Efficacy and safety of roflumilast cream 0.15% in adults and children aged ≥6 years with mild to moderate atopic dermatitis in two phase 3 trials (INTEGUMENT-1 and INTEGUMENT-2)

Eric Simpson,[1] Lawrence Eichenfield,[2] Melinda Gooderham,[3] Mercedes E. Gonzalez,[4] Adelaide Hebert,[5] Kim Papp,[6] Vimal H. Prajapati,[7] David Krupa,[8] Patrick Burnett,[8] David Berk,[8] Robert Higham[8]

[1]Oregon Health & Science University, Portland, OR, USA; [2]University of California, San Diego and Rady Children's Hospital, San Diego, CA, USA; [3]SKiN Centre for Dermatology, Probity Medical Research and Queen's University, Peterborough, ON, Canada; [4]Pediatric Skin Research, LLC Miami, FL, USA; [5]UT Health McGovern Medical School, Houston, TX, USA; [6]Probity Medical Research and Alliance Clinical Research, Waterloo, ON, Canada and University of Toronto, Toronto, ON, Canada; [7]Dermatology Research Institute, Skin Health & Wellness Centre, University of Calgary, and Probity Medical Research, Calgary, AB, Canada; [8]Arcutis Biotherapeutics, Inc., Westlake Village, CA, USA

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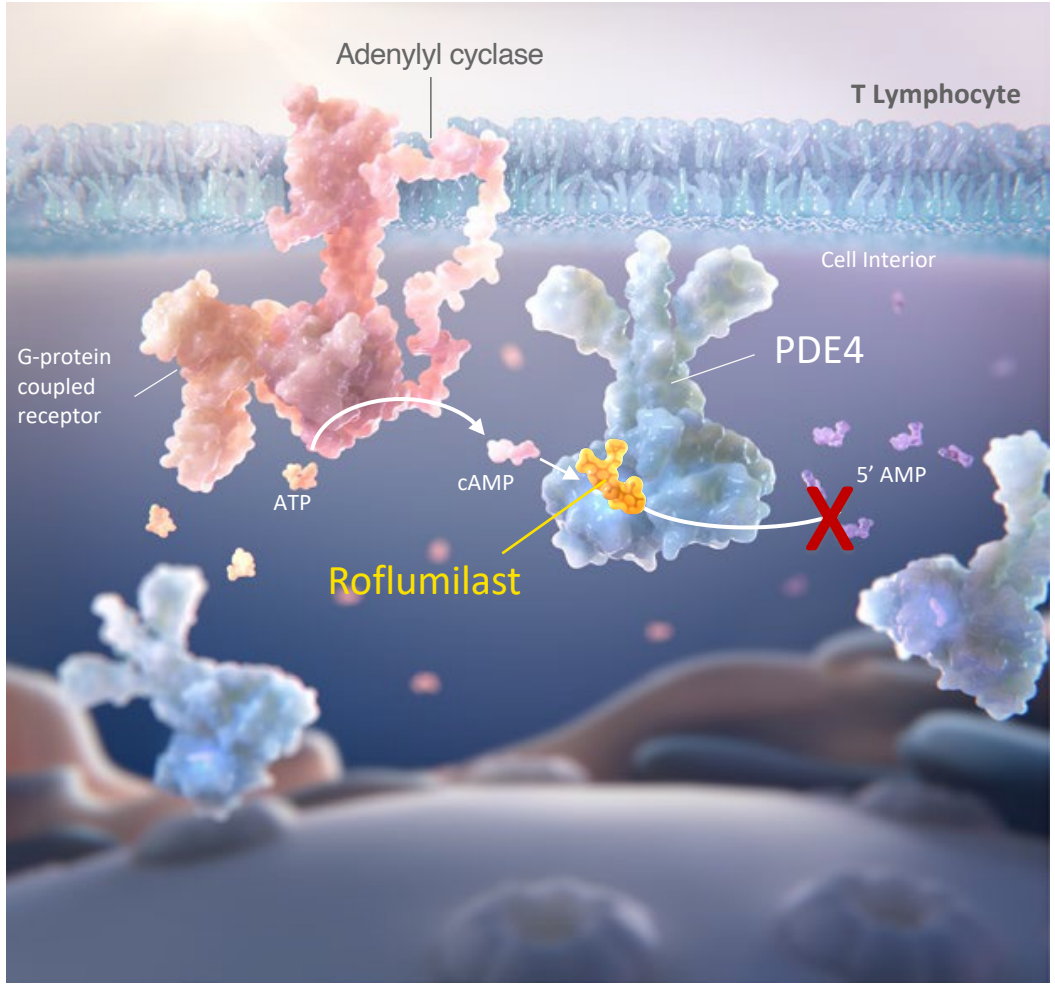
Introduction

- Topical roflumilast is being investigated as a once-daily, nonsteroidal treatment for long-term management of psoriasis (roflumilast cream 0.3% FDA-approved July 29, 2022), atopic dermatitis, and seborrheic dermatitis[1]
- Topical roflumilast is formulated as a water-based cream:
  - Excipients include an emulsifier novel to prescription topical products which does not extract epidermal lipids at safe skin temperatures[2]
  - The vehicle does not contain ethanol, propylene glycol, or fragrances that can irritate skin
- Objective: to present results of two phase 3 trials (INTEGUMENT-1 [NCT04773587] and INTEGUMENT-2 [NCT04773600]) of roflumilast cream 0.15% in patients aged ≥6 years of age with mild to moderate atopic dermatitis

FDA: Food and Drug Administration

1.. Gooderham et al. *J Drugs Dermatol*. 2023;22:139-147. 2. Berk and Osborne. Society for Investigative Dermatology 2022.

Roflumilast Mechanism of Action: A Selective and Potent PDE4 Inhibitor



- Roflumilast has a greater affinity for PDE4 than apremilast and crisaborole
  - 25- to >300-fold more potent in *in vitro* assays[1]
- Roflumilast modulates inflammatory cytokines through inhibition of PDE4[1]
  - Decreases conversion of cAMP[2]
  - Results in decreased expression of key pro-inflammatory cytokines:
    - Th1 (IFN-γ, TNF-α)
    - Th2 (IL-4)
    - Th17 (IL-17, IL-23)[1]

AC: adenylyl cyclase; AMP: adenosine monophosphate; ATP: adenosine triphosphate; cAMP: cyclic AMP; IL: interleukin; IFN: interferon; PDE4: phosphodiesterase 4; Th: T helper; TNF: tumor necrosis factor.

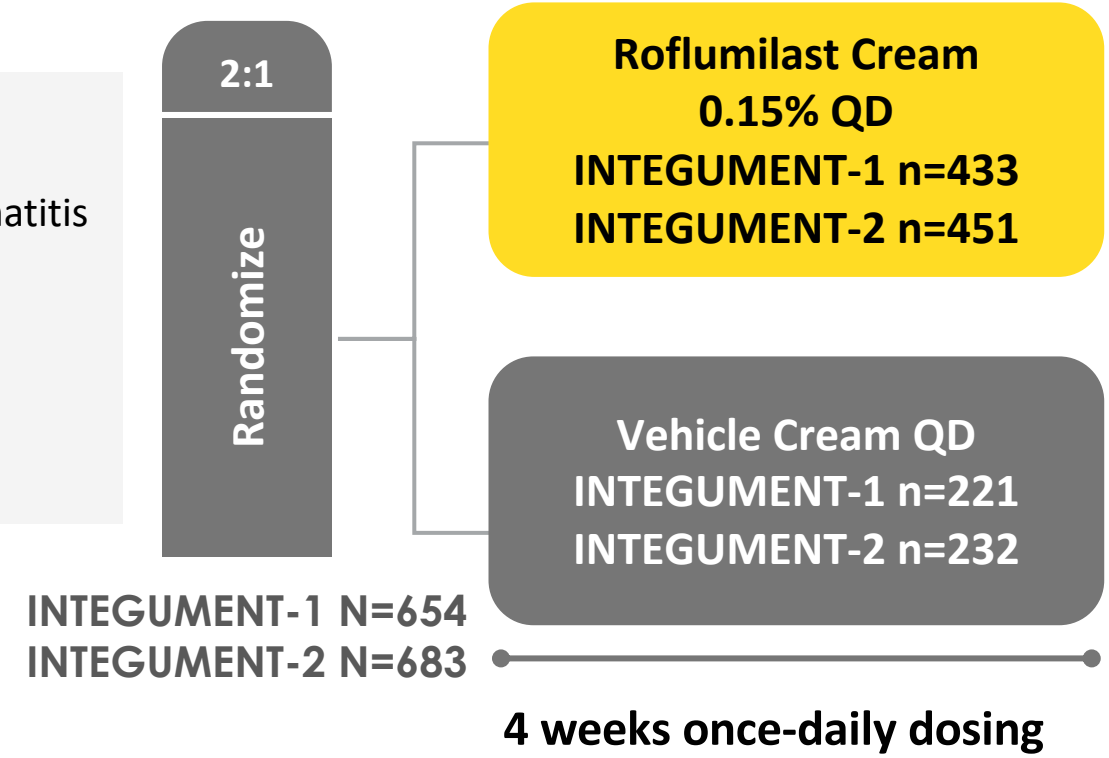
1. Dong et al. *J Pharmacol Exp Ther*. 2016:358:413-422. **2.** Schafer et al. *Cell Signal.* 2014;26:2016-2029.

Study Design

Randomized, Parallel group, Double-blind, Vehicle-controlled, Multicenter Study

Eligibility

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



Endpoints

Primary

- vIGA-AD Success* at Week 4

Secondary

- vIGA-AD Success at Week 1 and Week 2
- vIGA-AD = Clear (0) or Almost Clear (1)
- WI-NRS Success
- EASI-75

Safety and Tolerability

*vIGA-AD Success = Clear or Almost clear 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

Reason for Discontinuation

	INTEGUMENT-1		INTEGUMENT-2	
Patients, n (%)	**Roflumilast cream 0.15% (n=433)**	**Vehicle cream (n=221)**	**Roflumilast cream 0.15% (n=451)**	**Vehicle cream (N=232)**
Completed	404 (93.3)	208 (94.1)	410 (90.9)	211 (90.9)
Discontinued	29 (6.7)	13 (5.9)	41 (9.1)	21 (9.1)
Reason for discontinuation				
Lost to follow-up	11 (2.5)	3 (1.4)	10 (2.2)	6 (2.6)
Patient withdrawal of consent	4 (0.9)	5 (2.3)	15 (3.3)	9 (3.9)
Adverse event	6 (1.4)	3 (1.4)	8 (1.8)	2 (0.9)
Lack of efficacy	5 (1.2)	2 (0.9)	2 (0.4)	3 (1.3)
Non-compliance	1 (0.2)	0	2 (0.4)	0
Protocol violation	1 (0.2)	0	2 (0.4)	0
Request of primary care physician or investigator	0	0	0	1 (0.4)
Other	1 (0.2)	0	2 (0.4)	0
Early termination due to COVID-19 disruption	0	1 (0.5)	0	1 (0.4)

Patient Demographics

	INTEGUMENT-1		INTEGUMENT-2	
Patients	**Roflumilast cream 0.15% (n=433)**	**Vehicle cream (n=221)**	**Roflumilast cream 0.15% (n=451)**	**Vehicle cream (n=232)**
Age in years, mean (standard deviation)	28.1 (19.1)	28.5 (18.9)	27.7 (19.6)	26.2 (18.9)
Sex at birth, n (%)				
Male	196 (45.3)	92 (41.6)	199 (44.1)	89 (38.4)
Female	237 (54.7)	129 (58.4)	252 (55.9)	143 (61.6)
Ethnicity, n (%)				
Hispanic or Latino	99 (22.9)	56 (25.3)	51 (11.3)	16 (6.9)
Not Hispanic or Latino	333 (76.9)	164 (74.2)	397 (88.0)	213 (91.8)
Not reported	1 (0.2)	1 (0.5)	3 (0.7)	3 (1.3)
Race, n (%)				
American-Indian or Alaskan Native	2 (0.5)	0	5 (1.1)	1 (0.4)
Asian	63 (14.5)	32 (14.5)	51 (11.3)	30 (12.9)
Black or African-American	80 (18.5)	46 (20.8)	96 (21.3)	50 (21.6)
Native Hawaiian, Other Pacific Islander	1 (0.2)	0	0	0
White	261 (60.3)	129 (58.4)	268 (59.4)	138 (59.5)
Other	12 (2.8)	8 (3.6)	19 (4.2)	5 (2.2)
More than one race	14 (3.2)	6 (2.7	12 (2.7)	8 (3.4)
Fitzpatrick Skin Type at Screening, n (%)				
I to III	233 (53.8)	112 (50.7)	248 (55.0)	126 (54.3)
IV to VI	200 (46.2)	109 (49.3)	203 (45.0)	106 (45.7)

Baseline Disease Characteristics

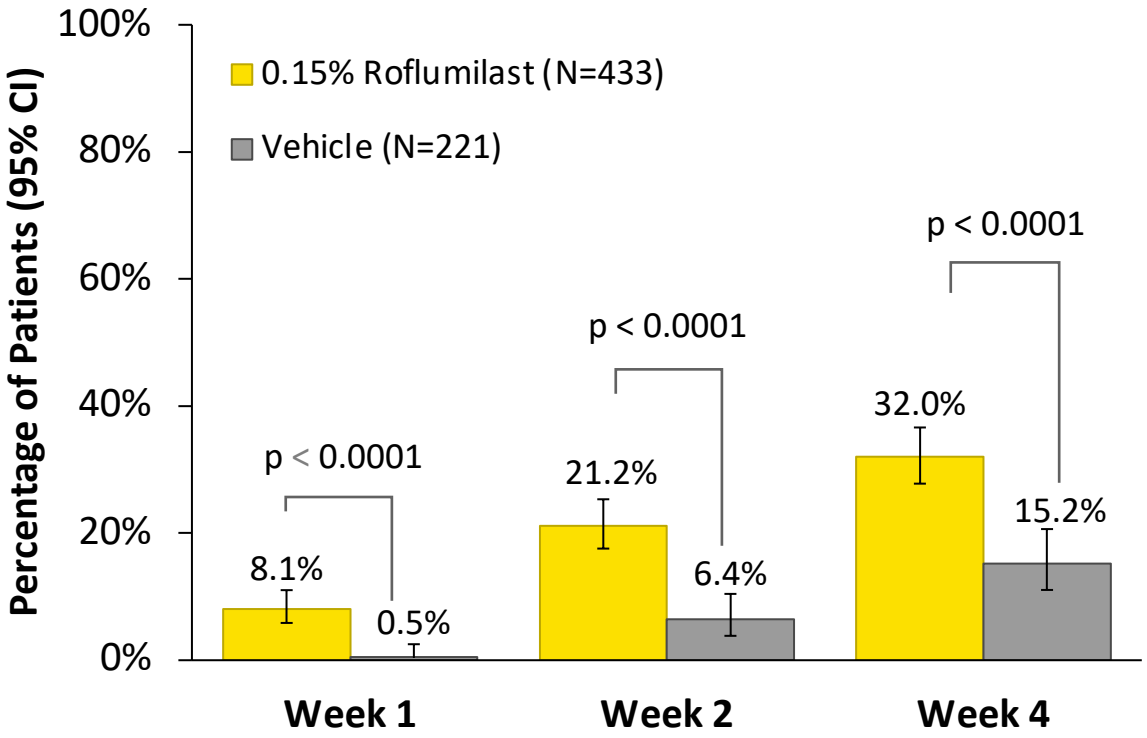
	INTEGUMENT-1		INTEGUMENT-2	
Patients	Roflumilast cream 0.15% (n=433)	Vehicle cream (n=221)	Roflumilast cream 0.15% (n=451)	Vehicle cream (n=232)
Baseline vIGA-AD				
2 (mild)	103 (23.8)	59 (26.7)	108 (23.9)	53 (22.8)
3 (moderate)	330 (76.2)	162 (73.3)	343 (76.1)	179 (77.2)
EASI				
Mean (SD)	9.9 (5.3)	9.8 (5.1)	10.3 (6.1)	10.2 (5.3)
Median (range)	8.2 (4.4, 47.4)	8.2 (4.2, 37.9)	8.5 (4.9, 52.5)	8.4 (3.4, 31.2)
BSA				
Mean (SD)	13.4 (11.9)	12.9 (11.1)	13.7 (11.6)	14.9 (11.3)
Median (range)	9.5 (3.0, 87.0)	3.0, 86.0)	10.0 (3.0, 88.0)	11.0 (3.0, 63.0)
WI-NRS, n	423	217	435	224
Mean (SD)	5.9 (2.1)	5.9 (2.4)	6.2 (2.2)	5.9 (2.1)
Median (range)	6.1 (0.0, 10.0)	6.0 (0.0, 10.0)	6.4 (0.0, 10.0)	6.1 (0.0, 10.0)
Average weekly baseline WI-NRS ≥4, n (%)	350 (80.8)	168 (76.0)	359 (79.6)	181 (78.0)

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

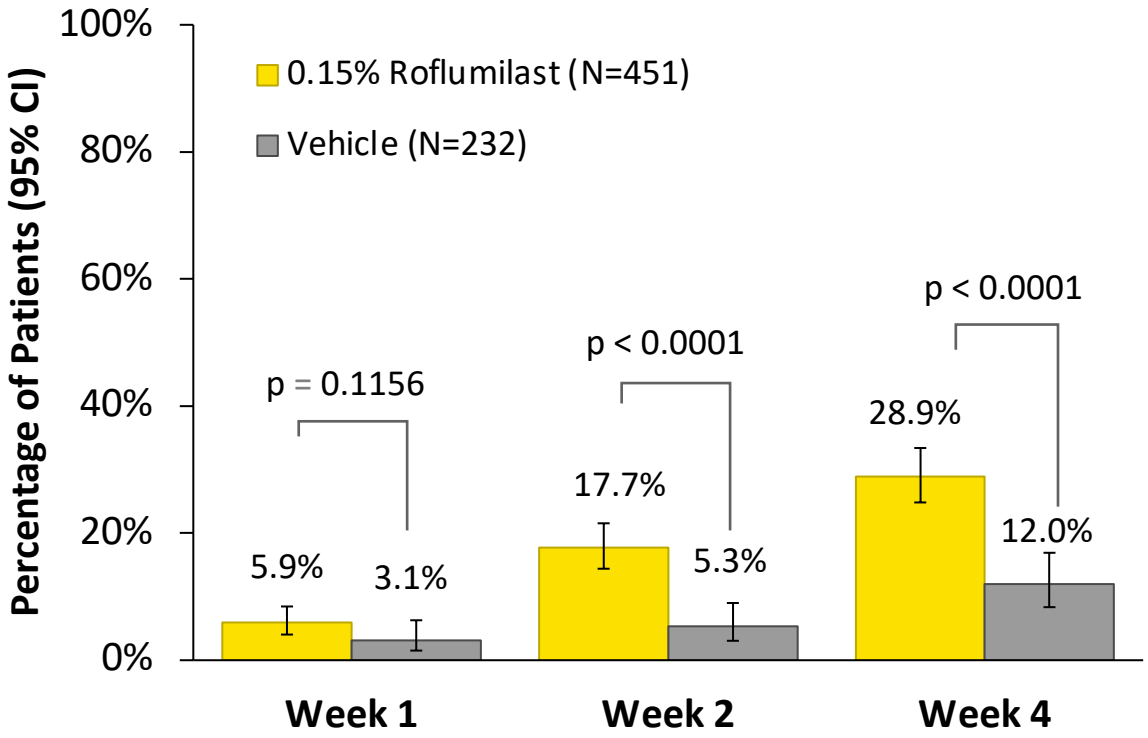
Percent of Patients Achieving vIGA-AD Success

Primary Endpoint: vIGA-AD Success at Week 4

32% of patients achieved vIGA-AD Success at Week 4 (INTEGUMENT-1)



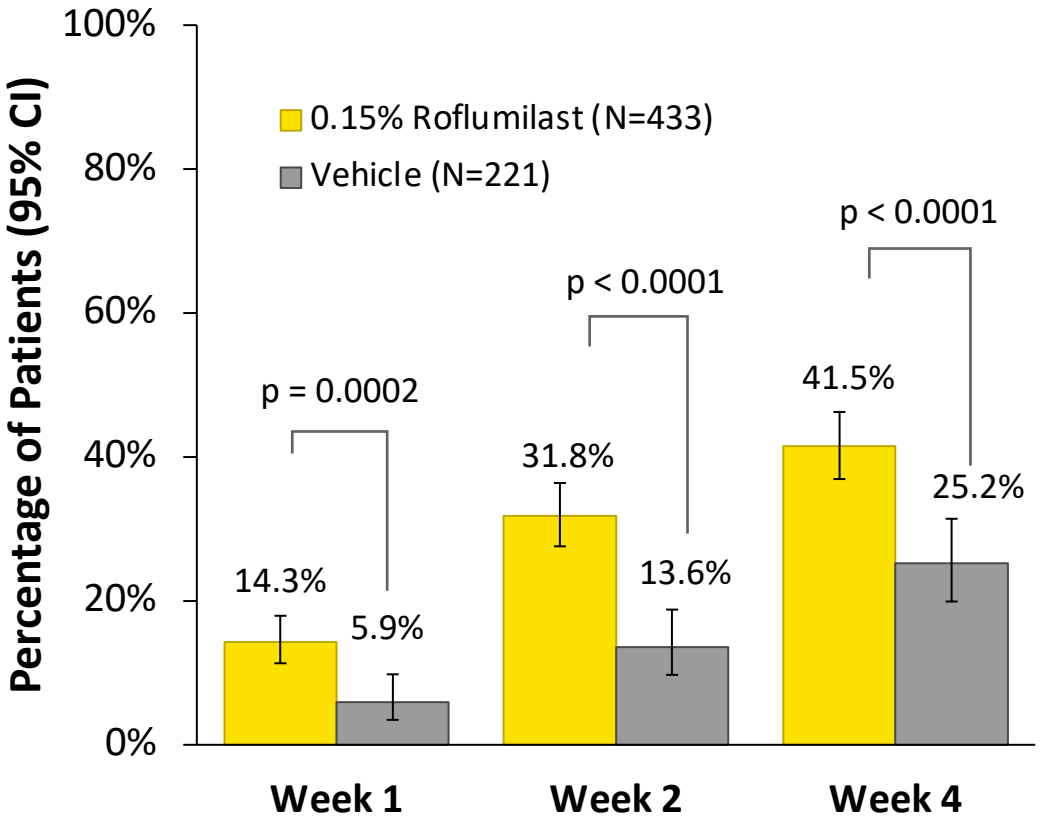
29% of patients achieved vIGA-AD Success at Week 4 (INTEGUMENT-2)



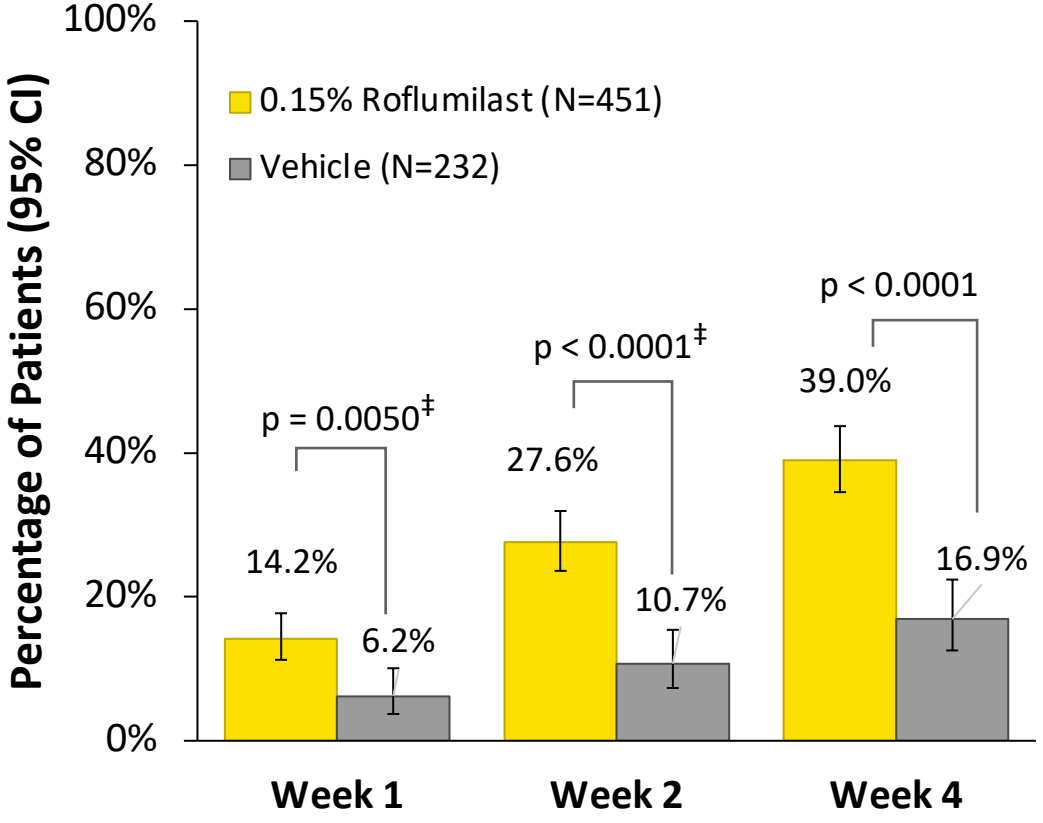
vIGA-AD Success = Clear or Almost clear plus 2-grade improvement from Baseline
CI: confidence interval; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis

Percent of Patients Achieving vIGA-AD Clear or Almost Clear

41.5% of patients achieved vIGA-AD 0/1 at Week 4 (INTEGUMENT-1)



39.0% of patients achieved vIGA-AD 0/1 at Week 4 (INTEGUMENT-2)

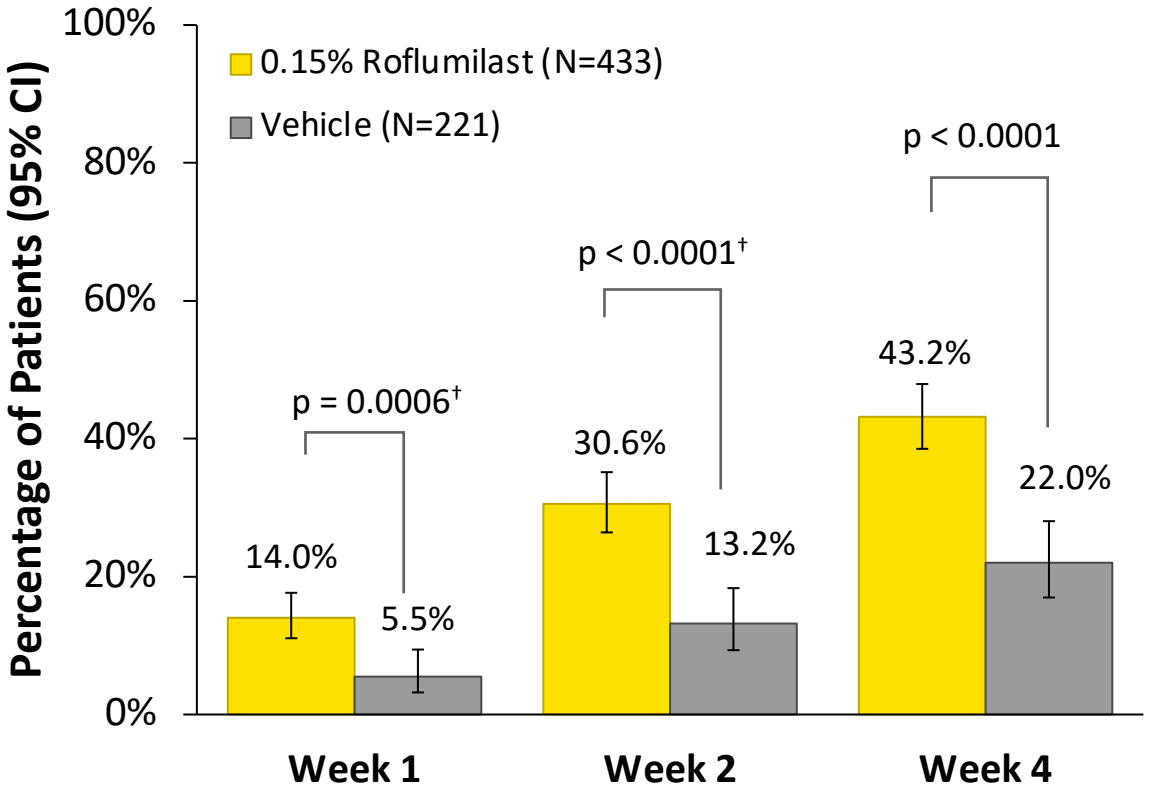


‡P-values are nominal

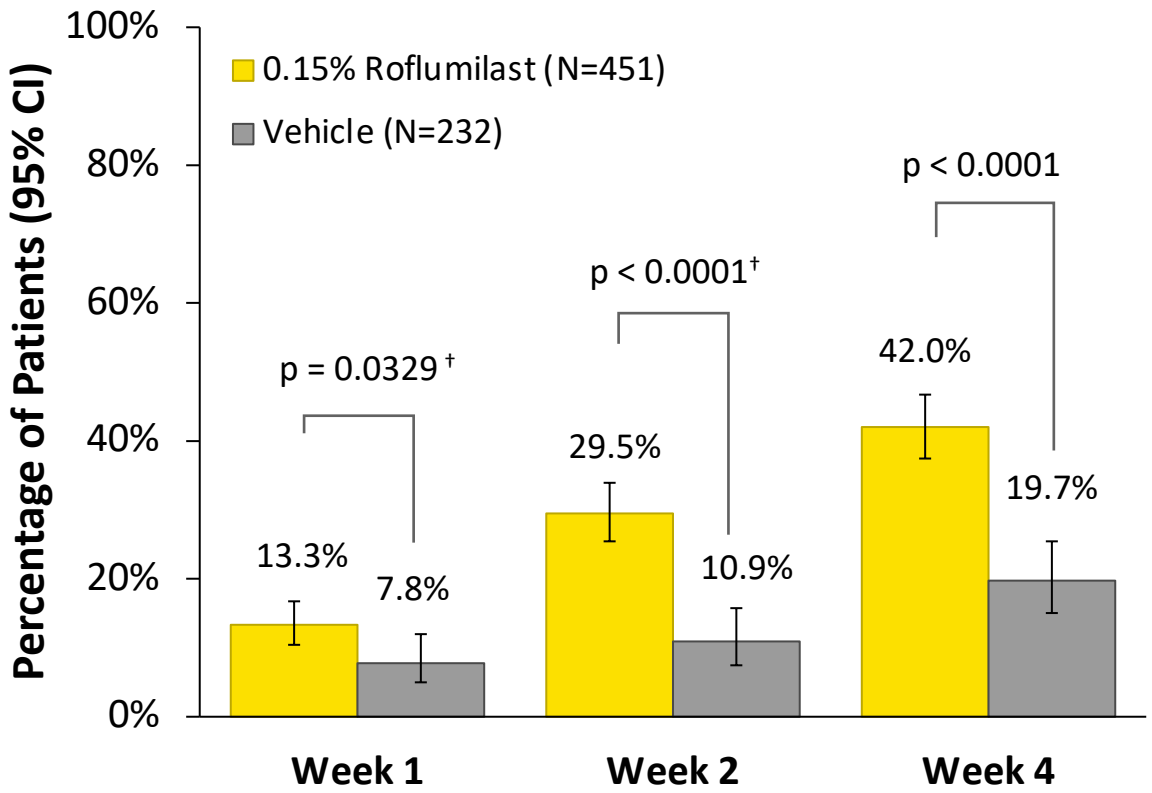
CI: confidence interval; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis

Percent of Patients Achieving 75% Improvement in EASI

43% of patients achieved EASI-75 at Week 4 (INTEGUMENT-1)



42% of patients achieved EASI-75 at Week 4 (INTEGUMENT-2)

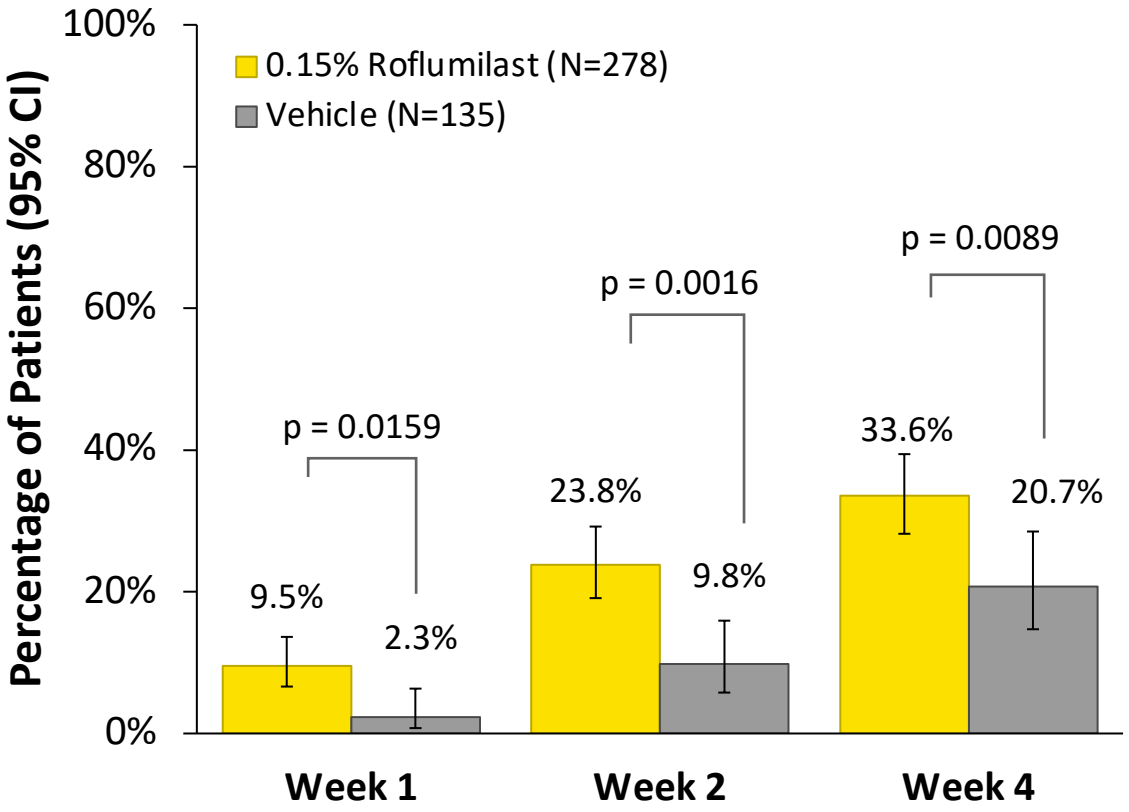


†P-values are nominal

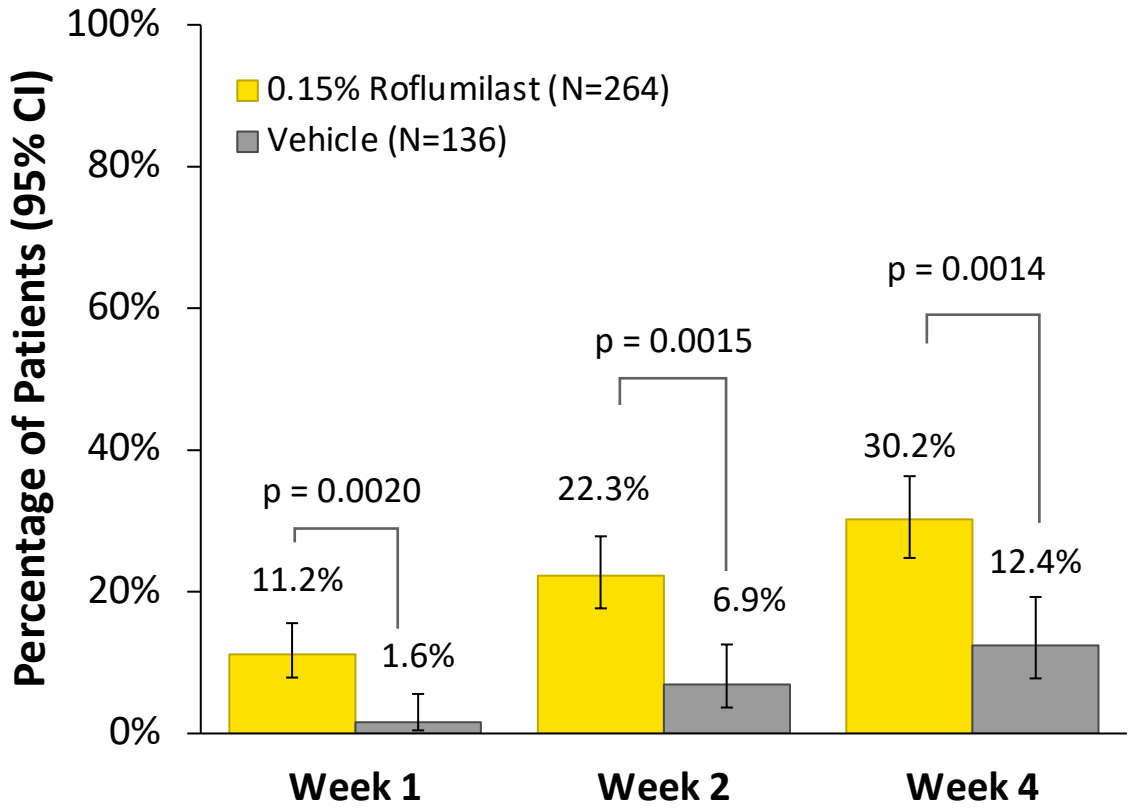
CI: confidence interval; EASI: Eczema Area and Severity Index; EASI-75: 75% reduction in EASI score from Baseline

Improvement in Pruritus
WI-NRS Success

33.6% of patients achieved WI-NRS Success at Week 4 (INTEGUMENT-1)



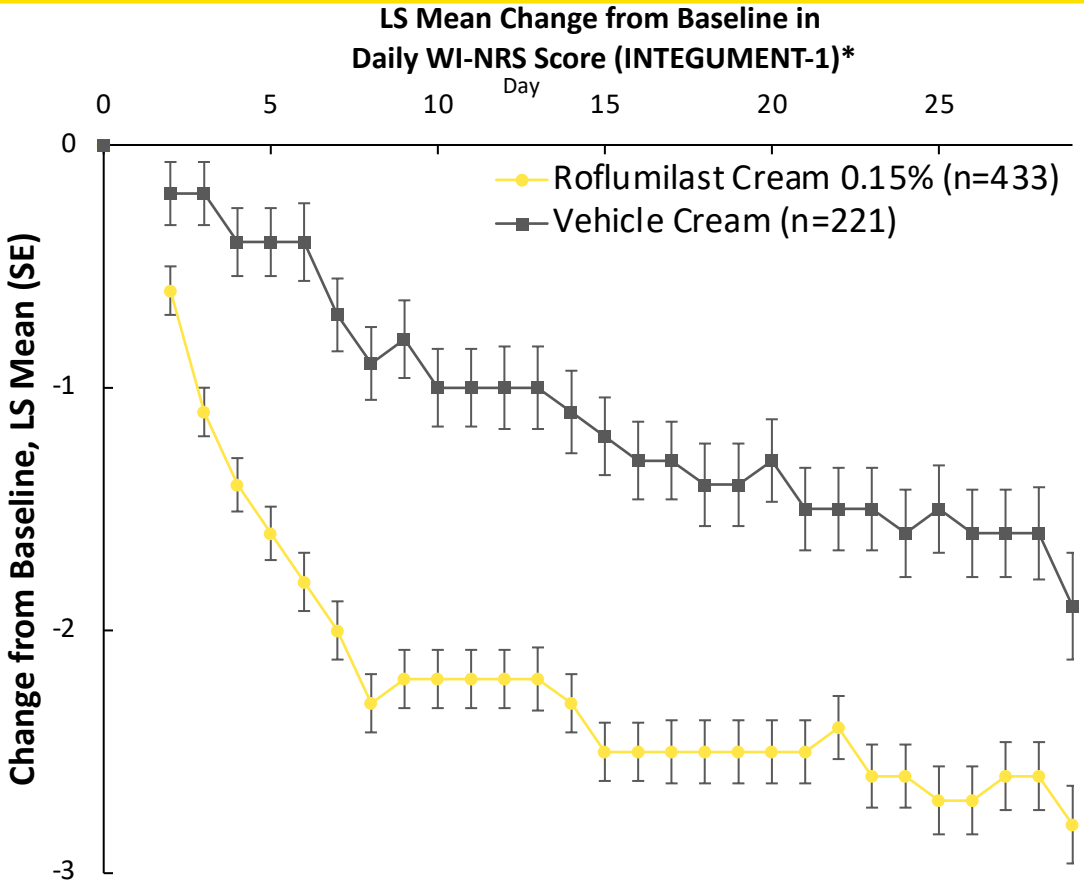
30.2% of patients achieved WI-NRS Success at Week 4 (INTEGUMENT-2)



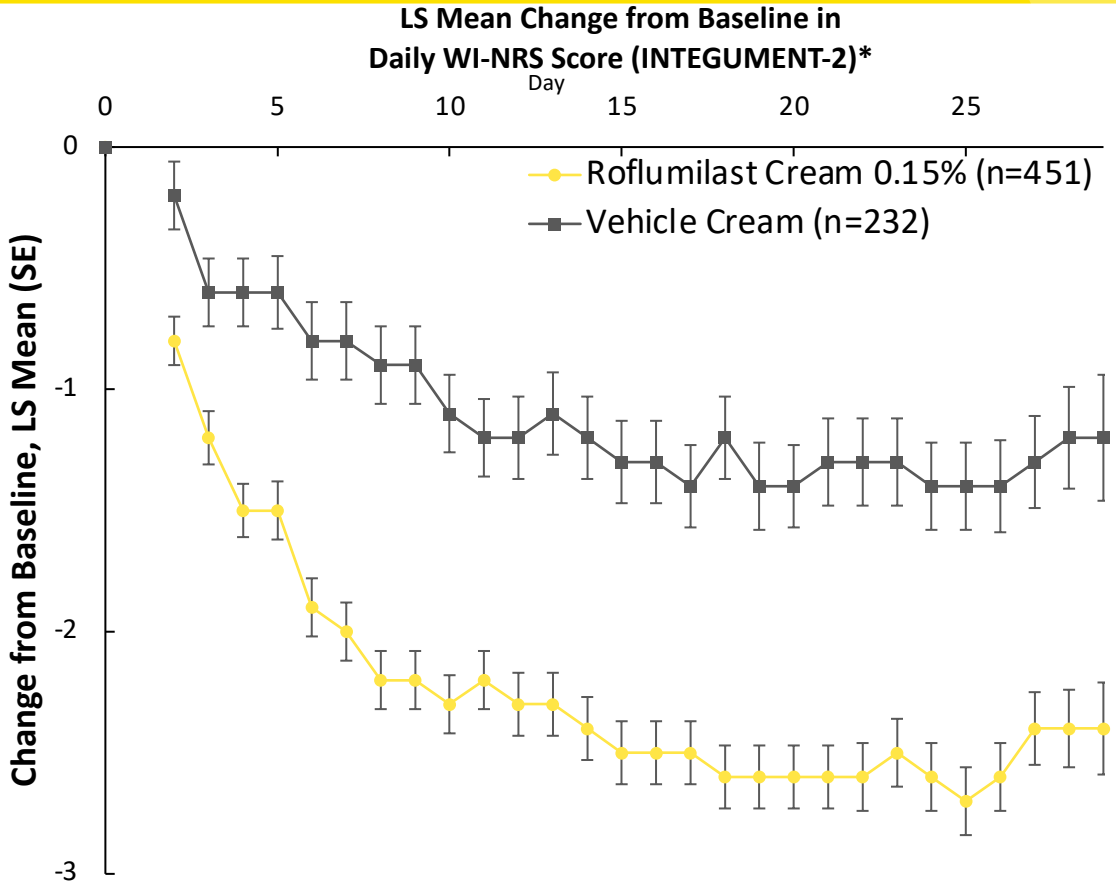
α = 0.03

WI-NRS Success: achievement of ≥4-point improvement in WI-NRS from baseline in patients with baseline WI-NRS ≥4; evaluated in patients ≥12 years of age

Daily Improvement in Pruritus
Daily Diary



Nominal P<0.05 for difference from Vehicle for all timepoints



Nominal P<0.05 for difference from Vehicle for all timepoints

Improvement in itch with roflumilast cream 0.15% was observed at 24 hours after first application (P<0.05)

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

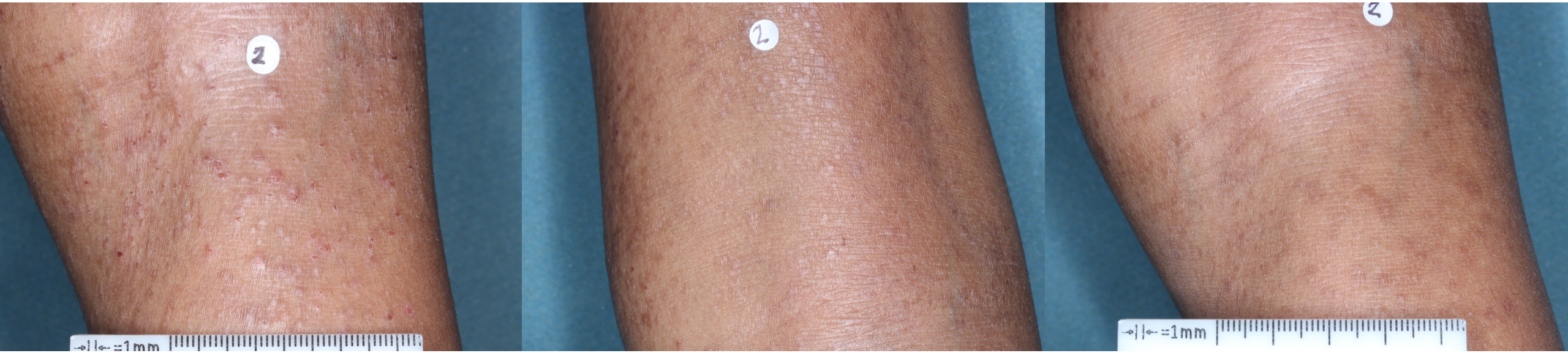
LS: least squares; SE: standard error; WI-NRS: Worst Itch Numerical Rating Scale

Response in AD Patients Treated with Roflumilast Cream 0.15%

Male, 10 years of age

Black or African American, White

Not Hispanic or Latino



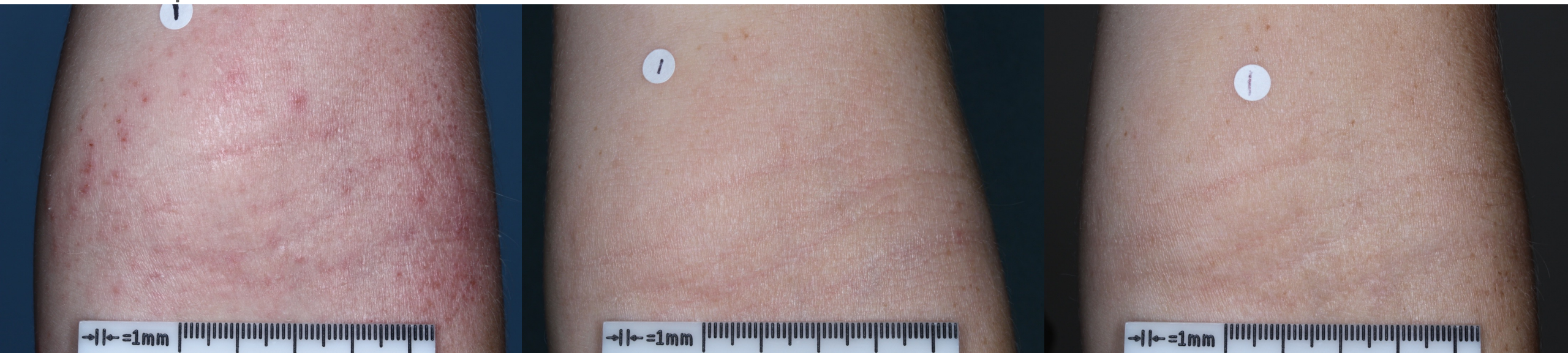
Baseline	Week 1	Week 4
IGA=3	IGA=3	IGA=1
WI-NRS=8.0	WI-NRS=5.3	WI-NRS=1.3

Response in AD Patients Treated with Roflumilast Cream 0.15%

Female, 14 years of age

White

Not Hispanic or Latino



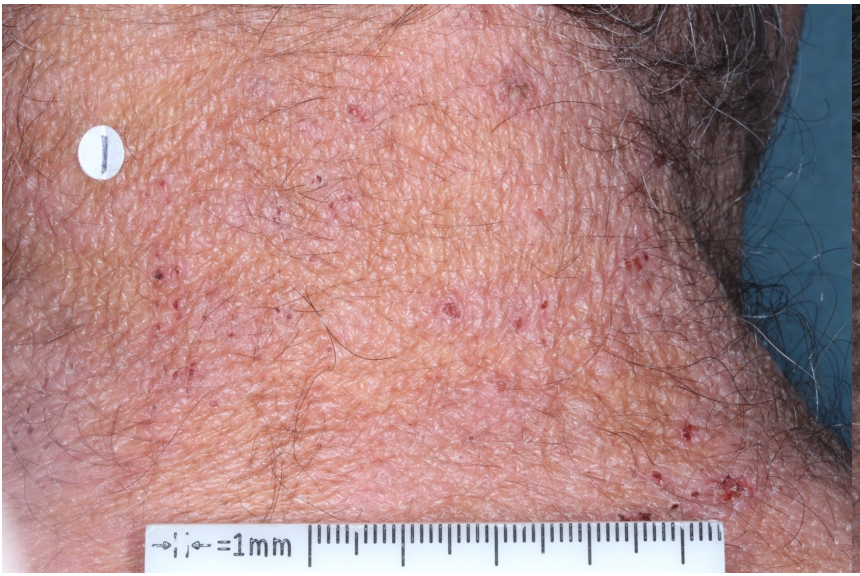
Baseline	Week 1	Week 4
IGA=3	IGA=1	IGA=1
WI-NRS=2.0	WI-NRS=1.9	WI-NRS=1.9

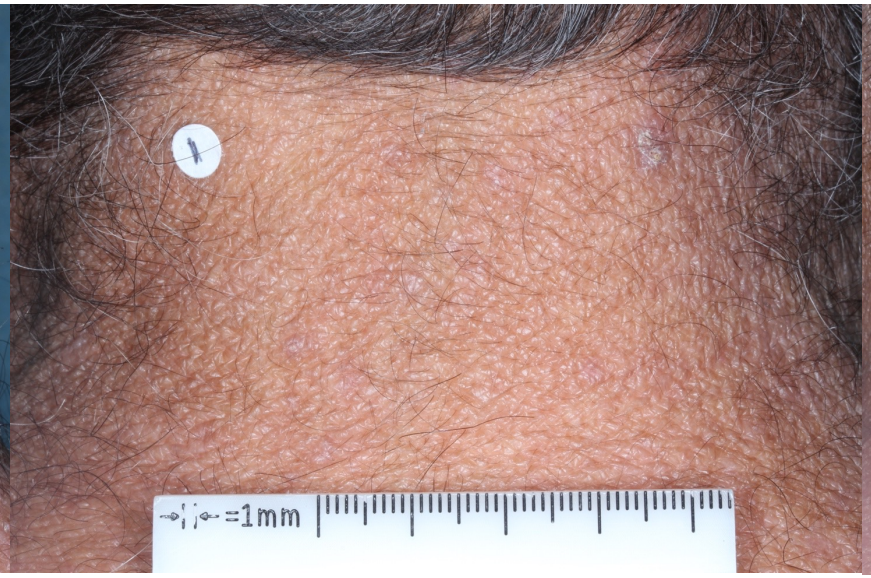
Response in AD Patients Treated with Roflumilast Cream 0.15%

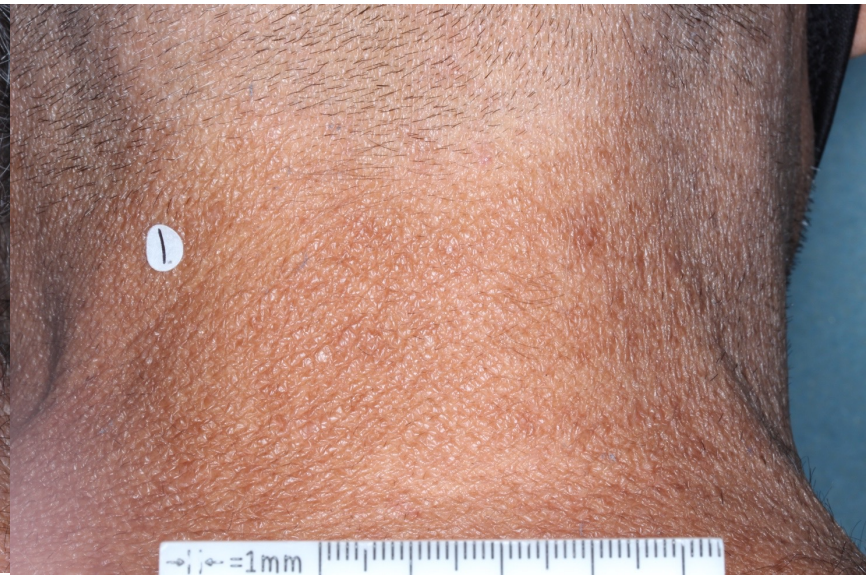
Male, 51 years of age

White

Not Hispanic or Latino







Baseline	Week 1	Week 4
IGA=3	IGA=2	IGA=1
WI-NRS=9.0	WI-NRS=4.0	WI-NRS=2.5

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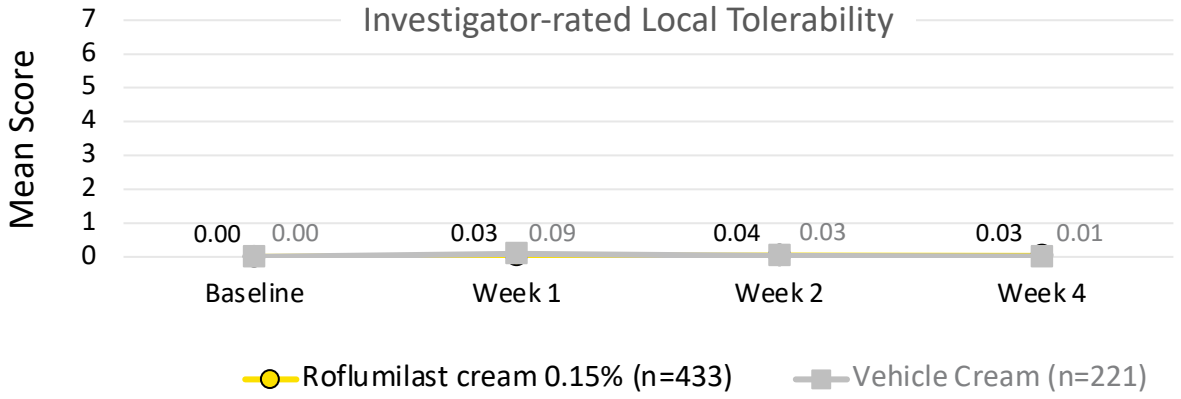
Safety

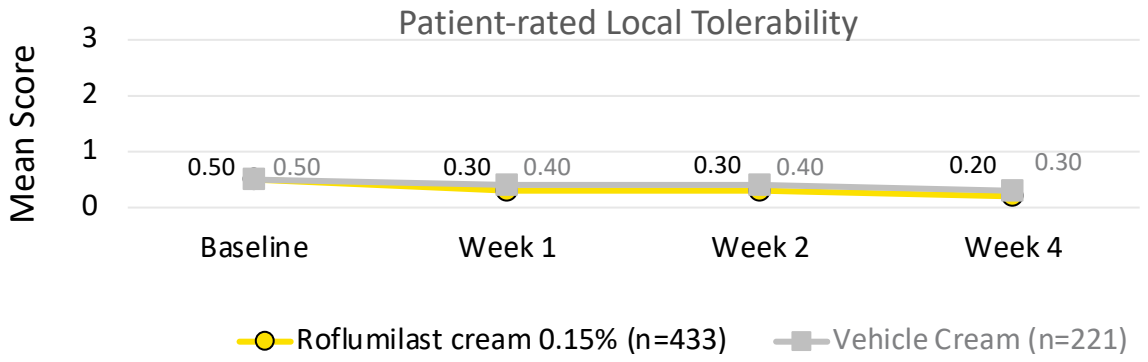
Patients, n (%)	INTEGUMENT-1		INTEGUMENT-2	
	Roflumilast cream 0.15% (n=433)	Vehicle cream (n=221)	Roflumilast cream 0.15% (n=452)	Vehicle cream (n=230)
Patients with any treatment-related TEAE	27 (6.2)	4 (1.8)	26 (5.8)	8 (3.5)
Patients with any treatment-emergent SAE*	4 (0.9)	0	4 (0.9)	0
Patients with any TEAE leading to discontinuation	6 (1.4)	3 (1.4)	8 (1.8)	2 (0.9)
Patients with any TEAE	92 (21.2)	35 (15.8)	102 (22.6)	30 (13.0)
Most Common TEAEs by Preferred Term, ≥1% in any group				
Headache	10 (2.3)	3 (1.4)	16 (3.5)	2 (0.9)
Nausea	8 (1.8)	2 (0.9)	9 (2.0)	0
Application site pain	9 (2.1)	1 (0.5)	4 (0.9)	2 (0.9)
Nasopharyngitis	8 (1.8)	2 (0.9)	0	1 (0.4)
COVID-19	4 (0.9)	5 (2.3)	4 (0.9)	3 (1.3)
Diarrhea	6 (1.4)	0	7 (1.5)	2 (0.9)
Vomiting	5 (1.2)	0	8 (1.8)	2 (0.9)
Upper respiratory tract infection	0	1 (0.5)	5 (1.1)	1 (0.4)

*SAEs were: diverticulitis, depression, suicidal ideation, pulmonary embolism, cutaneous nerve entrapment, staphylococcal scalded skin syndrome, general physical health deterioration, atopic dermatitis
AE: adverse event; TEAE: treatment-emergent adverse event; SAE: serious adverse event

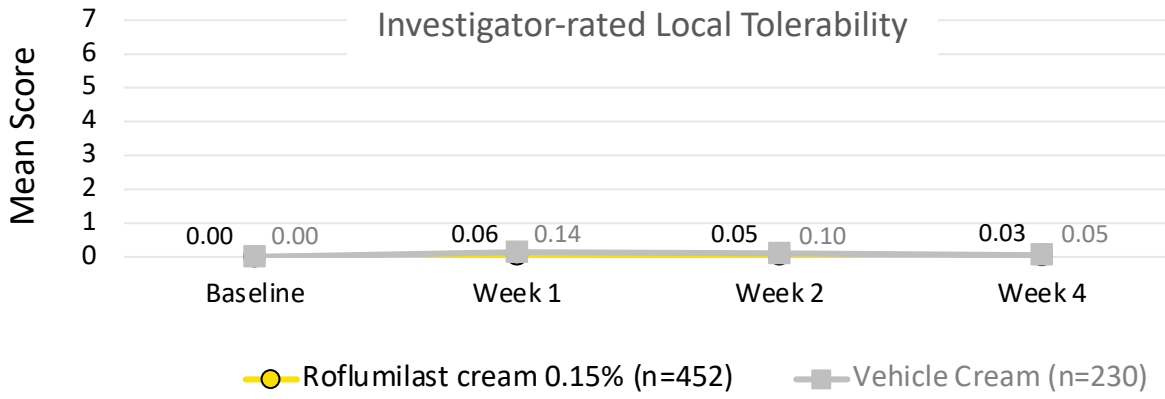
Investigator and Patient-Rated Local Tolerability

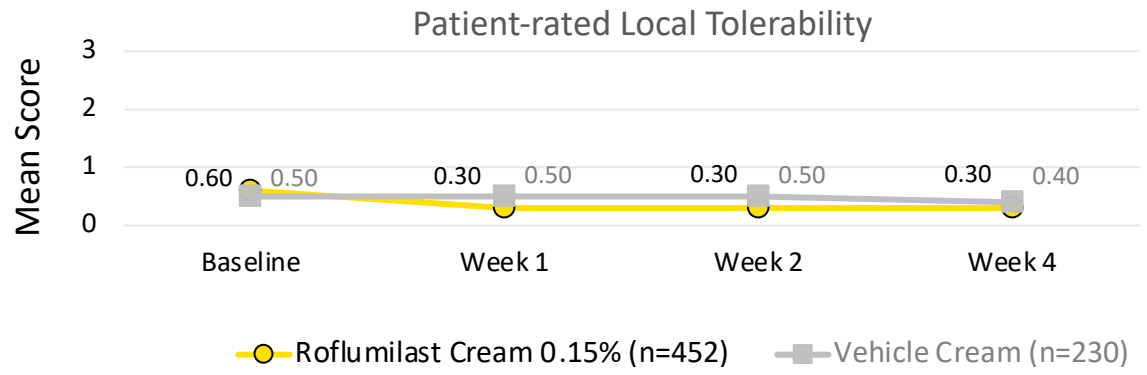
INTEGUMENT-1





INTEGUMENT-2





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

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Conclusions

- Once-daily, non-steroidal roflumilast cream 0.15% significantly improved atopic dermatitis
  - Significant improvement based on EASI-75 was observed as early as 1 week after treatment initiation
  - Reduction in pruritus was observed at 24 hours following the first application
- No AE occurred in more than 3.5% of patients in either arm with low rates of application site pain in both the roflumilast- and vehicle-treated patients
- Once-daily roflumilast cream 0.15% improved atopic dermatitis across multiple efficacy endpoints while demonstrating favorable safety and tolerability in two phase 3 trials

AE: adverse event; EASI: Eczema Area and Severity Index; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis