Pooled Efficacy, Patient-Reported Outcomes, and Safety of Roflumilast Cream 0.15% From the INTEGUMENT-1 and INTEGUMENT-2 Phase 3 Clinical Trials of Adults and Children With Atopic Dermatitis

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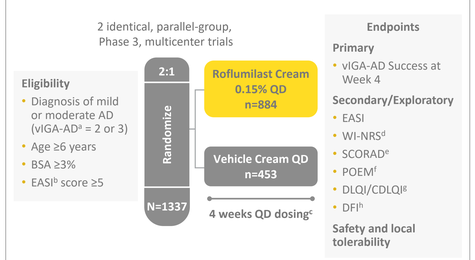
INTRODUCTION

- Atopic dermatitis (AD) is a chronic inflammatory skin disease affecting patient quality of life, with itch being the most burdensome symptom[1]
- Roflumilast is a potent phosphodiesterase 4 (PDE4) inhibitor formulated as a water-based cream and foam
  - Roflumilast potency is ~25- to >300-fold higher than apremilast and crisaborole, with roflumilast more closely mimicking cyclic adenosine monophosphate (cAMP) binding to PDE4[2,3]
  - Formulations do not contain ethanol, propylene glycol, or fragrances that can irritate skin
- Efficacy, including improvement in itch, local tolerability, and safety were demonstrated in 2 Phase 3 clinical trials of roflumilast cream 0.15% (INTEGUMENT-1 and INTEGUMENT-2)[4,5]
- While the main safety and efficacy (including WI-NRS Success and daily improvement in pruritus) data have been presented previously,[4,5] the attainment of other patient-reported outcome (PRO) thresholds has not yet been presented

METHODS

- INTEGUMENT-1 and INTEGUMENT-2 were identically designed, randomized, parallel-group, double-blind, vehicle-controlled, multicenter trials enrolling patients ≥6 years of age with mild to moderate AD (Validated Investigator Global Assessment for Atopic Dermatitis [vIGA-AD] score of 2 [Mild] or 3 [Moderate]; Figure 1)
  - The primary efficacy endpoint was vIGA-AD Success at Week 4, which was defined as achievement of Clear or Almost Clear IGA status plus ≥2-grade improvement from baseline
  - PROs included Worst Itch-Numeric Rating Scale (WI-NRS), SCORing Atopic Dermatitis (SCORAD), Patient-Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI)/Children's DLQI (CDLQI), and Dermatitis Family Impact (DFI)
  - Safety and local tolerability were also assessed

Figure 1. Study Design



vIGA-AD Success = Clear or Almost Clear IGA status plus ≥2-grade improvement from baseline.
[a]A 5-point scale ranging from 0 (Clear) to 4 (Severe) assessing inflammatory signs of AD. [b]A 72-point scale based on AD disease intensity and total affected body area. [c]Non-medicated emollients or moisturizers could be applied QD, but only to untreated areas of the patient's skin. [d]An 11-point scale ranging from 0 (no itch) to 10 (worst itch imaginable). [e]A 104-point scale based on extent of involvement, disease intensity, and subjective symptoms (including pruritus and sleep loss). [f]A 28-point scale measuring disease severity per patient reports of signs and symptoms, including pruritus, sleep, and local skin changes (bleeding, oozing, flaking, etc). [g]A 30-point scale assessing various aspects of patients' quality of life. [h]A 30-point scale evaluating the effect of AD on patients' family life and relationships.
AD: atopic dermatitis; BSA: body surface area; CDLQI: Children's Dermatology Life Quality Index; DFI: Dermatitis Family Impact; DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; POEM: Patient-Oriented Eczema Measure; QD: once daily; SCORAD: SCORing Atopic Dermatitis; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis; WI-NRS: Worst Itch-Numeric Rating Scale.

RESULTS

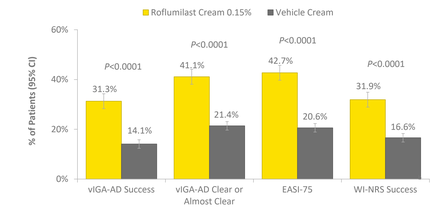
- Baseline disease characteristics were consistent between treatment groups (Table 1)
- Roflumilast cream 0.15% provided significant improvement in AD, as indicated by changes in the percentages of patients achieving the following (Figure 2):
  - vIGA-AD Success
  - vIGA-AD score of Clear or Almost Clear
  - 75% reduction in Eczema Area and Severity Index (EASI) score from baseline
  - WI-NRS Success (≥4-point improvement in patients with baseline score ≥4)

Table 1. Patient Baseline Demographics and Disease Characteristics

Patients	Roflumilast Cream 0.15% (n=884)	Vehicle Cream (n=453)
Age, years, mean (SD)	27.9 (19.4)	27.3 (19.0)
Sex at birth, n (%)		
Male	395 (44.7)	181 (40.0)
Female	489 (55.3)	272 (60.0)
Ethnicity, n (%)		
Hispanic or Latino	150 (17.0)	72 (15.9)
Not Hispanic or Latino	730 (82.6)	377 (83.2)
Not reported	4 (0.5)	4 (0.9)
Race, n (%)		
American Indian or Alaskan Native	7 (0.8)	1 (0.2)
Asian	114 (12.9)	62 (13.7)
Black or African American	176 (19.9)	96 (21.2)
Native Hawaiian or Other Pacific Islander	1 (0.1)	0
White	529 (59.8)	267 (58.9)
Other	33 (3.7)	13 (2.9)
>1 race	24 (2.7)	14 (13.1)
Fitzpatrick skin type at screening, n (%)		
I–III	481 (54.4)	238 (52.5)
IV–VI	403 (45.6)	215 (47.5)
Baseline vIGA-AD, n (%)		
2 (Mild)	211 (23.9)	112 (24.7)
3 (Moderate)	673 (76.1)	341 (75.3)
EASI		
Mean (SD)	10.1 (5.7)	10.0 (5.2)
WI-NRS, n	858	441
Mean (SD)	6.1 (2.2)	5.9 (2.2)
SCORAD		
Mean (SD)	45.5 (10.9)	45.1 (10.6)
SCORAD Pruritus		
Mean (SD)	6.2 (2.6)	6.2 (2.6)
SCORAD Sleep Loss		
Mean (SD)	3.7 (3.1)	3.4 (3.2)
POEM		
Mean (SD)	15.8 (6.3)	15.3 (6.4)
DLQI, n	498	258
Mean (SD)	8.6 (6.1)	8.5 (6.4)
CDLQI, n	383	195
Mean (SD)	7.8 (5.4)	7.2 (5.5)
DFI, n	406	208
Mean (SD)	6.5 (5.9)	6.5 (6.2)

SD: standard deviation.

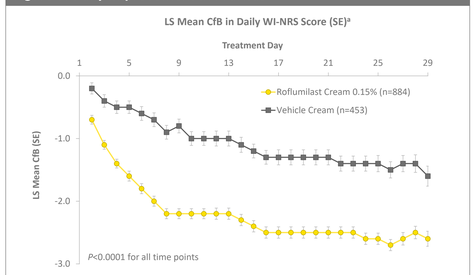
Figure 2. Percentage of Patients Achieving vIGA-AD Success, vIGA-AD Clear or Almost Clear, EASI-75, and WI-NRS Success at Week 4



Multiple imputation of missing data.
CI: confidence interval; EASI-75: 75% reduction in EASI score from baseline; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis; WI-NRS: Worst Itch-Numeric Rating Scale.

- Roflumilast-treated patients also showed greater improvements than vehicle-treated patients on several PROs (Figures 3–5), including itch and sleep loss
  - Of patients with baseline WI-NRS ≥2, more roflumilast- than vehicle-treated patients achieved a score of 0/1 at Week 4 (28.8% vs 18.5%; *P*=0.0087)
  - Patients treated with roflumilast experienced greater improvements in sleep than patients treated with vehicle, as illustrated by the sleep components of POEM (Figure 4) and SCORAD (Figure 5)
  - Differences favoring roflumilast over vehicle were also seen at all time points for changes in DLQI, CDLQI, and DFI
    - At Week 4, roflumilast-treated patients achieved greater improvements than vehicle-treated in DLQI (least squares mean change, −4.53 vs −3.43; *P*=0.0005), CDLQI (−3.75 vs −1.97; *P*<0.0001), and DFI (−3.12 vs −1.74; *P*<0.0001)

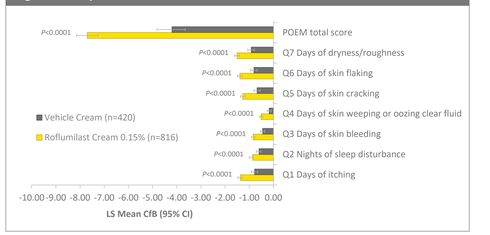
Figure 3. Daily Improvement in Pruritus



Roflumilast cream 0.15% improved (reduced) itch by 24 hours after first application compared with vehicle (*P*<0.0001)

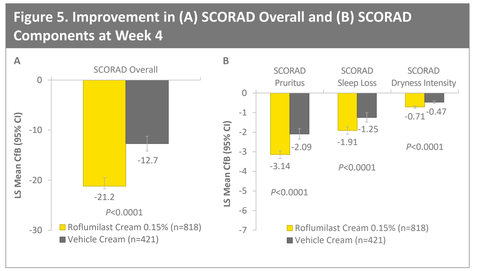
Missing data were not imputed.
[a]Evaluated in all patients, not just those with baseline WI-NRS score ≥4.
CfB: change from baseline; LS: least squares; SE: standard error.

Figure 4. Improvement in POEM at Week 4



Missing data were not imputed.
POEM is a 28-point scale measuring disease severity per patient reports of signs and symptoms, including pruritus, sleep, and local skin changes (bleeding, oozing, flaking, etc).
CfB: change from baseline; CI: confidence interval; LS: least squares; POEM: Patient-Oriented Eczema Measure.

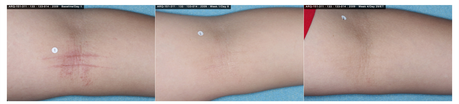
Figure 5. Improvement in (A) SCORAD Overall and (B) SCORAD Components at Week 4



Missing data were not imputed.
SCORAD assesses the severity (ie, extent, intensity) of AD taking into account (1) the overall BSA affected by AD, (2) severity (0 = absence to 3 = severe) of 6 signs of AD (erythema, edema/papulation, oozing/crusts, excoriation, lichenification, and dryness), and (3) 2 subjective scales (loss of sleep and intensity of pruritus) evaluated on a 10.0-cm visual analog scale (0 = none to 10 = highest). It ranges from 0 to 103, where higher scores indicate the most severe severity.
CfB: change from baseline; CI: confidence interval; LS: least squares.

- A series of photographs of a patient with improvement in AD following roflumilast treatment is shown in Figure 6

Figure 6. Improvement in Patient With AD Treated With Roflumilast Cream 0.15%



Baseline	Week 1	Week 4
vIGA-AD: 3	vIGA-AD: 2	vIGA-AD: 1
BSA: 6.0%	BSA: 2.5%	BSA: 0.5%
WI-NRS: 9	WI-NRS: 3	WI-NRS: 1

12-year-old male, White/Hispanic or Latino

SAFETY AND LOCAL TOLERABILITY

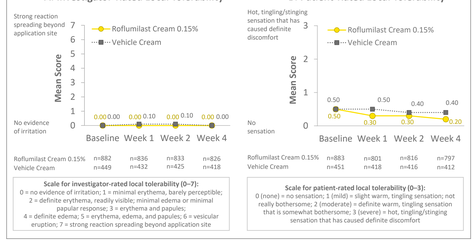
- Incidence of treatment-emergent adverse events (AEs) was low in both treatment groups (Table 2)
- Local tolerability was favorable (Figure 7)
  - >90% of patients reported no or mild sensation across both treatment groups at all time points

Table 2. Safety

Patients, n (%)	Roflumilast Cream 0.15% (n=885)	Vehicle Cream (n=451)
Patients with any treatment-related TEAE	53 (6.0)	12 (2.7)
Patients with any treatment-emergent SAE[a]	8 (0.9)	0
Patients with any TEAE leading to discontinuation of trial/trial drug	14 (1.6)	5 (1.1)
Patients with any TEAE	194 (21.9)	65 (14.4)
Most common TEAEs by Preferred Term, ≥1% in any group		
Headache	26 (2.9)	4 (0.9)
Nausea	17 (1.9)	2 (0.4)
Application site pain	13 (1.5)	3 (0.7)
Diarrhea	13 (1.5)	2 (0.4)
Vomiting	13 (1.5)	2 (0.4)
COVID-19	7 (0.8)	8 (1.8)

[a]SAEs were: atopic dermatitis, cutaneous nerve entrapment, depression, diverticulitis, general physical health deterioration, pulmonary embolism, staphylococcal scalded skin syndrome, suicidal ideation.
COVID-19, coronavirus disease 2019; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

Figure 7. (A) Investigator- and (B) Patient-Rated Local Tolerability



CONCLUSIONS

- Once-daily, nonsteroidal roflumilast cream 0.15% provided improvement across multiple efficacy endpoints and PROs versus vehicle in patients with AD
  - Statistically significant improvement in itch was observed as early as 24 hours after first application of roflumilast cream 0.15% compared with vehicle
- Patients treated with roflumilast achieved statistically significantly greater improvements in PROs, including itch, sleep loss, and quality of life
- Safety and local tolerability were favorable
  - There were low rates of AEs and discontinuations due to AEs, generally similar to vehicle

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DISCLOSURES

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