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]UTHealth McGovern Medical School, Houston, TX, USA; [6]Probity Medical Research and Alliance Clinical Research, Waterloo, ON, 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

INTRODUCTION

- Topical roflumilast is being investigated as a once-daily, nonsteroidal treatment for long-term management of psoriasis (roflumilast cream 0.3% U.S. Food and Drug Administration–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 that does not extract epidermal lipids at safe skin temperatures[2]
  - The vehicle does not contain ethanol, propylene glycol, or fragrances that can irritate skin
- Roflumilast has a greater affinity for phosphodiesterase 4 (PDE4) than apremilast and crisaborole
  - 25- to >300-fold more potent in in vitro assays[3]
- Roflumilast modulates inflammatory cytokines through inhibition of PDE4[4]
  - Decreases conversion of cAMP[4]
  - Results in decreased expression of key proinflammatory cytokines: T-helper (Th)1 (interferon [IFN]-γ, tumor necrosis factor [TNF]-α); Th2 (interleukin [IL]-4); Th17 (IL-17, IL-23)[3]

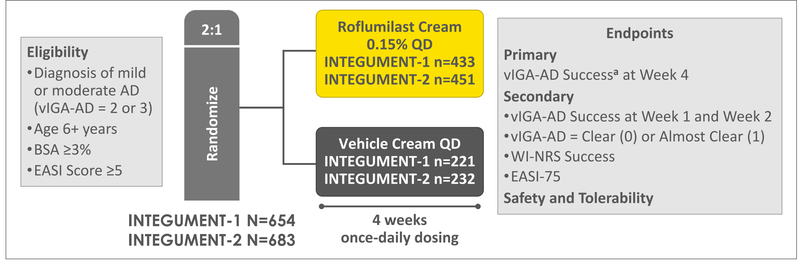
OBJECTIVE

- To present results of 2 phase 3 trials (INTEGUMENT-1 [NCT04773587] and INTEGUMENT-2 [NCT04773600]) of roflumilast cream 0.15% in patients aged ≥6 years with mild to moderate atopic dermatitis

METHODS

- These were randomized, parallel-group, double-blind, vehicle-controlled, multicenter studies (**Figure 1**)

Figure 1. Study Design



[a]vIGA-AD Success = Clear or Almost clear plus 2-grade improvement from baseline.
AD: atopic dermatitis; 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 scale for Atopic Dermatitis; WI-NRS: Worst Itch Numerical Rating Scale.

- Over 90.9% of patients completed the trial; completion rates were similar between treatment groups
  - Few patients discontinued due to adverse events (<1.8% in any treatment group) or due to lack of efficacy (≤1.3% in any treatment group)

RESULTS

- Overall, baseline demographics and disease characteristics were well-balanced (**Table 1**)

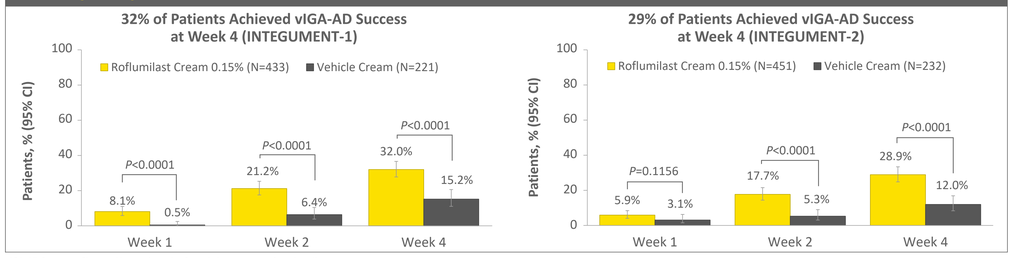
Table 1. Patient Baseline Demographics and Disease Characteristics

Patients	INTEGUMENT-1 Roflumilast Cream 0.15% (n=433)	INTEGUMENT-1 Vehicle Cream (n=221)	INTEGUMENT-2 Roflumilast Cream 0.15% (n=451)	INTEGUMENT-2 Vehicle Cream (n=232)
Age in years, mean (SD)	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 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)
BSA				
Mean (SD)	13.4 (11.9)	12.9 (11.1)	13.7 (11.6)	14.9 (11.3)
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)
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 scale for Atopic Dermatitis; WI-NRS: Worst Itch Numerical Rating Scale.

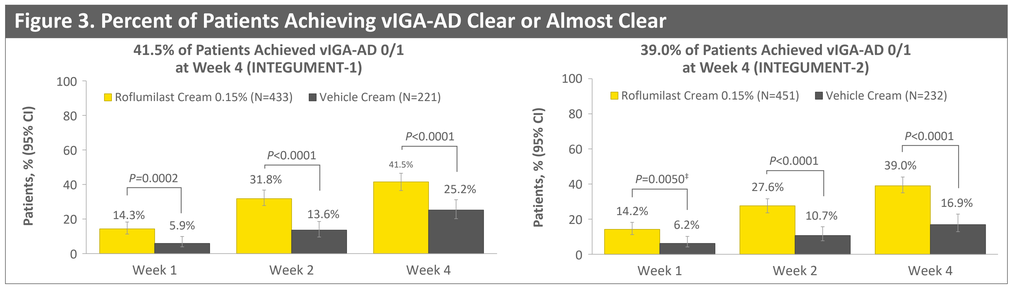
- Roflumilast cream 0.15% provided greater efficacy than vehicle across multiple endpoints (**Figures 2–7**)
- Incidence of treatment-emergent adverse events was low in both arms (**Table 2**) and local tolerability was favorable (**Figure 8**)

Figure 2. Percent of Patients Achieving vIGA-AD Success
Primary Endpoint: vIGA-AD Success at Week 4



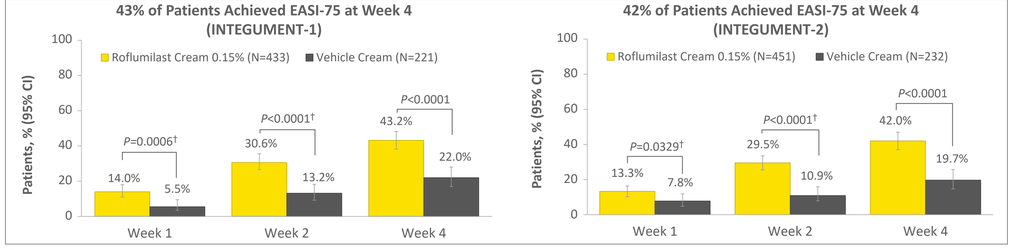
vIGA-AD Success = Clear or Almost clear plus 2-grade improvement from baseline.
CI: confidence interval; vIGA-AD: Validated Investigator Global Assessment scale for Atopic Dermatitis.

Figure 3. Percent of Patients Achieving vIGA-AD Clear or Almost Clear



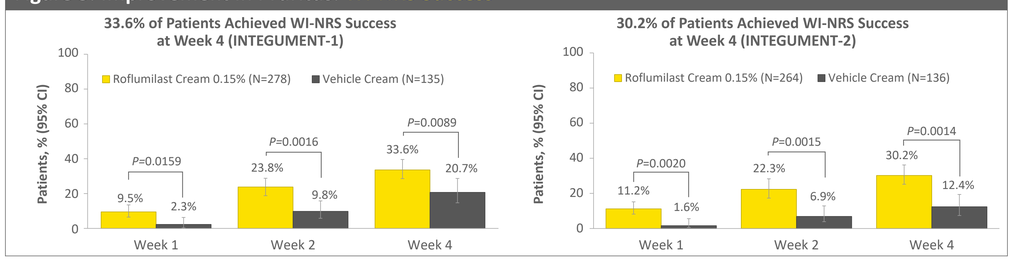
‡P-values are nominal.
CI: confidence interval; vIGA-AD: Validated Investigator Global Assessment scale for Atopic Dermatitis.

Figure 4. Percent of Patients Achieving 75% Improvement in EASI



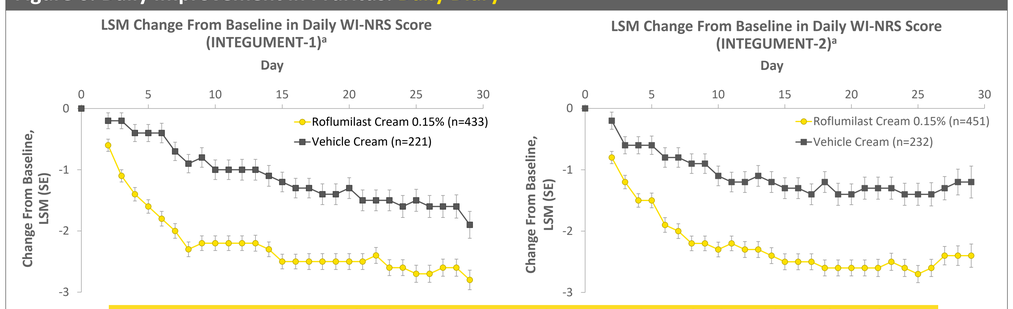
†P-values are nominal.
CI: confidence interval; EASI: Eczema Area and Severity Index; EASI-75: 75% reduction in EASI score from baseline.

Figure 5. Improvement in Pruritus: WI-NRS Success



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 aged ≥12 years.
CI: confidence interval; WI-NRS: Worst Itch Numerical Rating Scale.

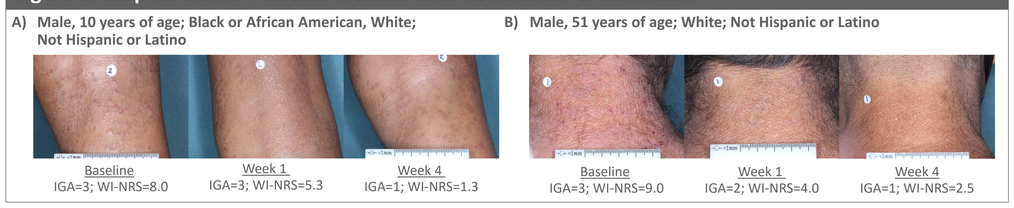
Figure 6. Daily Improvement in Pruritus: Daily Diary



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

[a]Evaluated in all patients, not just those with baseline WI-NRS ≥4.
LSM: least squares mean; SE: standard error; WI-NRS: Worst Itch Numerical Rating Scale.

Figure 7. Response in AD Patients Treated With Roflumilast Cream 0.15%



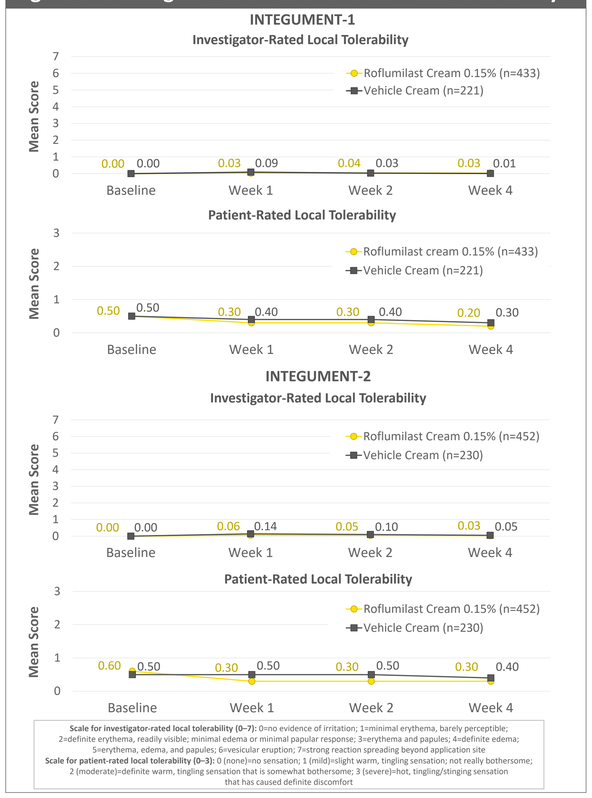
AD: atopic dermatitis; IGA: Investigator Global Assessment; WI-NRS: Worst Itch Numerical Rating Scale.

Table 2. Safety in AD Patients

Patients, n (%)	INTEGUMENT-1 Roflumilast Cream 0.15% (n=433)	INTEGUMENT-1 Vehicle Cream (n=221)	INTEGUMENT-2 Roflumilast Cream 0.15% (n=452)	INTEGUMENT-2 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.
SAE: serious adverse event; TEAE: treatment-emergent adverse event.

Figure 8. 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

CONCLUSIONS

- Once-daily, nonsteroidal roflumilast cream 0.15% significantly improved atopic dermatitis
  - Significant improvement based on 75% improvement in Eczema Area and Severity Index 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 2 phase 3 trials

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DISCLOSURES

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