Efficacy and Safety of Once-Daily Roflumilast Cream 0.05% in Pediatric Patients 2 to 5 Years of Age with Mild to Moderate Atopic Dermatitis (INTEGUMENT-PED): A Phase 3 Randomized Controlled Trial

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Introduction

- Current topical atopic dermatitis (AD) treatments are limited by dosing frequency, local tolerability issues, restrictions on application to the face/eyelids, use on large body surface areas, and use long-term
- Topical roflumilast, a potent PDE4 inhibitor, is formulated as a water-based, once-daily, nonsteroidal cream and foam
  - Demonstrated safety and efficacy in patients with psoriasis and AD (≥2 years of age)[1,2] and seborrheic dermatitis (≥9 years of age)[3]
  - Roflumilast potency is ~25 to >300-fold higher than apremilast and crisaborole, with roflumilast more closely mimicking cAMP binding to PDE4[4]
  - Formulations do not contain ethanol, propylene glycol, or fragrances that can irritate skin
- In two phase 3 trials (INTEGUMENT-1 and 2), roflumilast cream 0.15% was well tolerated and demonstrated efficacy in patients aged ≥6 years of age AD[3]
  - Here, we present results of a phase 3 trial (INTEGUMENT-PED) of roflumilast cream 0.05% in patients aged 2-5 years of age with AD

INTEGUMENT-1: NCT04773587; INTEGUMENT-2: NCT04773600; INTEGUMENT-PED: NCT04845620

1. Lebwohl MG, et al. *JAMA*. 2022;328:1073-1084. Gooderham M, et al. *J Drugs Dermatol*. 2023;22:139-147. 2. Blauvelt A, et al. *J Am Acad Dermatol*. 2024;S0190-9622(24)00107-5. 3. Eichenfield L, et al. Poster presented at: The American Academy of Dermatology Congress, Mar 17-21, 2023, New Orleans, LA.

Study Design

INTEGUMENT-PED:
Phase 3 multicenter trial

Eligibility

- Age 2-5 years
- vIGA-AD score 2 or 3
- BSA ≥ 3%†
- EASI score ≥5

2:1

Randomized

N=652

Roflumilast cream 0.05% QD n=437

Vehicle cream QD n=215

4-weeks QD dosing

Endpoints

Primary

- vIGA-AD Success at Week 4

Key Secondary

- vIGA-AD = Clear (0) or Almost Clear (1) at Weeks 1, 2, 4
- vIGA-AD Success at Weeks 1 and 2
- EASI-75 at Week 4

Pruritus

- Improvement in WI-NRS (≥4-point reduction vs baseline)
- Daily improvement in WI-NRS

Safety and tolerability

†No upper limit on BSA restriction.

vIGA-AD Success = Clear or Almost Clear IGA status plus ≥2-grade improvement from baseline.

BSA: body surface area; EASI: Eczema Area and Severity Index; EASI-75: 75% reduction in EASI score from baseline; QD: once daily; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis; WI-NRS: Worst Itch Numerical Rating Scale

Baseline Demographics
ITT population

	Roflumilast 0.05% (n=436)	Vehicle (n=215)
Age in years, mean (SD)	3.3 (1.1)	3.2 (1.1)
Male, n (%)	225 (51.6)	116 (54.0)
Race, n (%)		
Asian	37 (8.5)	17 (7.9)
Black or African American	68 (15.6)	32 (14.9)
White	294 (67.4)	156 (72.6)
Other or More than 1 race	37 (8.5)	10 (4.7)
Ethnicity, n (%)		
Hispanic or Latino	82 (18.8)	31 (14.4)
Not Hispanic or Latino	351 (80.5)	184 (85.6)
Not reported	3 (0.7)	0
Fitzpatrick Skin Type, n (%)		
I to III	279 (64.0)	148 (68.8)
IV to VI	157 (36.0)	66 (30.7)

ITT: intent-to-treat; SD: standard deviation

Baseline Demographics (cont'd)
ITT population

n (%)	Roflumilast 0.05% (n=436)	Vehicle (n=215)
Key body areas involved		
Face	226 (51.8)	119 (55.3)
Eyelids	90 (20.6)	51 (23.7)
Prior inadequate response, intolerance, or contraindication to:		
Topical corticosteroids	226 (51.8)	114 (53.0)
Topical calcineurin inhibitors	74 (17.0)	35 (16.3)
Crisaborole	40 (9.2)	18 (8.4)

ITT: intent-to-treat

Baseline Disease Characteristics
ITT population

	Roflumilast 0.05% (n=436)	Vehicle (n=215)
Baseline vIGA-AD, n (%)		
2 (mild)	99 (22.7)	43 (20.0)
3 (moderate)	337 (77.3)	172 (80.0)
EASI		
Mean (SD)	12.2 (6.9)	11.6 (6.2)
Median (min, max)	10.2 (4.6, 42.0)	9.5 (5.0, 32.9)
BSA		
Mean (SD)	22.5 (16.4)	21.2 (15.7)
Median (min, max)	17.3 (3.0, 82.0)	16.5 (4.0, 78.8)
Average weekly baseline WI-NRS		
Mean (SD)	6.2 (2.3)	5.9 (2.2)
Median (min, max)	6.6 (0, 10)	6.3 (0, 10)
Average weekly baseline WI-NRS ≥4, n (%)	347 (79.6)	160 (74.4)

Overall, 519 (79.7%) of patients had a baseline BSA ≥10%

BSA: body surface area; EASI: Eczema Area and Severity Index; ITT: intent-to-treat; SD: standard deviation; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis; WI-NRS: Worst Itch Numerical Rating Scale

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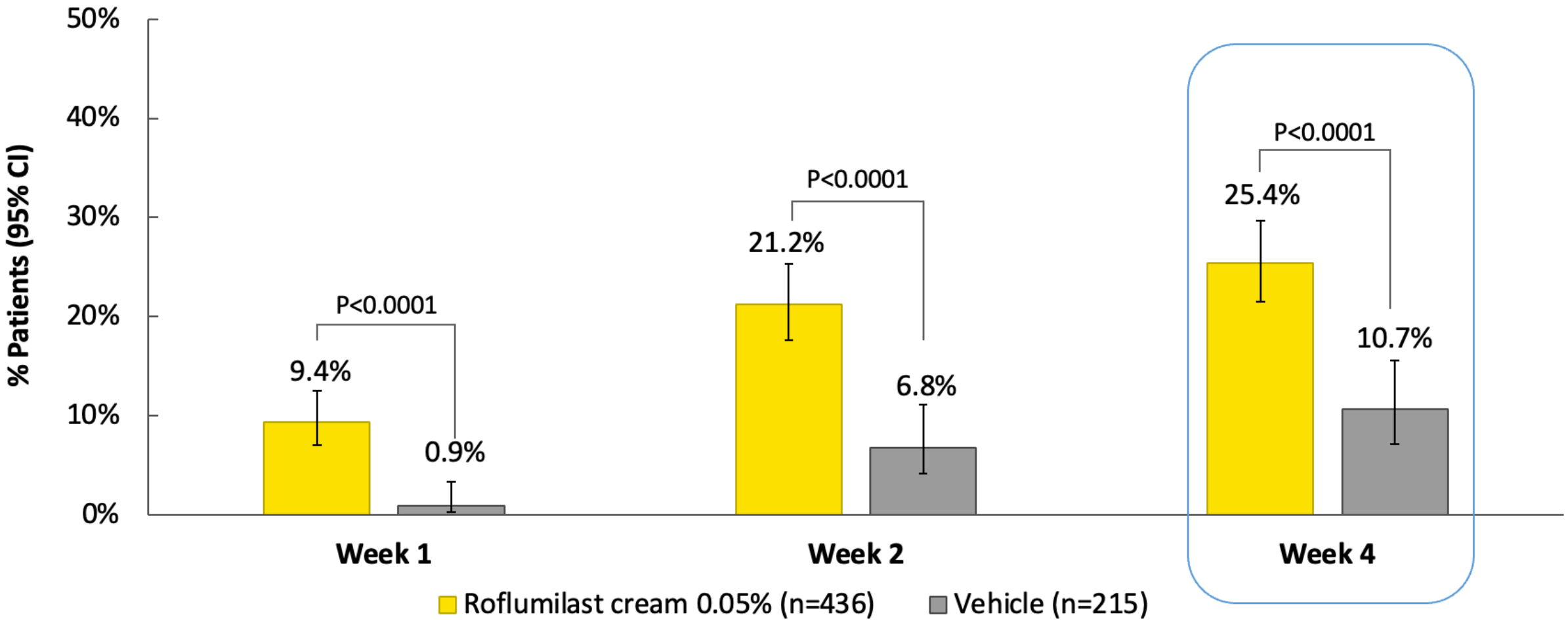
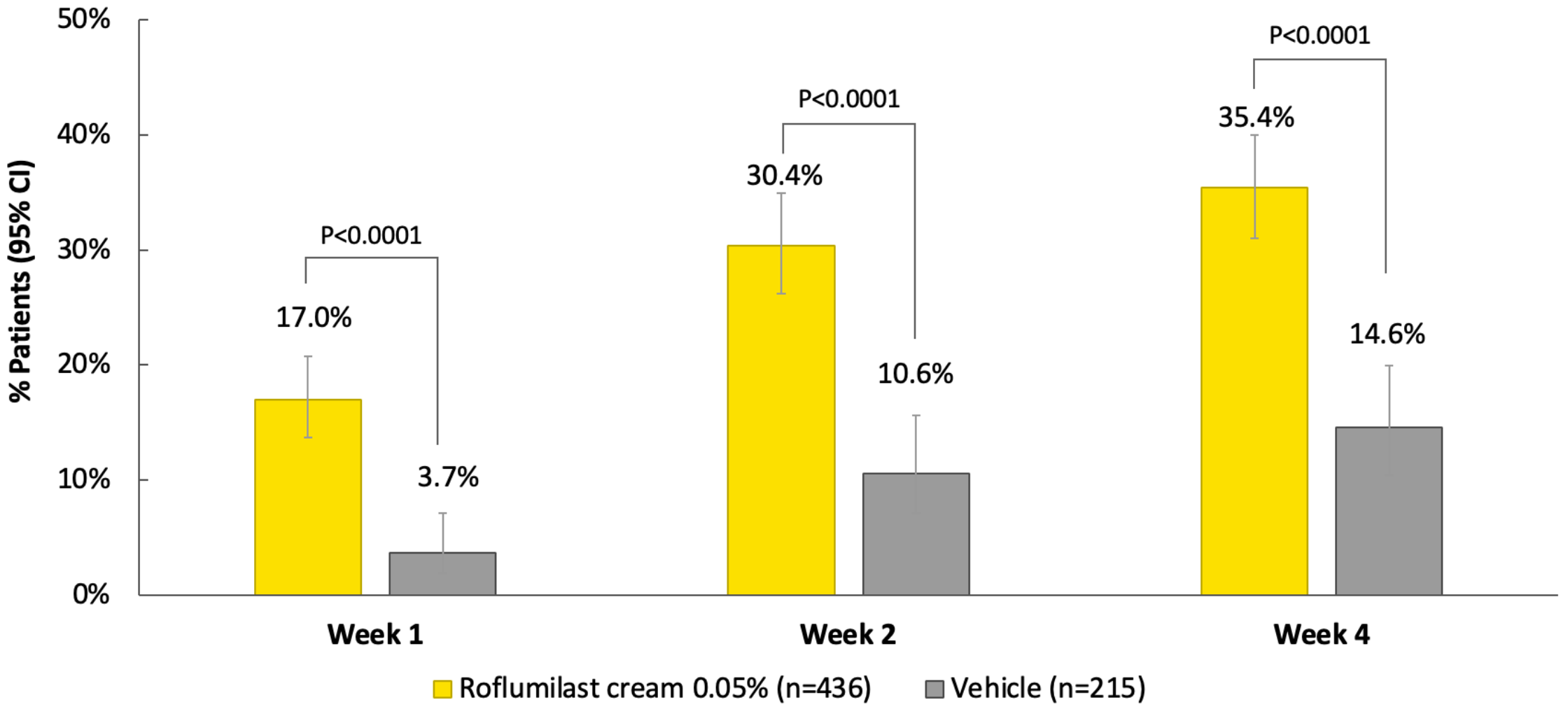
vIGA-AD Success



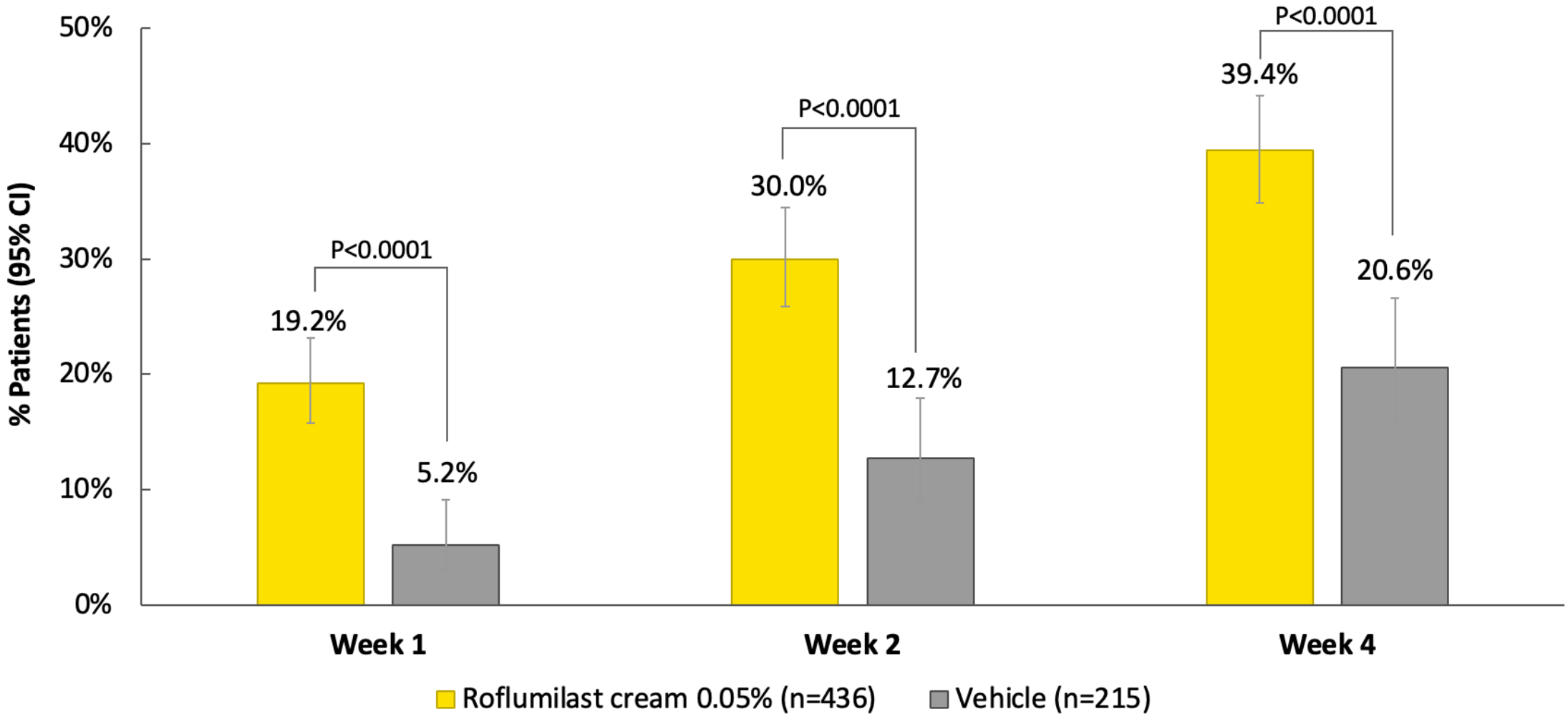
vIGA-AD Success = Clear or Almost Clear with at least a 2-grade improvement from baseline
CI: confidence interval; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis

vIGA-AD Clear or Almost Clear



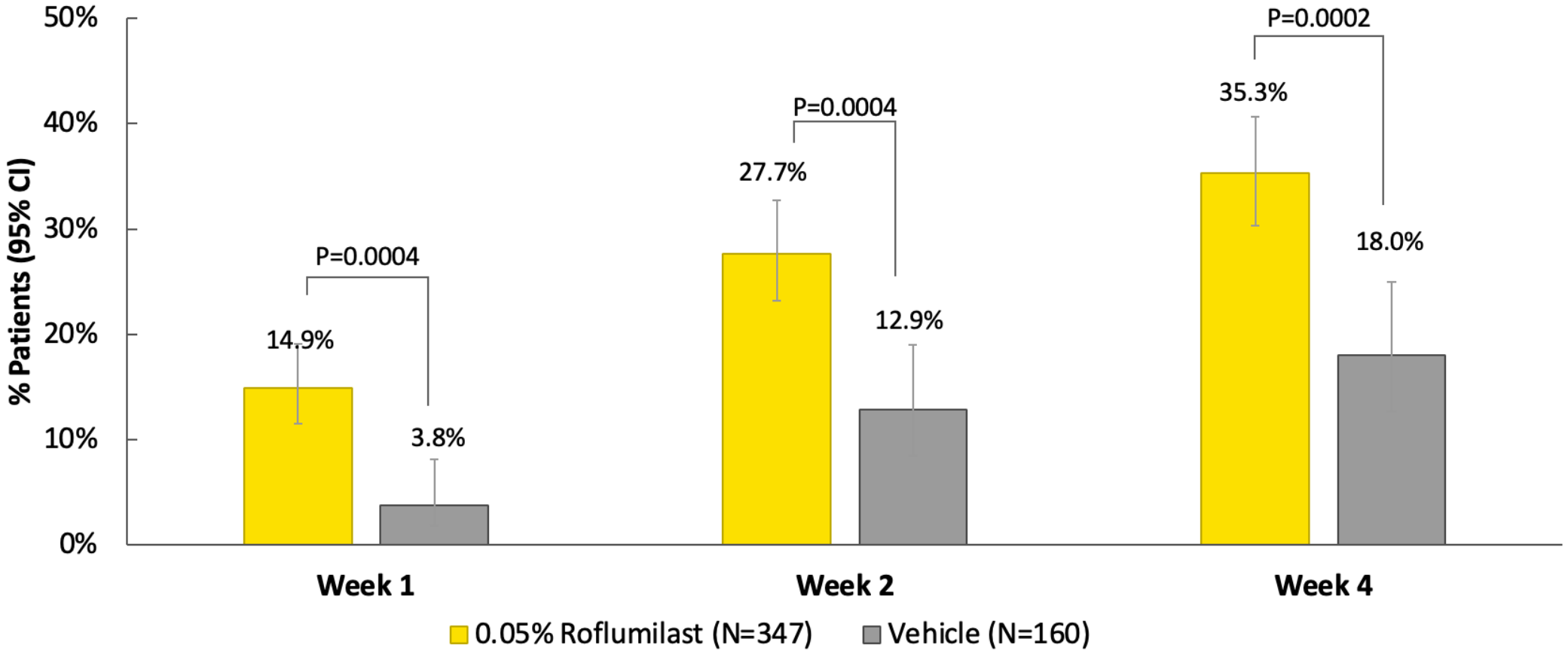
CI: confidence interval; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis

EASI-75



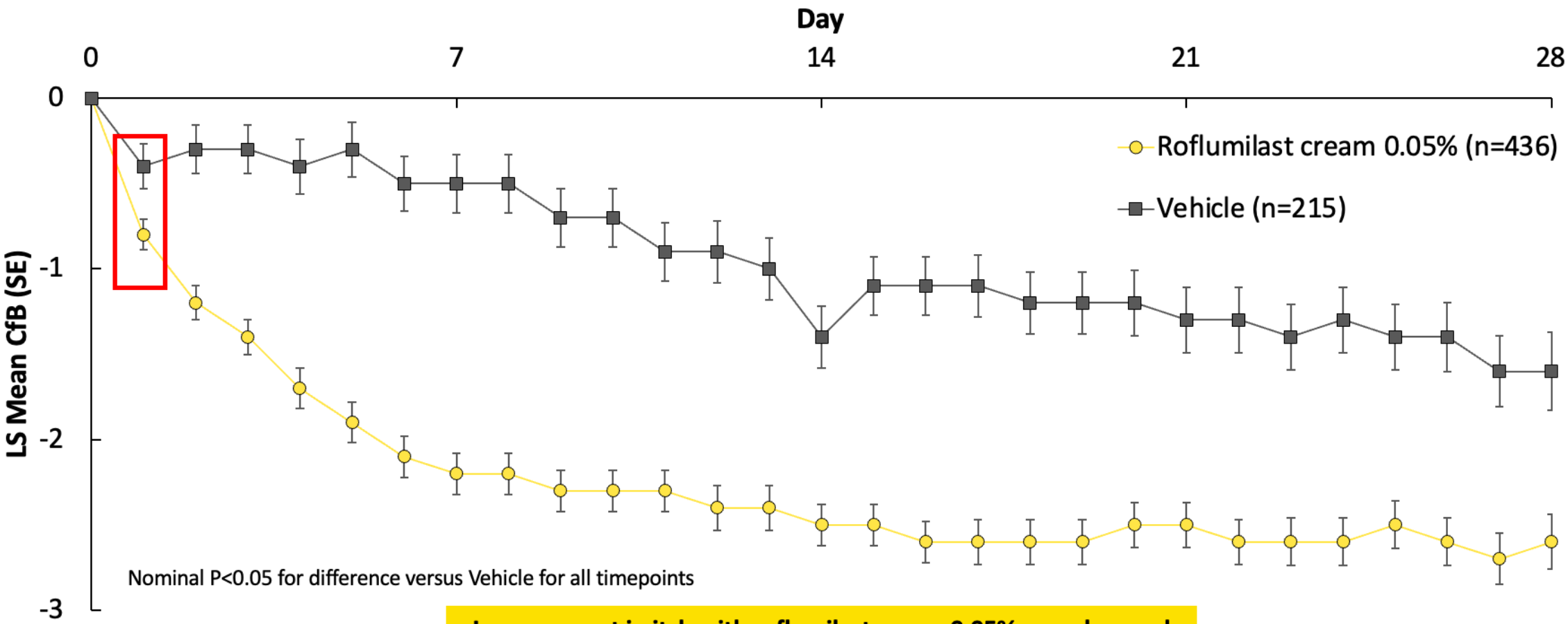
CI: confidence interval; EASI-75: 75% reduction in EASI score from baseline

WI-NRS Success



WI-NRS Success = ≥4-point reduction in weekly average WI-NRS score with WI-NRS ≥4 at baseline
CI: confidence interval; WI-NRS: Worst Itch Numerical Rating Scale

LS Mean Change from Baseline in Daily WI-NRS Score†



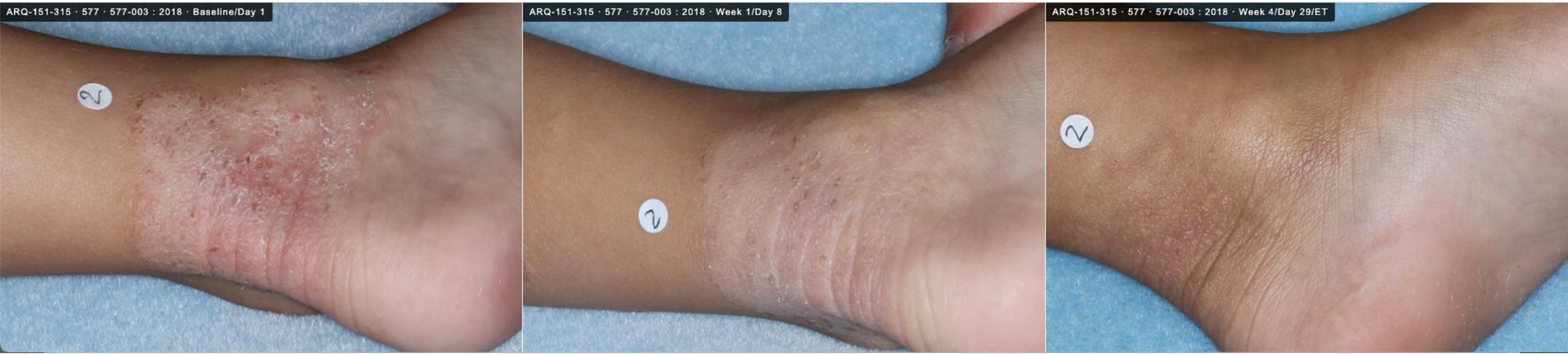
Improvement in itch with roflumilast cream 0.05% was observed at 24 hours after first application (P=0.0014 vs vehicle)

†Evaluated in all patients, not just those with baseline WI-NRS ≥4

CfB: change from baseline; LS: least squares; SE: standard error; WI-NRS: Worst Itch Numerical Rating Scale

Treatment with Roflumilast Cream 0.05% Once Daily

Baseline	**Week 1**	**Week 4**
vIGA-AD=3	vIGA-AD=1	vIGA-AD=1
EASI=24.6	EASI=2.6	EASI=1.3
BSA=39.0%	BSA=35.5%	BSA=7.0%
WI-NRS=5	WI-NRS=5	WI-NRS=0



3-year-old White Male, Hispanic or Latino

BSA: body surface area; EASI: Eczema Area and Severity Index; QD: once daily; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis; WI-NRS: Worst Itch Numerical Rating Scale.

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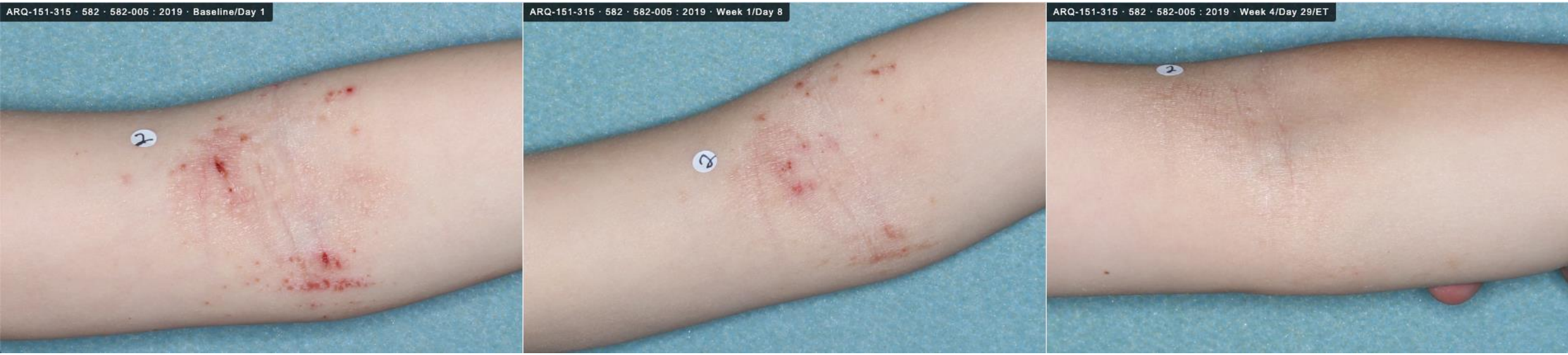
Treatment with Roflumilast Cream 0.05% Once Daily

Baseline	**Week 1**	**Week 4**
vIGA-AD=3	vIGA-AD=3	vIGA-AD=1
EASI=11.4	EASI=9.0	EASI=0.2
BSA=28.0%	BSA=16.0%	BSA=2.0%
WI-NRS=8	WI-NRS=3	WI-NRS=1



3-year-old White Female, Hispanic or Latino

BSA: body surface area; EASI: Eczema Area and Severity Index; QD: once daily; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis; WI-NRS: Worst Itch Numerical Rating Scale.

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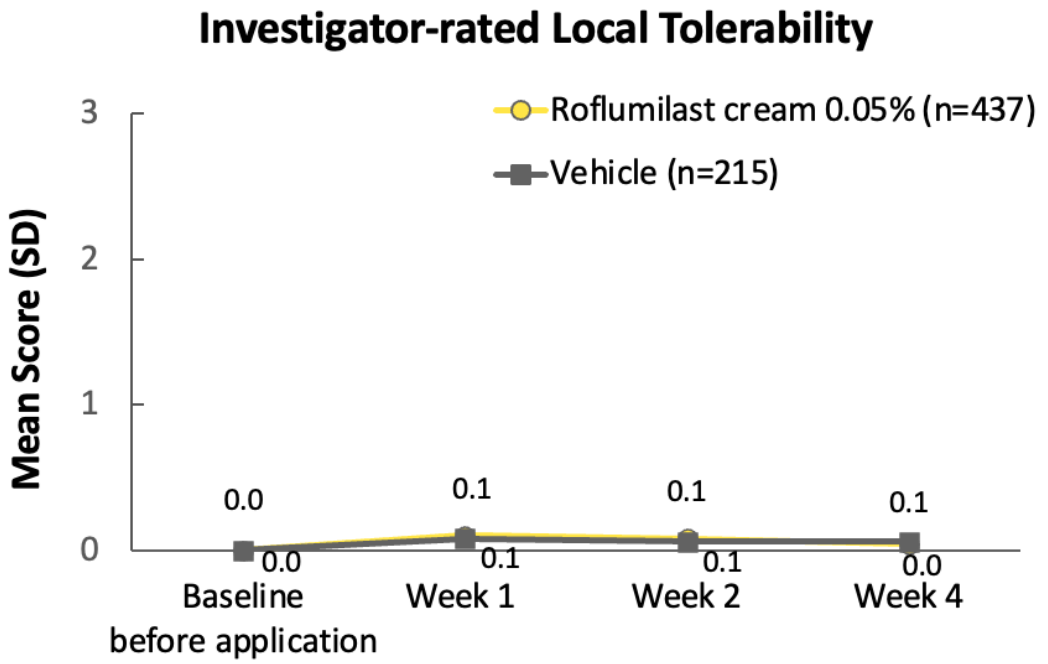
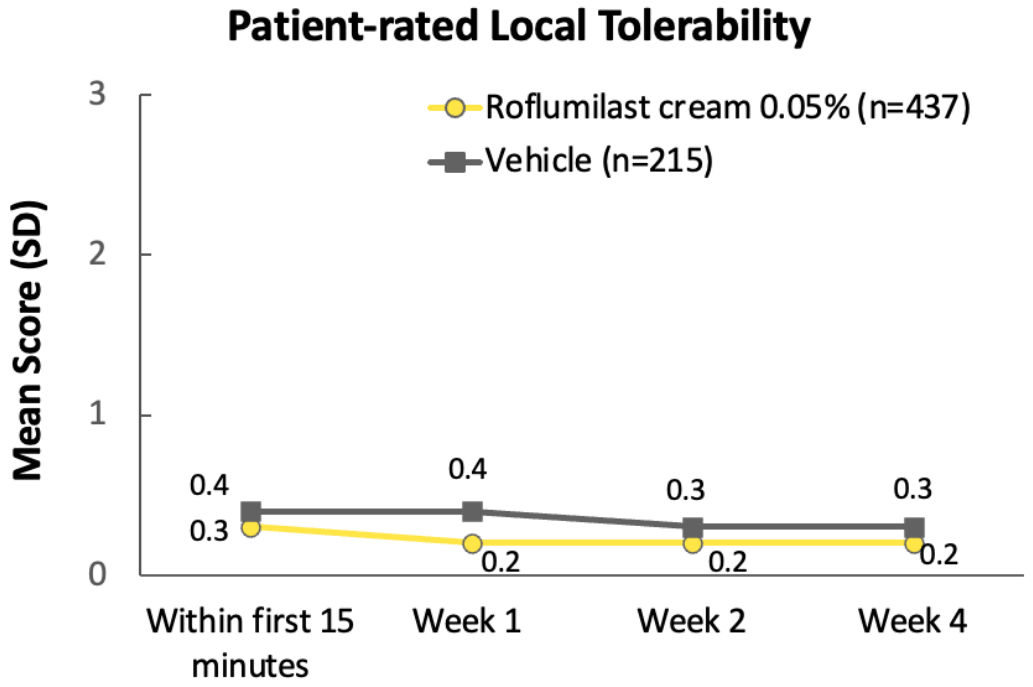
Safety

n (%)	Roflumilast 0.05% (n=437)	Vehicle (n=215)
Patients with at least one TEAE	130 (29.7)	47 (21.9)
Patients with any treatment-related TEAE	15 (3.4)	6 (2.8)
Patients with at least one treatment-emergent serious AE†	1 (0.2)	0
Patients with at least one TEAE leading to IP discontinuation††	5 (1.1)	5 (2.3)
Patients with at least one TEAE on an application site	23 (5.3)	13 (6.0)
Most Common TEAEs by Preferred Term, >2.0% in Either Group		
Upper respiratory tract infection	18 (4.1)	3 (1.4)
Pyrexia	12 (2.7)	6 (2.8)
Diarrhea	11 (2.5)	1 (0.5)
Vomiting	9 (2.1)	0
Atopic dermatitis	2 (0.5)	5 (2.3)

†Serious AE: 2 y/o F, Cellulitis of right leg- on non-eczematous skin, hospitalized 3 days for antibiotics. IP held for 5 days; SAE deemed unlikely related to study drug; event resolved.
††Roflumilast: application site pain, dermatitis atopic, impetigo, neurodermatitis, varicella; Vehicle: application site pain, dermatitis atopic, upper respiratory tract infection, urticaria.
AE: Adverse Event; IP, investigational product; SAE: Serious Adverse Event; TEAE: Treatment Emergent Adverse Event

Investigator and Patient-Rated Local Tolerability





Scale for investigator-rated local tolerability (0-7)

0 = no evidence of irritation; 1 = minimal erythema, barely perceptible; 2 = definite erythema, readily visible; minimal edema or minimal papular response; 3 = erythema and papules; 4 = definite edema; 5 = erythema, edema and papules; 6 = vesicular eruption; 7 = strong reaction spreading beyond application site

Scale for patient-rated local tolerability (0-3)

0 (none)= no sensation; 1 (mild) = slight warm, tingling sensation; not really bothersome; 2 (moderate) = definite warm, tingling sensation that is somewhat bothersome; 3 (severe) = hot, tingling/stinging sensation that has caused definite discomfort

59 (9%) of patients reported prior inadequate response, intolerance, or contraindication to crisaborole
35 of the 59 patients reported stinging, burning, and/or poor tolerability as a reason for stopping crisaborole
2 of 21 roflumilast-treated and 2 of 14 vehicle-treated patients reported any application site TEAE

SD: standard deviation; TEAE: Treatment Emergent Adverse Event

Conclusions

- Once-daily, nonsteroidal roflumilast cream 0.05% significantly improved AD in children 2-5 years of age
  - Significant improvement in AD was observed as early as 1 week after treatment initiation
  - Reduction in pruritus was observed 24 hours (P=0.0014) following the first application
- No AE occurred in more than 4.1% of patients in either arm
  - Low rates of application site pain in patients treated with roflumilast (1.6%) and vehicle (1.9%)
- Efficacy and safety are consistent with previous trials of roflumilast cream 0.15% in patients ≥6 years of age with AD (INTEGUMENT-1/2)
  - Continued improvement in efficacy over 56 weeks of treatment with roflumilast cream 0.15% in patients ≥6 years of age with AD (INTEGUMENT-OLE)
    - 61.5% and 66.2% of patients achieving EASI-75 after 28 and 56 weeks, respectively
  - Ongoing assessment of safety and efficacy of roflumilast cream 0.05% in patients 2-5 years of age with AD (INTEGUMENT-OLE)

AE: adverse event; EASI: Eczema Area and Severity Index; EASI-75: 75% reduction in EASI score from baseline

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