Pooled Safety and Local Tolerability of Roflumilast Cream 0.15% From the INTEGUMENT-1 and INTEGUMENT-2 Phase 3 Trials of Patients With Atopic Dermatitis: Subgroup Analysis of Patients With Prior Inadequate Response, Intolerance, and/or Contraindications to Topical Treatments

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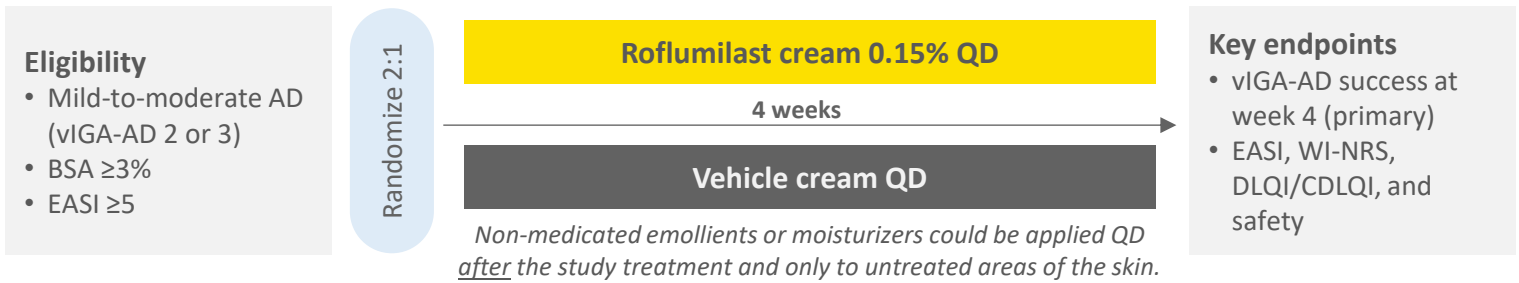
- Topical therapies available for treatment of AD (ie, TCS, TCI, and crisaborole) can have side effects and/or lack efficacy, which may negatively impact treatment adherence and disease control[1]
- Roflumilast cream 0.15%, a topical phosphodiesterase 4 inhibitor, was well tolerated and demonstrated efficacy in patients aged ≥6 years with AD in two phase 3 trials (INTEGUMENT-1 and -2), leading to its approval in that indication[2,3]



Safety, local tolerability, efficacy, and PROs of roflumilast in patients aged ≥6 years in the INTEGUMENT-1 and -2 trials are reported here for patients who had prior inadequate response, intolerance[a], and/or contraindications to a TCS, TCI, or crisaborole.

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[a]Intolerance included patient report of stinging, burning, and/or poor tolerability as a reason for stopping treatment with a TCI or crisaborole.

AD, atopic dermatitis; BSA, body surface area; CDLQI, Children's DLQI; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; PRO, patient-reported outcome; QD, once daily; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis; WI-NRS, Worst Itch-Numeric Rating Scale.

1. Butala S and Paller AS. *Ann Allergy Asthma Immunol.* 2022;128:488–504. 2. Simpson EL, et al. *JAMA Dermatol.* 2024;160:1161–1170. 3. ZORYVE® (roflumilast) cream 0.15%. Prescribing information. Arcutis Biotherapeutics, Inc.; July 2024. https://www.arcutis.com/wp-content/uploads/USPI-roflumilast-cream.pdf.

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Baseline Characteristics and 4-Week Safety Summary

- Of 1337 patients pooled from INTEGUMENT-1 and -2, prior inadequate response, intolerance, and/or contraindications to a TCS, TCI, or crisaborole was reported for 60.8%, 18.1%, and 7.3% of patients at baseline, respectively
  - Demographics and baseline disease characteristics were generally similar across treatment groups with a mean age of 28 years
    - A comparable proportion of patients had Fitzpatrick skin type I-III and type IV-VI
    - Intolerance to a TCI and crisaborole because of stinging, burning, and/or poor tolerability was reported for 67/242 (27.7%) and 47/98 (48.0%) patients, respectively

Roflumilast was well tolerated, regardless of prior inadequate response, intolerance, and/or contraindications to a TCS, TCI, or crisaborole.

- Severe or serious TEAEs were reported for ~1% of patients across roflumilast subgroups
- Most frequently reported TEAEs (≥1% in either overall group, and greater in roflumilast group) were headache, nausea, diarrhea, vomiting, and application-site pain
  - Application-site pain in the overall and prior[a] TCS, TCI, and crisaborole groups who received roflumilast was reported in 1.5%, 1.5%, 1.8%, and 1.4% of patients, respectively, and in 0.7%, 0.7%, 2.5%, and 0% of patients in the vehicle groups

Clinical characteristics		Overall		Prior inadequate response, intolerance, and/or contraindications					
				TCS		TCI		Crisaborole	
		Roflumilast 0.15% (N=884)	Vehicle (N=453)	Roflumilast 0.15% (n=545)	Vehicle (n=268)	Roflumilast 0.15% (n=161)	Vehicle (n=81)	Roflumilast 0.15% (n=68)	Vehicle (n=30)
vIGA-AD, n (%)	Mild (2)	211 (23.9)	112 (24.7)	134 (24.6)	68 (25.4)	35 (21.7)	22 (27.2)	14 (20.6)	4 (13.3)
	Moderate (3)	673 (76.1)	341 (75.3)	411 (75.4)	200 (74.6)	126 (78.3)	59 (72.8)	54 (79.4)	26 (86.7)
BSA, %, mean (SD) [range]		13.5 (11.8) [3–88]	13.9 (11.3) [3–86]	14.3 (12.7) [3–88]	14.3 (10.9) [3–63]	16.4 (14.5) [3–88]	15.9 (10.7) [3–47]	16.7 (13.0) [3–76]	16.7 (9.6) [4–44]
EASI, mean (SD)		10.1 (5.7)	10.0 (5.2)	10.6 (6.3)	10.2 (4.9)	11.7 (7.2)	10.7 (4.8)	12.3 (8.1)	10.8 (3.9)
Average weekly WI-NRS score, mean (SD)		6.1 (2.2)	5.9 (2.2)	6.1 (2.0)	6.0 (2.2)	6.2 (2.1)	6.3 (2.0)	6.4 (1.9)	6.1 (2.2)
Involvement, n (%)	Face	370 (41.9)	197 (43.5)	252 (46.2)	131 (48.9)	105 (65.2)	57 (70.4)	36 (52.9)	15 (50.0)
	Eyelid	178 (20.1)	99 (21.9)	126 (23.1)	64 (23.9)	63 (39.1)	29 (35.8)	17 (25.0)	8 (26.7)
Safety; patients, n (wINR, %)		**Roflumilast 0.15% (N=885)**	**Vehicle (N=451)**	**Roflumilast 0.15% (n=545)**	**Vehicle (n=267)**	**Roflumilast 0.15% (n=161)**	**Vehicle (n=80)**	**Roflumilast 0.15% (n=68)**	**Vehicle (n=30)**
≥1 TEAE		194 (21.9)	65 (14.4)	141 (25.9)	39 (14.6)	47 (29.3)	13 (16.3)	17 (25.1)	6 (21.0)
≥1 Treatment-related TEAE		53 (6.0)	12 (2.7)	40 (7.3)	7 (2.6)	19 (11.7)	6 (7.4)	2 (2.8)	2 (6.6)
≥1 TEAE leading to study/study drug discontinuation		14 (1.6)	5 (1.1)	10 (1.8)	3 (1.1)	4 (2.5)	2 (2.5)	1 (1.6)	0

[a]Subgroups had prior inadequate response, intolerance, and/or contraindications to a TCS, TCI, or crisaborole.

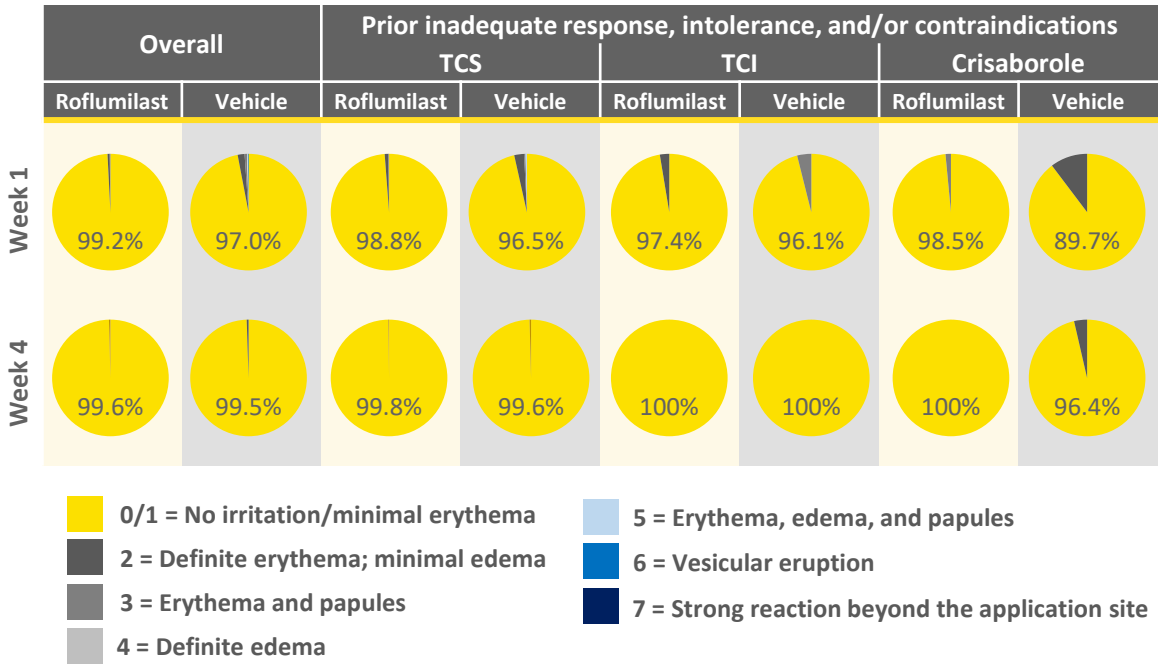
BSA, body surface area; EASI, Eczema Area and Severity Index; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; TEAE, treatment-emergent adverse events; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis; WI-NRS, Worst Itch-Numeric Rating Scale; wINR, weighted incidence rate.

Local Tolerability

Local tolerability was comparable for roflumilast and vehicle among those with prior inadequate response, intolerance, and/or contraindications to a TCS, TCI, or crisaborole and the overall population.

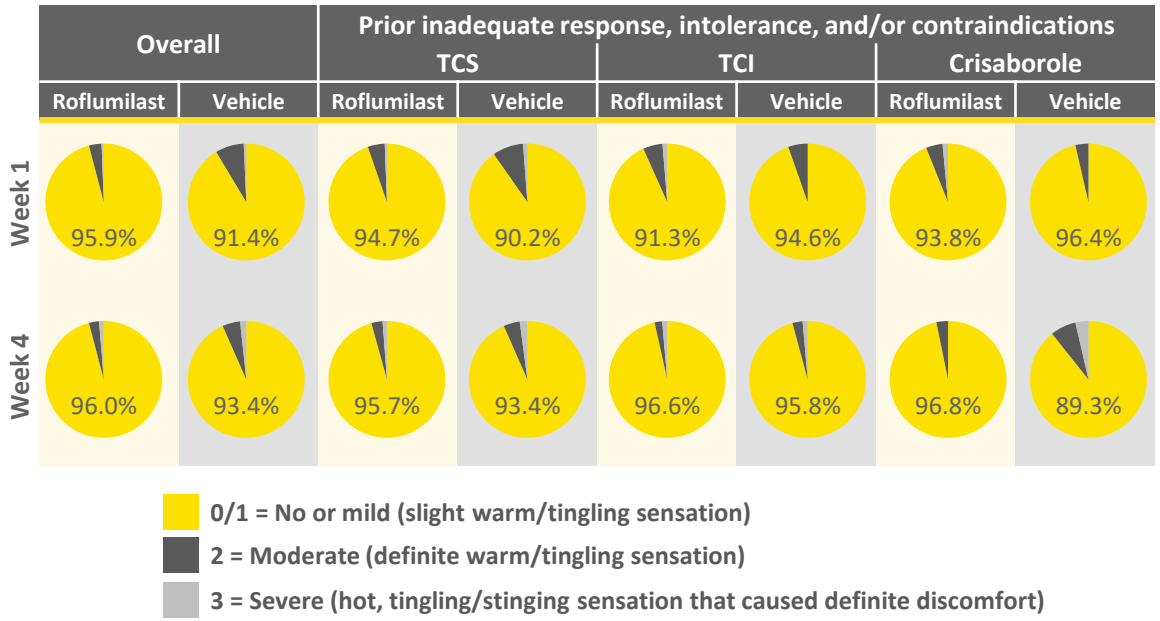
Investigator-rated

- No irritation/minimal erythema was reported by investigators in ≥97% of patients in each of the roflumilast-treated groups at all time points assessed



Patient-rated

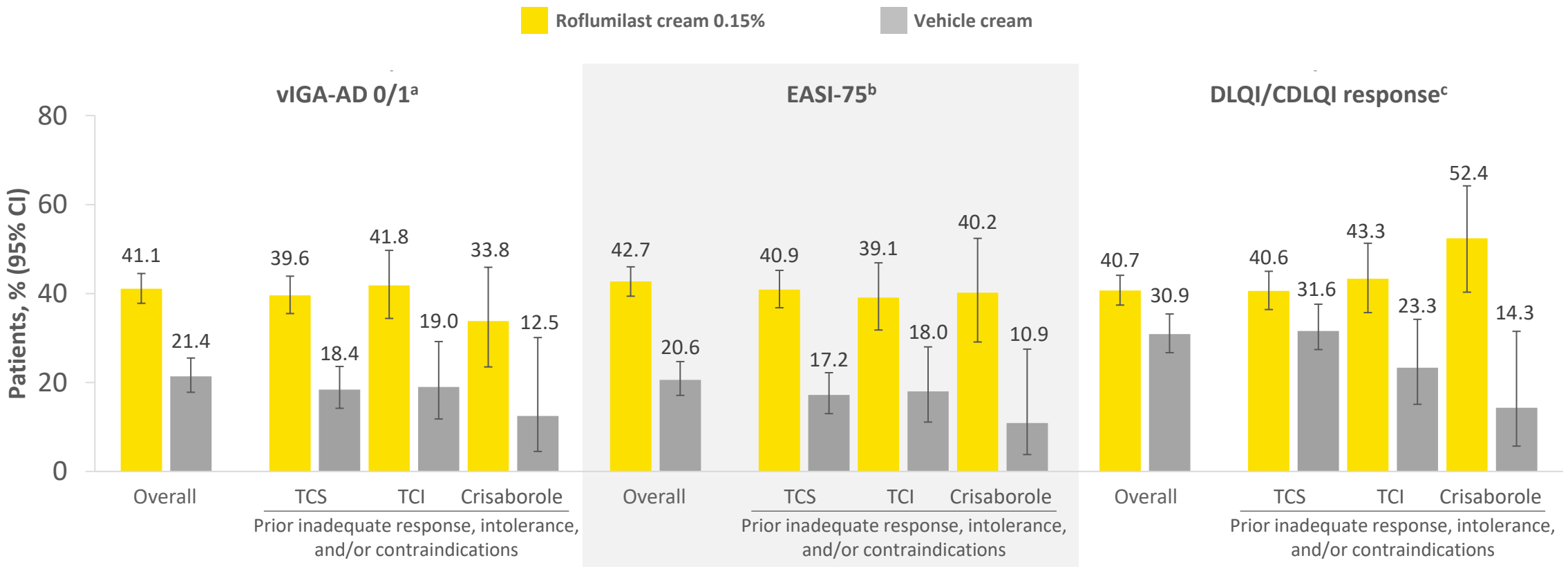
- No or mild sensation at the application site of roflumilast cream 0.15% was reported in ≥91% of patients across prior treatment subgroups at week 4



Investigator-rated local tolerability was assessed prior to application at baseline and at clinic visits on weeks 1, 2, and 4. Patient-rated local tolerability was assessed via feedback on burning/stinging sensation 10–15 minutes after the 1st application and at weeks 1, 2, and 4.
TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Efficacy and Patient-Reported Outcomes

Over 4 weeks, roflumilast improved AD across multiple efficacy endpoints in those with prior inadequate response, intolerance, and/or contraindications to a TCS, TCI, or crisaborole, including improvements in quality of life.



ITT population. [a]Patients achieved clear (0) or almost clear (1) skin. [b]Defined as ≥75% improvement from parent trial baseline. [c]Quality of life outcomes presented from combined observed data of DLQI ≥4-point and CLDQI ≥6-point improvement (minimally important difference) from baseline.

AD, atopic dermatitis; CDLQI, Children's DLQI; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis.

Conclusions

Roflumilast cream 0.15% was well tolerated, including at the application site, in patients with AD and prior inadequate response, intolerance, and/or contraindications to a TCS, TCI, or crisaborole, as reported by both investigators and patients.

- After 4 weeks, ≥91% of patients in the roflumilast subgroups reported no or mild sensation (eg, warmth, tingling) at the application site
- Investigators reported no irritation or minimal erythema for ≥97% of patients in the roflumilast subgroups at each assessment

Once-daily roflumilast cream 0.15% demonstrated a positive risk-benefit profile, regardless of prior inadequate response, intolerance, and/or contraindications to topical treatment, and outcomes among subgroups were consistent with the overall population.[1]

- Treatment-related, serious, and severe TEAEs were limited
- No new safety signals were identified in the subpopulations assessed
- Improvements in AD were observed across a variety of efficacy endpoints
- Roflumilast cream 0.15% improved disease-related quality-of-life

The results of this subpopulation analysis from the phase 3 INTEGUMENT-1 and -2 studies indicate that roflumilast can provide a potential treatment option for those with AD who may be unable to use other topical therapies.

AD, atopic dermatitis; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; TEAE, treatment-emergent adverse event.

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1. Simpson EL, et al. *JAMA Dermatol.* 2024;160:1161–1170.