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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INTRODUCTION

- 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
- Phosphodiesterase-4 (PDE-4) is the predominant cyclic adenosine monophosphate–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]

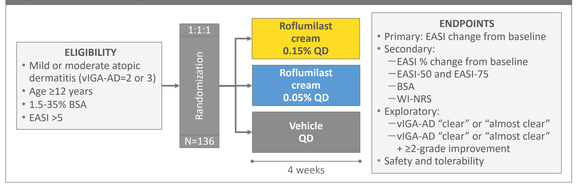
OBJECTIVE

- To assess the short-term safety and efficacy of once-daily (QD) topical roflumilast cream in patients with mild to moderate atopic dermatitis

METHODS

- Randomized, double-blind, vehicle-controlled, multicenter phase 2 study (ClinicalTrials.gov NCT03916081; **Figure 1**)

Figure 1. Study Design



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.

Statistical Analysis

- 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 test
- Comparisons were specified at the 0.05 level and were not adjusted for multiplicity

RESULTS

- Overall, patients were recruited from 3 sites in Canada and 19 sites in the United States and randomized to roflumilast 0.15% (n=45), roflumilast 0.05% (n=46), or vehicle (n=45)
- Completion rate was over 90% in all treatment groups
- Baseline characteristics are presented in **Table 1**

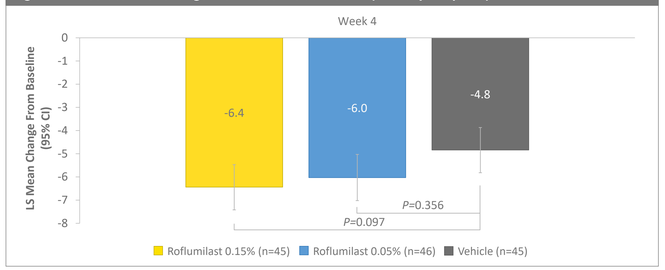
Table 1. Baseline Characteristics

	Roflumilast 0.15% (n=45)	Roflumilast 0.05% (n=46)	Vehicle (n=45)
Age, mean (SD), years	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.

- At the early timepoint of 4 weeks, roflumilast cream improved severity of atopic dermatitis as measured by absolute change from baseline in Eczema Area and Severity Index (EASI), yet was not statistically significant (**Figure 2**)
- A robust response to vehicle was observed

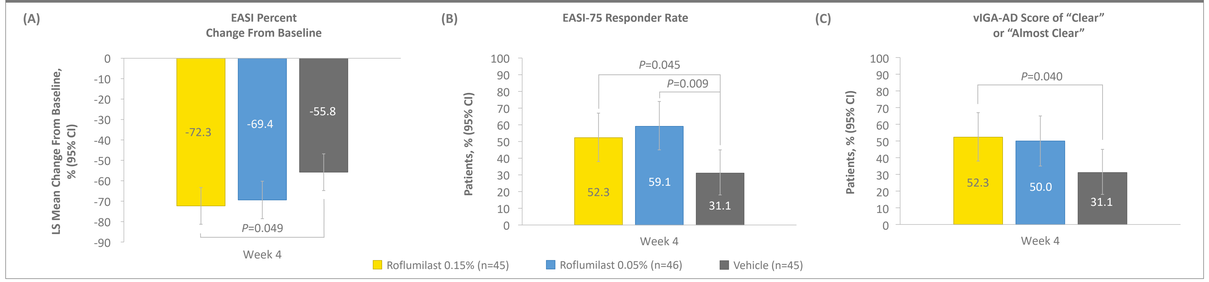
Figure 2. Absolute EASI Change From Baseline at Week 4 (Primary Endpoint)



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

- Secondary and exploratory endpoints showed significant improvement with roflumilast cream over vehicle at Week 4 (**Figure 3**)

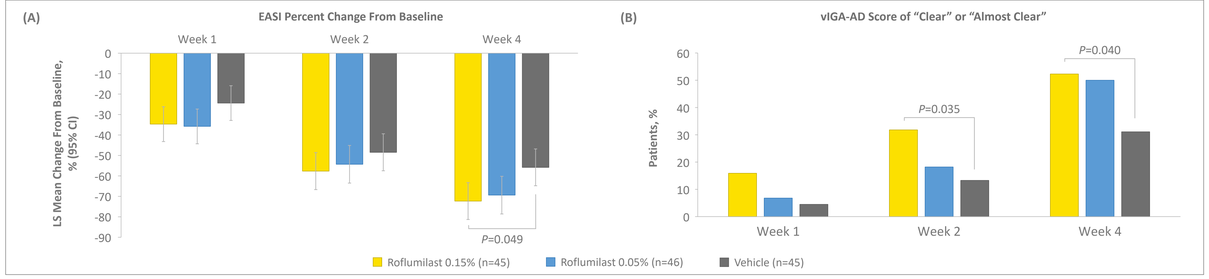
Figure 3. Secondary (A, B) and Exploratory (C) Efficacy Endpoints at Week 4



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.

- Efficacy of roflumilast cream continued to improve through Week 4 (**Figure 4**)

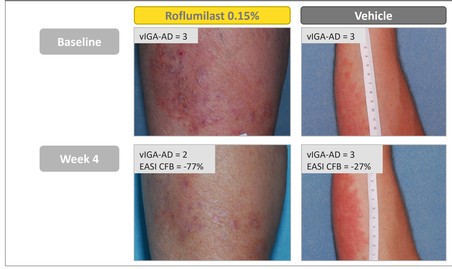
Figure 4. Secondary (A) and Exploratory (B) Efficacy Endpoints at Weeks 1 Through 4



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.

- Patient cases illustrating improvement in severity of atopic dermatitis with roflumilast cream are shown in **Figure 5**

Figure 5. Patient Cases Representative of the Efficacy of Roflumilast Cream 0.15% at Week 4 Compared With Vehicle



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

Safety and Tolerability

- Treatment-emergent adverse events (TEAEs) were uncommon in this study (**Table 2**)
- Safety and tolerability of roflumilast was similar to vehicle group
- All TEAEs were mild or moderate
- Low rates of application-site adverse events
- No psychiatric TEAEs
- No unintentional weight loss of more than 5%

Table 2. Summary of AEs

TEAE, 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 0.05%: 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; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

CONCLUSIONS

- In this small proof-of-concept study, roflumilast cream QD demonstrated efficacy compared with vehicle cream in atopic dermatitis
  - Primary endpoint showed a trend toward, 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 was observed
  - 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

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DISCLOSURES

MJG, **LHK**, **MZ**, **ML**, **SEK**, **ZDD**, **LF**, **TMJ**, **ES-CP**, **RB**, **NB**, **STG**, and **RAK**: Investigator, consultant, and/or advisory board member for Arcutis Biotherapeutics, Inc. **ZDD** has received grant support from Arcutis Biotherapeutics, Inc. **HW** has a patent application relevant to this work. **CM**, **ME**, **LN**, **RCH**, **MG**, and **DRB**: Employees of Arcutis Biotherapeutics, Inc.

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