

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

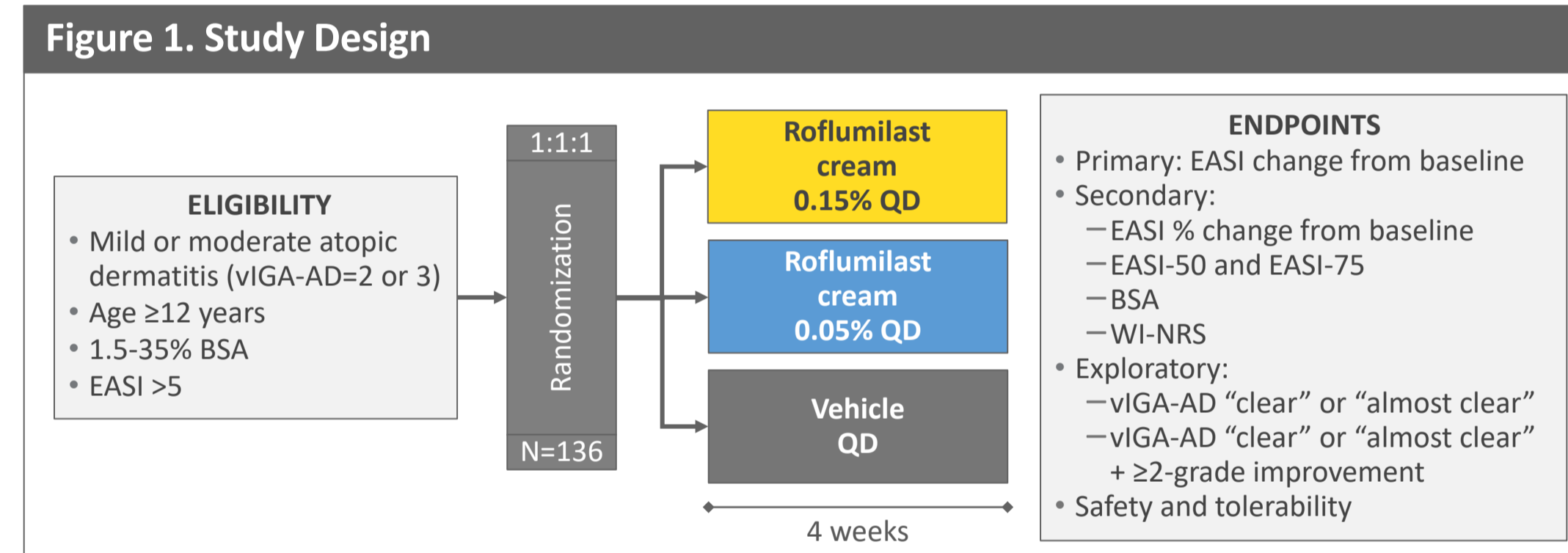
- Majority of patients with atopic dermatitis are treated with topical anti-inflammatory therapy: corticosteroids or calcineurin inhibitors, in combination with emollients¹
 - Side effects and poor adherence limit long-term use of topical corticosteroids
 - Topical calcineurin inhibitors may cause local 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 inhibitors⁴
 - Roflumilast cream is in phase 3 development for plaque psoriasis⁵

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**)



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

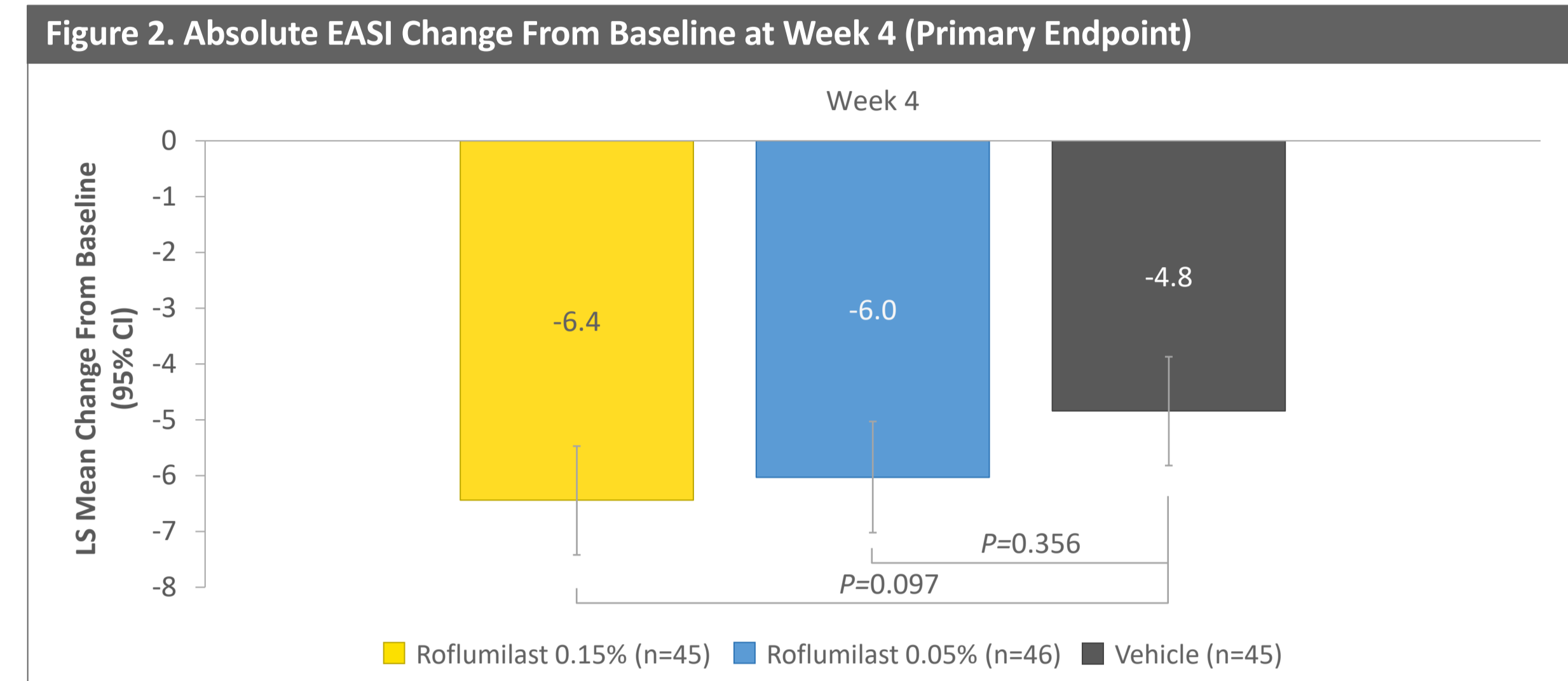
- Overall, patients were recruited from 3 sites in Canada and 19 sites in the United States and randomized to roflumilast 0.15% (n=45), roflumilast 0.05% (n=46), or vehicle (n=45)
- Completion rate was over 90% in all treatment groups
- Baseline characteristics are presented in **Table 1**

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)

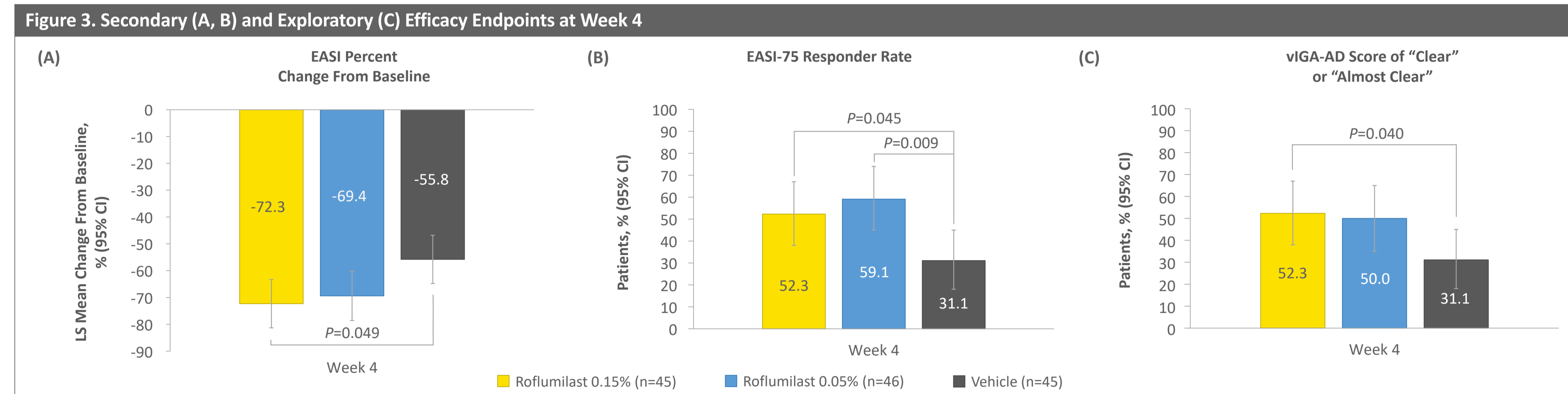
Data are presented for safety population. BSA: body surface area; EASI: Eczema Area and Severity Index; SD: standard deviation; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis; WI-NRS: Worst Itch Numeric Rating Scale.

- 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



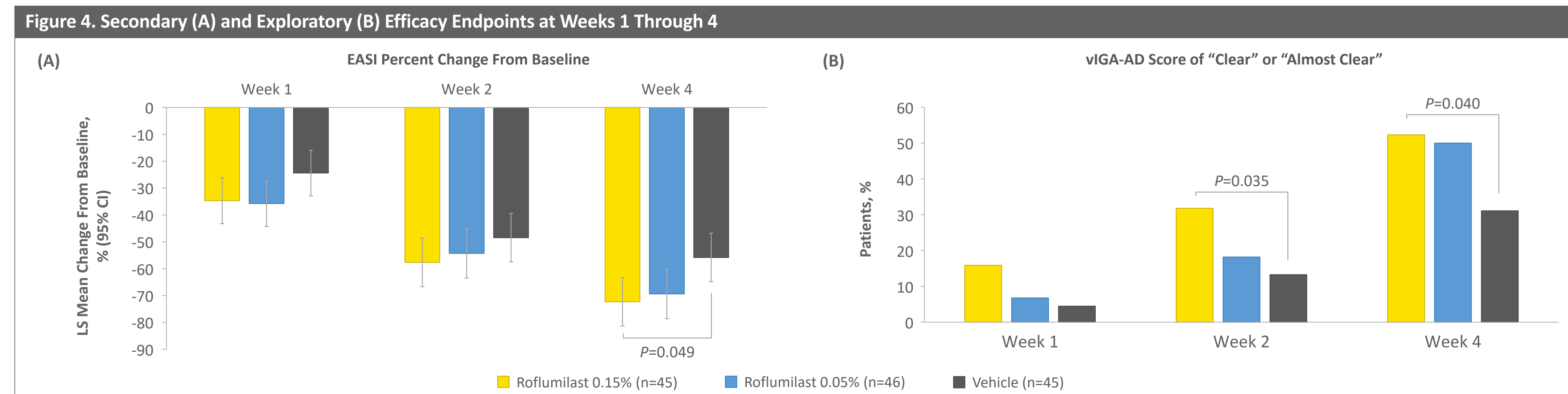
Data presented for intent-to-treat population. CI: confidence interval; EASI: Eczema Area and Severity Index; LS: least squares.

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



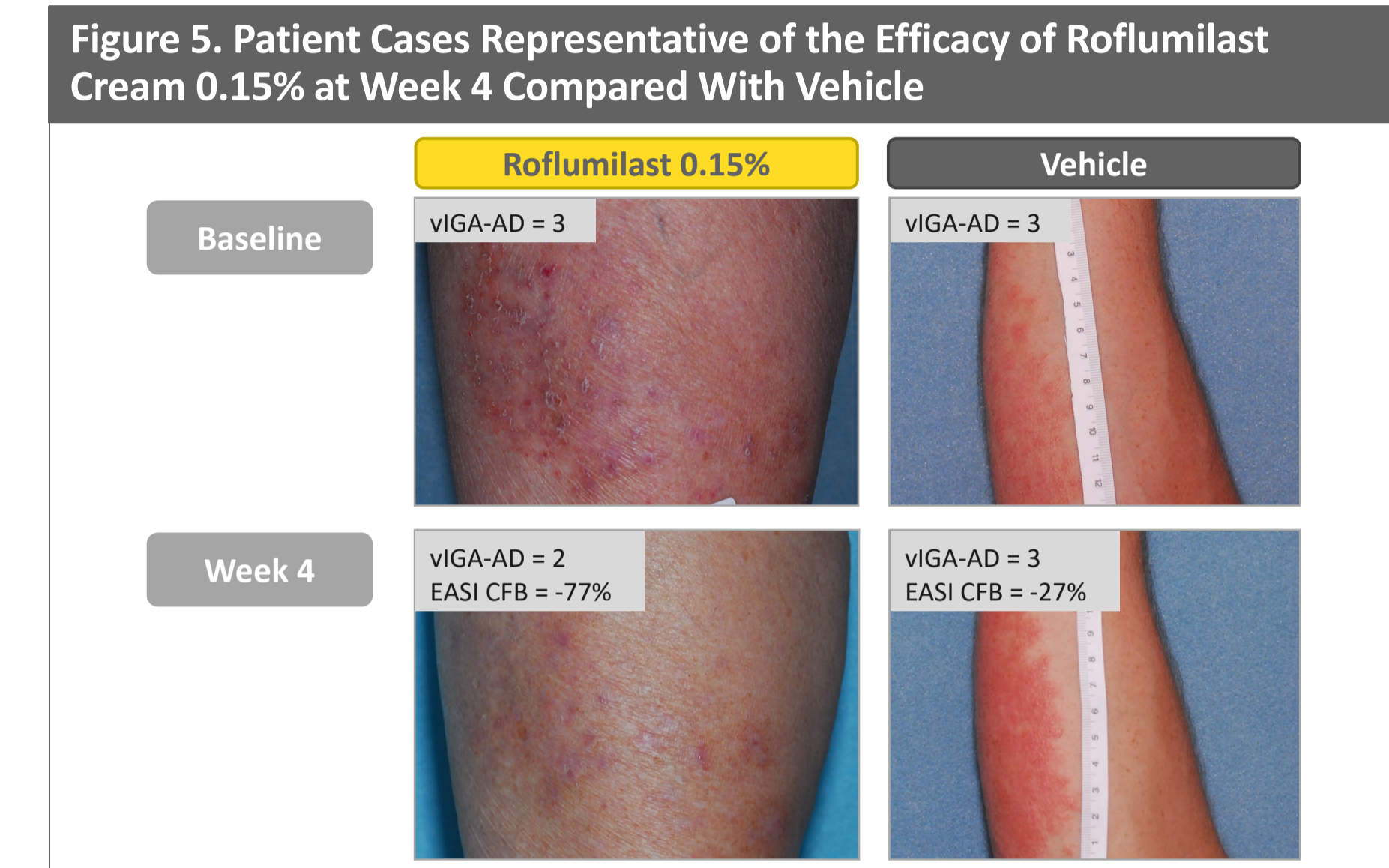
Data presented for intent-to-treat population. Only significant P-values (P<0.05) shown. CI: confidence interval; EASI: Eczema Area and Severity Index; LS: least squares; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis.

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



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**



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

^aRoflumilast 0.05%: moderate application site pain; vehicle: moderate worsening of AD. ^bRoflumilast 0.05%: mild traumatic spinal cord compression that was considered unrelated to the study drug. ^cUnrelated 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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ACKNOWLEDGEMENTS

- This study was supported by Arcutis Biotherapeutics, Inc.
- Thank you to the investigators and their staff for their participation in the trial
- We are grateful to the study participants and their families for their time and commitment
- Writing support was provided by Aleksandra Adomas, PhD, CMPP, Alligent Biopharm Consulting LLC, Philadelphia, PA, and funded by Arcutis Biotherapeutics, Inc.

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.