Once-Daily Roflumilast Cream 0.15% for Atopic Dermatitis: Pooled Results From INTEGUMENT-1/2 Phase 3 Trials

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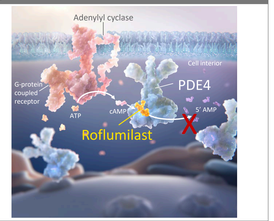
INTRODUCTION

- Topical roflumilast is a once-daily, nonsteroidal treatment being investigated in cream and foam formulations for long-term management of:
  - Psoriasis (for which the US Food and Drug Administration approved a 0.3% cream formulation on July 29, 2022)[1]
  - Seborrheic dermatitis[2]
  - Atopic dermatitis[3]
- Topical roflumilast is intentionally formulated to maintain the skin barrier[4]:
  - Excipients include an emulsifier commonly used in cosmetic products but novel to prescription topical products
  - The water-based vehicle does not contain fragrances, propylene glycol, isopropyl alcohol, ethanol, or formaldehyde-releasing preservatives that can irritate skin

Figure 1. Roflumilast Mechanism of Action



- Roflumilast inhibits PDE4, modulating inflammatory cytokines[5] (Figure 1)
  - Decreased conversion of cAMP[6]
  - Decreased expression of key proinflammatory cytokines[5]:
    - Th1 (IFN-γ, TNF-α)
    - Th2 (IL-4)
    - Th17 (IL-17, IL-23)
- Roflumilast binds to PDE4 using the same 3 points of stabilization as cAMP[7]
  - 25- to >300-fold more potent than crisaborole and apremilast in in vitro assays[1]

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

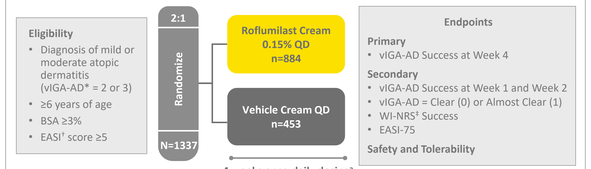
OBJECTIVE

- To present pooled results of two 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 identically designed, randomized, parallel-group, double-blind, vehicle-controlled, multicenter studies (Figure 2)

Figure 2. Study Design



vIGA-AD Success = Clear or Almost Clear ≥2-grade improvement from baseline. WI-NRS Success = ≥4-point improvement in patients with baseline WI-NRS score ≥4.
*A 5-point scale ranging from 0 (Clear) to 4 (Severe) assessing inflammatory signs of atopic dermatitis; †A 72-point scale based on AD disease intensity and total affected body area; ‡An 11-point scale ranging from 0 (no itch) to 10 (worst itch imaginable).
[a]Nonmedicated emollients or moisturizers could be applied, but only to untreated areas of the patient's skin.
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-Numeric Rating Scale.

RESULTS

- >92.1% of patients completed the trials; completion rates were similar between treatment groups
  - Few patients discontinued due to adverse events (≤1.6% in any treatment group) or due to lack of efficacy (≤1.1% in any treatment group)
- Overall, baseline demographics and disease characteristics were well balanced (Table 1)

Table 1. Patient Baseline Demographics and Disease Characteristics

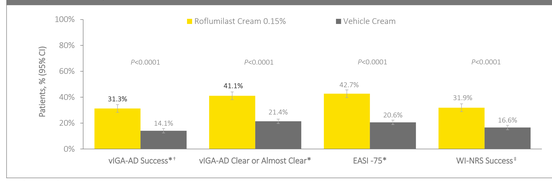
Patients	Roflumilast Cream 0.15% (n=884)	Vehicle Cream (n=453)
Age, years, mean (SD)	27.9 (19.4)	27.3 (19.0)
Sex at birth, n (%)		
Male	395 (44.7)	181 (40.0)
Female	489 (55.3)	272 (60.0)
Ethnicity, n (%)		
Hispanic or Latino	150 (17.0)	72 (15.9)
Not Hispanic or Latino	730 (82.6)	377 (83.2)
Not reported	4 (0.5)	4 (0.9)
Race, n (%)		
American Indian or Alaskan Native	7 (0.8)	1 (0.2)
Asian	114 (12.9)	62 (13.7)
Black or African American	176 (19.9)	96 (21.2)
Native Hawaiian, Other Pacific Islander	1 (0.1)	0
White	529 (59.8)	267 (58.9)
Other	33 (3.7)	13 (2.9)
More than one race	24 (2.7)	14 (13.1)
Fitzpatrick skin type at screening, n (%)		
I to III	481 (54.4)	238 (52.5)
IV to VI	403 (45.6)	215 (47.5)
Baseline vIGA-AD,* n (%)		
2 (mild)	211 (23.9)	112 (24.7)
3 (moderate)	673 (76.1)	341 (75.3)
EASI†		
Mean (SD)	10.1 (5.7)	10.0 (5.2)
Median (range)	8.4 (4.4, 52.5)	8.4 (3.4, 37.9)
BSA		
Mean (SD)	13.5 (11.8)	13.9 (11.3)
Median (range)	9.7 (3.0, 88.0)	10.0 (3.0, 86.0)
Facial involvement, n (%)	370 (41.9)	197 (43.5)
WI-NRS,‡ n	858	441
Mean (SD)	6.1 (2.2)	5.9 (2.2)
Median (range)	6.3 (0.0, 10.0)	6.0 (0.0, 10.0)
≥12 years of age with average weekly baseline WI-NRS ≥4, n (%)	542 (61.3)	271 (59.8)

*A 5-point scale ranging from 0 (Clear) to 4 (Severe) assessing inflammatory signs of atopic dermatitis; †A 72-point scale based on AD disease intensity and total affected body area; ‡An 11-point scale ranging from 0 (no itch) to 10 (worst itch imaginable).
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-Numeric Rating Scale.

EFFICACY

- At Weeks 1, 2, and 4 (Figure 3), more roflumilast- than vehicle-treated patients achieved:
  - Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) Success (defined as vIGA-AD Clear (0) or Almost Clear (1) plus ≥2-grade improvement from baseline)
  - vIGA-AD Clear or Almost Clear
  - 75% reduction in the Eczema Area and Severity Index from baseline (EASI-75)
  - Worst Itch-Numeric Rating Scale (WI-NRS) Success (defined as ≥4-point reduction on the WI-NRS score in patients with baseline WI-NRS ≥4)
- Roflumilast-treated patients experienced greater improvement in itch beginning as early as 24 hours following first application (Figure 4)
- Photographs of patients with improvement in AD following roflumilast treatment are shown in Figure 5

Figure 3. Percentage of Patients Achieving vIGA-AD Success, vIGA-AD Clear or Almost Clear, EASI-75, and WI-NRS Success at Week 4



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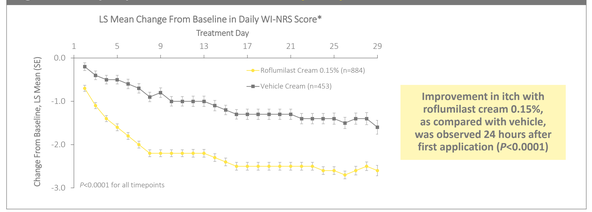
*ITT population (roflumilast [n=884], vehicle [n=453]); †vIGA-AD Success = Clear or Almost Clear plus ≥2-grade improvement from baseline; ‡WI-NRS Success = ≥4-point improvement in patients with baseline WI-NRS score ≥4 (roflumilast [n=542], vehicle [n=271]).
CI: confidence interval; EASI: Eczema Area and Severity Index; EASI-75: 75% reduction in EASI score from baseline; ITT: intent-to-treat; MI: multiple imputation; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis; WI-NRS: Worst Itch-Numeric Rating Scale.

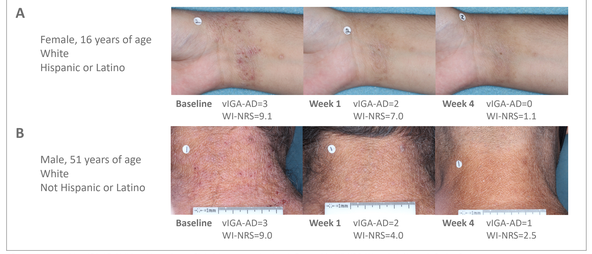
Figure 4. Daily Improvement in Pruritus: Daily Diary



Improvement in itch with roflumilast cream 0.15%, as compared with vehicle, was observed 24 hours after first application (*P*<0.0001)

*ITT population (roflumilast [n=884], vehicle [n=453]).
ITT: intent-to-treat; LS: least squares; SE: standard error; WI-NRS: Worst Itch-Numeric Rating Scale.

Figure 5. Response in Patients With AD Treated With Roflumilast Cream 0.15%



AD: atopic dermatitis; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis; WI-NRS: Worst Itch-Numeric Rating Scale.

SAFETY AND TOLERABILITY

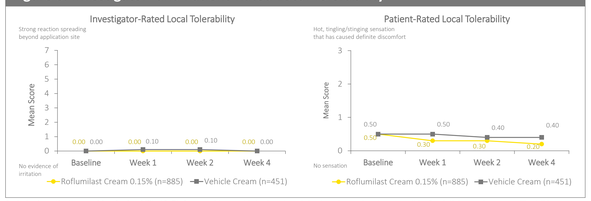
- Incidence of treatment-emergent adverse events was low in both arms (Table 2)
- Local tolerability was favorable (Figure 6)
  - >90% of patients reported no or mild sensation across both treatment groups at all timepoints

Table 2. Safety

Patients, n (%)	Roflumilast Cream 0.15% (n=885)	Vehicle Cream (n=451)
Patients with any treatment-related TEAE	53 (6.0)	12 (2.7)
Patients with any treatment-emergent SAE*	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	194 (21.9)	65 (14.4)
Most common TEAEs by Preferred Term, ≥1% in any group		
Headache	26 (2.9)	4 (0.9)
Nausea	17 (1.9)	2 (0.4)
Application site pain	13 (1.5)	3 (0.7)
Diarrhea	13 (1.5)	2 (0.4)
Vomiting	13 (1.5)	2 (0.4)
COVID-19	7 (0.8)	8 (1.8)

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

Figure 6. 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 vIGA-AD and EASI-75 at Week 4
  - Reduction in pruritus was observed 24 hours following the first application
- No adverse event occurred in >2.9% of patients in either arm, with low rates of:
  - Application site pain (reported by patients as an adverse event)
  - Application site stinging/burning (per the patient-reported local tolerability scale)
- Once-daily roflumilast cream 0.15% improved atopic dermatitis across multiple efficacy endpoints while demonstrating favorable safety and tolerability in two Phase 3 trials

REFERENCES

1. Lebwohl MG, et al. *JAMA* 2022;328:1073–1084.
2. Ziwas MJ, et al. *JAMA Dermatol* 2023;159:613–620.
3. Gooderham MJ, et al. *J Drugs Dermatol* 2023;22:139–147.
4. Berk DR, Osborne DW. Society for Investigative Dermatology 2022.
5. Dong C, et al. *J Pharmacol Exp Ther* 2016;358:413–422.
6. Schafer PH, et al. *Cell Signal* 2014;26:2016–2029.
7. Wang J, Bunick CG. International Societies for Investigative Dermatology 2023.

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DISCLOSURES

LFE, **ELS**, **AB**, **MG**, and **EL** are investigators and/or consultants for Arcutis Biotherapeutics, Inc. and received grants/research funding and/or honoraria; **MB** is a consultant for Arcutis Biotherapeutics, Inc.; **DHC** and **RCH** are employees of Arcutis Biotherapeutics, Inc. Additional disclosures provided on request.