



# 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

**M.J. Gooderham** has been a speaker, advisory board member, investigator and/or consultant for AbbVie, Akros, Amgen, Arcutis, BMS, Boehringer Ingelheim, Celgene, Dermavant, Dermira, Eli Lilly, Galderma, GSK, Incyte, Janssen, Kyowa Kirin, LEO Pharma, Medimmune, Merck, Novartis, Pfizer, Regeneron, Sanofi Genzyme, UCB Pharma, and Valeant/Bausch.

**L.H. Kircik** is an investigator, consultant, speaker, and/or serves on advisory boards for Abbott Laboratories, Acambis, Aclaris, Allergan, Inc., Almirall, Amgen Inc., Anacor Pharmaceuticals, Assos Pharma, Astellas Pharma US, Inc., Asubio, Berlex Laboratories (Bayer HealthCare Pharmaceuticals), Biogen-Idec, Biolife, Biopelle, Boehringer Ingelheim, Breckinridge Pharma, Colbar, Celgene, Centocor, Inc., Cellceutix, CIPHER, Coherus, CollaGenex, Combinatrix, Connetics Corporation, Coria, Dermavant, Dermira, Dermik Laboratories, Dow Pharmaceutical Sciences, Inc., Dusa, Eli Lilly, Embil Pharmaceuticals, EOS, Exeltis, Ferndale Laboratories, Inc., Foamix, Genentech, Inc., GlaxoSmithKline, PLC, Health Point, LTD, Idera, Intendis, Innocutis, Innovail, Isdin, Johnson & Johnson, Laboratory Skin Care Inc., Leo Pharma, L'Oreal, 3M, Maruho, Medical International Technologies, Merck, Medicis Pharmaceutical Corp., Merz, Nano Bio, Novartis AG, Noven Pharmaceuticals, Nucrust Pharmaceuticals Corp., Obagi, Onset, OrthoNeutrogena, Promius, PediaPharma, PharmaDerm, Pfizer, PuraCap, QLT, Inc., Quinova, Quatrix, Serono (Merck Serono International SA), SkinMedica, Inc., Stiefel Laboratories, Inc., Sun Pharma, Taro, TolerRx, Triax, UCB Pharma, Valeant Pharmaceuticals Intl, Warner-Chilcott, XenoPort, and ZAGE.

**M. Zirwas** is an investigator, consultant, and/or speaker for AbbVie, Arcutis, Asana, Avillion, Dermavant, DS Biopharma, Edessa Biotech, Fit Bit, Foamix, Galderma, Genentech/Novartis, Incyte, Janssen, Leo Pharma, L'Oreal, Lilly, Menlo, Ortho Derm, Pfizer, Regeneron/Sanofi, and UCB Pharma, and is part owner of AsepticMD. **M. Lee** is an investigator for AbbVie, Arcutis, Bausch Health, Boehringer Ingelheim, Dermavant, Dermira, Eli Lilly, Incyte, Foamix, Pfizer, and UCB. **S.E. Kempers** is an investigator for Arcutis, and serves as a consultant for Foamix and Kinex.

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# Background

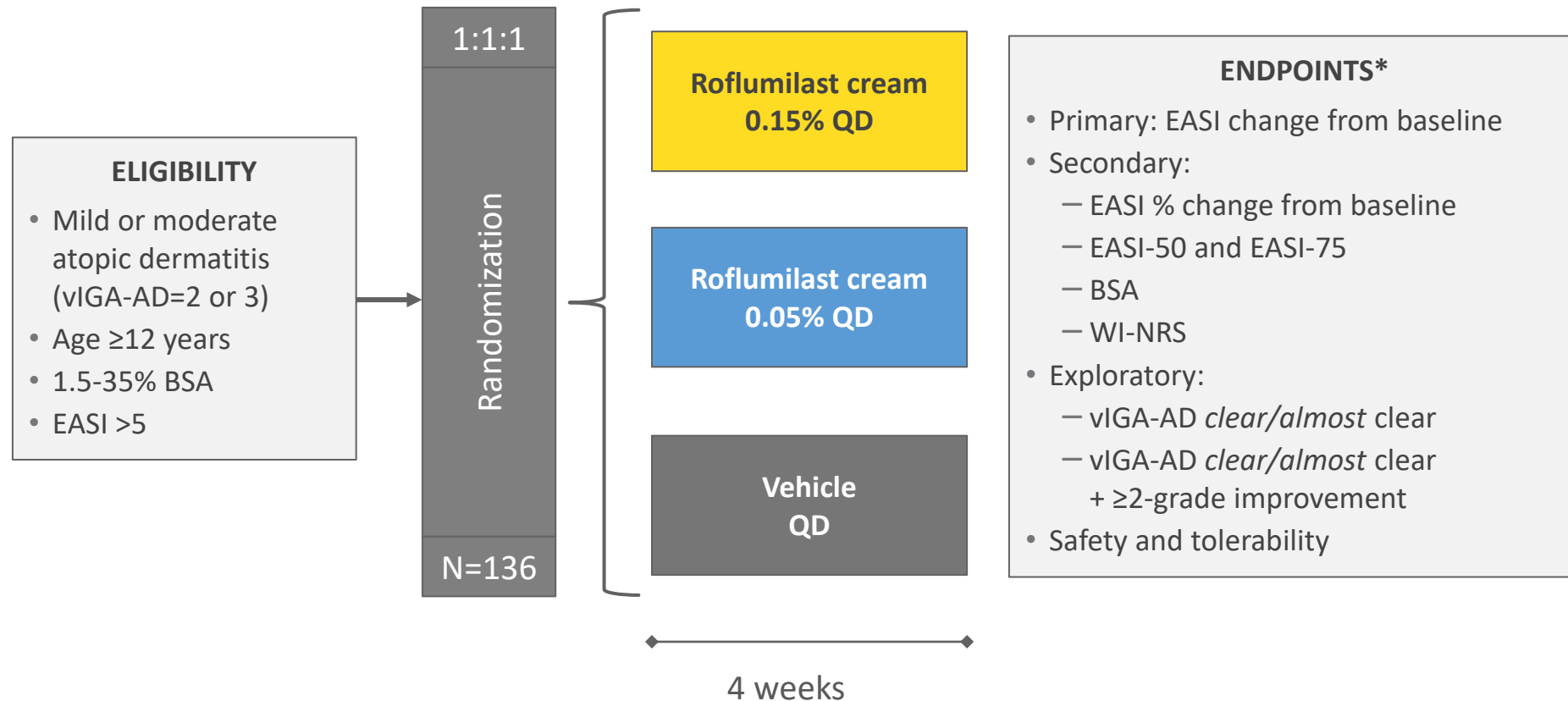
- Majority of patients with atopic dermatitis are treated with topical anti-inflammatory therapy: corticosteroids or calcineurin inhibitors, in combination with emollients<sup>1</sup>
  - Side effects and poor adherence limit long-term use of topical corticosteroids
  - Topical calcineurin inhibitors 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<sup>2,3</sup>
- Roflumilast cream is a highly potent PDE-4 inhibitor with ~25- to >300-fold higher potency than other approved PDE-4 inhibitors<sup>4</sup>
  - Roflumilast cream is in Phase 3 development for plaque psoriasis<sup>5</sup>
- 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.

<sup>1</sup>Silverberg JI, et al. *J Dermatolog Treat.* 2016;27:568-576. <sup>2</sup>Bäumer W, et al. *Inflamm Allergy Drug Targets.* 2007;6:17-26. <sup>3</sup>Guttman-Yassky E, et al. *Exp Dermatol.* 2019;28:3-10. <sup>4</sup>Dong C, et al. *J Pharmacol Exp Ther.* 2016;358:413-422. <sup>5</sup>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.

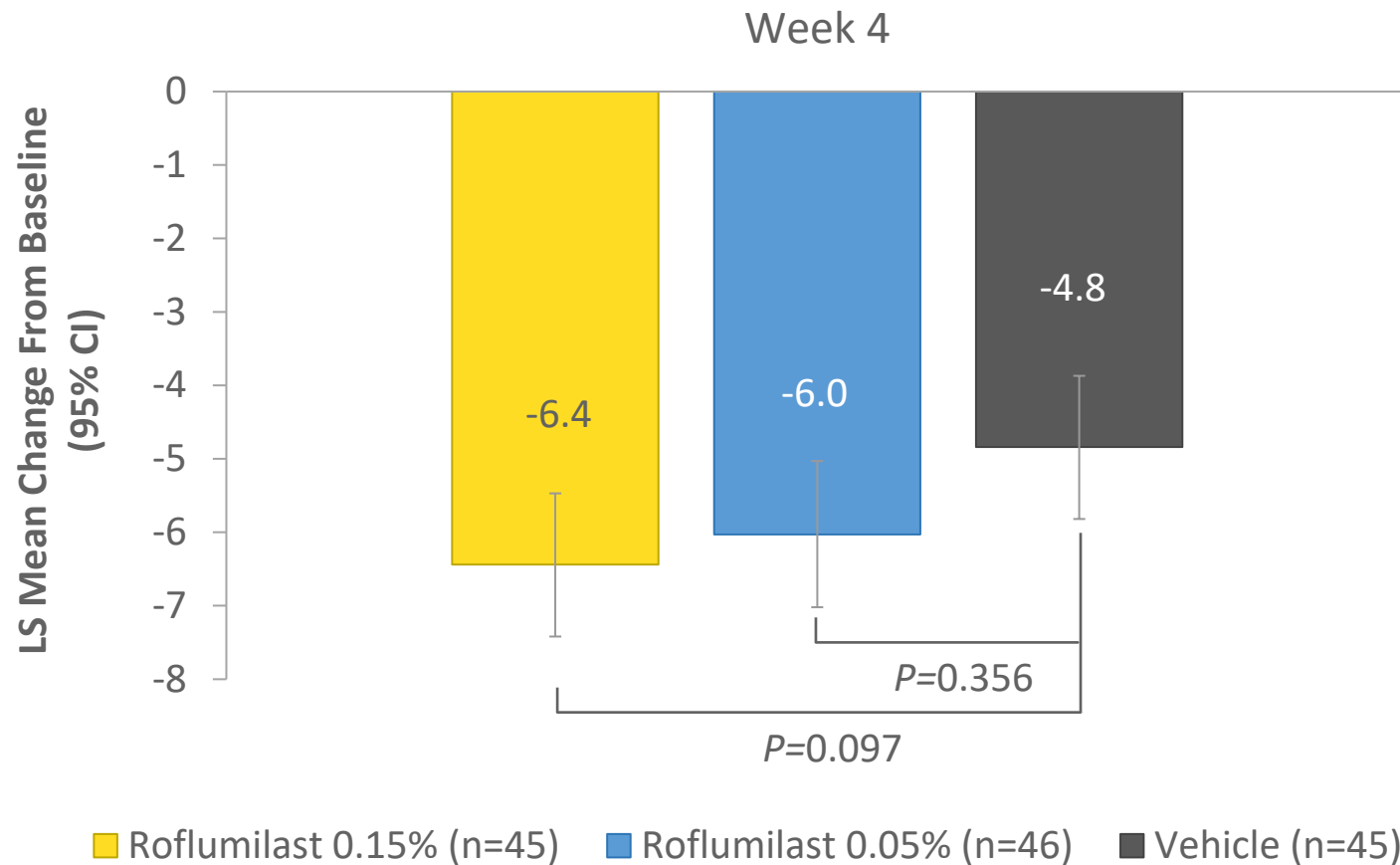
# Baseline Characteristics

	Roflumilast 0.15% (n=45)	Roflumilast 0.05% (n=46)	Vehicle (n=45)
<b>Age, mean years (SD)</b>	38.0 (16.5)	44.3 (17.0)	42.4 (17.6)
<b>Sex, female, n (%)</b>	33 (73.3)	31 (67.4)	29 (64.4)
<b>Race, n (%)</b>			
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)
<b>vIGA-AD score, mean (SD)</b>	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)
<b>EASI, mean score (SD)</b>	9.5 (4.1)	8.4 (4.1)	9.2 (3.9)
<b>BSA, mean (SD), %</b>	9.6 (6.0)	8.4 (7.1)	10.5 (6.6)
<b>WI-NRS, mean score (SD)</b>	6.6 (2.0)	6.5 (2.0)	7.2 (2.1)
WI-NRS score $\geq 6$ , 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.

# Severity of Atopic Dermatitis Improved With Roflumilast Cream

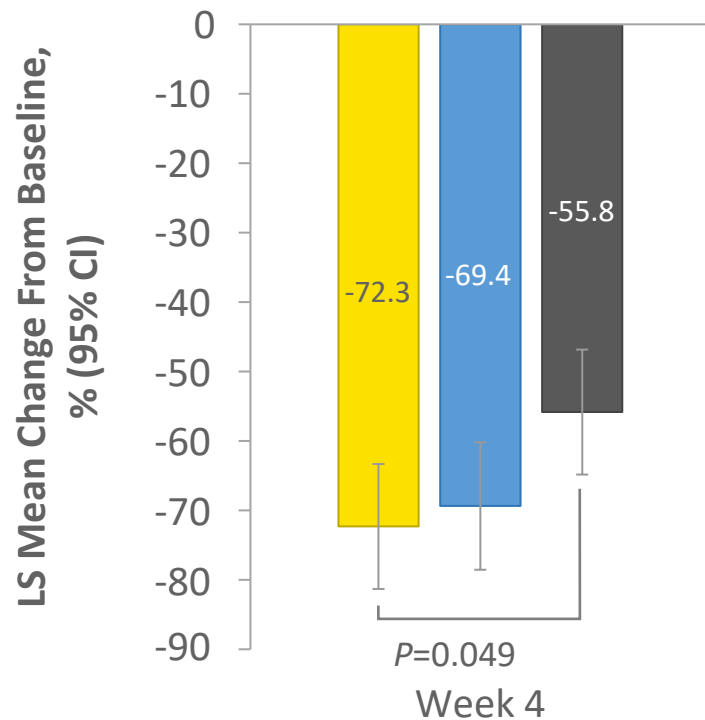
## Absolute EASI Change From Baseline (Primary Endpoint)



- 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

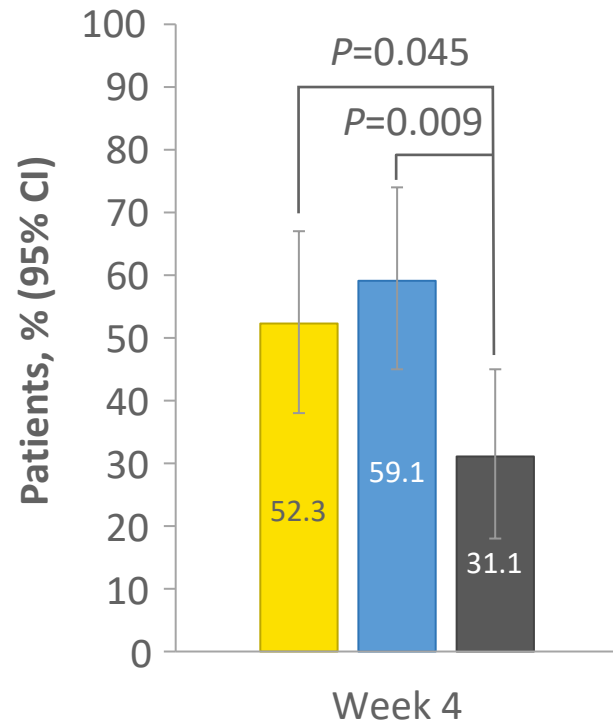
# Secondary and Exploratory Endpoints Showed Significant Improvement With Roflumilast Cream Over Vehicle

**EASI Percent Change From Baseline**



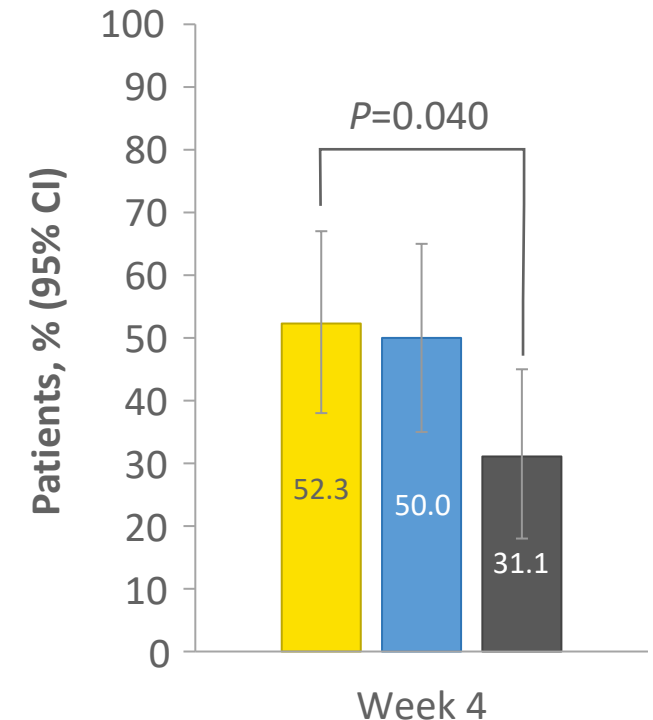
■ Roflumilast 0.15% (n=45)

**EASI-75 Responder Rate**



■ Roflumilast 0.05% (n=46)

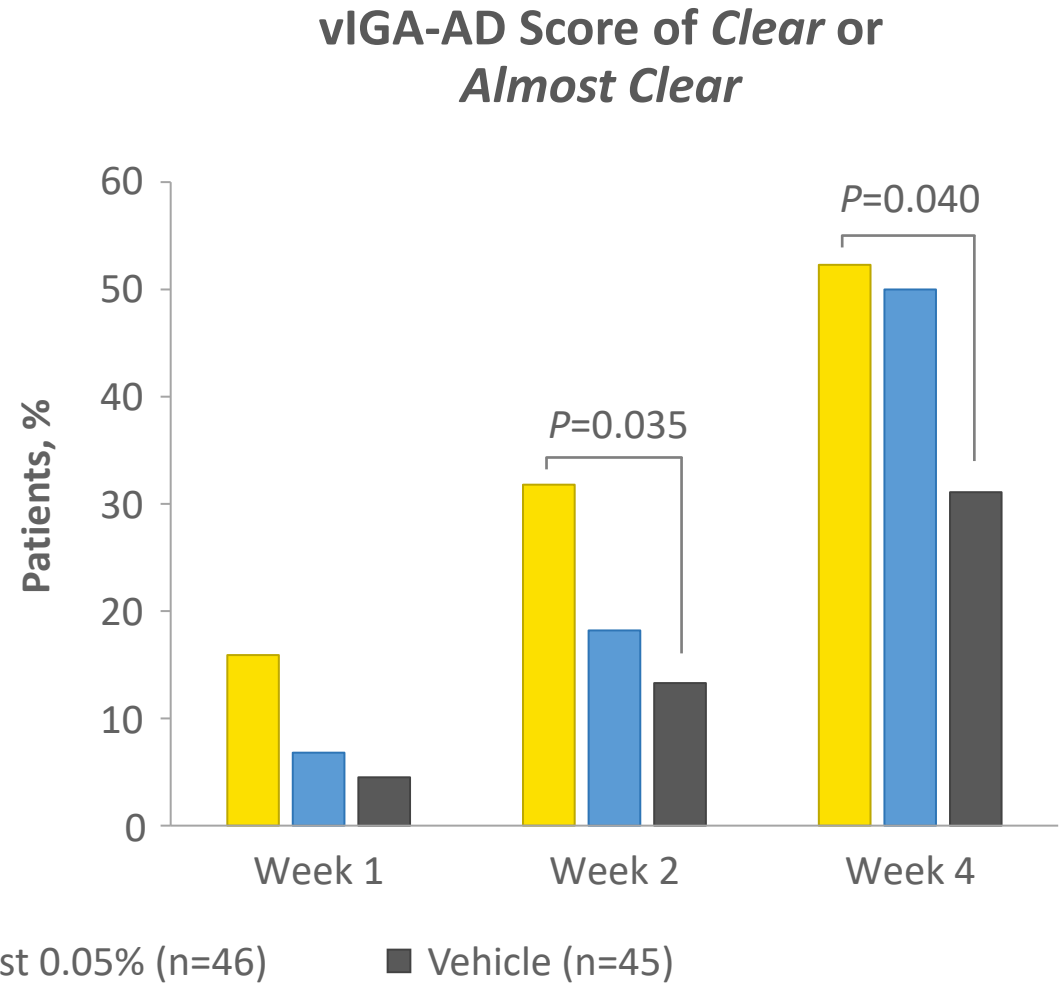
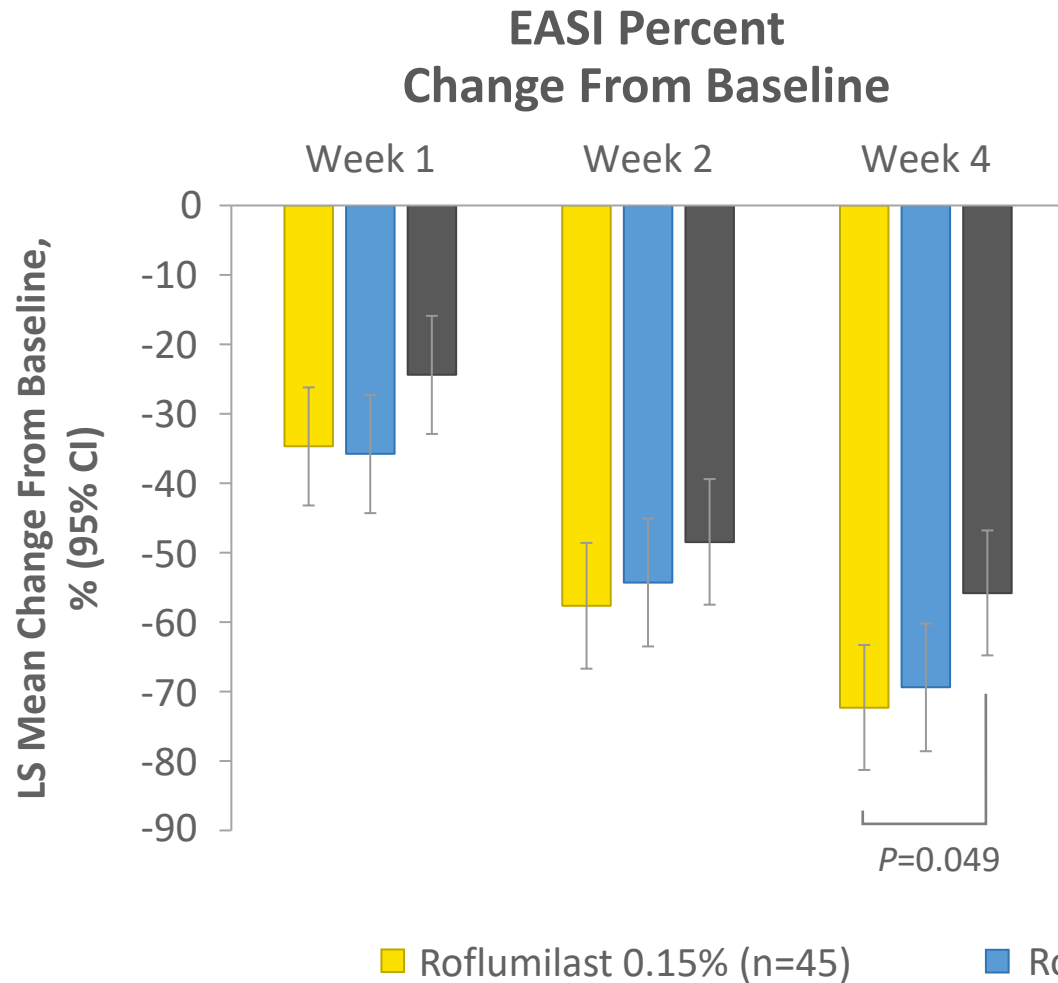
**vIGA-AD Score of *Clear* or *Almost Clear***



■ Vehicle (n=45)

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.

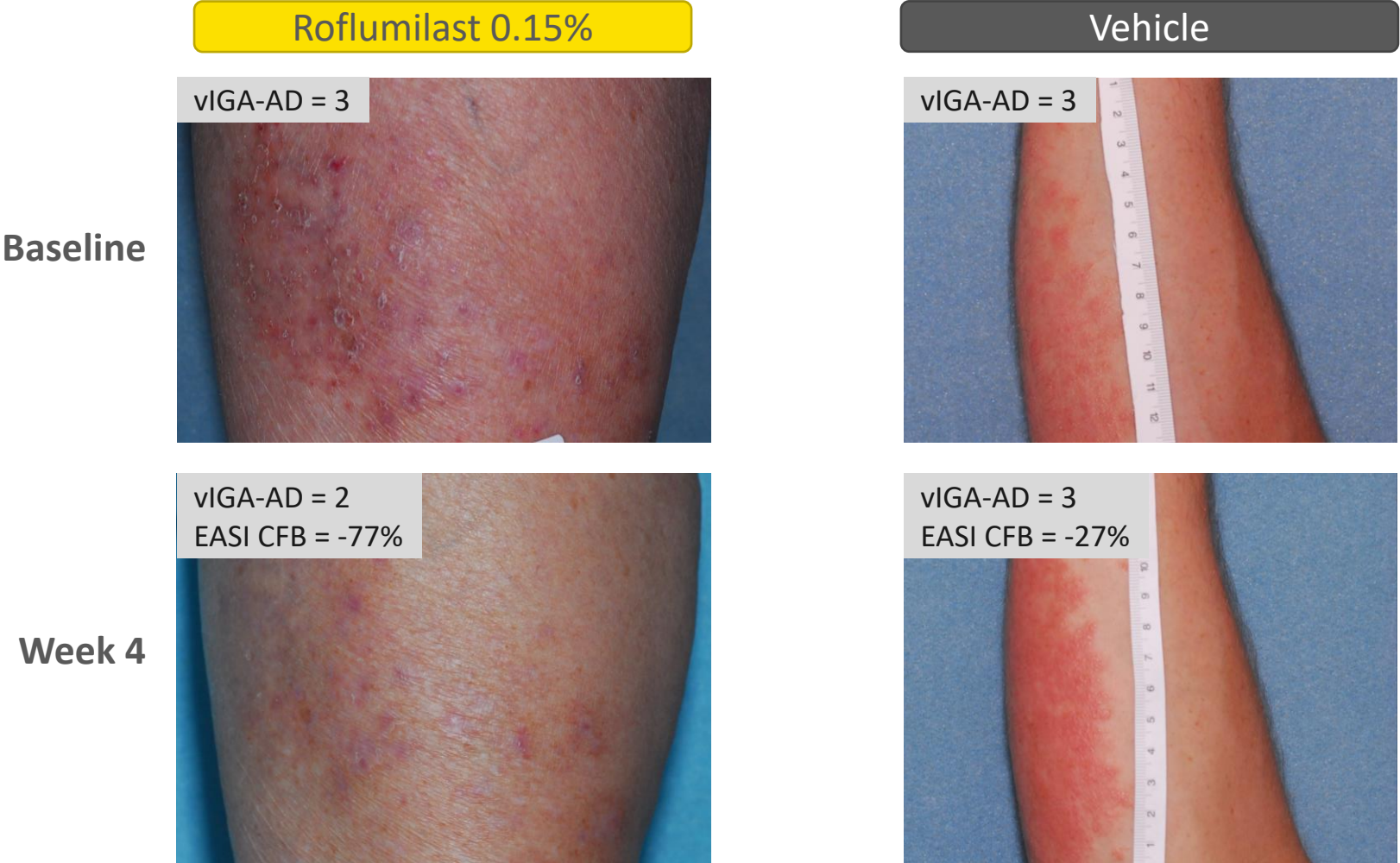
# Efficacy of Roflumilast Cream Continued to Improve Through Week 4



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.



# Roflumilast Cream Improved Severity of Atopic Dermatitis



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

# 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 <sup>a</sup>	0	1 (2.2)	1 (2.2)
SAE <sup>b</sup>	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 <sup>c</sup>	0	1 (2.2)	0

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

# 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

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