Roflumilast Cream 0.15% and 0.05% Effects on Sleep in Patients With Atopic Dermatitis

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ABBREVIATIONS

AD, atopic dermatitis; AE, adverse event; BSA, body surface area affected; CDLQI, Children's Dermatology Life Quality Index; CMH, Cochran-Mantel-Haenszel; DFI, Dermatitis Family Impact; EASI, Eczema Area and Severity Index; h, hour; IDQoL, Infant Dermatology Life Quality Index; ITT, intention to treat; LSM, least squares mean; m, minutes; NA, not applicable; PDE4, phosphodiesterase 4; PED, pediatric; POEM, Patient-Oriented Eczema Measure; PRO, patient-reported outcome; QD, once daily; QoL, quality of life; SAE, serious AE; SCORAD, SCORing Atopic Dermatitis; SE, standard error; TCIs, topical calcineurin inhibitors; TCS, topical corticosteroids; 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 condition that is commonly diagnosed in childhood[1,2] and includes symptoms (eg, itch and mental/physical comorbidities) that can cause sleep disturbance for both patients and their families[3,4]
- Topical therapies commonly used to treat AD (eg, TCS and TCIs) often have complicated application regimens, as well as treatment limitations[5,6]
  - Caregivers, patients, and physicians may also have concerns over side effects from topical therapies, which can lead to reduced adherence and/or prolong AD symptoms, especially in children[5–7]
  - TCS are not approved for long-term use and potent TCS are not recommended for thin-skinned areas with higher absorption[5]
  - A burning/stinging sensation at the site of application has been reported with the use of topical crisaborole and TCIs[5]
- Roflumilast cream is an advanced targeted topical treatment that is a PDE4 inhibitor and does not contain potentially skin-irritating excipients, such as fragrances, ethanol, or propylene glycol[8]
- The efficacy, safety, and tolerability of roflumilast cream 0.15% and 0.05% were demonstrated in 4-week, vehicle-controlled, phase 3 trials, INTEGUMENT-1 and -2 (patients aged ≥6 years)[9] and INTEGUMENT-PED (patients 2–5 years),[10] respectively

OBJECTIVE

- The impact of roflumilast cream 0.15%/0.05% on sleep outcomes for patients and their families who participated in INTEGUMENT-1/2 or INTEGUMENT-PED are reported here

METHODS

Study design

- INTEGUMENT-1/2 and INTEGUMENT-PED were 4-week, phase 3, randomized, vehicle-controlled trials of once-daily roflumilast cream 0.15% and 0.05% in patients aged ≥6 years and 2–5 years with mild-to-moderate AD

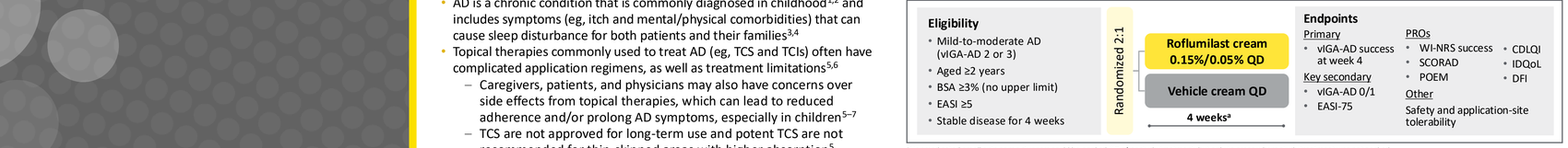
Assessments

- PROs were assessed at weeks 1, 2, and 4; *P* values are nominal
  - Parents/caregivers completed assessments for patients aged <6 years
- WI-NRS: measure of worst itch severity in the previous 24 hours; scores range from 0 (no itch) to 10 (worst itch imaginable)
- Sleep-related PROs were determined for the following assessments:
  - SCORAD: sleep loss over the past 3 days/nights; scores ranging from 0 (none) to 10 (most severe) are reported as LSM improvement from baseline
  - POEM: sleep disturbance over the past week for 0 days, 1–2 days, 3–4 days, 5–6 days, or every day
  - CDLQI: patients aged 4–16 years; sleep affected in the past week rated as not at all, a little, a lot, or very much
  - IDQoL (INTEGUMENT-PED only, patients aged <4 years)
    - Total time of sleep disturbance in the past week rated as <1 hour, 1–2 hours, 3–4 hours, or ≥5 hours
    - Average time to get a child to fall asleep each night in the past week rated as 0–15 minutes, 15 minutes to 1 hour, 1–2 hours, or >2 hours
  - DFI: parent/caregiver of patients aged ≤17 years; sleep disturbance and tiredness/exhaustion of family members/caregivers rated as not at all, a little, a lot, or very much
- The CMH test of rank scores was used to evaluate the association between treatment and response for POEM, CDLQI, IDQoL, and DFI assessments

RESULTS

- Demographics and baseline clinical characteristics were balanced among patients randomized to receive roflumilast cream 0.15%/0.05% or vehicle cream in the INTEGUMENT-1/2 (n=884; n=453) and INTEGUMENT-PED (n=436; n=215) trials
  - 59.5% and 69.1% of patients in the INTEGUMENT-1/2 and INTEGUMENT-PED trials, respectively, were White
- Roflumilast cream 0.15% and 0.05% versus vehicle cream significantly improved WI-NRS scores within 24 hours of the first application (*P*<0.005) in both INTEGUMENT-1/2 and INTEGUMENT-PED[9,10]
  - LSM improvements were greater with roflumilast cream versus vehicle throughout both INTEGUMENT-1/2 (2.6 vs 1.6; *P*<0.001) and INTEGUMENT-PED (2.6 vs 1.6; *P*<0.01), including at week 4
- Roflumilast cream, compared with vehicle cream, improved individual PRO component scores related to impact of AD on sleep loss/disturbance for patients and families throughout INTEGUMENT-1/2 and INTEGUMENT-PED
- Roflumilast cream was well tolerated
  - Treatment-related AEs and SAEs were reported by ≤6% and <1% of patients, respectively, in the roflumilast group, from either study
  - Application-site pain AEs were reported for 13 (1.5%) and 7 (1.6%) patients in the roflumilast group in INTEGUMENT-1/2 and INTEGUMENT-PED, respectively

Study Design



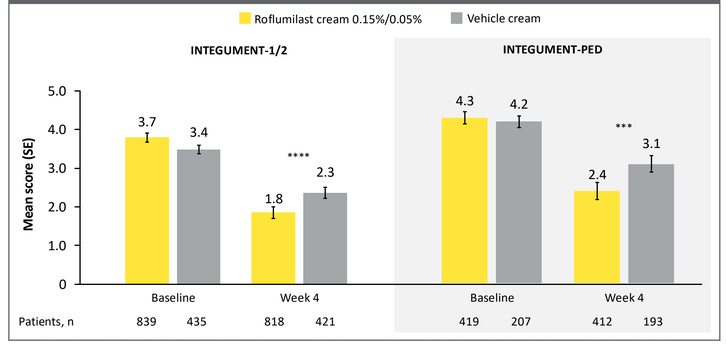
[a]Nonmedicated emollients or moisturizers could be applied QD after study treatment, but only to areas where study treatment was not applicable.

Patient Demographics and Baseline Disease Characteristics

		INTEGUMENT-1/2		INTEGUMENT-PED	
		Roflumilast cream 0.15% (n=884)	Vehicle cream (n=453)	Roflumilast cream 0.05% (n=436)	Vehicle cream (n=215)
Age, years, mean (median) [range]		27.9 (20.0) [6–91]	27.3 (20.0) [6–84]	3.3 (3.0) [2–5]	3.2 (3.0) [2–5]
Female sex at birth, n (%)		489 (55.3)	272 (60.0)	211 (48.4)	99 (46.0)
Not Hispanic or Latino, n (%)		730 (82.6)	377 (83.2)	351 (80.5)	184 (85.6)
vIGA-AD, n (%)	Mild (2)	211 (23.9)	112 (24.7)	103 (23.6)	44 (20.5)
	Moderate (3)	673 (76.1)	341 (75.3)	333 (76.4)	171 (79.5)
Mean (median) [range]	WI-NRS[a]	6.1 (6.3) [0–10]	5.9 (6.0) [0–10]	6.2 (6.6) [0–10]	5.9 (6.3) [0–10]
	SCORAD	45.5 (45.3) [18–82]	45.1 (43.9) [21–84]	46.9 (45.9) [18–93]	46.2 (45.1) [18–80]
	POEM	15.8 (16.0) [0–28]	15.3 (15.0) [0–28]	16.2 (17.0) [0–28]	15.8 (16.0) [0–28]
	CDLQI	7.8 (6.0) [0–28]	7.2 (6.0) [0–26]	10.7 (9.0) [0–30]	8.9 (8.0) [0–27]
	IDQoL	NA	NA	10.6 (10.0) [1–30]	10.2 (10.0) [0–25]
	DFI	6.5 (5.0) [0–27]	6.5 (5.0) [0–30]	9.6 (8.0) [0–30]	9.2 (8.0) [0–28]

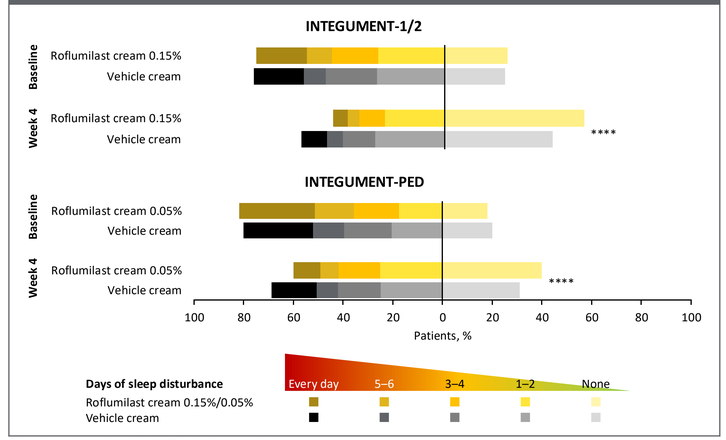
ITT population. [a]Weekly average.

Mean Sleep Loss With Roflumilast Cream (SCORAD)



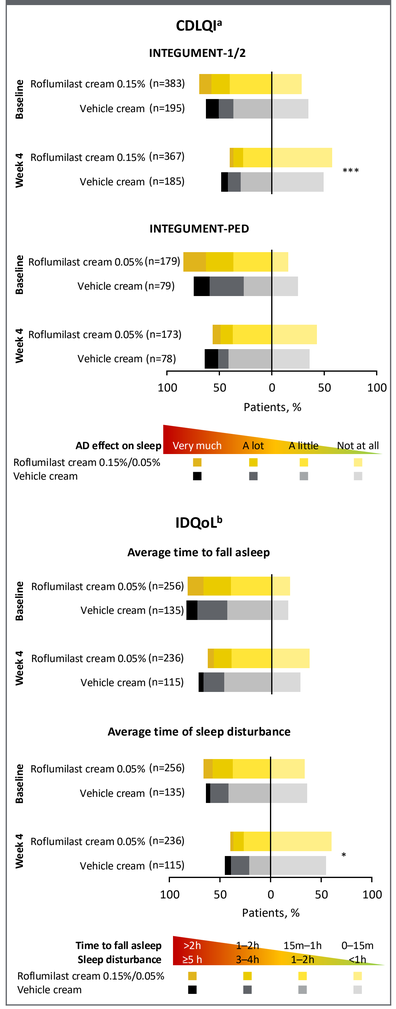
ITT population, observed data. ***P<0.001; ****P<0.0001; *P* values are nominal and represent difference in LSM change from baseline between roflumilast and vehicle.

Improvement in Sleep Disturbance With Roflumilast Cream (POEM)



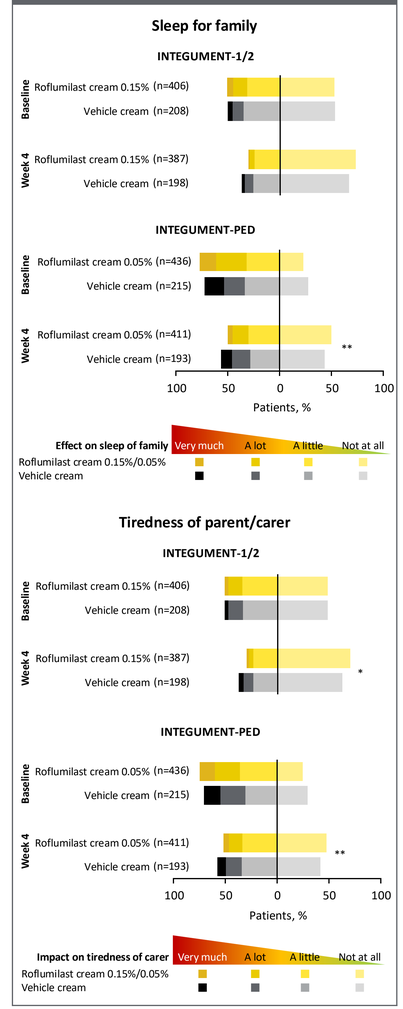
ITT population, observed data. ****P<0.0001; *P* values are nominal.

Improvement in Sleep-related QoL



ITT population, observed data. *P<0.05; ***P<0.001; *P* values are nominal. [a]Patients aged 4–16 years at baseline. [b]INTEGUMENT-PED only; patients aged <4 years at baseline.

Improvements in Impact on Family Sleep and Tiredness (DFI)[a]



ITT population, observed data. *P<0.05; **P<0.01; *P* values are nominal. [a]For family members of patients aged ≤17 years.

CONCLUSIONS

- Roflumilast cream 0.15% and 0.05% improved itch and reduced the negative impact of AD on sleep in patients aged ≥6 years and 2–5 years with AD throughout 4 weeks of treatment
  - Improvements were observed across multiple PRO assessments, including greater proportions of patients with no impact on sleep loss/disturbance with roflumilast cream compared with vehicle cream
- The reduced impact of AD on sleep for patients (and their family, in patients aged ≤17 years) was similar among the ≥6-year and 2–5-year-old age groups
- Roflumilast was well tolerated with low rates of treatment-related AEs
- Sleep disturbance was reduced across multiple PRO assessments with roflumilast cream 0.15% and 0.05% in patients aged ≥6 years and 2–5 years with mild-to-moderate AD, providing a treatment alternative to current common topical therapies (ie, TCS and TCIs)