The Safety and Efficacy of Roflumilast Cream 0.15% and 0.05% in Atopic Dermatitis: Phase 2 Proof-of-Concept Study

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Disclosures

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Background

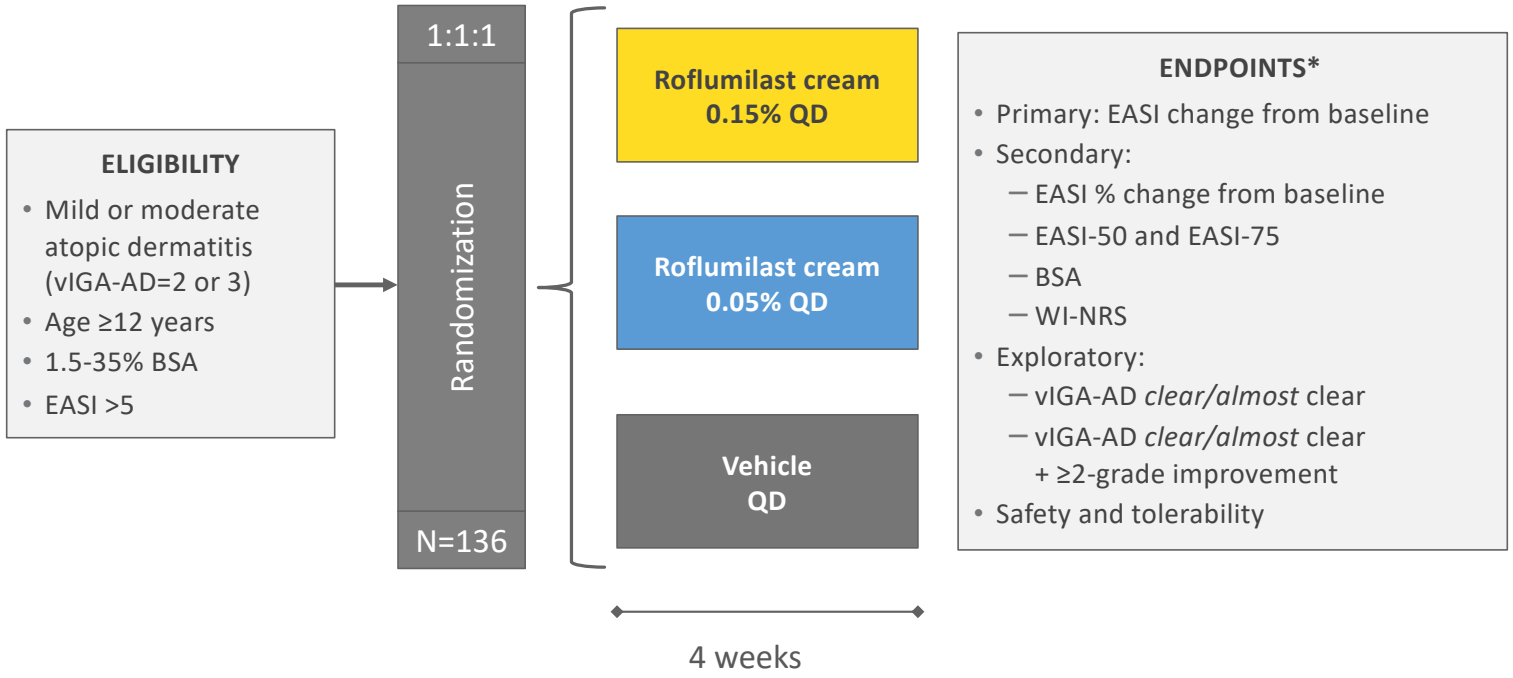
- Majority of patients with atopic dermatitis are treated with topical anti-inflammatory therapy: corticosteroids or calcineurin inhibitors, in combination with emollients[1]
  - Side effects and poor adherence limit long-term use of topical corticosteroids
  - Topical calcineurin inhibitors may cause local tolerability reactions
- PDE-4 is the predominant cAMP-degrading enzyme in inflammatory cells, including lymphocyte subsets, and has increased activity in inflammatory skin disorders like atopic dermatitis[2,3]
- Roflumilast cream is a highly potent PDE-4 inhibitor with ~25- to >300-fold higher potency than other approved PDE-4 inhibitors[4]
  - Roflumilast cream is in Phase 3 development for plaque psoriasis[5]
- The objective of this study was to assess the short-term safety and efficacy of QD topical roflumilast cream in patients with mild to moderate atopic dermatitis

cAMP: cyclic adenosine monophosphate; PDE-4: phosphodiesterase-4; QD: once daily.

[1]Silverberg JI, et al. *J Dermatolog Treat.* 2016;27:568-576. [2]Bäumer W, et al. *Inflamm Allergy Drug Targets.* 2007;6:17-26. [3]Guttman-Yassky E, et al. *Exp Dermatol.* 2019;28:3-10. [4]Dong C, et al. *J Pharmacol Exp Ther.* 2016;358:413-422. [5]Lebwohl MG, et al. *N Engl J Med.* 2020;383:229-239.

The Safety and Efficacy of Roflumilast Cream in Atopic Dermatitis: Study Design

Randomized, double-blind, vehicle-controlled, multicenter study



*The primary endpoint was analyzed with a mixed-effects model for repeated measures, as were other continuous endpoints. Categorical endpoints were analyzed with a Cochran-Mantel-Haenszel (CMH) test. Comparisons were specified at the 0.05 level and were not adjusted for multiplicity. 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 Numeric Rating Scale.

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Baseline Characteristics

	Roflumilast 0.15% (n=45)	Roflumilast 0.05% (n=46)	Vehicle (n=45)
Age, mean years (SD)	38.0 (16.5)	44.3 (17.0)	42.4 (17.6)
Sex, female, n (%)	33 (73.3)	31 (67.4)	29 (64.4)
Race, n (%)			
White	24 (53.3)	32 (69.6)	32 (71.1)
Black	14 (31.1)	11 (23.9)	11 (24.4)
Multiple/other	7 (15.6)	3 (6.5)	2 (4.4)
vIGA-AD score, mean (SD)	2.8 (0.4)	2.8 (0.4)	2.8 (0.4)
2 (mild), n (%)	10 (22.2)	11 (23.9)	9 (20.0)
3 (moderate), n (%)	35 (77.8)	35 (76.1)	36 (80.0)
EASI, mean score (SD)	9.5 (4.1)	8.4 (4.1)	9.2 (3.9)
BSA, mean (SD), %	9.6 (6.0)	8.4 (7.1)	10.5 (6.6)
WI-NRS, mean score (SD)	6.6 (2.0)	6.5 (2.0)	7.2 (2.1)
WI-NRS score ≥6, n (%)	32 (71.1)	31 (67.4)	38 (84.4)

Data are presented for safety population. 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.

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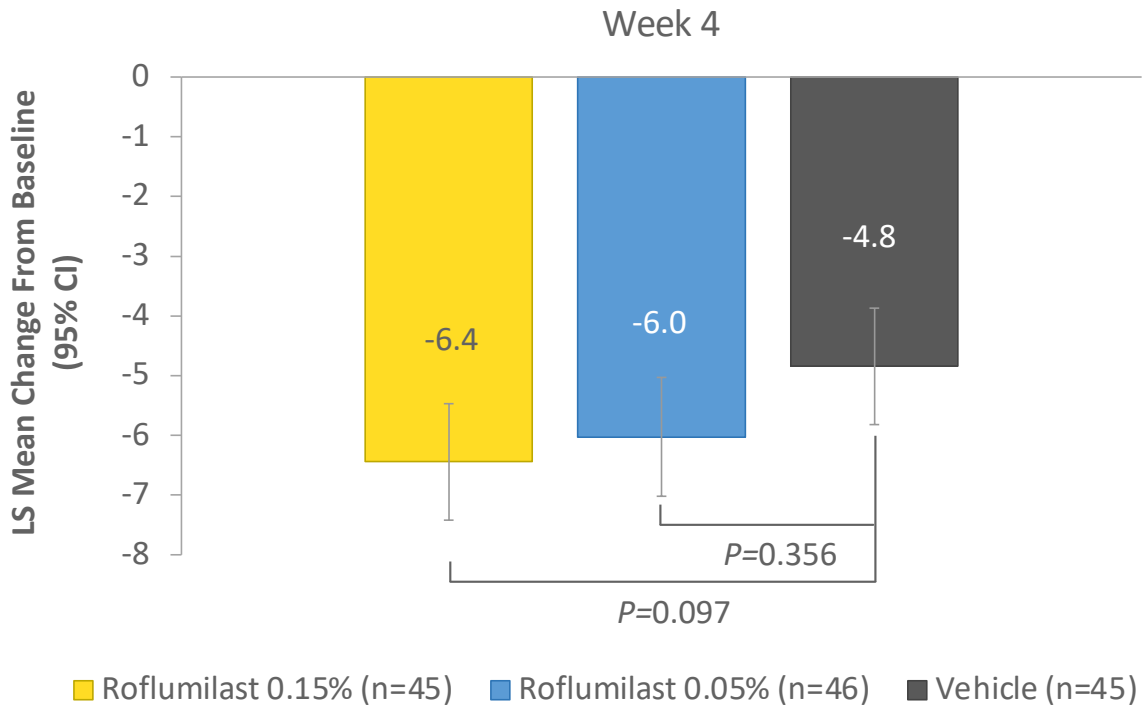
Severity of Atopic Dermatitis Improved With Roflumilast Cream

Absolute EASI Change From Baseline (Primary Endpoint)



- At this early timepoint of 4 weeks, there was improvement in atopic dermatitis severity, yet not statistically significant
- A robust response to vehicle was observed

Data presented for intent-to-treat population. CI: confidence interval; EASI: Eczema Area and Severity Index; LS: least squares.

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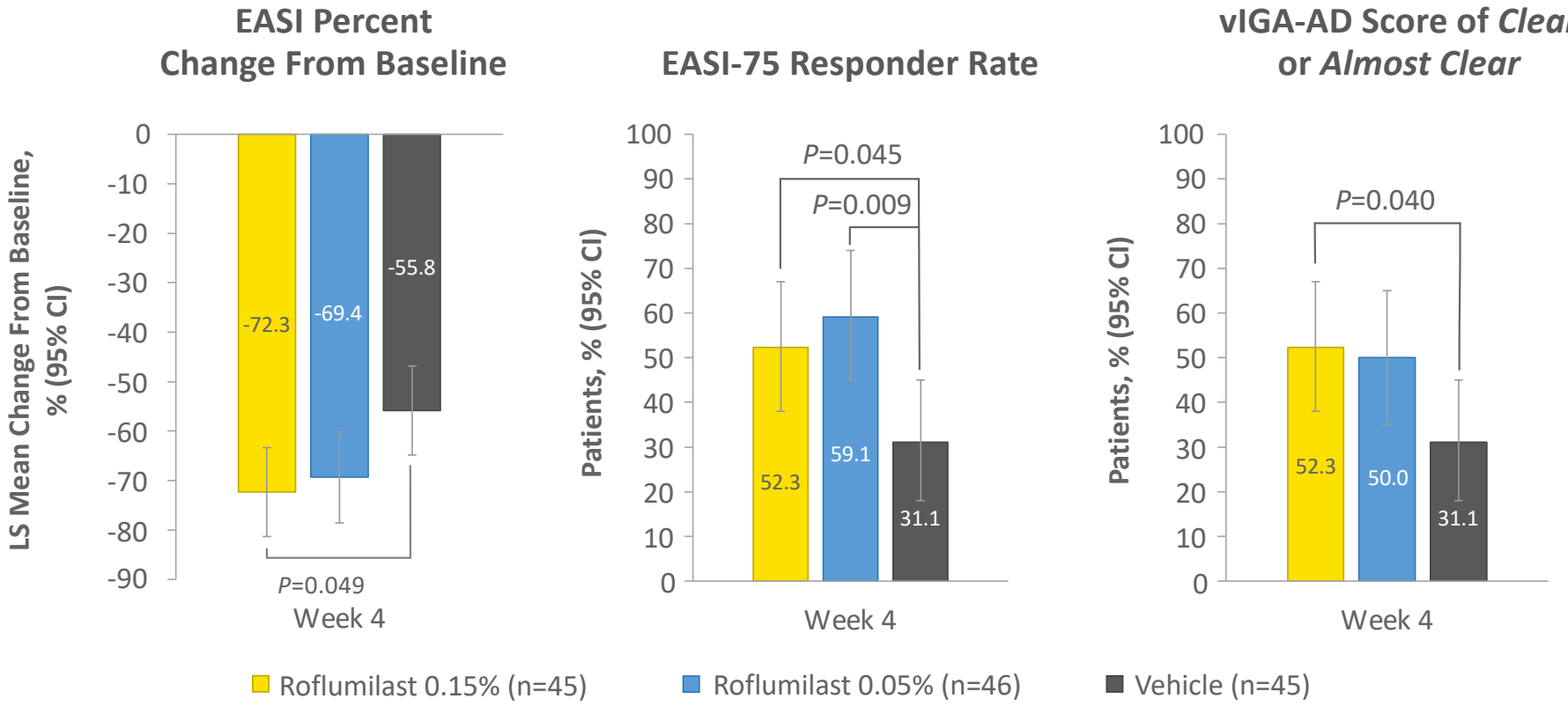
Secondary and Exploratory Endpoints Showed Significant Improvement With Roflumilast Cream Over Vehicle



Data presented for intent-to-treat population. Only significant *P*-values ($P<0.05$) shown. CI: confidence interval; EASI: Eczema Area and Severity Index; LS: least squares; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis.

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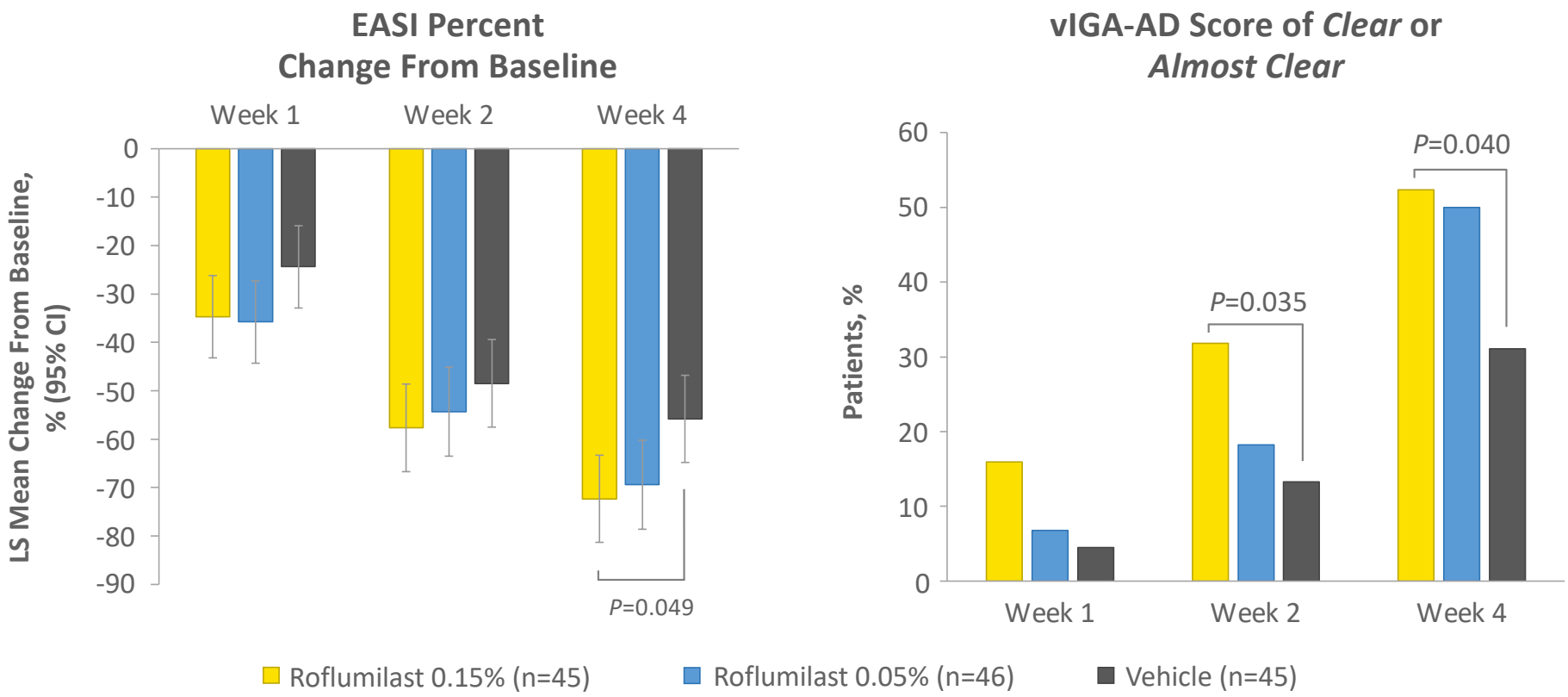
Efficacy of Roflumilast Cream Continued to Improve Through Week 4



Data presented for intent-to-treat population. Only significant P-values (P<0.05) shown. CI: confidence interval; EASI: Eczema Area and Severity Index; LS: least squares; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis.

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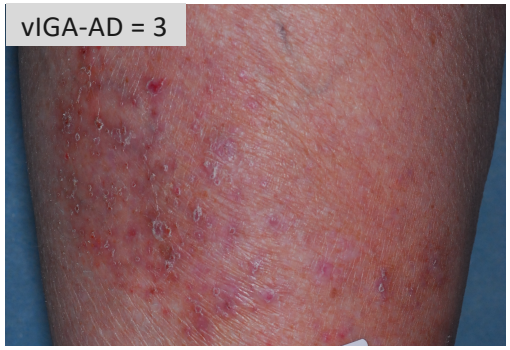
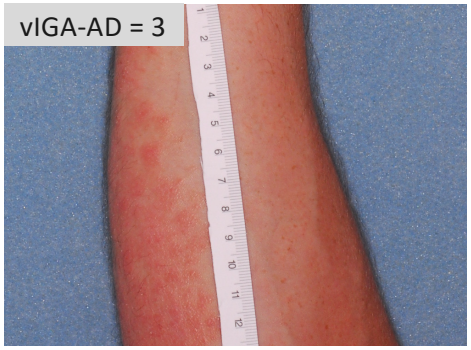
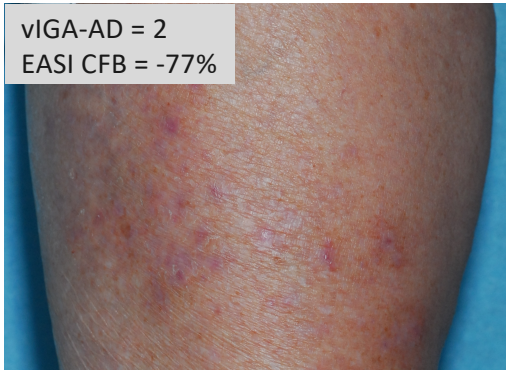
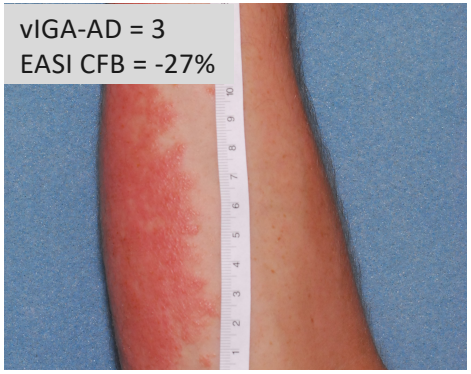
Roflumilast Cream Improved Severity of Atopic Dermatitis

	Roflumilast 0.15%	Vehicle
Baseline	vIGA-AD = 3 	vIGA-AD = 3 
Week 4	vIGA-AD = 2 EASI CFB = -77% 	vIGA-AD = 3 EASI CFB = -27% 

CFB: change from baseline; EASI: Eczema Area and Severity Index; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis.

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TEAEs Uncommon; Similar Incidence Across Groups

- Safety and tolerability of roflumilast was similar to vehicle group
- All TEAEs were mild or moderate
- Low rates of application site AEs
- No psychiatric TEAEs
- No unintentional weight loss of more than 5%

Category, n (%)	Roflumilast 0.15% (n=45)	Roflumilast 0.05% (n=46)	Vehicle (n=45)
Patients with			
Any TEAE	12 (26.7)	10 (21.7)	6 (13.3)
Any treatment-related TEAE	0	2 (4.3)	2 (4.4)
TEAE leading to study discontinuation[a]	0	1 (2.2)	1 (2.2)
SAE[b]	0	1 (2.2)	0
Maximum severity of TEAEs			
Mild	10 (22.2)	6 (13.0)	5 (11.1)
Moderate	2 (4.4)	4 (8.7)	1 (2.2)
Application site TEAEs			
Application site pain	0	1 (2.2)	1 (2.2)
Atopic dermatitis worsening	0	0	1 (2.2)
Skin laceration[c]	0	1 (2.2)	0

[a]Roflumilast 0.05%: moderate application site pain; vehicle: moderate worsening of AD. [b]Roflumilast 0.03%: mild traumatic spinal cord compression that was considered unrelated to the study drug. [c]Unrelated to the study drug.

Data presented for safety population. AE: adverse event; AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

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Conclusions

- In this small proof-of-concept study, once-daily roflumilast cream demonstrated efficacy compared with vehicle cream in atopic dermatitis
  - Primary endpoint showed a trend towards, but did not reach, statistical significance
  - Statistical significance was reached for other efficacy endpoints
  - Substantial efficacy noted, with 72.3% EASI improvement and >50% of patients achieving *clear* or *almost clear* skin on vIGA-AD at Week 4 for roflumilast cream 0.15%
  - Continued efficacy through Week 4
  - High response rate with cream vehicle in this study may have been a factor in not reaching statistical significance in the primary endpoint
- Roflumilast cream was well-tolerated, with a low rate of application site reactions, and no signs of local irritation

Roflumilast cream, a potent PDE-4 inhibitor, represents a potential effective QD topical treatment for atopic dermatitis. Favorable safety profile and encouraging efficacy results warrant further investigation of roflumilast cream in larger studies over longer times

EASI: Eczema Area and Severity Index; PDE-4: phosphodiesterase-4; QD: once daily; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis.

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