

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 & Objectives

Atopic dermatitis (AD) is commonly treated with topical anti-inflammatory therapy (corticosteroids or calcineurin inhibitors) in combination with emollients. However, side effects limit long-term use of topical corticosteroids and alternative treatments are needed. Roflumilast cream (ARQ-151) is a highly potent phosphodiesterase-4 (PDE-4) inhibitor with ~25- to >300-fold higher potency than the approved PDE-4 inhibitors, crisaborole and apremilast. Roflumilast cream 0.3% is currently in Phase 3 development for plaque psoriasis. The objective of this Phase 2, proof-of-concept study was to assess the safety and efficacy of once-daily (QD) roflumilast 0.15% and 0.05% in patients with mild to moderate AD.

Materials & Methods

This randomized, parallel-group, double-blind, vehicle-controlled study enrolled 136 patients (≥12 years of age) from North America who had 1.5-35% body surface area (BSA) affected by AD, with a validated investigator global assessment-AD (vIGA-AD) score of 2 (mild) or 3 (moderate), and eczema area and severity index (EASI) score of ≥5. Patients were randomized (1:1:1) to roflumilast 0.15%, roflumilast 0.05% or vehicle QD for 4 weeks. The primary efficacy endpoint was absolute change from baseline in EASI score at Week 4. Other efficacy assessments included EASI percent change from baseline and responder rates, and vIGA-AD. Safety was evaluated through local tolerability assessments and adverse events (AEs). Testing of secondary endpoints was not adjusted for multiplicity.

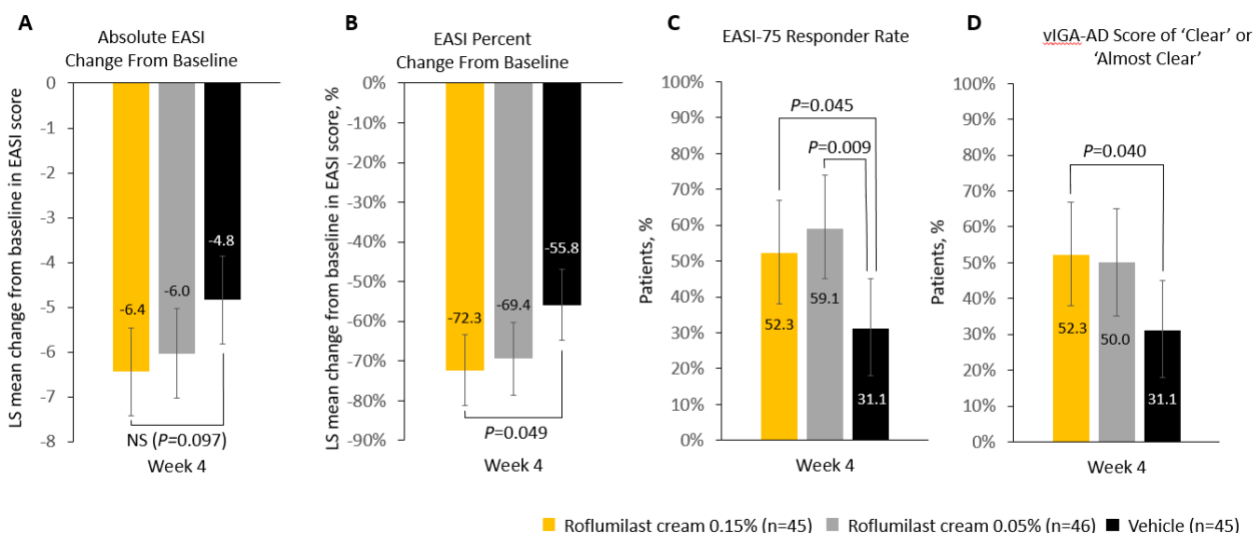
Results

At baseline, 22.1% of patients had a vIGA-AD of mild, 77.9% had a vIGA-AD of moderate, and mean BSA was 9.5%. Completion rate was over 90% in all treatment groups. At Week 4, the mean changes in EASI scores from baseline of 9.5, 8.4, and 9.2 were -6.4 ($P=0.097$ compared with vehicle), -6.0 ($P=0.356$), and -4.8 with roflumilast 0.15%, roflumilast 0.05%, and vehicle, respectively (primary endpoint; Figure). Statistically significant improvements compared with vehicle were observed at Week 4 for % change from baseline in EASI score (-72.3% [$P=0.049$], -69.4% [$P=0.164$], and -55.8% for roflumilast 0.15%, roflumilast 0.05%, and vehicle, respectively); patients reaching EASI-75 (52.3% [$P=0.045$], 59.1% [$P=0.009$], and 31.1%); and patients achieving vIGA-AD score of *clear* or *almost clear* (52.3% [$P=0.040$], 50.0 [$P=0.076$], and 31.1%; Figure). At Week 4, there was no evidence of efficacy plateau as measured by EASI and vIGA-AD. Overall, 4 patients experienced a treatment-related TEAE: none in the roflumilast 0.15% group, 2 patients (4.3%) in the roflumilast 0.05% group, and 2 patients (4.4%) in the vehicle group. All TEAEs were mild or moderate. Only 2 patients (1 in roflumilast 0.05% and 1 in vehicle group) discontinued study drug due to an AE. Application site pain was reported in just 2 patients: 1 (2.2%) in the roflumilast 0.05% group and 1 (2.2%) in the vehicle group.

Discussion

In this small, proof-of-concept study, the primary endpoint showed a trend towards, but did not reach, statistical significance. However, statistical significance was reached for other efficacy endpoints including % change from baseline in EASI score, EASI-75 responders, and patients achieving vIGA-AD score of *clear* or *almost clear*. Both doses of roflumilast (0.15% and 0.05%) had a favorable safety profile, with a low rate of application site reactions. This study suggests that roflumilast cream, a potent PDE-4 inhibitor, represents a potential effective QD treatment for AD.

Figure. Primary (A), secondary (B, C), and exploratory (D) efficacy endpoints.



Data presented for intent-to-treat population. Error bars represent 95% confidence intervals. Only significant P -values ($P<0.05$) shown for secondary and exploratory endpoints. EASI: eczema area and severity index; LS: least squares; NS: not significant; vIGA-AD: validated investigator global assessment—atopic dermatitis.