Skirting Steroids in Atopic Dermatitis

Don’t Go Chasing Flares: New Therapies and Expert Strategies for Long-term Control

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LiVDerm
REVOLUTIONIZING DERMATOLOGY EDUCATION

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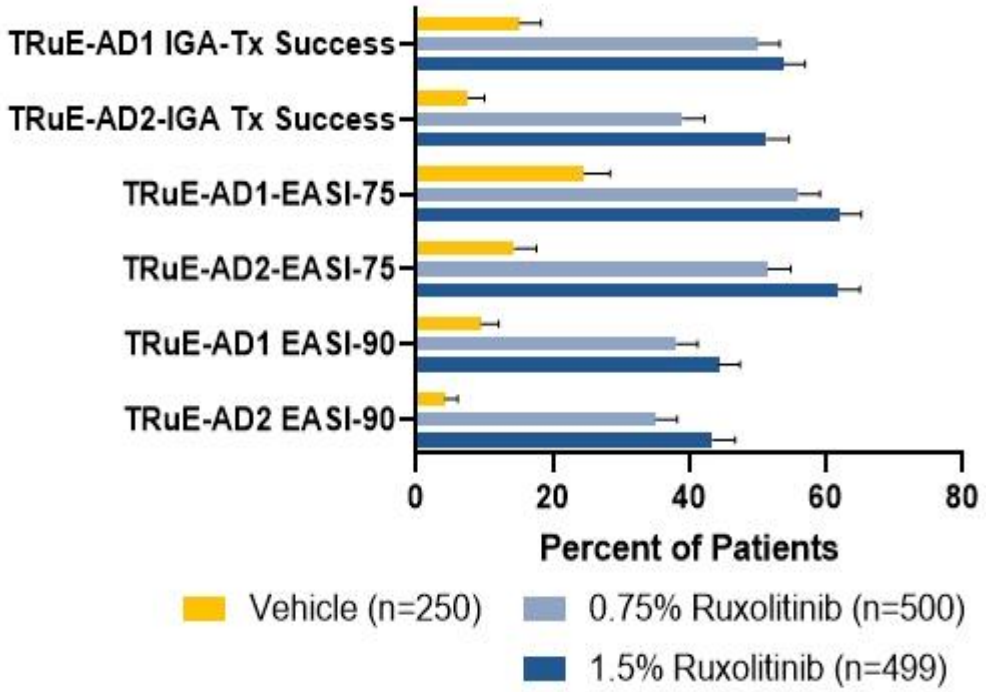
Non-Steroidal Topical Agents

Drug Name	Mechanism	Status
Crisaborole	PDE-4 inhibitor	Approved by FDA for AD patients aged 3 months and older
Ruxolitinib	JAK1/2 inhibitor	Approved by FDA for AD patients aged 12 years and older
Roflumilast	PDE-4 inhibitor	Approved by FDA for AD patients aged 6 years and older
Tapinarof	AhR agonist	Pending FDA approval for AD patients aged 2 years and older
Delgocitinib	pan-JAK inhibitor	Investigated in global phase 3 study for chronic hand eczema (CHE) patients aged 12 years and older

Topical Ruxolitinib

- Predominantly JAK1/2 inhibition
- TRuE-AD1 and 2 consisted of more than 1200 patients age 12 and up
- Endpoints at 8 weeks
- Studied in 0.75 and 1.5% strengths
- Approved in 1.5% cream
- BID as needed use



Ruxolitinib Cream

396

Presented at
Revolutionizing Atopic Dermatitis
Washington, DC · April 29–May 1, 2023

Rapid, Substantial, and Sustained Reduction of Itch in Adults With Atopic Dermatitis Applying Ruxolitinib Cream

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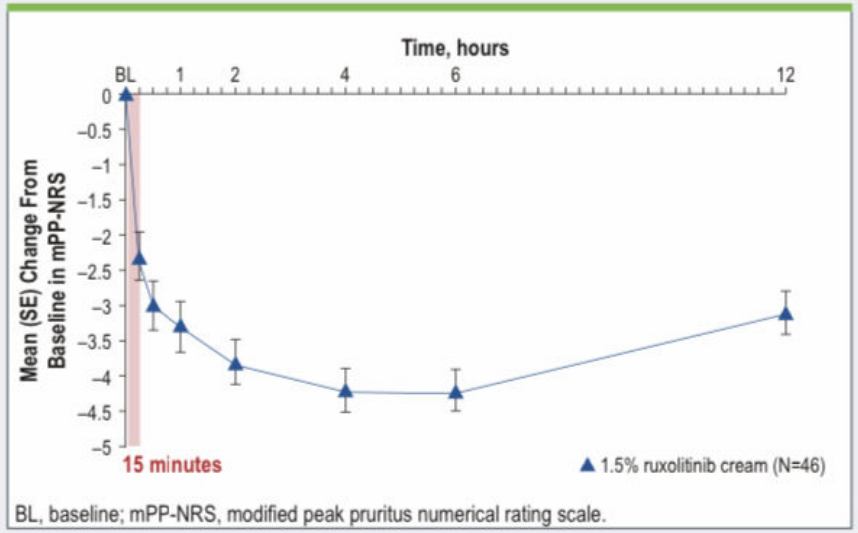
*Presenting Author

Figure 3. Mean (SE) Change From Baseline in mPP-NRS Score



BL, baseline; mPP-NRS, modified peak pruritus numerical rating scale.

- The mean (SE) changes from baseline in IGA score on Days 8, 15, and 29 were –1.4 (0.11), –2.0 (0.13), and –2.2 (0.14), respectively (**Figure 4**)

Conclusions

- **Participants with AD applying 1.5% ruxolitinib cream in this study experienced rapid, substantial improvement in itch, which was sustained and further improved through 28 days of treatment**
  - **Itch reduction was observed as early as 15 minutes after first ruxolitinib cream application, and peak reduction was observed at 4 hours after first application**
- **These results are consistent with the established data on ruxolitinib cream as an effective, well-tolerated topical treatment for AD**

Topical Ruxolitinib

Abstract #6746
Presented at the 32nd European Academy of Dermatology and Venereology (EADV) Congress
11–14 October 2023, Berlin, Germany

A Phase 3 Study of Ruxolitinib Cream in Children Aged 2–<12 Years with Atopic Dermatitis (TRuE-AD3): 8-Week Analysis

Lawrence F. Eichenfield, MD,[1] Linda F. Stein Gold, MD, PhD,[2] Eric L. Simpson, MD, MCR,[3] Andrea L. Zaenglein, MD,[4] April W. Armstrong, MD, PhD, MPH,[5] Megha M. Tollefson, MD,[6] Weily Soong, MD,[7] Lara Wine Lee, MD, PhD,[8] Alim R. Devani, MD,[9] Seth B. Forman, MD,[10] Dareen D. Siri, MD,[11] Brett Angel, MD,[12] Howard Kallender, PhD,[12] Qian Li, PhD,[12] Amy S. Paller, MD[13]

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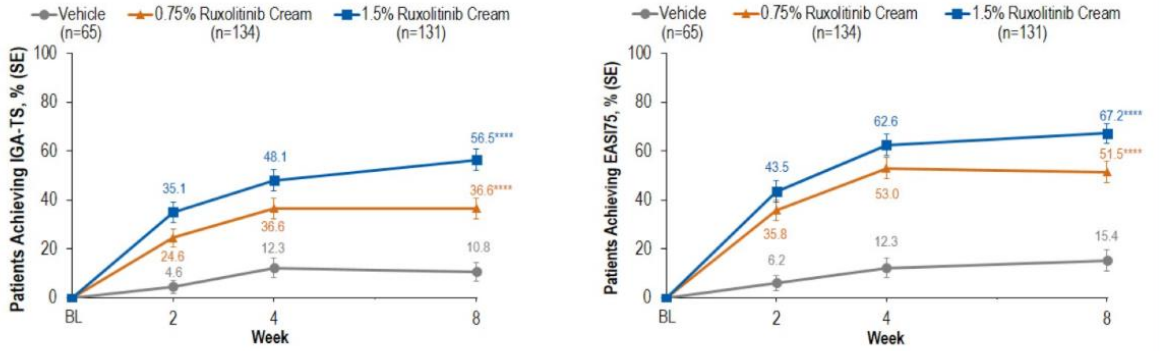
Topical Ruxolitinib

Percentage of Patients Achieving IGA-TS (Primary Endpoint) and EASI75

- Clinical improvement was observed in patients applying 0.75%/1.5% ruxolitinib cream vs vehicle at Week 2, with efficacy increasing through Week 8 for IGA-TS and EASI75

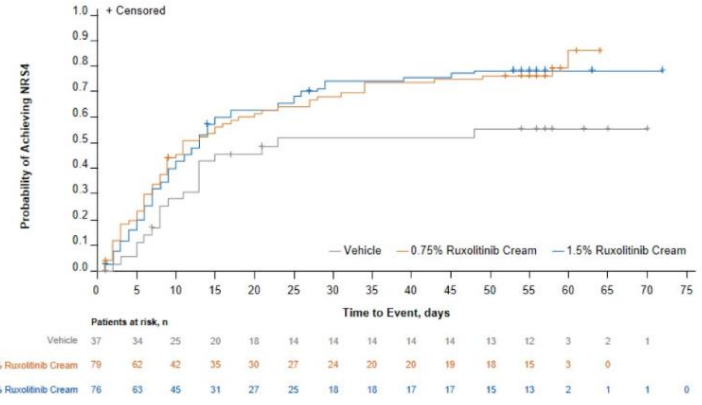


BL, baseline.
**** $P \leq 0.0001$ vs vehicle.

13

Time to Achieve NRS4

- In patients aged 6 to <12 years with a baseline daily itch NRS ≥4 (n=192), median time to achieve NRS4 was 11.0/13.0 days vs 23.0 days (HR, 1.74/1.77; $P<0.05$ vs vehicle for both)



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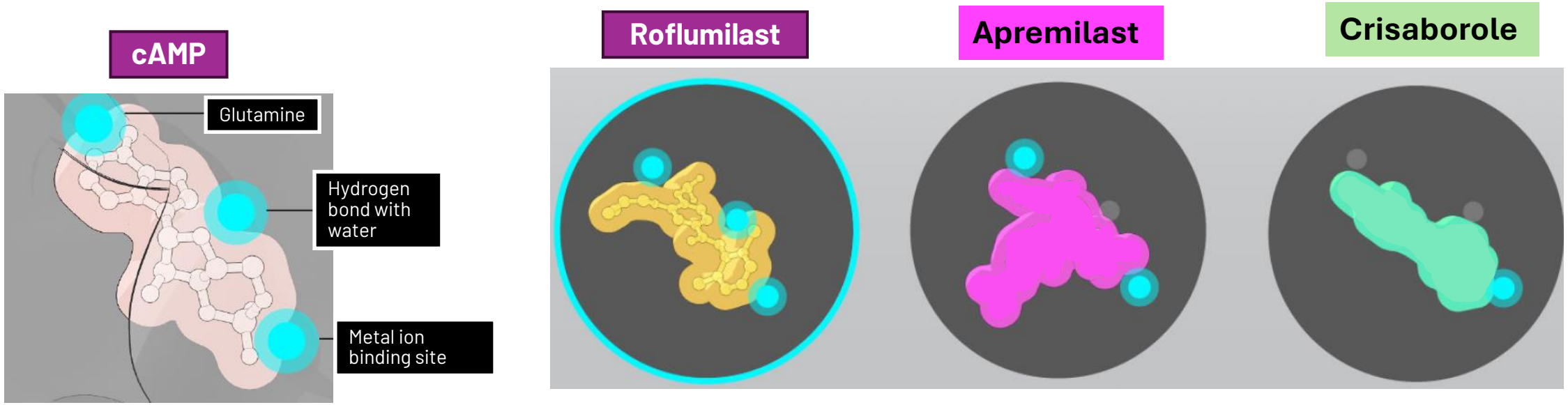
PDE4 inhibitors are molecularly distinct

Roflumilast binding to PDE4 mimics cAMP binding well



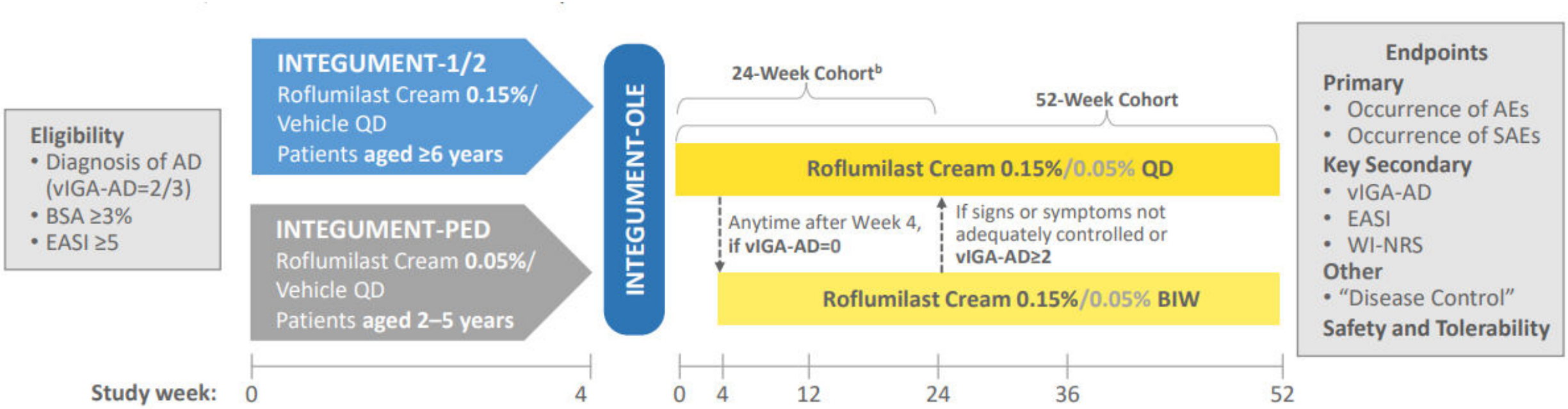
Roflumilast has not been studied in head-to-head clinical trials and the comparative clinical significance is unknown. Efficacy and safety cannot be derived from these data.

Wang J, et al. International Societies for Investigative Dermatology (ISID) Meeting 2023.

Topical Roflumilast

INTEGUMENT-OLE TRIAL - STUDY DESIGN

- 52-week, phase 3, multicenter, open-label extension trial in adults and children ≥2 years of age with AD (INTEGUMENT-OLE [NCT04804605])
  - Here we present results for patients who previously completed INTEGUMENT-1/2 (n=658; 299 in the 24-week cohort, 359 in the 52-week cohort)



Simpson E. et al, Long-term Safety and Efficacy of Roflumilast Cream 0.15% in Adults and Children Aged ≥6 Years With Mild to Moderate Atopic Dermatitis: A 52-week, Phase 3, Open-Label Safety Trial. RAD Conference, Chicago, IL, June 8-10, 2024.

Topical Roflumilast

PATIENT BASELINE DEMOGRAPHICS

		Roflumilast 0.15% to Roflumilast 0.15% (n=439)	Vehicle to Roflumilast 0.15% (n=218)
Age, years, mean (SD) [range]		19.4 (16.4) [6–82]	20.5 (17.9) [6–84]
Age group, n (%)	6–11 years 12–17 years ≥18 years	183 (41.7) 140 (31.9) 116 (26.4)	79 (36.2) 79 (36.2) 60 (27.5)
Female at birth, n (%)		244 (55.6)	122 (56.0)
Not Hispanic or Latino, n (%)		361 (82.2)	182 (83.5)
Race, n (%)	White Asian Black or African-American American-Indian or Alaskan Native Native Hawaiian or Other Pacific Islander More than one race Other	272 (62.0) 63 (14.4) 58 (13.2) 6 (1.4) 1 (0.2) 20 (4.6) 19 (4.3)	139 (63.8) 35 (16.1) 31 (14.2) 0 0 7 (3.2) 6 (2.8)
Fitzpatrick Skin Type, n (%)	I to III IV to VI	245 (55.8) 194 (44.2)	120 (55.0) 98 (45.0)
Baseline vIGA-AD,[a] n (%)	2 (mild) 3 (moderate)	115 (26.2) 324 (73.8)	57 (26.0) 162 (74.0)
Disease characteristics,[a] mean (median) [range]	EASI BSA, % WI-NRS[b]	10.4 (8.8) [5.0–52.5] 14.4 (10.0) [3.0–88.0] 5.8 (6) [0–10]	10.6 (8.8) [5.0–37.9 15.6 (11.0) [3.0–86.0] 5.5 (6.0) [0.0–10.0]

Topical Roflumilast

LONG-TERM SAFETY

- No new safety signals observed over up to 56 weeks of treatment
- 96.3% of patients who experienced TEAEs had AEs of mild or moderate severity
- At each visit, ≥98.1% of patients showed no evidence of irritation on investigator assessment of local tolerability
- Application site pain was reported in for 3 (0.5%) patients, and 0.4%–2.1% of patients reported severe stinging and/or burning at any visit

Patients, n (%)	Roflumilast cream 0.15% (n=657)
Patients with any TEAE	241 (36.7)
Patients with any treatment-related TEAE	31 (4.7)
Patients with any SAE[b]	8 (1.2)
Patients with any treatment-related SAE	0
Patients who discontinued trial because of AE[c]	20 (3.0)

Most Common TEAEs
by Preferred Term (≥2% Overall)

Patients, n (%)	Roflumilast cream 0.15% (n=657)
COVID-19	30 (4.6)
Upper respiratory tract infection	21 (3.2)
Nasopharyngitis	20 (3.0)
Headache	18 (2.7)

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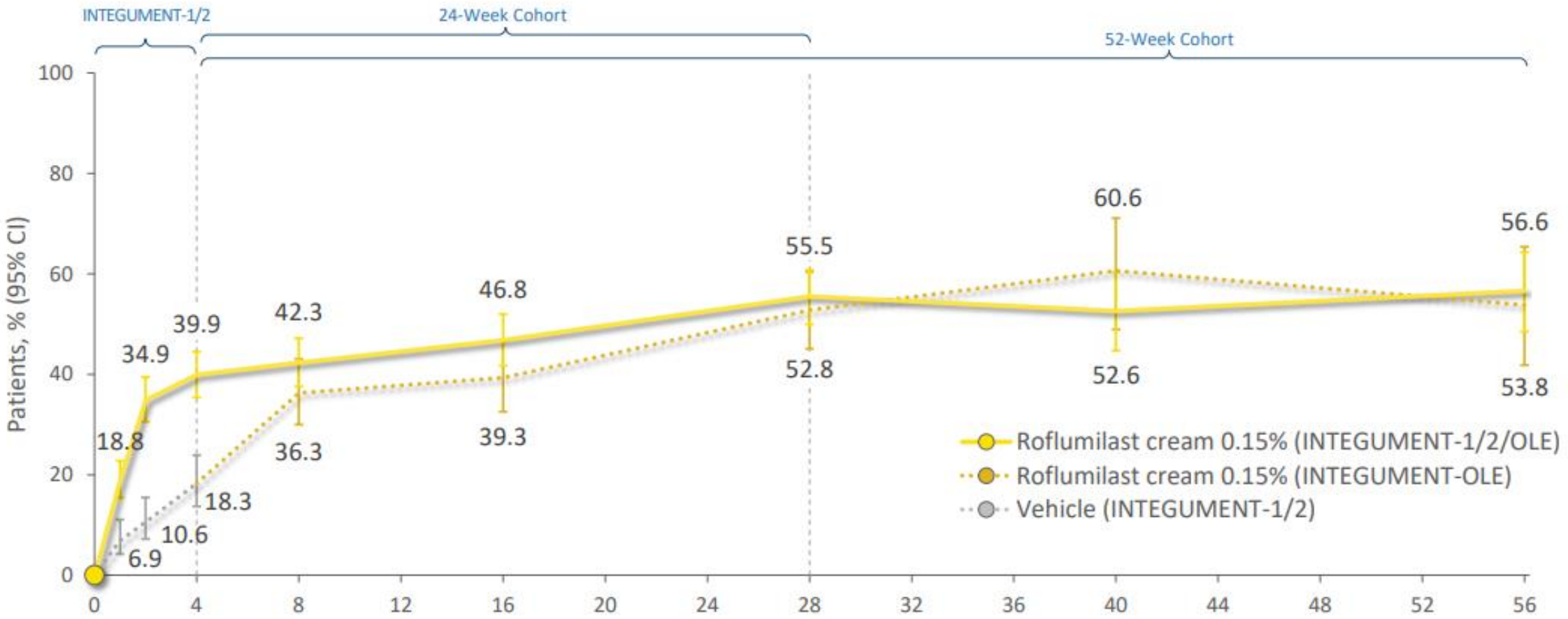
Topical Roflumilast

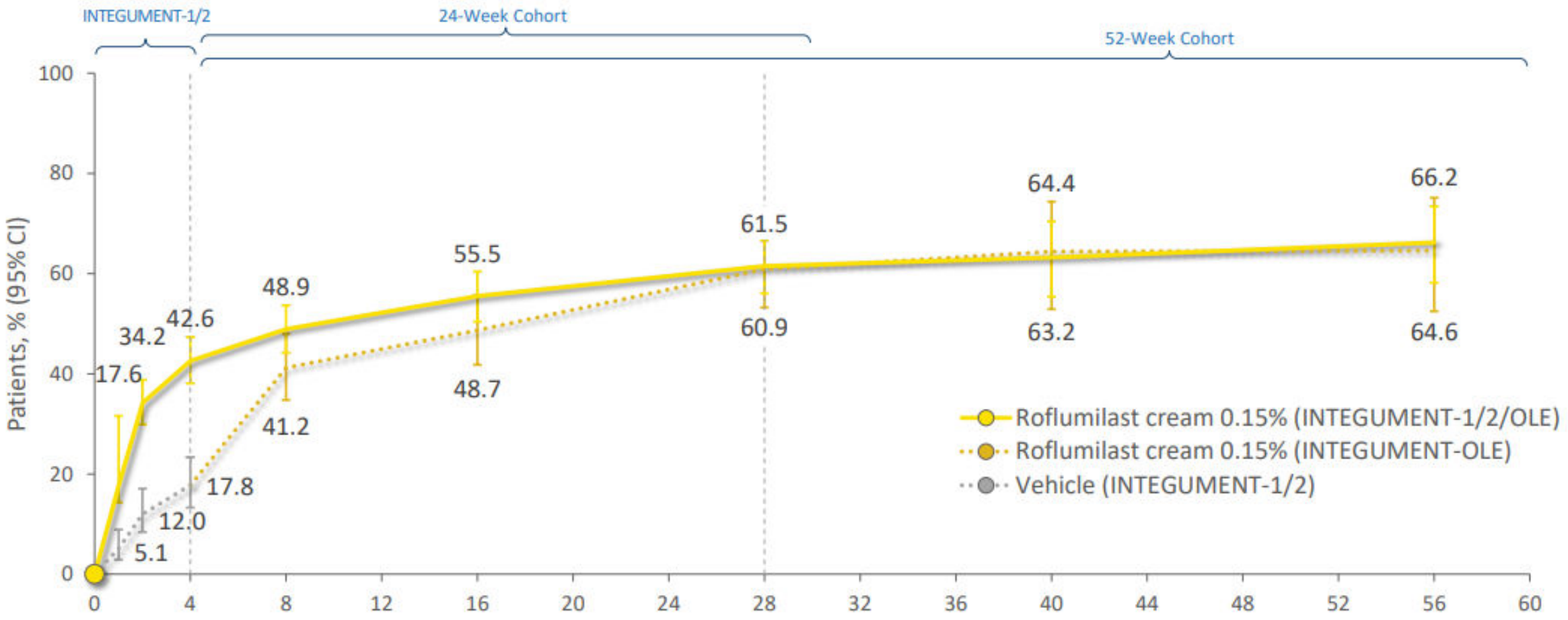
Proportion of Patients Achieving vIGA-AD of 0 (Clear) or 1 (Almost Clear)



Simpson E. et al, Long-term Safety and Efficacy of Roflumilast Cream 0.15% in Adults and Children Aged ≥6 Years With Mild to Moderate Atopic Dermatitis: A 52-week, Phase 3, Open-Label Safety Trial. RAD Conference, Chicago, IL, June 8-10, 2024.

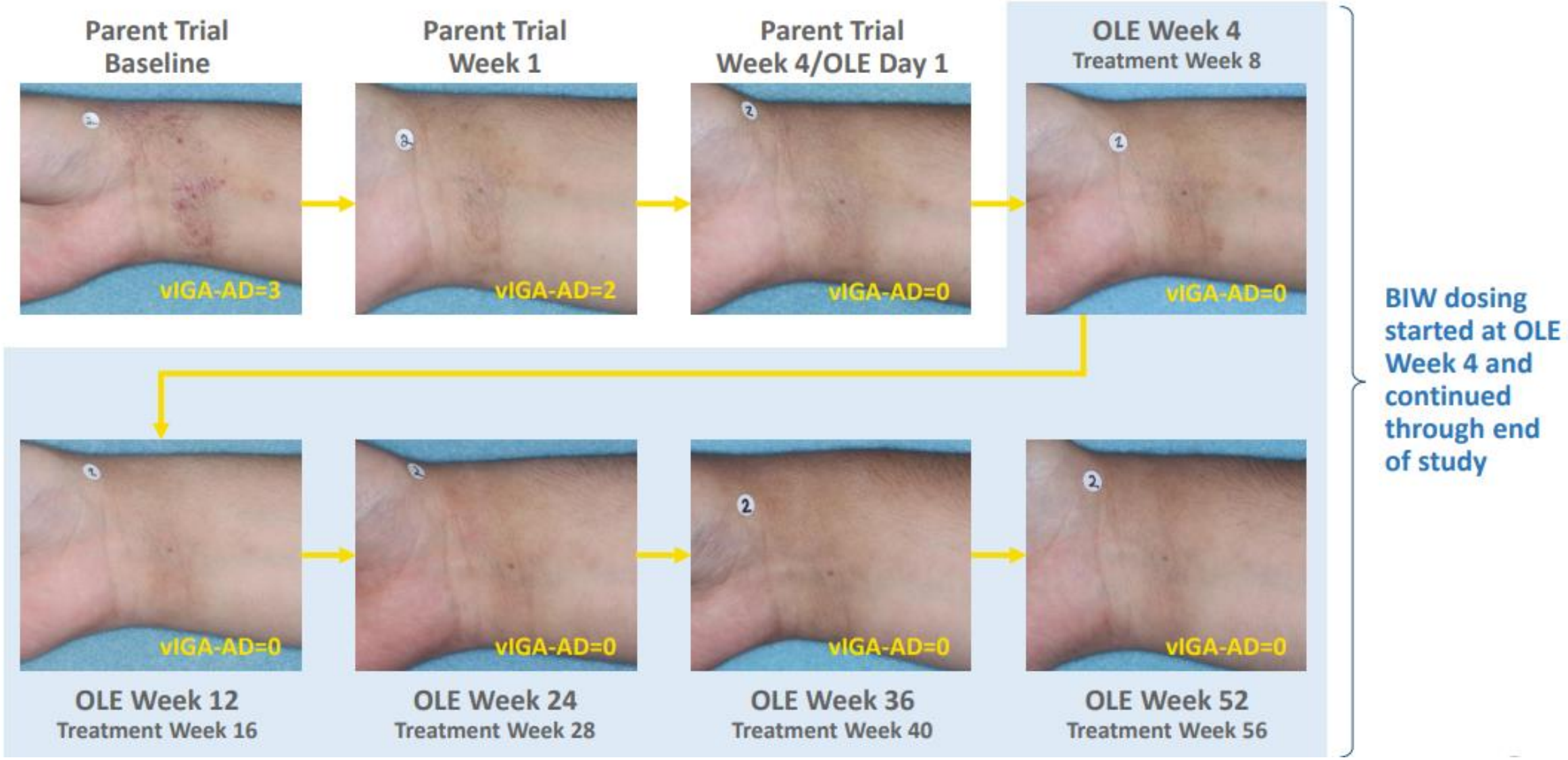
Topical Roflumilast

Proportion of Patients Achieving EASI-75



Simpson E. et al, Long-term Safety and Efficacy of Roflumilast Cream 0.15% in Adults and Children Aged ≥6 Years With Mild to Moderate Atopic Dermatitis: A 52-week, Phase 3, Open-Label Safety Trial. RAD Conference, Chicago, IL, June 8-10, 2024.

Topical Roflumilast



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Emerging Non-Steroidal Topical Agents

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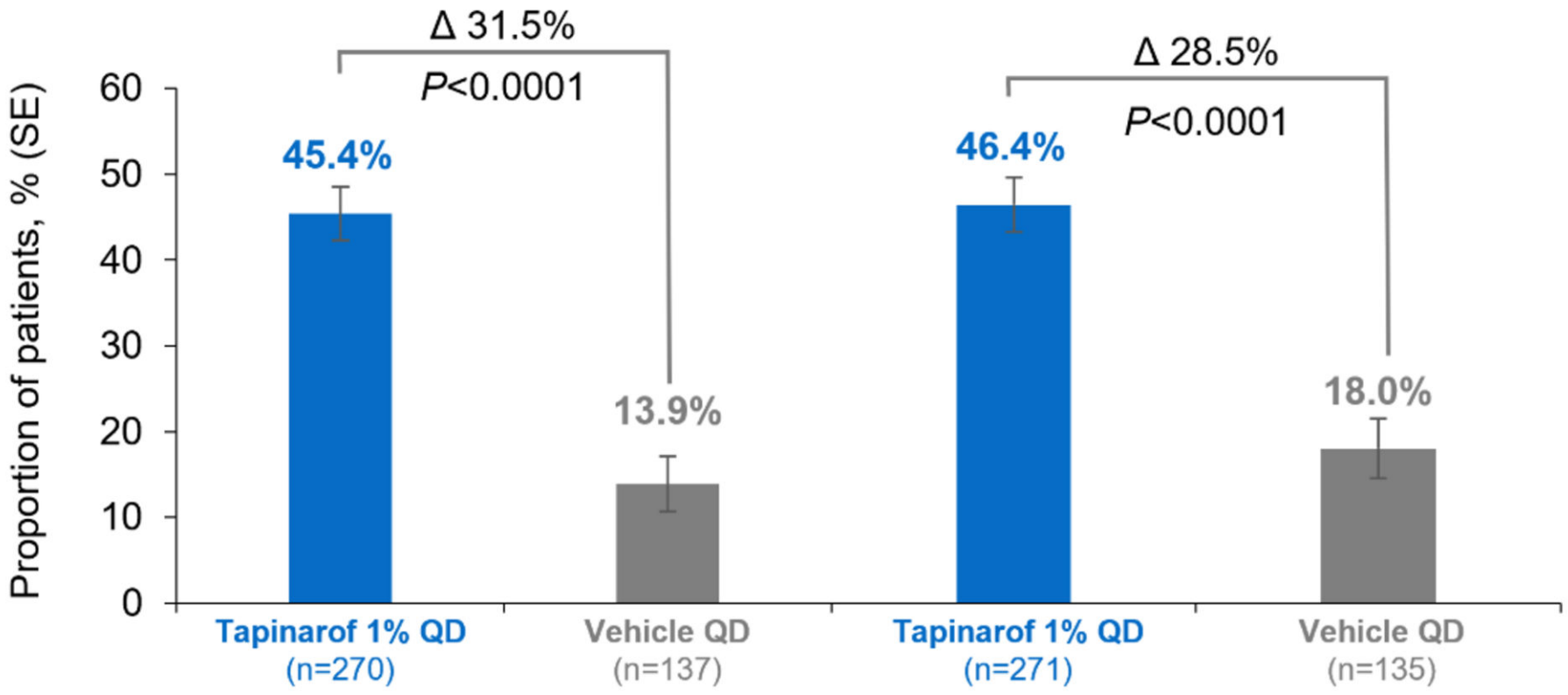
Topical Tapinarof

- 813 patients randomized to tapinarof or vehicle QD in two 8-week trials
- Primary endpoint (vIGA 0 or 1 and ≥2-grade improvement at Week 8)
- Both trials met this endpoint: 45.4% vs 13.9% and 46.4% vs 18.0% tapinarof vs vehicle; both P<0.0001
- EASI75 responses with tapinarof vs vehicle: 55.8% vs 22.9% and 59.1% vs 21.2%, both P<0.0001

Silverberg JI, Eichenfield LF, Hebert AA, Simpson EL, Gold LS, Bissonnette R, Papp KA, Browning J, Kwong P, Korman NJ, Brown PM. Tapinarof Cream 1% Once Daily: Significant Efficacy in the Treatment of Moderate to Severe Atopic Dermatitis in Adults and Children Down to 2 Years of Age in the Pivotal Phase 3 ADORING Trials. Journal of the American Academy of Dermatology. 2024 May 20.

Topical Tapinarof



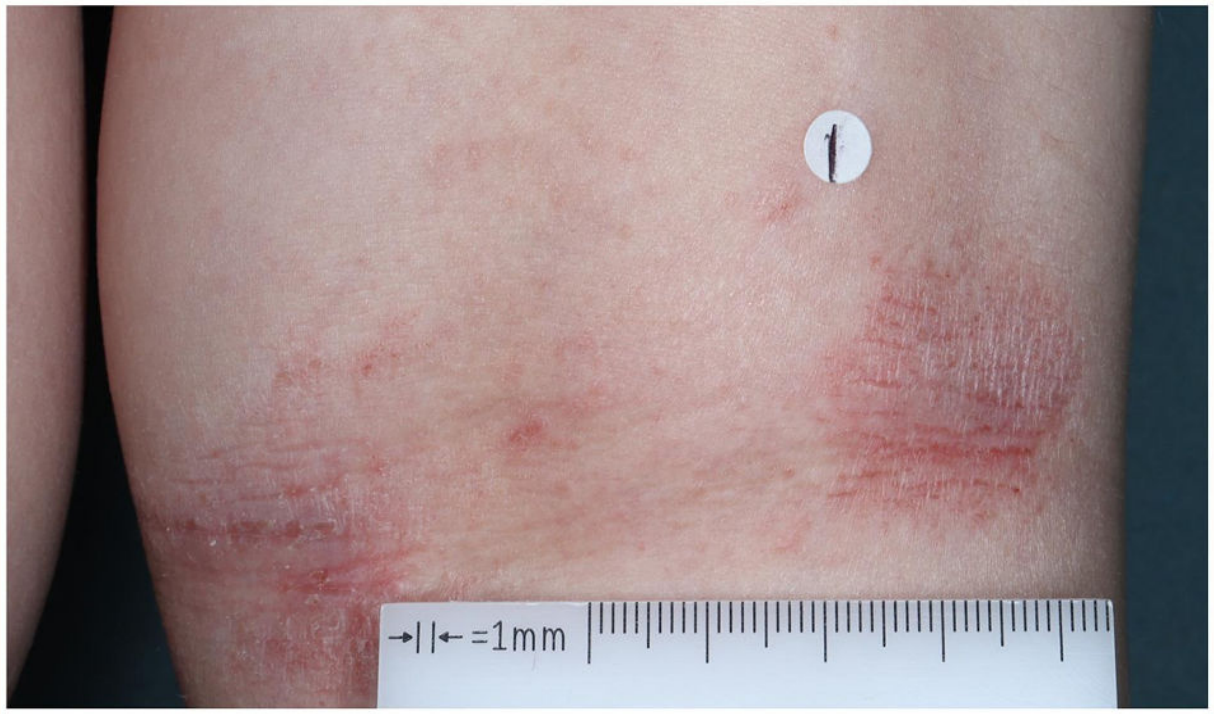
ADORING 1

ADORING 2

Silverberg JI, Eichenfield LF, Hebert AA, Simpson EL, Gold LS, Bissonnette R, Papp KA, Browning J, Kwong P, Korman NJ, Brown PM. Tapinarof Cream 1% Once Daily: Significant Efficacy in the Treatment of Moderate to Severe Atopic Dermatitis in Adults and Children Down to 2 Years of Age in the Pivotal Phase 3 ADORING Trials. Journal of the American Academy of Dermatology. 2024 May 20.

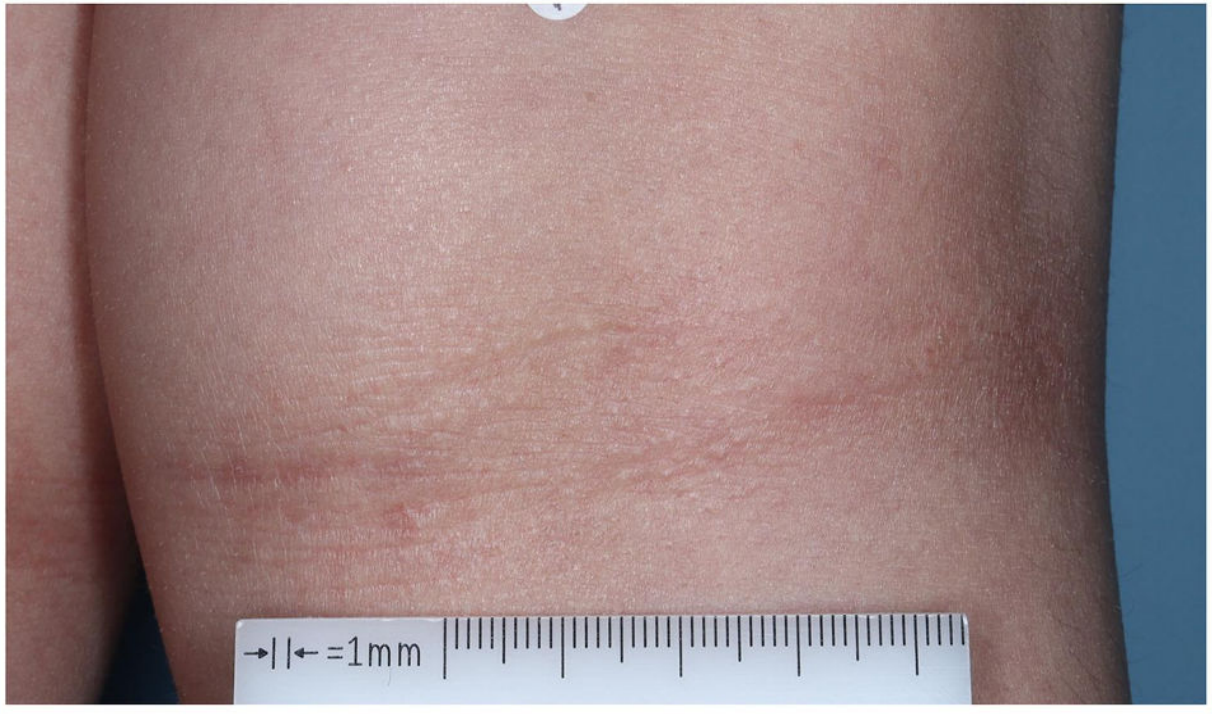
Topical Tapinarof

Baseline



- vIGA-AD™=3
- EASI=6.5
- PP-NRS=9

Week 8



- vIGA-AD™=1
- EASI=0.9
- PP-NRS=0.3

Silverberg JI, Eichenfield LF, Hebert AA, Simpson EL, Gold LS, Bissonnette R, Papp KA, Browning J, Kwong P, Korman NJ, Brown PM. Tapinarof Cream 1% Once Daily: Significant Efficacy in the Treatment of Moderate to Severe Atopic Dermatitis in Adults and Children Down to 2 Years of Age in the Pivotal Phase 3 ADORING Trials. Journal of the American Academy of Dermatology. 2024 May 20.

Topical pan-JAK inhibitor Delgocitinib for Chronic Hand Eczema – Delta 1 and 2 Trials

PATIENT BASELINE DEMOGRAPHICS

Previous CHE treatments

	Total (N=960)	Delgocitinib cream 20 mg/g (N=639)	Cream vehicle (N=321)
TCS			
Inadequate response in last 12 months, n (%)	950 (99.0)	634 (99.2)	316 (98.4)
Medically inadvisable, n (%)	195 (20.3)	127 (19.9)	68 (21.2)
TCI, n (%)	349 (36.4)	234 (36.6)	115 (35.8)
Phototherapy and other procedures, n (%)	191 (19.9)	125 (19.6)	66 (20.6)
Oral retinoids, n (%)	143 (14.9)	97 (15.2)	46 (14.3)
Oral corticosteroids, n (%)	137 (14.3)	96 (15.0)	41 (12.8)
Oral methotrexate, n (%)	50 (5.2)	35 (5.5)	15 (4.7)
Oral cyclosporine, n (%)	31 (3.2)	20 (3.1)	11 (3.4)
Other previous CHE treatments*, n (%)	212 (22.1)	144 (22.5)	68 (21.2)

*The most frequently reported (>2% of patients) included antihistamines, select emollients and protectives, and antibiotics.

. Baseline demographics and characteristics

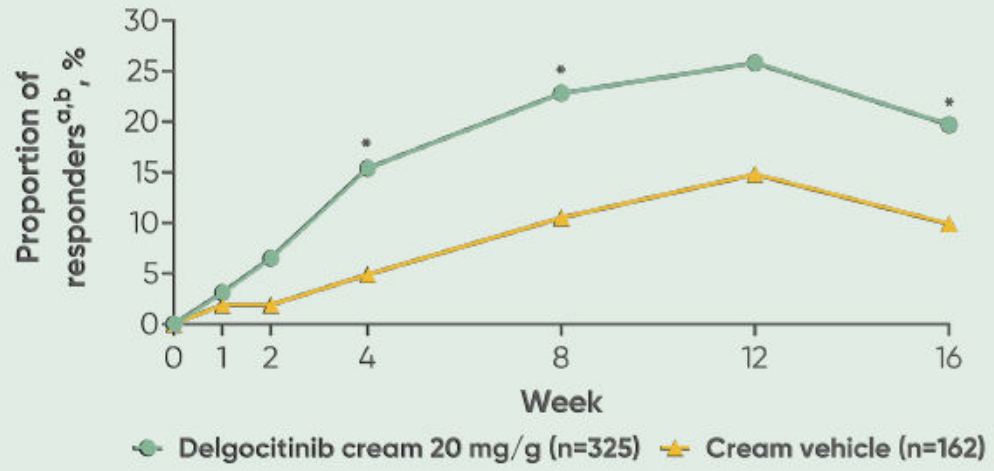
	Total (N=960)	Delgocitinib cream 20 mg/g (N=639)	Cream vehicle (N=321)
Age, median years (min-max)	44.0 (18-87)	45.0 (18-87)	42.0 (18-86)
Sex, n (%)			
Male	342 (35.6)	233 (36.5)	109 (34.0)
Female	618 (64.4)	406 (63.5)	212 (66.0)
Race, n (%)			
White	868 (90.4)	578 (90.5)	290 (90.3)
Black or African American	7 (0.7)	5 (0.8)	2 (0.6)
Asian	34 (3.5)	22 (3.4)	12 (3.7)
Other/Not reported	51 (5.3)	34 (5.3)	17 (5.3)
Age at onset of CHE, median years (min-max)	33.0 (0-87)	34.0 (0-87)	32.0 (0-77)
Duration of CHE, median years (min-max)	5.0 (0-61)	5.0 (0-61)	5.0 (0-53)
IGA-CHE, n (%)			
Moderate	687 (71.6)	457 (71.5)	230 (71.7)
Severe	273 (28.4)	182 (28.5)	91 (28.3)
HECSI, median (min-max)	62.0 (7-280)	63.0 (7-275)	60.0 (8-280)
DLQI			
Median (min-max)	11.0 (0-30)	11.0 (0-30)	11.0 (2-30)
≥4, n (%)	905 (95.5)	604 (95.7)	301 (95.0)

Bissonnette R. et al, Efficacy and safety of delgocitinib cream in adults with moderate to severe Chronic Hand Eczema: pooled results of the Phase 3 DELTA 1 and 2 trials. AAD Annual Conference, San Diego, CA, March 8-11, 2024.

Topical Delgocitinib

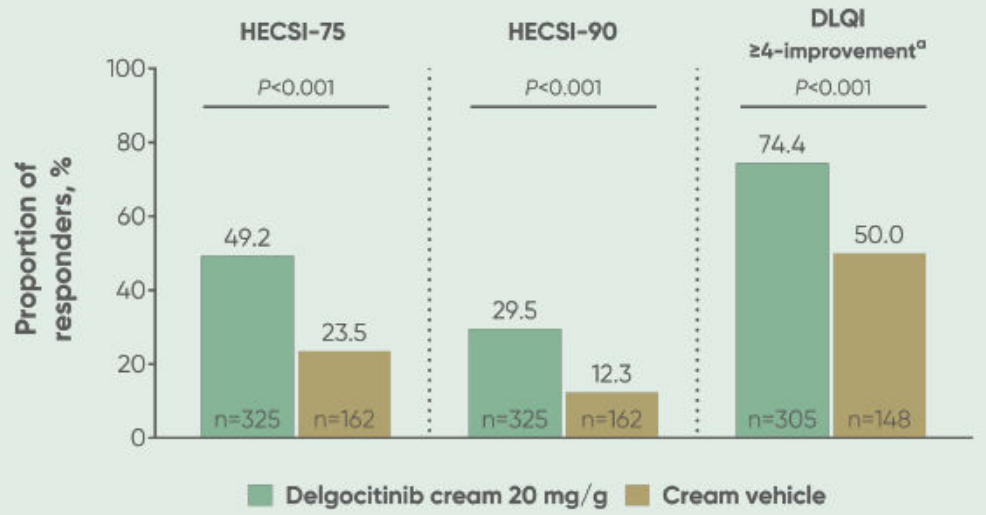
DELTA 1 TRIAL RESULTS

Proportion of patients achieving IGA-CHE treatment success from baseline to Week 16 in the DELTA 1 trial



[a]IGA-CHE treatment success by visit; [b]Treatment success is defined as IGA-CHE score of 0/1 (clear/almost clear , i.e., no/barely perceptible erythema and no other signs) with at least a two-step improvement from baseline. *P*-values compare delgocitinib cream 20 mg/g vs cream vehicle. Binary endpoints were analyzed using Cochran–Mantel–Haenszel test. *$P<0.01$.

Proportion of patients achieving HECSI-75, HECSI-90, and ≥4-point DLQI improvement from baseline at Week 16 in the DELTA 1 trial



[a]Among patients with baseline ≥4 points DLQI score. *P*-values compare delgocitinib cream 20 mg/g vs cream vehicle. The number of patients are represented within each respective bar. Binary endpoints were analyzed using Cochran–Mantel–Haenszel test

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Topical Delgocitinib

JAK Kinase Domain (JH1) Inhibitor Selectivity (IC50, nM)

JAKi	JAK1	JAK2	JAK3	TYK2
Delgocitinib	2.8 nM	2.6 nM	13.0 nM	58.0 nM
Ruxolitinib	6.4 nM	8.8 nM	487.0 nM	30.1 nM

Shawky AM, Almalki FA, Abdalla AN, Abdelazeem AH, Gouda AM. A Comprehensive Overview of Globally Approved JAK Inhibitors. Pharmaceutics. 2022 May 6;14(5):1001.

Miot HA, Criado PR, de Castro CCS, Ianhez M, Talhari C, Ramos PM. JAK-STAT pathway inhibitors in dermatology. An Bras Dermatol. 2023 Sep-Oct;98(5):656-677. doi: 10.1016/j.abd.2023.03.001. Epub 2023 May 23. PMID: 37230920; PMCID: PMC10404561.