Caregiver-Reported Outcomes From the Phase 3 INTEGUMENT-PED Trial of Children Aged 2–5 Years With Atopic Dermatitis and Treated With Roflumilast Cream 0.05%

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INTRODUCTION

- AD is a chronic inflammatory skin disease, often diagnosed in childhood[1,2]
  - Disease symptoms (eg, itch), chronic mental/physical comorbidities resulting from inflammation and itch-related sleep deprivation, and life-long treatment regimens can decrease quality of life, including negatively impacting the entire family[3,4]
- Despite side effects and/or treatment limitations of some topical therapies (eg, TCS and TCIs), they are still being used to treat AD[5,6]
  - Potent TCS are not recommended for thin-skinned areas with higher absorption and TCS are not approved for long-term use[5]
  - Reports of burning/stinging sensation with the use of TCIs[5] can be a concern, especially when treating children
- Concerns about side effects and difficulties with application can adversely affect adherence, prolonging AD symptoms[6,7]
- Alternatives to mainstay treatment regimens with the potential for proactive, long-term use to maintain disease control are needed[4,8]
- Roflumilast is a potent PDE4 inhibitor, formulated as a water-based cream and foam, neither of which contain potentially skin-irritating excipients, such as fragrances, ethanol, or propylene glycol[9]
- Roflumilast cream 0.15% and 0.05% has demonstrated a favorable efficacy-safety profile and application-site tolerability versus vehicle cream in patients with AD aged ≥6 years and aged 2–5 years in the phase 3 INTEGUMENT-1/2 and INTEGUMENT-PED trials, respectively[10,11]
- This analysis evaluated QoL changes with roflumilast cream 0.05% versus vehicle cream in patients aged 2–5 years who participated in the INTEGUMENT-PED trial

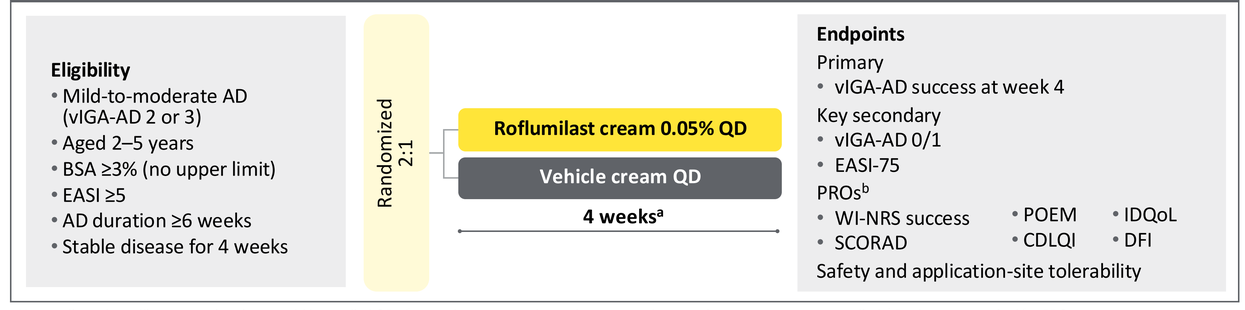
METHODS

- INTEGUMENT-PED (NCT04845620) was a 4-week, randomized, parallel-group, double-blind, vehicle-controlled, multicenter trial in children aged 2–5 years with mild-to-moderate AD; roflumilast cream 0.05% or vehicle cream was applied once daily by a parent/caregiver for 4 weeks

Endpoints

- vIGA-AD success (clear/almost clear [0/1] plus ≥2-grade improvement from baseline) at week 4 (primary endpoint)
- vIGA-AD 0/1
- WI-NRS success, defined as ≥4-point improvement from baseline, among patients with baseline score ≥4
- EASI-75, defined as ≥75% improvement in EASI from baseline
- PROs, evaluated by parents/caregivers weekly and reported here as LSM improvement from baseline
  - SCORAD: evaluation of AD sign/symptom severity; total scores range from 0 (none) to 103 (most severe)
  - POEM: measure of AD severity and symptom impact; total scores range from 0 (no impact) to 28 (greatest symptom impact)
  - CDLQI (aged 4–5 years) or IDQoL (aged 2–3 years): assessments of the impact of AD on QoL over the prior week; total scores for both range from 0 (no impact) to 30 (highest impact)
  - DFI: measure of how having a child with AD affects QoL of the family; total scores range from 0 (no impact) to 30 (highest impact)
- Safety and application-site tolerability

Study Design



[a]Nonmedicated emollients or moisturizers could be applied QD after study treatment, but only to areas where study treatment was not applied. [b]*P* values are nominal for PROs.

RESULTS

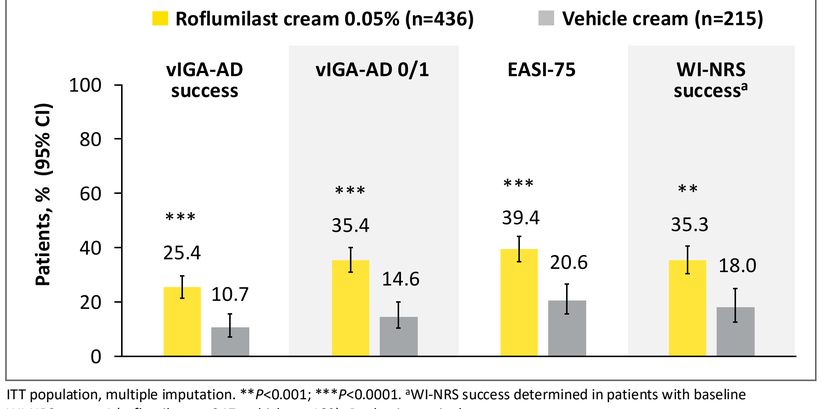
- Among 651 enrolled patients, demographics and baseline disease characteristics were consistent between groups
  - Most patients were not Hispanic or Latino (82.2%) and White (69.1%); 52.4% of patients were male
- After 4 weeks, significantly higher proportions of patients in the roflumilast cream 0.05% group versus vehicle group achieved vIGA-AD success, vIGA-AD 0/1, and EASI-75[11]
- Patients who received roflumilast versus vehicle had greater improvements across various PROs assessing signs, symptoms, and severity of AD, as well as improving QoL
  - A significantly higher proportion of patients achieved WI-NRS success after 4 weeks[11]
    - Pruritus symptoms improved with roflumilast versus vehicle within 24 hours after the first application ($P \leq 0.0014$)
  - Improvements with roflumilast were observed for both overall and individual component and symptom scores for SCORAD and POEM
- Roflumilast was well tolerated, with treatment-related AEs reported for 15 (3.4%) patients
  - Across time points, investigators reported no evidence of irritation at the application site in ≥93.3% of patients treated with roflumilast
  - A hot, tingling/stinging sensation that caused definite discomfort was reported by caregivers of 2 (0.5%) patients after the first application of roflumilast and <1% of patients at subsequent assessments
  - Application-site pain AEs were reported for 7 (1.6%) and 4 (1.9%) patients in the roflumilast and vehicle groups, respectively

Patient Demographics and Baseline Disease Characteristics

		Roflumilast cream 0.05% (n=436)	Vehicle cream (n=215)
Age, mean (SD) [range], years		3.3 (1.1) [2–5]	3.2 (1.1) [2–5]
Male at birth, n (%)		225 (51.6)	116 (54.0)
Ethnicity, n (%)	Not Hispanic or Latino	351 (80.5)	184 (85.6)
Race, n (%)	White	294 (67.4)	156 (72.6)
	Black or African American	68 (15.6)	32 (14.9)
	Asian	37 (8.5)	17 (7.9)
	Multiple	28 (6.4)	4 (1.9)
	Other	9 (2.1)	6 (2.8)
Fitzpatrick skin type, n (%)[a]	Type I–III	279 (64.0)	148 (68.8)
	Type IV–VI	157 (36.0)	66 (30.7)
vIGA-AD, n (%)	Mild (2)	103 (23.6)	44 (20.5)
	Moderate (3)	333 (76.4)	171 (79.5)
Mean (median) [range]	EASI	12.2 (10.3) [4.6–42.0]	11.6 (9.5) [5.0–32.9]
	BSA, %	22.5 (17.3) [3.0–82.0]	21.2 (16.5) [4.0–78.8]
	WI-NRS[b]	6.2 (6.6) [0–10]	5.9 (6.3) [0–10]
	SCORAD	46.9 (45.9) [17.7–92.9]	46.2 (45.1) [17.9–80.4]
	CDLQI	10.7 (9.0) [0–30]	8.9 (8.0) [0–27]
	IDQoL	10.6 (10.0) [1–30]	10.2 (10.0) [0–25]
	POEM	16.2 (17.0) [0–28]	15.8 (16.0) [12.0–20.0]
	DFI	9.6 (8.0) [0–30]	9.2 (8.0) [0–28]

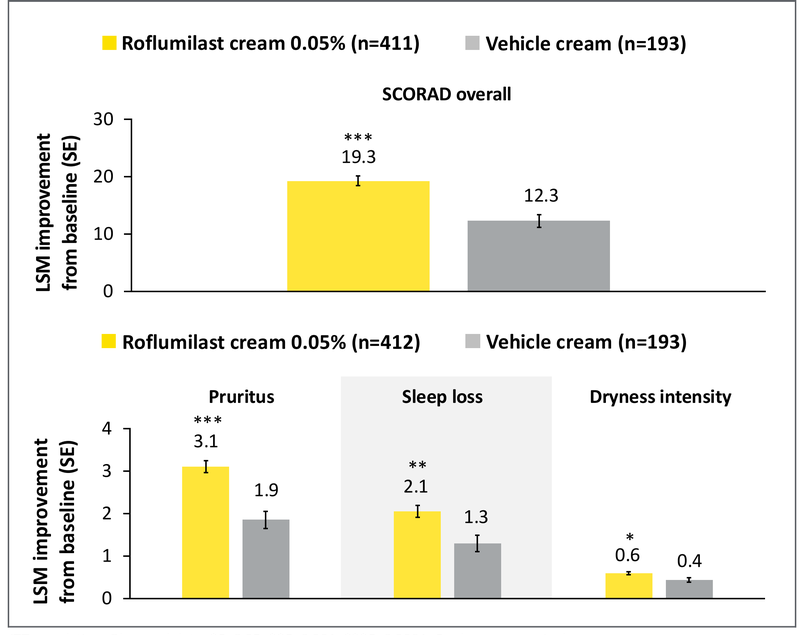
ITT population. [a]There was 1 patient in the vehicle group with a missing baseline Fitzpatrick skin type. [b]Weekly average.

Improvement in Signs and Symptoms of AD at Week 4



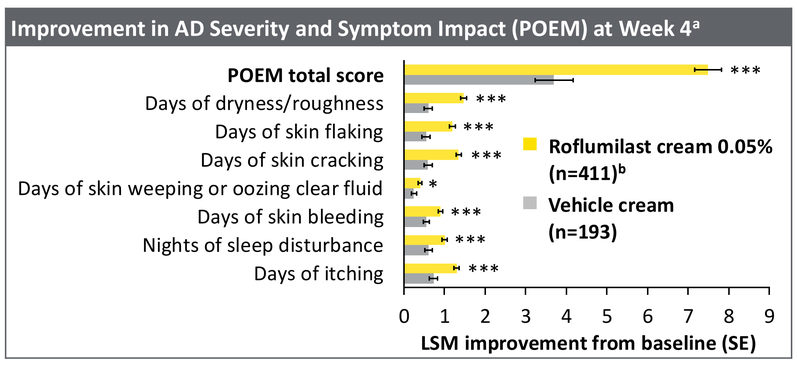
ITT population, multiple imputation. **P<0.001; ***P<0.0001. [a]WI-NRS success determined in patients with baseline WI-NRS score ≥4 (roflumilast, n=347; vehicle, n=160); *P* value is nominal.

Improvement in AD Severity (SCORAD) at Week 4



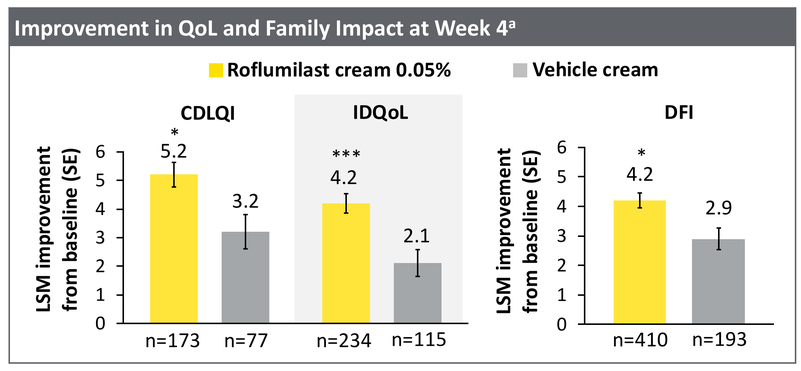
ITT population. Observed data. *P<0.05; **P<0.001; ***P<0.0001; *P* values are nominal.

Improvement in AD Severity and Symptom Impact (POEM) at Week 4[a]



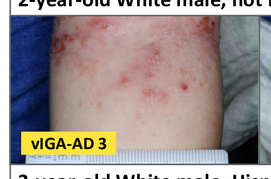
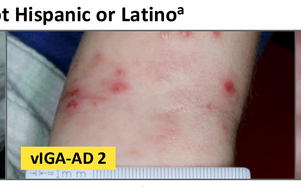
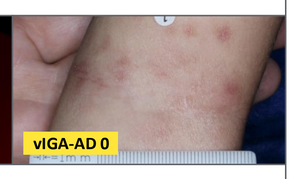
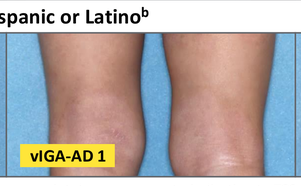
ITT population; observed data. *P<0.05; ***P<0.0001; *P* values are nominal. [a]POEM questions assess the frequency of 7 symptoms in the preceding week. [b]n=410 for POEM total score in the roflumilast group.

Improvement in QoL and Family Impact at Week 4[a]



ITT population. Observed data. *P<0.05; ***P<0.0001; *P* values are nominal.
[a]CDLQI, IDQoL, and DFI are each 10-question surveys.

Improvement With Roflumilast Cream 0.05%

Baseline	Week 1	Week 4
2-year-old White male, not Hispanic or Latino[a]		
 vIGA-AD 3	 vIGA-AD 2	 vIGA-AD 0
3-year-old White male, Hispanic or Latino[b]		
 vIGA-AD 3	 vIGA-AD 1	 vIGA-AD 1

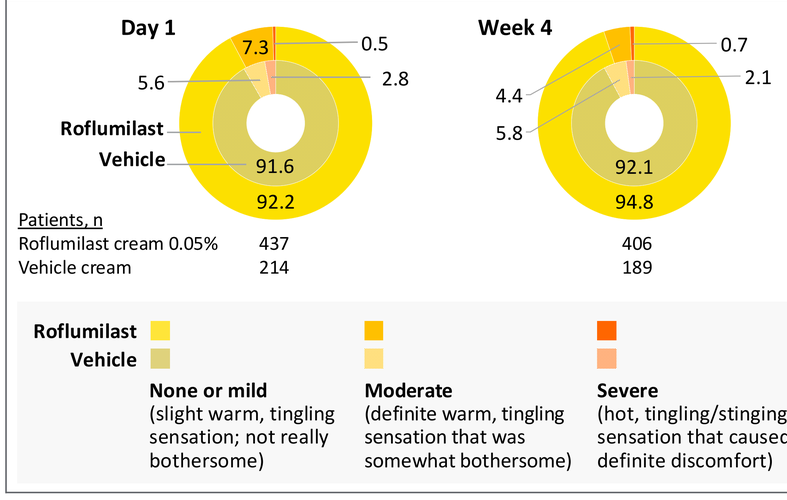
[a]Patient had a history of inadequate response, intolerance, or contraindication to TCS and 2-year history of AD. [b]Patient had a 3-year history of AD.

Safety Summary

Patients, n (%)	Roflumilast cream 0.05% (n=437)	Vehicle cream (n=215)
≥1 TEAE	130 (29.7)	47 (21.9)
≥1 treatment-related AE	15 (3.4)	6 (2.8)
≥1 SAE[a]	1 (0.2)	0
≥1 TEAE leading to discontinuation of study/study drug	5 (1.1)/5 (1.1)	5 (2.3)/4 (1.9)
Most common TEAEs by preferred term, ≥2% in either group		
Upper respiratory tract infection	18 (4.1)	3 (1.4)
Pyrexia	12 (2.7)	6 (2.8)
Diarrhea	11 (2.5)	1 (0.5)
Vomiting	9 (2.1)	0
Dermatitis atopic[b]	2 (0.5)	5 (2.3)

Safety population. [a]SAE in the roflumilast group was cellulitis in an area to which treatment was not applied; it was considered unlikely to be related to study treatment.[10] [b]Worsening atopic dermatitis.

Caregiver-rated Application-site Tolerability



CONCLUSIONS

- Roflumilast cream 0.05%, compared with vehicle cream, significantly improved multiple efficacy endpoints and PROs after 4 weeks of once-daily application
  - Improvements were observed in SCORAD total and component scores (ie, itch, sleep loss, and dryness intensity) and in disease severity and impact (ie, POEM)
  - Roflumilast improved QoL in patients and decreased the negative impact on family
- Roflumilast was well tolerated with no or minimal irritation at the application site, including after the first application
- Outcomes are consistent with those reported for patients aged ≥6 years with AD who participated in the 4-week INTEGUMENT-1 and -2 trials[12]
- These results demonstrate that roflumilast cream 0.05% improves signs and symptoms of AD, decreases disease severity and impact, and improves QoL in both children aged 2–5 years with AD and their families

ABBREVIATIONS

AD, atopic dermatitis; AE, adverse event; BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; DFI, Dermatitis Family Impact; EASI, Eczema Area and Severity Index; IDQoL, Infant Dermatology Life Quality Index; ITT, intention-to-treat; LSM, least-squares mean; PDE4, phosphodiesterase 4; POEM, Patient-Oriented Eczema Measure; PRO, patient-reported outcome; QD, once daily; QoL, quality of life; SAE, serious adverse event; SCORAD, SCORing Atopic Dermatitis; TCIs, topical calcineurin inhibitors; TCS, topical corticosteroids; TEAE, treatment-emergent adverse event; vIGA-AD, Validated Investigator Global Assessment for AD; WI-NRS, Worst Itch-Numeric Rating Score.

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DISCLOSURES

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