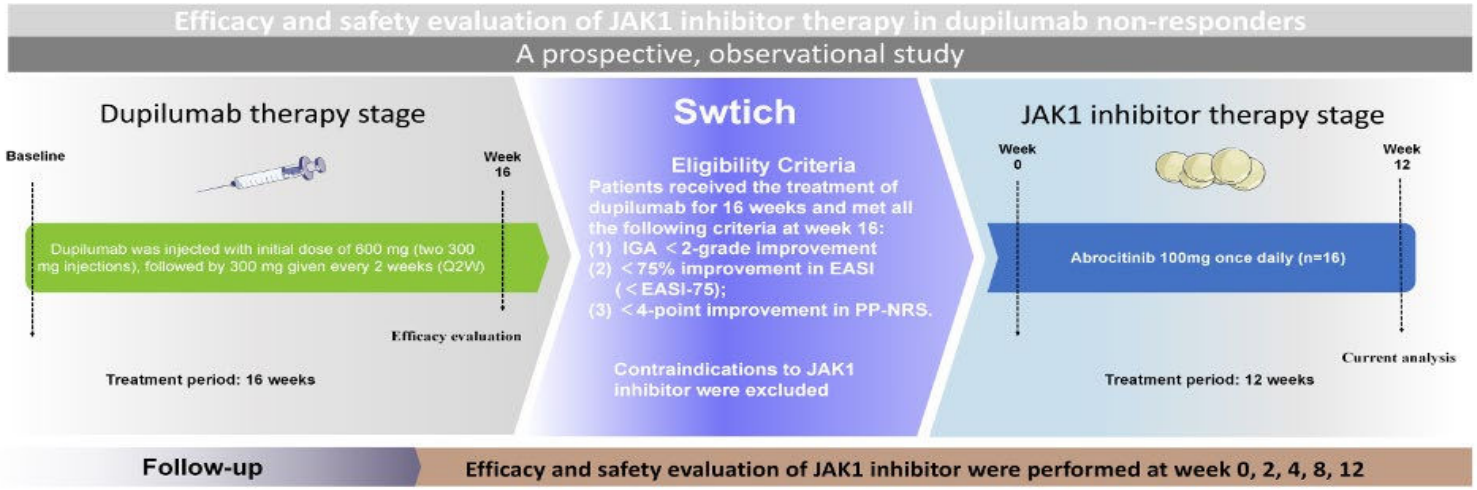
Observational study of abrocitinib in adults with moderate-to-severe atopic dermatitis after switching from dupilumab







Tong Z, Zhang Y, Zhou K, Zou Y, Wu Z, Chen J, Zhuang Z, Zhao Y, Gong T, Ji C. An observational study of abrocitinib in adults with moderate-to-severe atopic dermatitis after switching from dupilumab. J Am Acad Dermatol. 2023 Oct;89(4):826-828. doi: 10.1016/j.jaad.2023.05.077. Epub 2023 Jun 10. PMID: 37307992.

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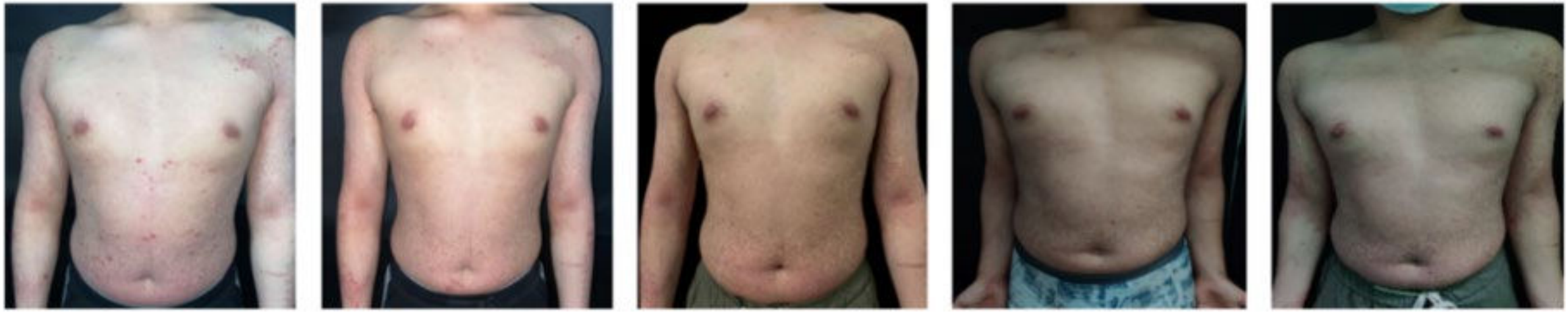

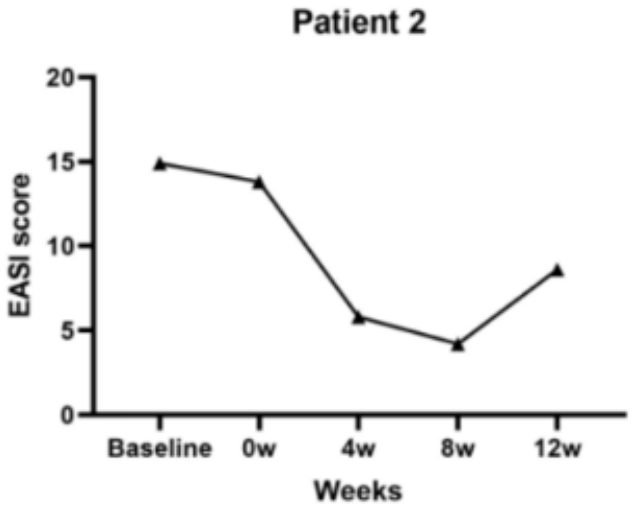

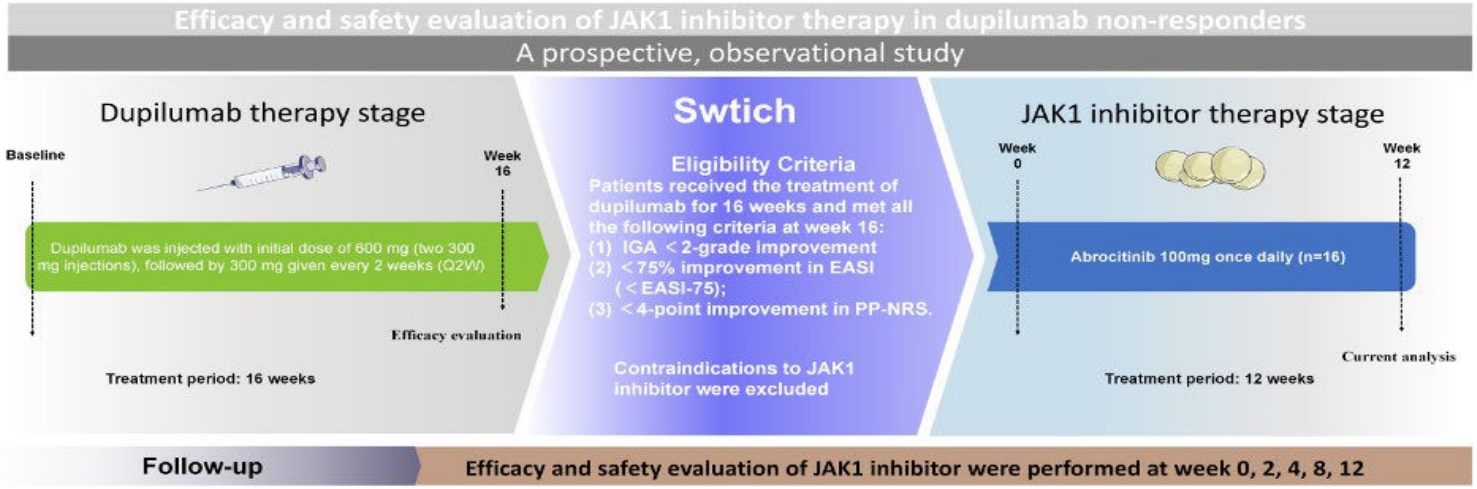

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Observational study of abrocitinib in adults with moderate-to-severe atopic dermatitis after switching from dupilumab

Scale	Primary outcomes		Secondary outcomes			
Time	SCORAD	EASI score	IGA score	PP-NRS score	DLQI score	ADCT score
Baseline	56.20 ± 8.16∗	19.16 ± 4.63^{ns}	4 (IQR 4-4)∗	8.5 (IQR 8-9)∗	21.50 ± 4.66^{ns}	20.25 ± 3.36^{ns}
Week 0	50.42 ± 6.59	16.63 ± 4.48	3 (IQR 3-3.75)	7 (IQR 7-8)	18.69 ± 4.08	18.38 ± 3.01
Week 2	40.33 ± 7.94∗	13.46 ± 4.01^{ns}	3 (IQR 2-3)^{ns}	3 (IQR 2-5.5)∗	12.88 ± 5.20∗	12.88 ± 2.42∗
Week 12	23.54 ± 11.12∗	7.14 ± 3.97∗	1 (IQR 1-2)∗	1 (IQR 1-2)∗	3.56 ± 2.80∗	4.81 ± 2.23∗

Six scale measurements of 16 patients during the follow-up
The score at each follow-up visit was compared to that obtained at week 0. (ns: no significance, $*P < .05$).
AD, Atopic dermatitis; *ADCT*, Atopic Dermatitis Control Tool; *DLQI*, Dermatology Life Quality Index; *EASI*, Eczema Area and Severity Index; *IGA*, Investigator Global Assessment; *IQR*, interquartile range; *PP-NRS*, Peak Pruritus Numerical Rating Scale; *SCORAD*, Scoring Atopic Dermatitis Index.

Tong Z, Zhang Y, Zhou K, Zou Y, Wu Z, Chen J, Zhuang Z, Zhao Y, Gong T, Ji C. An observational study of abrocitinib in adults with moderate-to-severe atopic dermatitis after switching from dupilumab. J Am Acad Dermatol. 2023 Oct;89(4):826-828. doi: 10.1016/j.jaad.2023.05.077. Epub 2023 Jun 10. PMID: 37307992.