Patient-Reported Outcomes and Family Impact With Roflumilast Cream in Atopic Dermatitis: Pooled Phase 3 Results

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Introduction

- Atopic dermatitis (AD) is a chronic inflammatory skin disease that has a substantial impact on patients' quality of life[1,2]
  - Families/parents/caregivers of children and adolescents with AD are also negatively impacted[2,3]
- Roflumilast, a potent phosphodiesterase 4 inhibitor (PDE4), is formulated as a water-based cream and foam
  - Roflumilast potency is ~25 to >300-fold higher than other PDE4 inhibitors apremilast and crisaborole, with roflumilast more closely mimicking cyclic adenosine monophosphate binding[4,5]
  - Roflumilast cream 0.15% was recently approved by the US Food and Drug Association for treatment of mild-to-moderate AD in patients aged ≥6 years
- The safety, efficacy, and patient-reported outcomes from two identically designed Phase 3 trials (INTEGUMENT-1/INTEGUMENT-2) of once-daily roflumilast cream 0.15% in patients aged ≥6 years with AD have been published[6]; here, we present the overall improvement in AD signs and symptoms as well as the impact on families and caregivers

AD: atopic dermatitis; cAMP: cyclic adenosine monophosphate; PDE4: phosphodiesterase 4 inhibitor.

1. Silverberg JI, et al. *Ann Allergy Asthma Immunol.* 2018;121:340–347. **2.** Rønnstad ATM, et al. *J Am Acad Dermatol.* 2018;79:448–456.e30. **3.** Ramirez FD, et al. *JAMA Pediatr.* 2019;173:e190025. **4.** Dong C, et al. *J Pharmacol Exp Ther.* 2016;358:413–422. **5.** Wang J, Bunick CG. International Societies for Investigative Dermatology Meeting 2023. **6.** Simpson EL, et al. *JAMA Dermatol.* Published online ahead of print September 18, 2024. doi:10.1001/jamadermatol.2024.3121.

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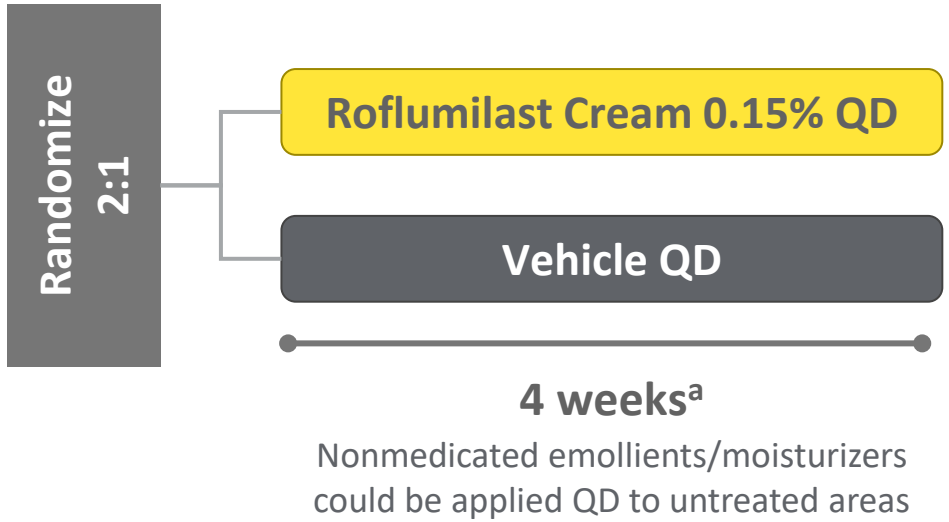
INTEGUMENT-1/-2 Study Design

Identically designed, parallel, phase 3 multicenter trials
(NCT04773587, NCT04773600)

Eligibility

- Diagnosis of mild or moderate AD (vIGA-AD = 2 or 3)
- Age ≥6 years
- BSA ≥3%
- EASI ≥5



- The primary endpoint was Validated Investigator Global Assessment for AD (vIGA-AD) Success (0 [Clear] or 1 [Almost Clear] plus ≥2-grade improvement from baseline) at Week 4
- Other outcome measures included Worst Itch-Numeric Rating Scale (WI-NRS), SCORing AD (SCORAD) total score, Patient-Oriented Eczema Measure (POEM), and Dermatitis Family Impact (DFI; patients aged ≤17 years)
- Safety and local tolerability were also assessed

AD: atopic dermatitis; BSA: body surface area; DFI: Dermatitis Family Impact; EASI: Eczema Area and Severity Index; POEM: Patient-Oriented Eczema Measure; QD: once daily; SCORAD: SCORing AD; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis; WI-NRS: Worst Itch-Numeric Rating Scale.

Simpson EL, et al. *JAMA Dermatol*. Published online ahead of print September 18, 2024. doi:10.1001/jamadermatol.2024.3121.

Patient Demographics and Baseline Disease Characteristics

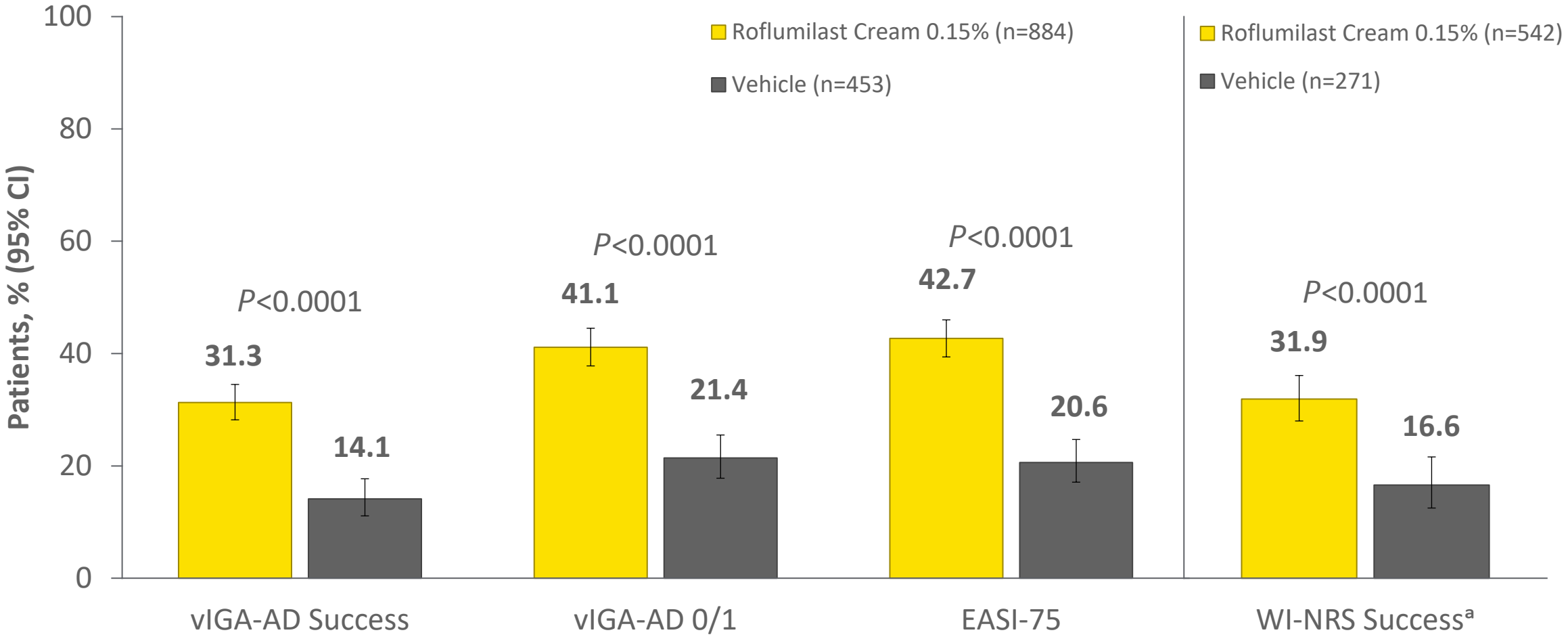
		Roflumilast Cream 0.15% (n=884)	Vehicle (n=453)
Age, years, mean (SD)		27.9 (19.4)	27.3 (19.0)
Age group, n (%)	6–11 years	214 (24.2)	103 (22.7)
	12–17 years	192 (21.7)	106 (23.4)
	18–64 years	434 (49.1)	223 (49.2)
	≥65 years	44 (5.0)	21 (4.6)
Female at birth, n (%)		489 (55.3)	272 (60.0)
Hispanic or Latino, n (%)		150 (17.0)	72 (15.9)
Race, n (%)	White	529 (59.8)	267 (58.9)
	Asian	114 (12.9)	62 (13.7)
	Black/African American	176 (19.9)	96 (21.2)
	American Indian/ Alaskan Native	7 (0.8)	1 (0.2)
	Native Hawaiian/ Other Pacific Islander	1 (0.1)	0
	>1 race	24 (2.7)	14 (3.1)
	Other	33 (3.7)	13 (2.9)

		Roflumilast Cream 0.15% (n=884)	Vehicle (n=453)
Fitzpatrick skin type, n (%)	I to III	481 (54.4)	238 (52.5)
	IV to VI	403 (45.6)	215 (47.5)
vIGA-AD,[a] n (%)	2 (mild)	211 (23.9)	112 (24.7)
	3 (moderate)	673 (76.1)	341 (75.3)
BSA, mean (median) [range]		13.5 (9.7) [3.0–88.0]	13.9 (10.0) [3.0–86.0]
WI-NRS[b]	Mean (median)	6.1 (6.3)	5.9 (6.0)
	Average weekly baseline score ≥4, n (%)	542 (61.3)	271 (59.8)
SCORAD,[c] mean (median) [range]		45.5 (45.3) [18.2–81.5]	45.1 (43.9) [20.9–83.5]
POEM,[d] mean (median)		15.8 (16) [0–28]	15.3 (15) [0–28]
DFI,[e] mean (median) [range]		6.5 (5) [0–27]	6.5 (5) [0–30]

[a]5-point scale ranging from 0 (Clear) to 4 (Severe) assessing inflammatory signs of AD. [b]11-point scale ranging from 0 (no itch) to 10 (worst itch imaginable) assessed only in patients aged ≥12 years. [c]Scored up to 103 based on extent of involvement, disease intensity, and subjective symptoms. [d]Scale ranging from 0–2 (Clear/Almost Clear) to 28 (Very Severe) measuring disease severity per patient reports of signs and symptoms. [e]Scored up to 30 evaluating the effect of AD on patients' family life and relationships for patients aged ≤17 years.

AD: atopic dermatitis; BSA: body surface area; DFI: Dermatitis Family Impact Questionnaire; POEM: Patient-Oriented Eczema Measure; SCORAD: SCORing AD; SD: standard deviation; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis; WI-NRS: Worst Itch-Numeric Rating Scale.

Proportion of Patients Achieving vIGA-AD Success, vIGA-AD 0/1, EASI-75, and WI-NRS Success at Week 4



Intent-to-treat population. Multiple imputation of missing data. All *P* values are nominal.

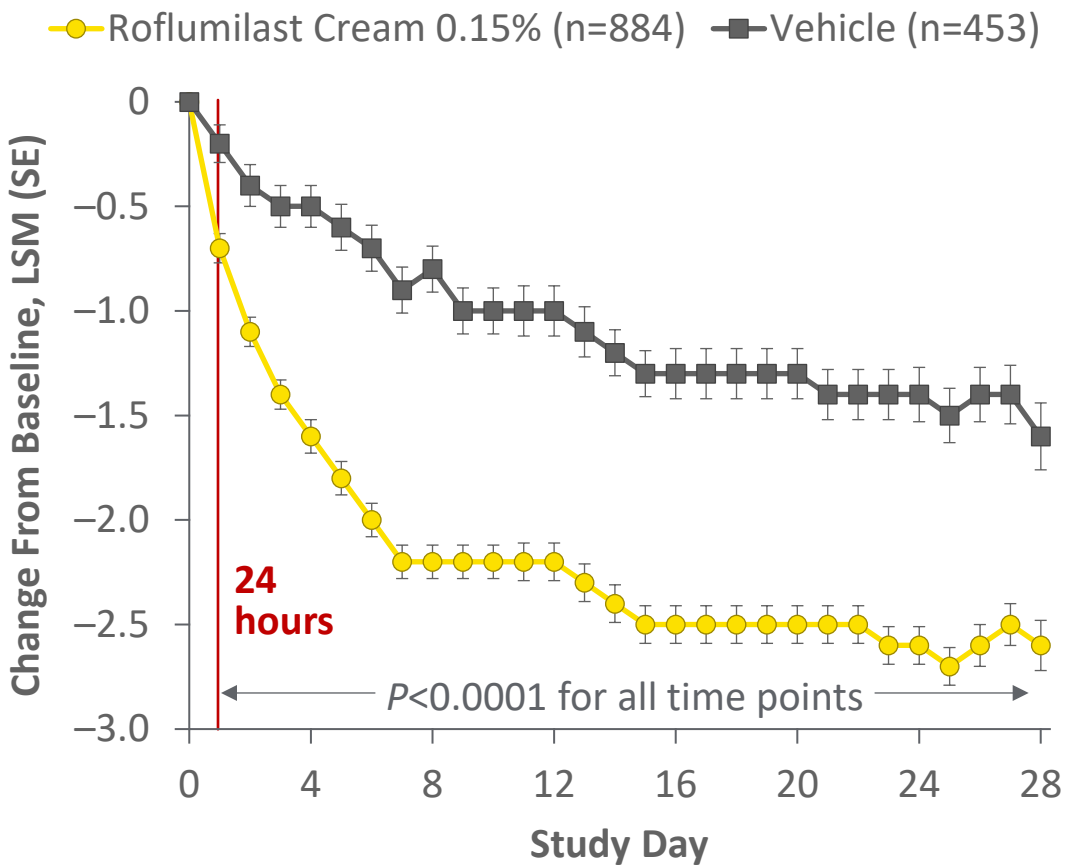
[a]WI-NRS success was evaluated in patients aged >12 years with baseline WI-NRS ≥4.

vIGA-AD Success = 0 (Clear) or 1 (Almost Clear) plus ≥2-grade improvement from baseline. EASI-75 = ≥75% reduction from baseline. WI-NRS Success = ≥4-point improvement in patients with baseline WI-NRS score ≥4.

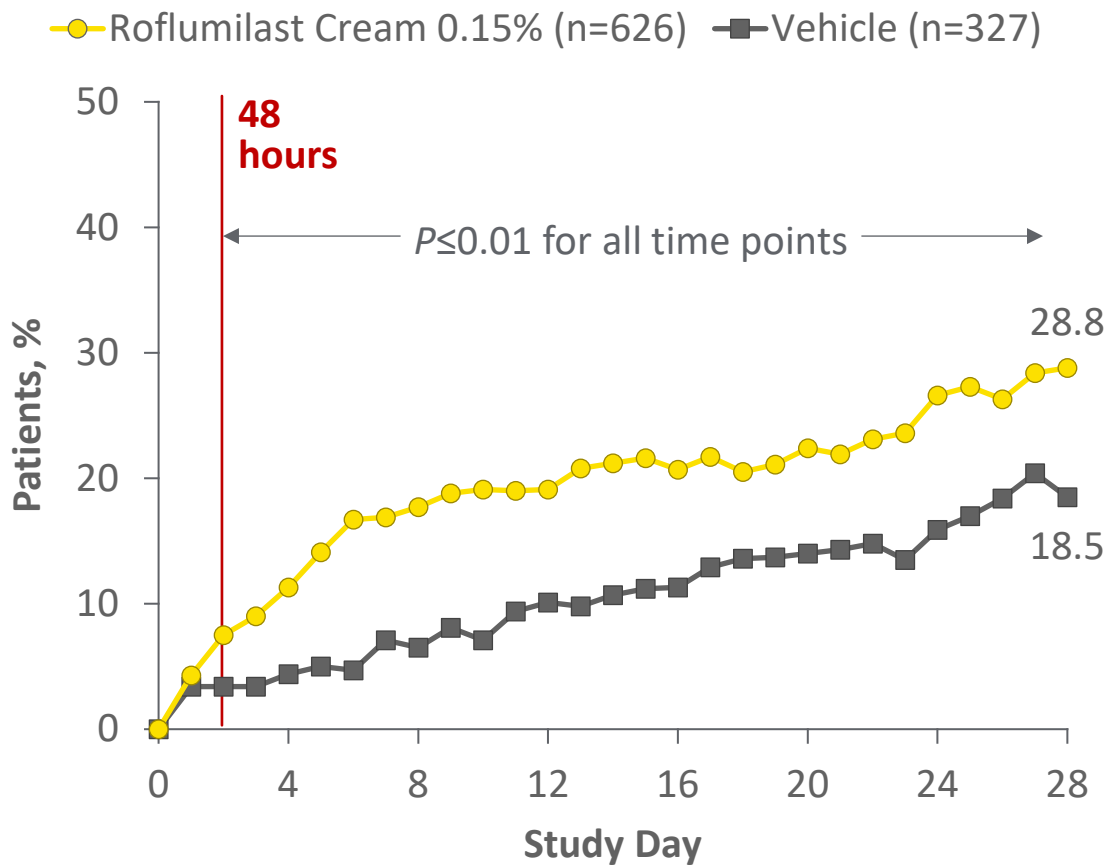
CI: confidence interval; EASI: Eczema Area and Severity Index; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis; WI-NRS: Worst Itch-Numeric Rating Scale.

Improvements in Pruritus

Change From Baseline in Daily WI-NRS Score[a]



Proportion of Patients Achieving WI-NRS 0/1[b]



All *P* values are nominal.

[a]Evaluated in all patients, not just those with baseline WI-NRS ≥4. [b]Evaluated in patients aged >12 years with baseline WI-NRS ≥2.

LSM: least squares mean; SE: standard error; WI-NRS: Worst Itch-Numeric Rating Scale

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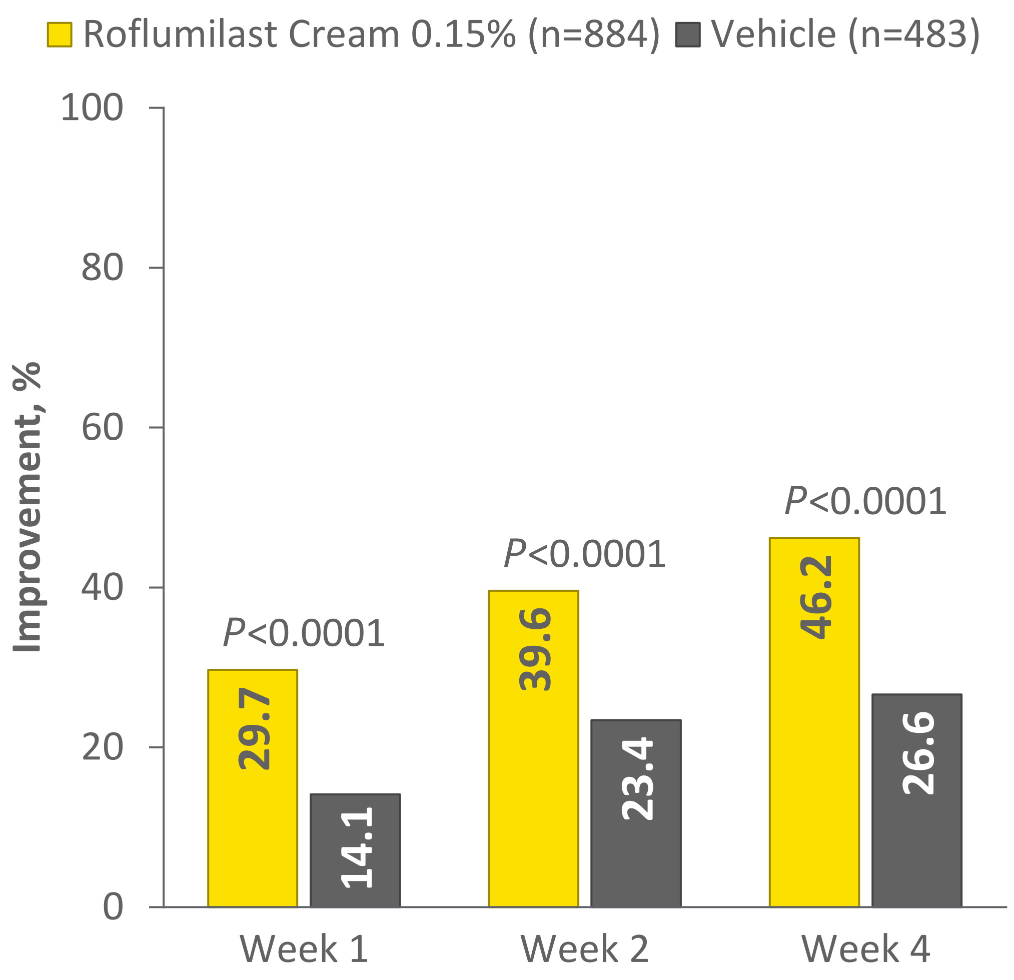
Improvements in SCORing AD (SCORAD) Total Score



Area

Estimate the portion of each of the following body areas affected by eczema.

Head and neck (9% BSA)
Upper limbs (left; 9% BSA)
Upper limbs (right; 9% BSA)
Genitals (1% BSA)
Lower limbs (left; 18% BSA))
Lower limbs (right; 18% BSA)
Anterior torso (18% BSA)
Posterior torso (18% BSA)

☐ 0% ☐ 25% ☐ 50% ☐ 75% ☐ 100%

Intensity

Rate the following for a representative area of eczema.

Redness
Swelling
Oozing/crusting
Scratch marks
Skin thickening (lichenification)
Dryness

☐ None (0) ☐ Mild (1) ☐ Moderate (2) ☐ Severe (3)

Subjective symptoms

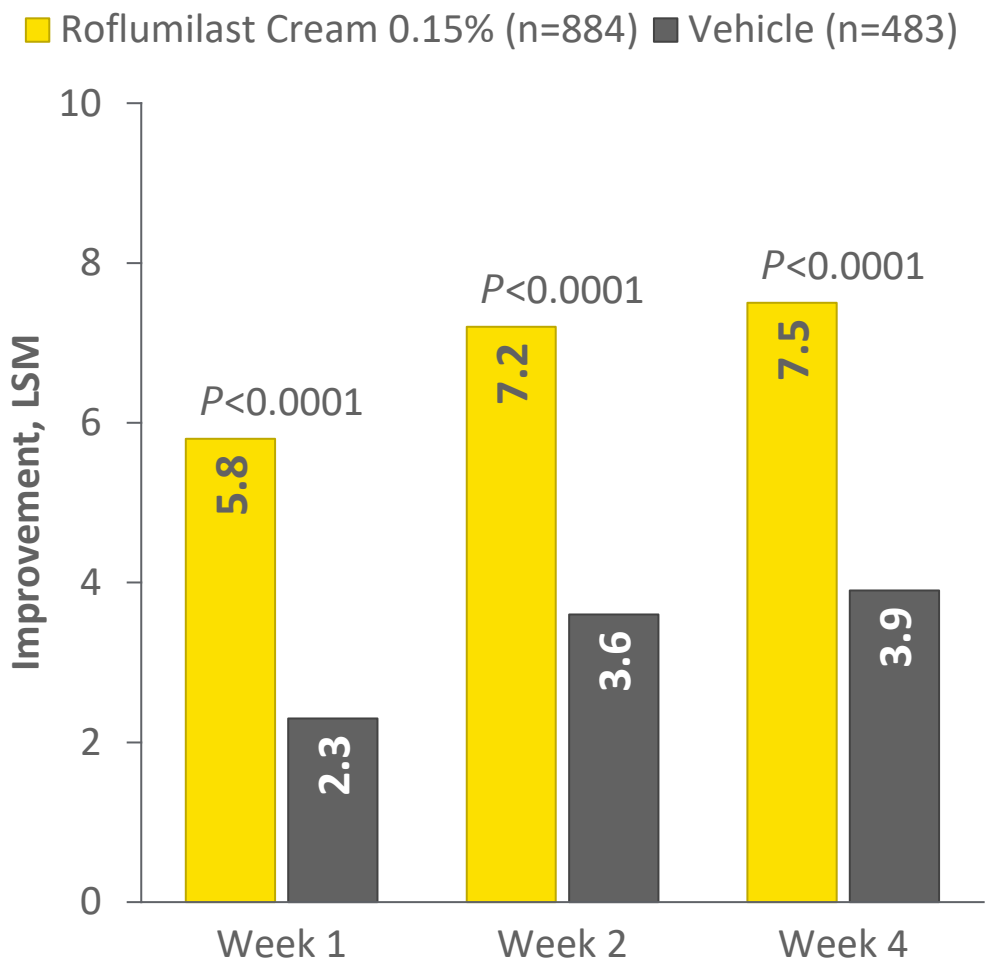
Rate the following for the last 3 days/nights.

Itch
Sleep loss

0 (None) • **10 (Worst Imaginable)**

All *P* values are nominal.
AD: atopic dermatitis; SCORAD: SCORing AD.

Improvements in Patient-Oriented Eczema Measure (POEM)



Over the last week, on how many days [or nights] has your/your child's…because of the eczema?

…skin been itchy…

…sleep been disturbed…

…skin been bleeding…

…skin been weeping or oozing clear fluid…

…skin been cracked…

…skin been flaking off…

…skin felt dry or rough…

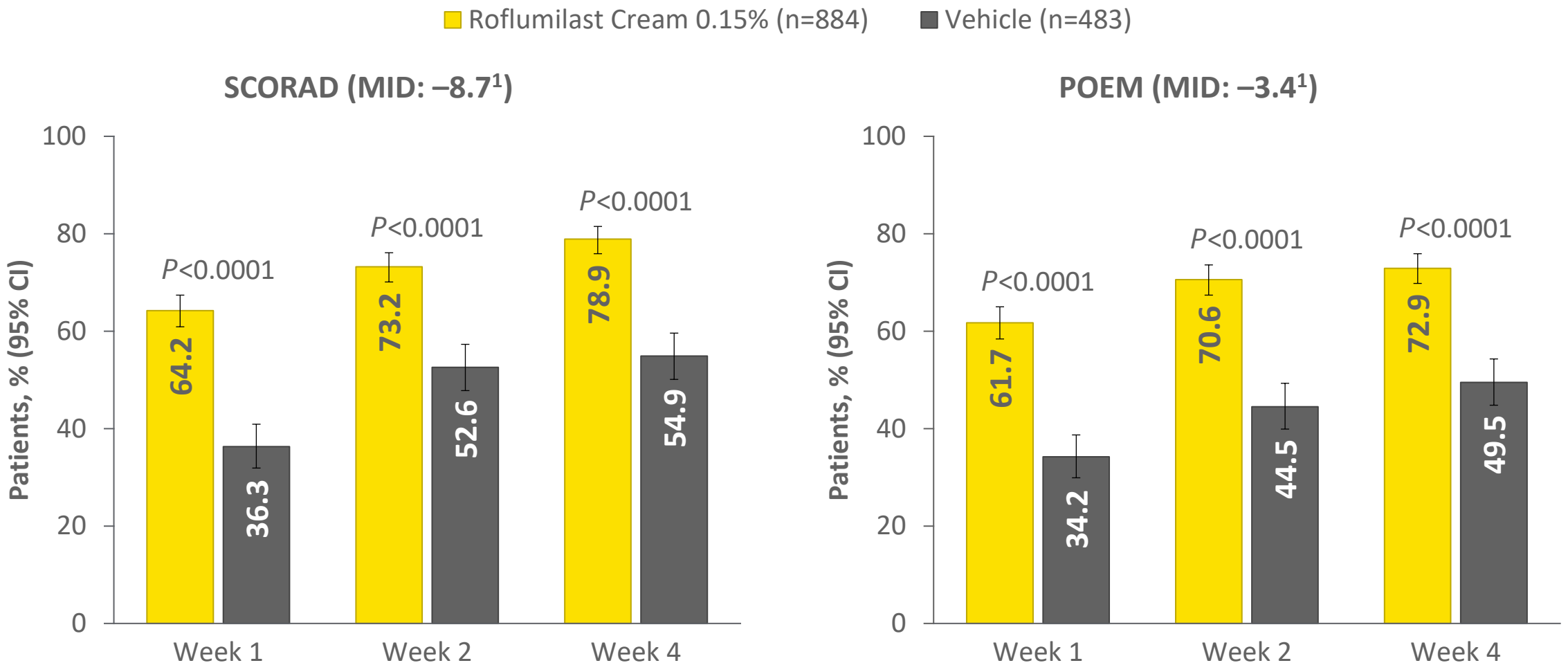
☐ **No days (0)** ☐ **1–2 days (1)** ☐ **3–4 days (2)** ☐ **5–6 days (3)** ☐ **Every day (4)**

0–2: clear/ almost clear	3–7: mild	8–16: moderate	17–24: severe	24–28: very severe

Baseline: 15.3–15.8

All *P* values are nominal.
LSM: least squares mean; POEM: Patient-Oriented Eczema Measure.

Proportions of Patients Achieving Minimally Important Differences (MIDs)

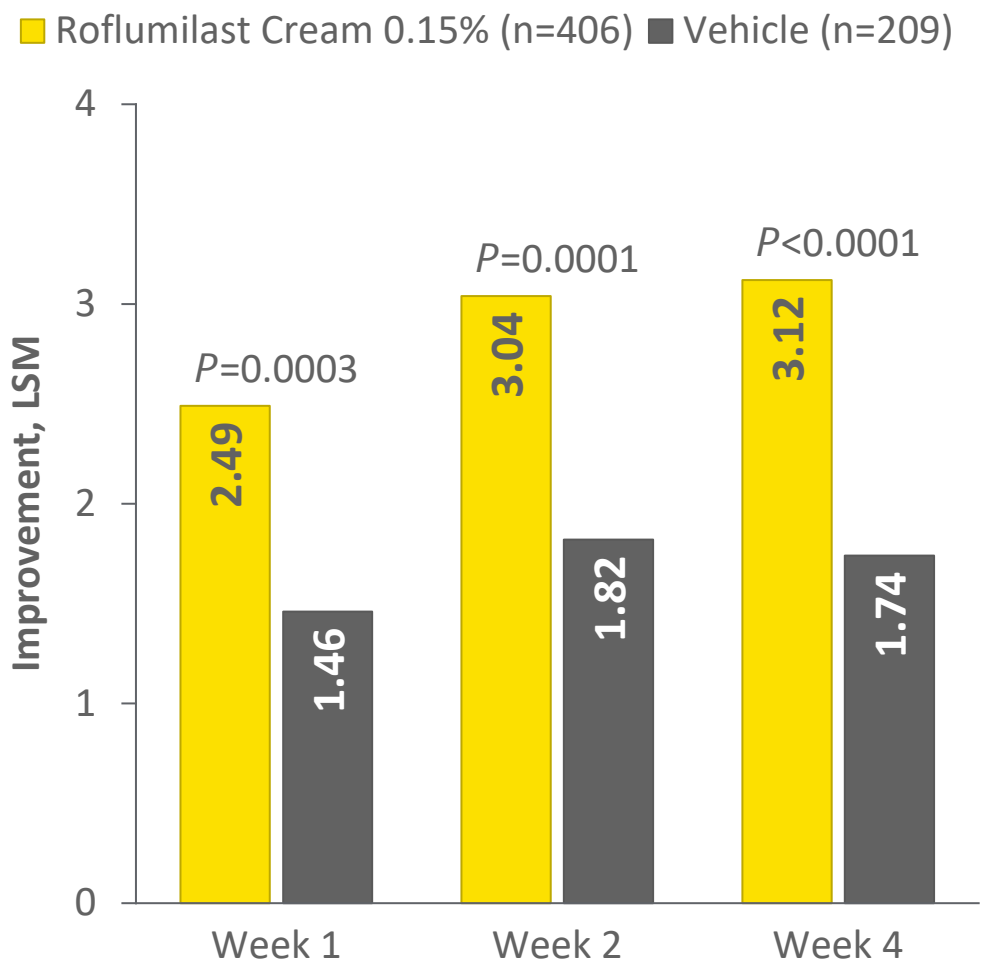


All *P* values are nominal.

AD: atopic dermatitis; CI: confidence interval; MID: minimal important difference; POEM: Patient-Oriented Eczema Measure; SCORAD: SCORing AD.

1. Schram MS, et al. *Allergy.* 2012;67:99–106.

Improvements in Dermatitis Family Impact (DFI)



Over the last week, how much effect has your child having eczema had on…

…**housework**?

…**food preparation** and **feeding**?

…the **sleep of others in the family**?

…**family leisure activities**?

…**time spent on shopping for the family**?

…**expenditure**?

…causing **tiredness** or **exhaustion** in your child's parents/carers?

…causing **emotional distress** in your child's parents/carers?

…**relationships** between the **main carer and partner** or between the **main carer and other children** in the family?

Over the last week, how much effect has **helping with your child's treatment** had on the main carer's life?

☐ **Not at all (0)** ☐ **A little (1)** ☐ **A lot (2)** ☐ **Very much (3)**

0: no impact on life of family — 30: max impact on life of family

Baseline: 6.5

All *P* values are nominal.
DFI was evaluated in patients aged ≤17 years.
DFI: Dermatitis Family Impact; LSM: least squares mean.

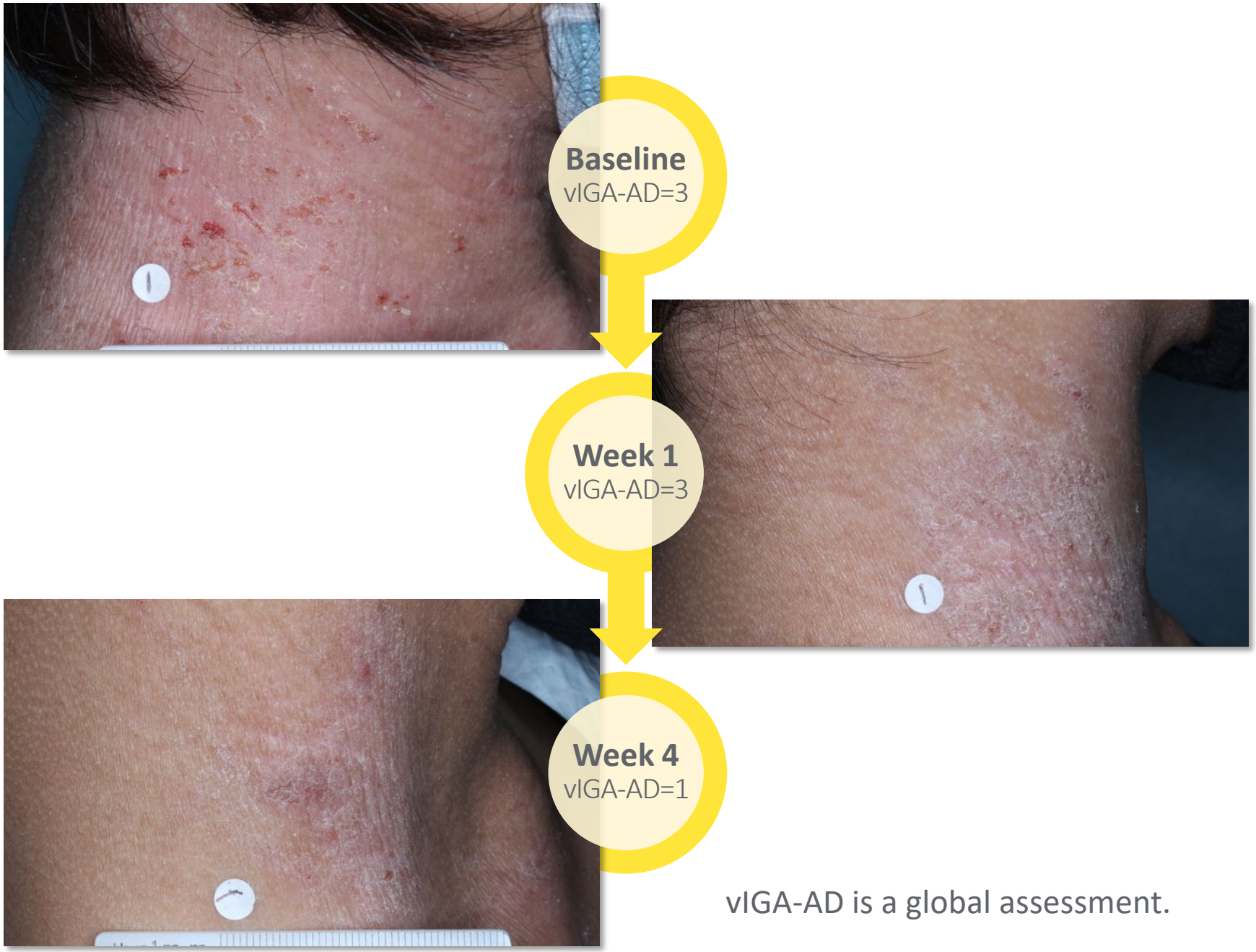
Neck of an 11-year-old female with AD treated with roflumilast cream 0.15%

Asian, Not Hispanic/Latino

Fitzpatrick skin type V

Duration of AD: 6 years

Prior intolerance, inadequate response, or contraindication to TCS



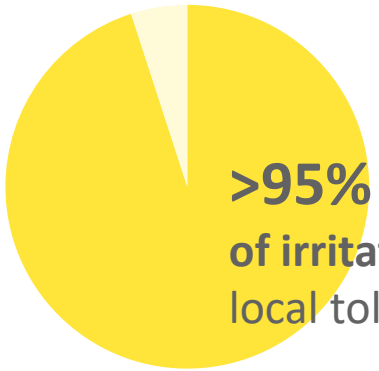
vIGA-AD is a global assessment.

AD: atopic dermatitis; TCS: topical corticosteroids; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis.

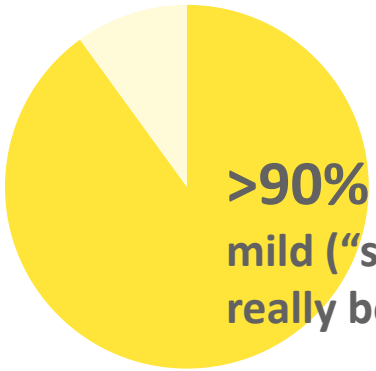
Safety and Local Tolerability

Patients, n (%)	Roflumilast Cream 0.15% (n=885)	Vehicle (n=451)
Patients with any treatment-related TEAE	53 (6.0)	12 (2.7)
Patients with any treatment-emergent SAE[a]	8 (0.9)	0
Patients with any TEAE leading to discontinuation of trial/trial drug	14 (1.6)	5 (1.1)
Patients with any TEAE[b]	194 (21.9)	65 (14.4)

- Incidence of TEAEs was low in both treatment groups
- Local tolerability was similar for roflumilast and vehicle. Across both treatment groups at all time points:



>95% of patients showed **no signs of irritation** on investigator-rated local tolerability assessments



>90% of patients reported **no or mild ("slight warm tingling; not really bothersome") sensation**

[a]SAEs were: atopic dermatitis, cutaneous nerve entrapment, depression, diverticulitis, general physical health deterioration, pulmonary embolism, staphylococcal scalded skin syndrome, and suicidal ideation. [b]Most frequently reported TEAEs (≥1% in either group) were (roflumilast / vehicle): headache (2.9% / 0.9%), nausea (1.9% / 0.4%), application site pain (1.5% / 0.7%), diarrhea (1.5% / 0.4%), vomiting (1.5% / 0.4%), and COVID-19 (0.8% / 1.8%).
SAE: serious adverse event; TEAE: treatment-emergent adverse event.

Conclusions

- Once-daily nonsteroidal roflumilast cream 0.15% provided meaningful improvements in signs and symptoms of AD, including improvement in pruritus within 24 hours of application
- Roflumilast cream also improved the impact of AD on patients' families and patient-reported measures
- Roflumilast cream was well tolerated, with low rates of discontinuations because of AEs occurring in both groups
- Local tolerability with roflumilast was generally similar to that of patients treated with vehicle

AD: atopic dermatitis; AE: adverse event.