Once-Daily Roflumilast Cream 0.15% and 0.05% Improve Atopic Dermatitis Signs and Symptoms That Can Be Maintained With Proactive Twice-Weekly Treatment: Results From the 52-Week Phase 3 INTEGUMENT-OLE Trial in Patients Aged ≥2 Years

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ABBREVIATIONS

AD, atopic dermatitis; AE, adverse event; BIW, twice weekly; BSA, body surface area affected; EASI, Eczema Area and Severity Index; FAS, full analysis set; K-M, Kaplan-Meier; NE, not evaluable; OLE, open-label extension; PDE4, phosphodiesterase 4; PED, pediatric; QD, once daily; SAE, serious AE; TCS, topical corticosteroids; TCI, topical calcineurin inhibitor; TEAE, treatment-emergent AE; vIGA-AD, Validated Investigator Global Assessment for AD; WI-NRS, Worst Itch-Numeric Rating Scale.

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DISCLOSURES

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SYNOPSIS

- AD is a chronic inflammatory skin disease that is often first diagnosed during childhood and can persist into adulthood[1,2]
- Complicated treatment regimens and limitations to topical therapies that are commonly used (ie, TCS and TCIs) can impact adherence to treatment and prolong signs and symptoms of AD[3–5]
  - Because of increased risk of cutaneous and systemic AEs, TCS are not approved for long-term use and higher potency TCS are not recommended for thin-skinned areas (eg, face, younger skin) where there is greater systemic absorption[3,4,6]
  - Children with less developed skin barriers and greater BSA-to-weight ratios are at even greater risk for AEs[6]
  - A burning/stinging sensation at the site of application has been reported with the use of topical crisaborole and TCIs[3]
- Alternative topical treatment options with the potential for proactive, long-term use to maintain disease control are needed[7,8]
- Topical roflumilast, a potent, advanced targeted PDE4 inhibitor, has been formulated as a cream or foam that does not include propylene glycol, formaldehyde, fragrances, or other potential cutaneous irritants[9]
- Efficacy, safety, and tolerability of once-daily roflumilast cream 0.15% and 0.05% in patients with AD aged ≥6 years and 2–5 years, respectively, were demonstrated in the 4-week, phase 3 INTEGUMENT-1/2 (NCT04662487/NCT04773600)[10] and INTEGUMENT-PED (NCT04845620)[11] trials
  - Use of roflumilast cream 0.15%/0.05% for up to 56 weeks in patients aged ≥2 years with AD was investigated in the INTEGUMENT-OLE (NCT04804605) study
  - Primary safety and efficacy outcomes in patients aged ≥6 years from the OLE study are reported by Simpson, et al[12]

OBJECTIVE

- Long-term outcomes, including changes in BSA, disease clearance, and disease control, of patients who participated in the INTEGUMENT-OLE trial are reported here

METHODS

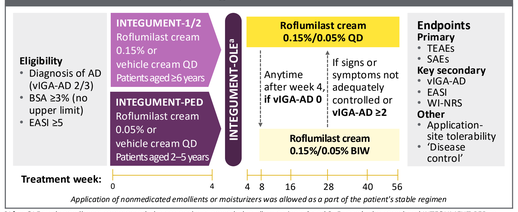
Study design

- INTEGUMENT-OLE was a 52-week, phase 3, multicenter, OLE trial in patients aged ≥2 years with mild-to-moderate AD
- Patients who completed 4 weeks in one of the parent studies (INTEGUMENT-1/2, ≥6 years [no upper limit] or INTEGUMENT-PED, 2–5 years) with no safety concerns were eligible to enroll in the INTEGUMENT-OLE trial and initiate or continue roflumilast cream 0.15% or 0.05%, respectively, once daily
  - Patients who 'aged up' from 5 to 6 years during the study were switched to roflumilast cream 0.15% at their first scheduled visit after their 6th birthday
- Patients could switch to BIW application any time at/after week 4, if they achieved vIGA-AD clear (0)
  - BIW treatment was maintained as long as signs and symptoms of AD were adequately controlled and vIGA-AD remained clear or almost clear (0/1)

Assessments in this analysis

- vIGA-AD 0/1
- WI-NRS 0/1 (no/minimal pruritus)
- BSA over time
- Rates of disease clearance (ie, vIGA-AD 0) and proportions of patients switching to BIW application
- Duration of 'disease control', defined as vIGA-AD 0/1 and adequate control of signs and symptoms with BIW application
- Safety and application-site tolerability

INTEGUMENT-OLE Study Design

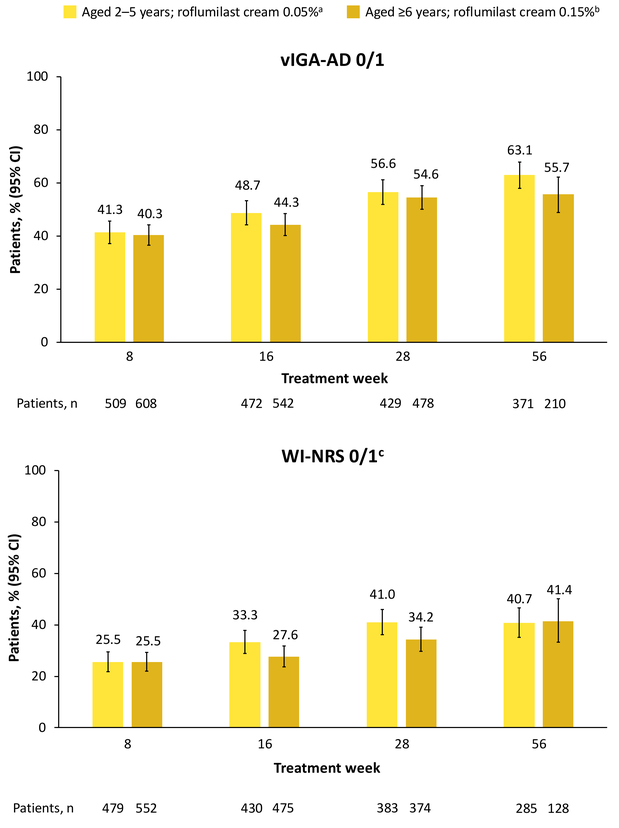


[a]After OLE study enrollment commenced, the protocol was amended to allow patients (aged 2–5 years) who completed INTEGUMENT-PED to enroll. Patients must have completed 4 weeks in a parent trial with no safety concerns.

RESULTS

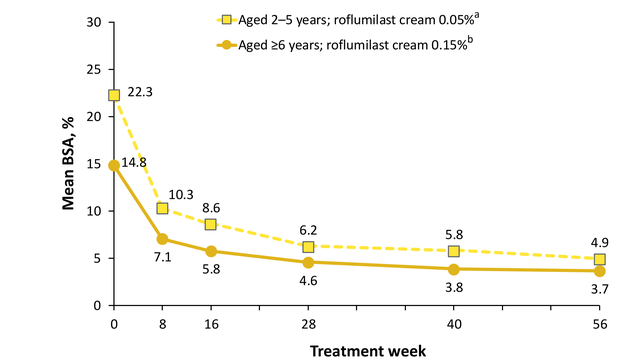
- 562 patients from INTEGUMENT-PED and 658 patients from INTEGUMENT-1/2 completed one of these parent studies and enrolled in INTEGUMENT-OLE
  - Mean BSA (at parent-study baseline) for patients entering the OLE, respectively, was 13.9% and 20.8%; ~82% of patients were not Hispanic or Latino and 63%–71% were White
  - Patient demographics and baseline clinical characteristics were balanced among the populations who continued in the OLE study
- Improvements in AD observed in the parent trials were maintained or continued to improve through the end of the OLE study
  - vIGA-AD 0/1 was achieved by 63.1% of patients from INTEGUMENT-PED and 55.7% of patients from INTEGUMENT-1/2
  - Mean BSA decreased from baseline of each parent study through the end of the OLE
- Approximately 1/3 patients achieved vIGA-AD 0 at/after OLE week 4 and were eligible to switch to BIW application
  - The majority of patients who achieved vIGA-AD 0 and did not switch to BIW application achieved vIGA-AD 0 at their last study visit and, therefore, were not able to switch to BIW application
- Patients from INTEGUMENT-PED and INTEGUMENT-1/2 who switched to BIW application maintained a median duration of 'disease control' (K-M estimates) of 238 days (34 weeks) and 281 days (>40 weeks), respectively
- Roflumilast cream 0.15%/0.05% was well tolerated, as previously reported[10–12]
  - Application-site pain was reported as an AE for 0.7% of patients from INTEGUMENT-PED and 0.5% of patients from INTEGUMENT-1/2[12]

Durable Improvements in AD Outcomes



FAS, as observed. [a]Patients entering the OLE from INTEGUMENT-PED. [b]Patients entering the OLE from INTEGUMENT-1/2. [c]Patients with WI-NRS ≥2 at parent-study baseline.

BSA Over Time



FAS, as observed. [a]Patients entering the OLE from INTEGUMENT-PED. [b]Patients entering the OLE from INTEGUMENT-1/2.

'Disease Control' With Proactive BIW Application

	Achieved vIGA-AD 0 at/after OLE week 4		Achieved vIGA-AD 0 and switched to proactive BIW application	Median duration of 'disease control'[c] with BIW application
	Through OLE week 24 (Treatment week 28)	*Through OLE week 52 (Treatment week 56)*		
Aged 2–5 years; roflumilast cream 0.05%[a] (n=562)	26.7% (150 patients)	35.7% (201 patients)	30.2% (170 patients)	238 days (95% CI, 146–331)
Aged ≥6 years; roflumilast cream 0.15%[b] (n=658)	26.1% (172 patients)	31.5% (207 patients)	19.8% (130 patients)	281 days (95% CI, 147–NE)

[a]Patients entering the OLE from INTEGUMENT-PED. [b]Patients entering the OLE from INTEGUMENT-1/2. [c]K-M median.

Safety Summary

Patients, n (%)		Aged 2–5 years; roflumilast cream 0.05%[a] (n=562)	Aged ≥6 years; roflumilast cream 0.15%[b] (n=657)
≥1 TEAE		280 (49.8)	241 (36.7)
≥1 treatment-related AE		14 (2.5)	31 (4.7)
≥1 SAE		18 (3.2)	8 (1.2)
≥1 treatment-related SAE		0	0
≥1 TEAE leading to discontinuation of study/study drug		17 (3.0)/18 (3.2)	20 (3.0)/21 (3.2)
Most common TEAEs by preferred term, ≥4.0% of patients in either group	Upper respiratory tract infection	49 (8.7)	21 (3.2)
	Nasopharyngitis	28 (5.0)	20 (3.0)
	Pyrexia	28 (5.0)	5 (0.8)
	COVID-19	18 (3.2)	30 (4.6)

Safety population. Summary of TEAEs occurring during INTEGUMENT-OLE. [a]Patients entering the OLE from INTEGUMENT-PED. [b]Patients entering the OLE from INTEGUMENT-1/2.

CONCLUSIONS

- Once-daily and proactive BIW roflumilast cream 0.15% and 0.05% decreased signs and symptoms of AD and maintained improvements through up to 56 weeks of treatment in patients aged ≥2 years
- In addition to durable improvements in vIGA-AD and itch symptoms (WI-NRS), BSA decreased through 4 weeks of treatment in parent trials, and was maintained or improved further over 52 weeks of treatment in the OLE
- Approximately 1/3 patients achieved clear skin (vIGA-AD 0) with once-daily application
  - Patients from INTEGUMENT-PED and INTEGUMENT-1/2 who achieved clear skin and transitioned to proactive BIW application were able to maintain 'disease control' for a median of 238 and 281 days (K-M estimates), respectively
- Overall, these results indicate that roflumilast cream is well tolerated and an appropriate alternative to topical therapies that are not recommended for long-term continuous use (eg, TCS or TCIs) for patients with AD