Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

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eMETHODS

PATIENTS

Key exclusion criteria were inability to discontinue treatment with therapies for atopic dermatitis before the baseline visit and during the trial; planned excessive exposure of treated area(s) to natural or artificial sunlight, tanning bed, or other light emitting device; previous treatment with roflumilast cream or foam; and treatment with oral roflumilast within the previous 4 weeks.

SAFETY ENDPOINTS

A serious adverse event was defined as any adverse event that, in the view of either the investigator or sponsor, met at least one of the following serious criteria: fatal; life-threatening (places the patient at immediate risk of death); requires inpatient hospitalization or prolongation of existing hospitalization; results in a persistent or significant incapacity/disability; congenital anomaly/birth defect; and other important medical events that, based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the end points listed in the above definition.

Local tolerability at application sites was assessed by investigators (prior to study drug application in the clinic) and patients (10-15 minutes after application of the study drug) at baseline and weeks 1, 2, and 4. Investigator-rated local tolerability assessments were conducted on an eight-point scale (range 0 [no evidence of irritation] to 7 [strong reaction spreading beyond the application site]). Patient-rated local tolerability was evaluated on a four-point scale (range 0 [none] to 3 [severe]).

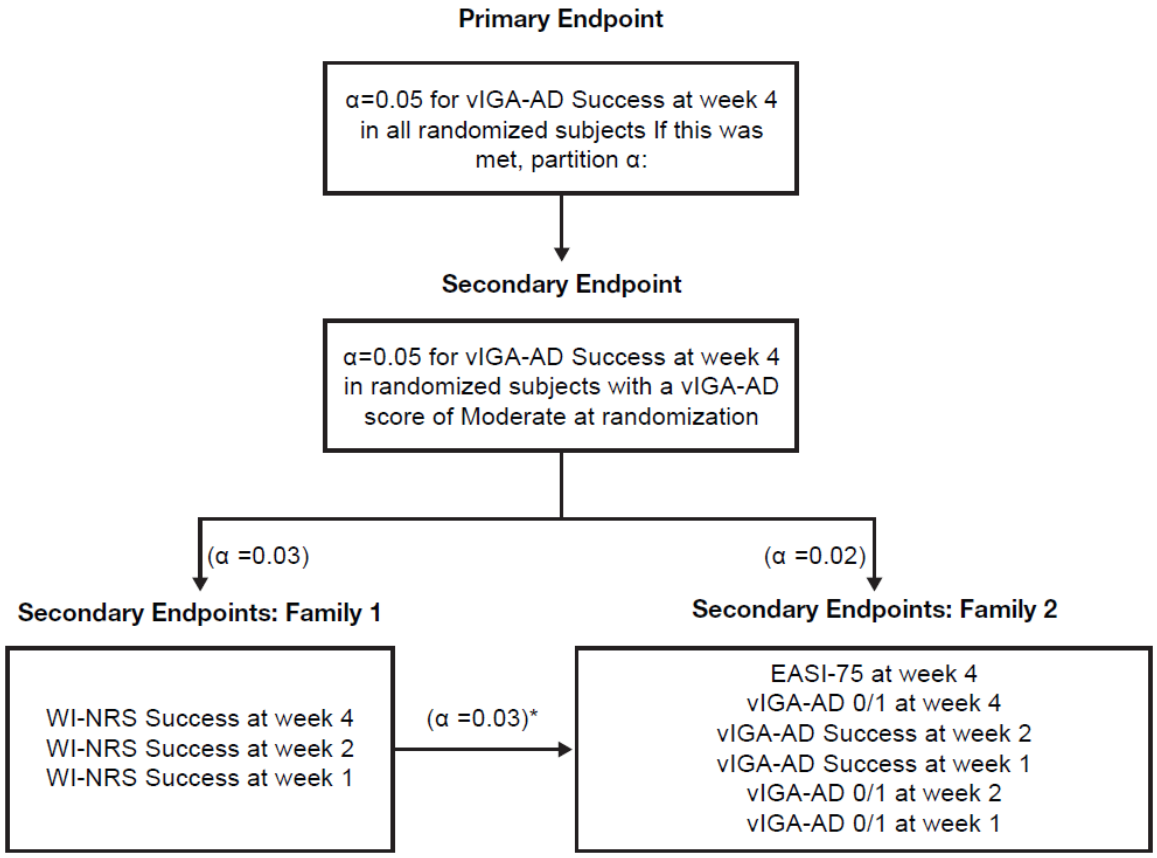
As depression and suicidal ideation have been reported with oral PDE4 inhibitors,[1,2] these adverse events were monitored by changes on the Children's Depression Inventory 2, Patient Health Questionnaire Depression Scale (including the modified version for adolescents), and Columbia-Suicide Severity Rating Scale.

STATISTICAL ANALYSIS

Categorical secondary efficacy analyses were performed in the same manner as the primary end point. Continuous secondary end points were analyzed by analysis of covariance with treatment, the randomization stratification factors, and baseline value as independent variables.

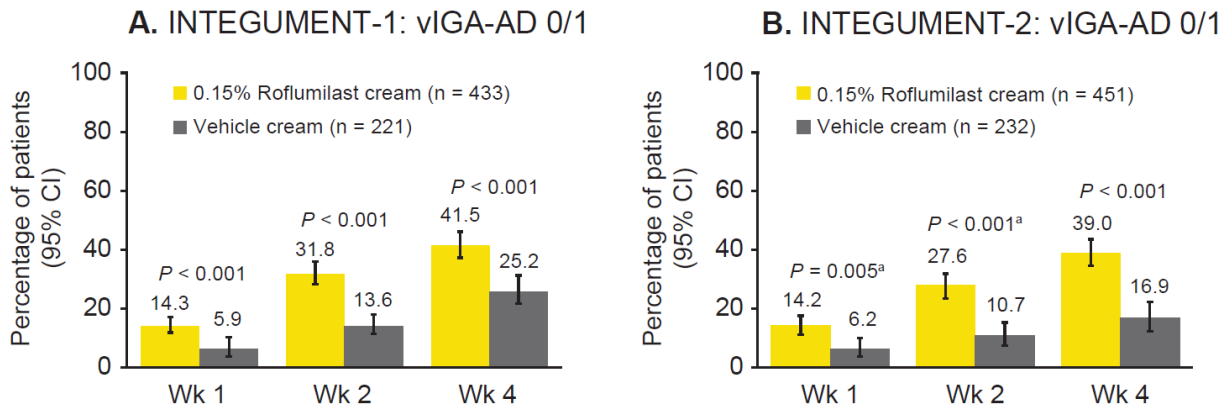
Upon successful demonstration of statistical significance for Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) Success at week 4 in the intent-to-treat (ITT) population (defined as all randomized patients) and vIGA-AD Success at week 4 in the subset of the ITT population with vIGA-AD score of 3 (Moderate), the remaining end points were grouped into 2 secondary end point families. Secondary end point family 1 comprised a 4-point reduction on the Worst Itch-Numeric Rating Scale end point at week 4, week 2 and week 1. Secondary end point family 2 comprised a 75% reduction in the Eczema Area and Severity Index at week 4, vIGA-AD 0 (Clear)/1 (Almost Clear) at week 4, vIGA-AD Success at week 2 and week 1, vIGA-AD 0/1 at week 2 and week 1. In addition, the Fallback Method was applied. First, testing proceeded at the 0.03 level sequentially within family 1. Should all end points in family 1 be statistically significant at the 0.03 level, then the full alpha (0.03) was carried to family 2. Family 2 was then tested at alpha = 0.05 (0.02+0.03). A *P* value > 0.03 in family 1 would end testing within family 1, and no additional alpha would be carried over to family 2.

eFigure 1. Statistical Testing Hierarchy



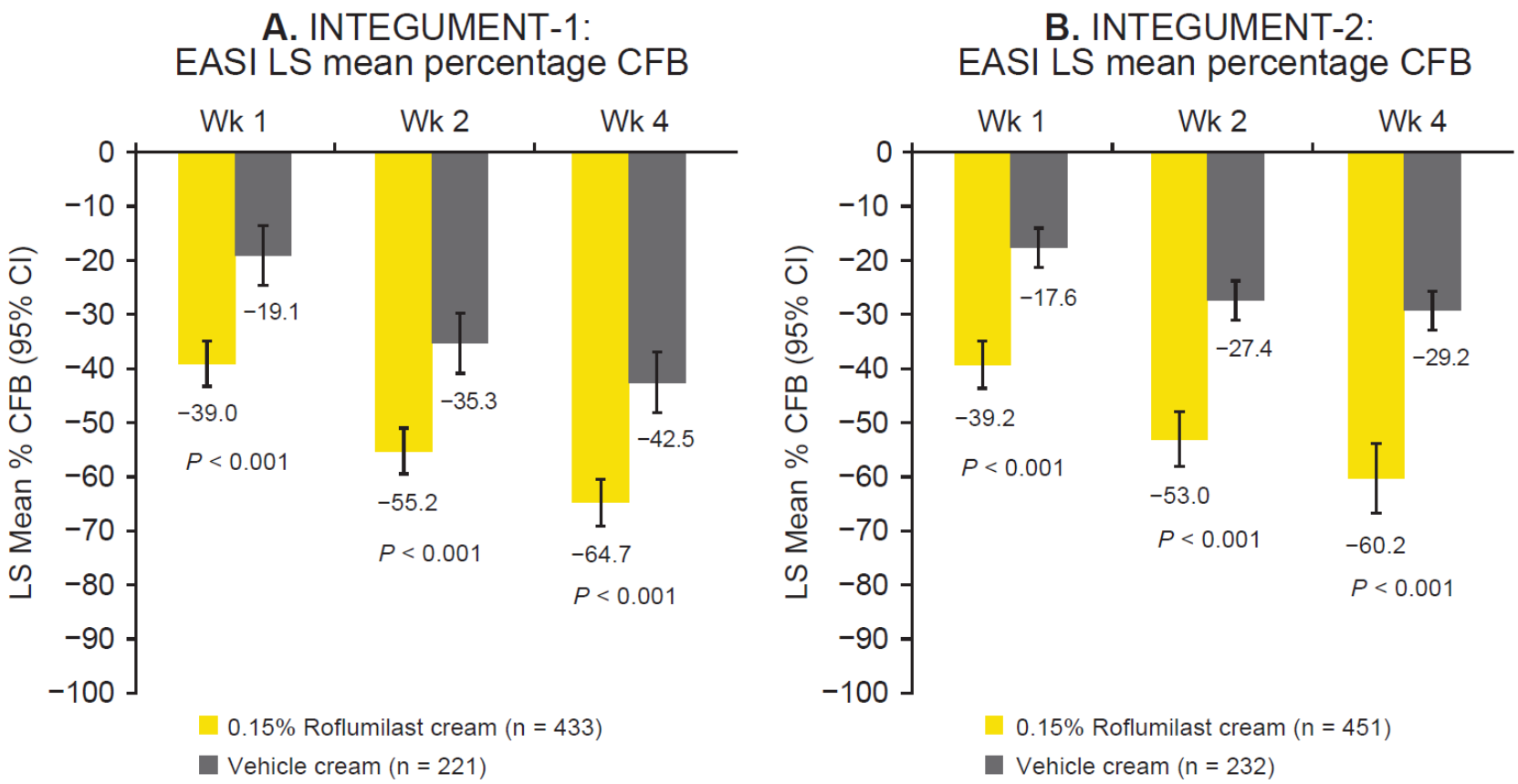
vIGA-AD was evaluated on a 5-point scale: 0 (Clear), 1 (Almost Clear), 2 (Mild), 3 (Moderate), 4 (Severe).
vIGA-AD Success = vIGA-AD score of 0 or 1 plus ≥2-grade improvement from baseline.
WI-NRS was evaluated on an 11-point scale ranging from 0 (no itch) to 10 (worst itch imaginable).
WI-NRS Success = ≥4-point reduction in the average weekly WI-NRS in the subset of the ITT population with baseline ≥4 and age ≥12 years.
EASI, Eczema Area and Severity Index; EASI-75, ≥4-point reduction in EASI; ITT, Intent-to-treat; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis; WI-NRS, Worst Itch-Numeric Rating Scale.
*Family 1 testing proceeded at the α = 0.03 level. Should all family 1 end points be statistically significant at the 0.03 level, then the full 0.03 alpha was carried to family 2. Family 2 was then tested at α = 0.05 (0.02 + 0.03). If anywhere in the sequential testing of family 1 there was a *P* value >0.03, testing within family 1 was stopped and no additional alpha carried over to family 2.

eFigure 2. Percentage of Patients with vIGA-AD 0/1 in INTEGUMENT-1 (A) and INTEGUMENT-2 (B)



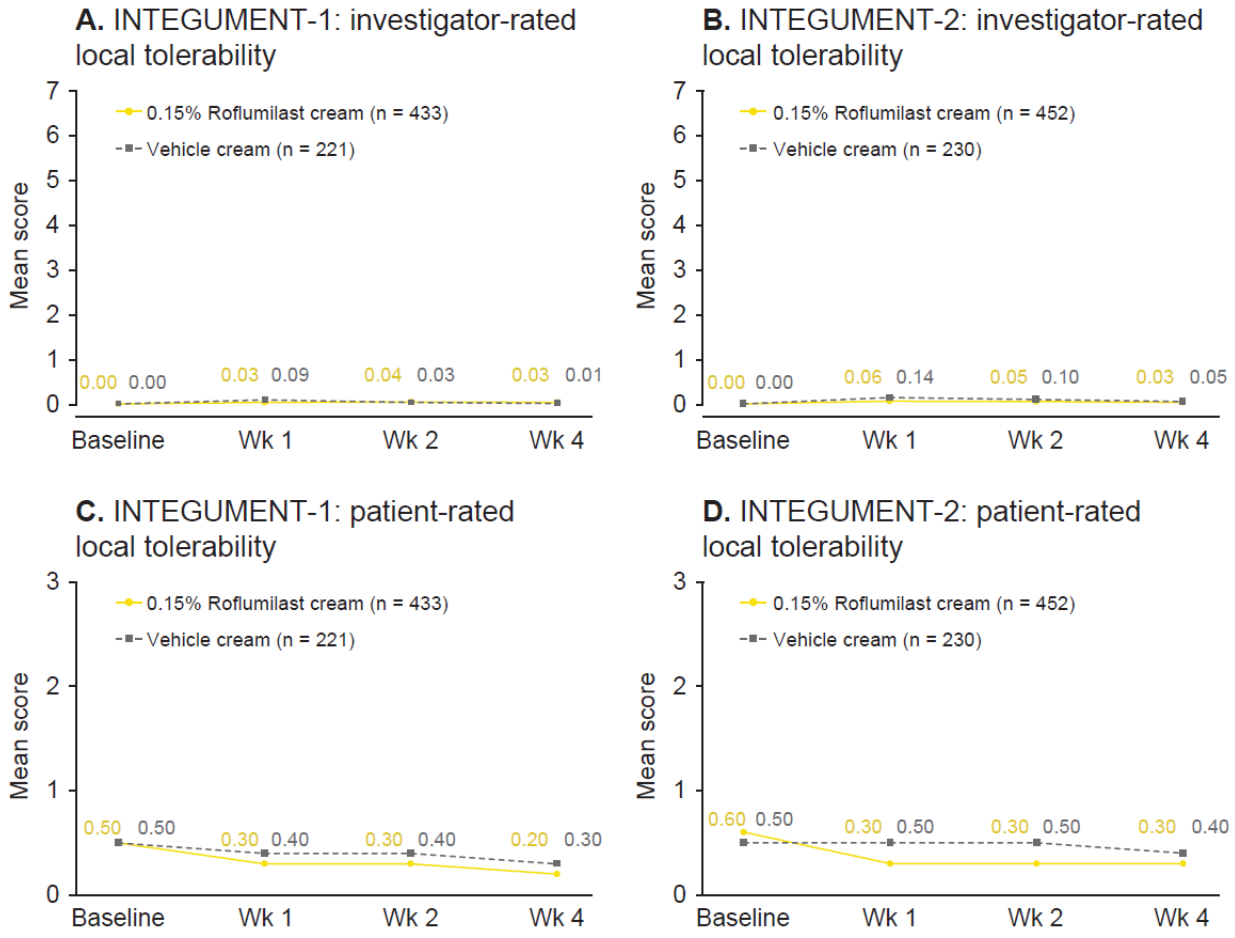
CI, Confidence interval; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis.
[a]*P* values are nominal.

eFigure 3. LS Mean Percentage CFB in EASI[a]



[a]EASI is a measurement that combines disease severity and the area affected into one score; scores range from 0 (no disease) to 72 (maximal disease);[3] however, due to the exclusion of the scalp, the maximum score was 70.8.
CFB, Change From Baseline; CI, confidence interval; EASI, Eczema Area and Severity Index; LS, least-squares.

eFigure 4. Investigator- (A, B) and Patient-Rated (C, D) Local Tolerability



Scale for investigator-rated local tolerability (0–7): 0 = no evidence of irritation; 1 = minimal erythema, barely perceptible; 2 = definite erythema, readily visible; minimal edema or minimal papular response; 3 = erythema and papules; 4 = definite edema; 5 = erythema, edema and papules; 6 = vesicular eruption; 7 = strong reaction spreading beyond application site.
Scale for patient-rated local tolerability (0–3): 0 (none) = no sensation; 1 (mild)= slight warm, tingling sensation; not really bothersome; 2 (moderate) = definite warm, tingling sensation that is somewhat bothersome; 3 (severe) = hot, tingling/stinging sensation that has caused definite discomfort.

eTable 1. vIGA-AD Scale

Score	Description
0 (Clear)	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Postinflammatory hyperpigmentation and/or hypopigmentation may be present.
1 (Almost Clear)	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2 (Mild)	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.
3 (Moderate)	Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4 (Severe)	Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

Abbreviation: vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis.

eTable 2. Patient Demographic and Baseline Characteristics[a]

Characteristic	INTEGUMENT-1		INTEGUMENT-2	
	Roflumilast Cream 0.15% (n = 433)	Vehicle Cream (n = 221)	Roflumilast Cream 0.15% (n = 451)	Vehicle Cream (n = 232)
Age, mean (SD), y	28.1 (19.1)	28.5 (18.9)	27.7 (19.6)	26.2 (18.9)
Age, No. (%)[b], y				
6–11	88 (20.3)	42 (19.0)	126 (27.9)	61 (26.3)
12–17	112 (25.9)	54 (24.4)	80 (17.7)	52 (22.4)
18–65	209 (48.3)	115 (52.0)	225 (49.9)	108 (46.6)
≥65	24 (5.5)	10 (4.5)	20 (4.4)	11 (4.7)
Sex at birth, No. (%)				
Male	196 (45.3)	92 (41.6)	199 (44.1)	89 (38.4)
Female	237 (54.7)	129 (58.4)	252 (55.9)	143 (61.6)
Ethnicity, No. (%)				
Hispanic or Latino	99 (22.9)	56 (25.3)	51 (11.3)	16 (6.9)
Not Hispanic or Latino	333 (76.9)	164 (74.2)	397 (88.0)	213 (91.8)
Not reported	1 (0.2)	1 (0.5)	3 (0.7)	3 (1.3)
Race, No. (%)[b]				
American Indian or Alaska Native	2 (0.5)	0 (0.0)	5 (1.1)	1 (0.4)
Asian	63 (14.5)	32 (14.5)	51 (11.3)	30 (12.9)
Black or African American	80 (18.5)	46 (20.8)	96 (21.3)	50 (21.6)
Native Hawaiian or other Pacific Islander	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
White	261 (60.3)	129 (58.4)	268 (59.4)	138 (59.5)
Multiple	12 (2.8)	6 (2.7)	12 (2.7)	8 (3.4)

Other[c]	14 (3.2)	8 (3.6)	19 (4.2)	5 (2.2)
Inadequate response, intolerance, or contraindication to prior medication, No. (%)				
Topical corticosteroids	285 (65.8)	136 (61.5)	260 (57.6)	132 (56.9)
Topical calcineurin inhibitors	77 (17.8)	35 (15.8)	84 (18.6)	46 (19.8)
Crisaborole	23 (5.3)	14 (6.3)	45 (10.0)	16 (6.9)
Fitzpatrick skin type at screening[d], No. (%)				
I–III	233 (53.8)	112 (50.7)	248 (55.0)	126 (54.3)
IV–VI	200 (46.2)	109 (49.3)	203 (45.0)	106 (45.7)
Baseline vIGA-AD[e], No. (%)				
2 (Mild)	103 (23.8)	59 (26.7)	108 (23.9)	53 (22.8)
3 (Moderate)	330 (76.2)	162 (73.3)	343 (76.1)	179 (77.2)
EASI[f]				
Mean (SD)	9.9 (5.3)	9.8 (5.1)	10.3 (6.1)	10.2 (5.3)
Median (Range)	8.2 (4.4, 47.4)	8.2 (4.2, 37.9)	8.5 (4.9, 52.5)	8.4 (3.4, 31.2)
BSA				
Mean (SD)	13.4 (11.9)	12.9 (11.1)	13.7 (11.6)	14.9 (11.3)
Median (Range)	9.5 (3.0, 87.0)	9 (3.0, 86.0)	10.0 (3.0, 88.0)	11.0 (3.0, 63.0)
Areas involved, No. (%)				
Facial	181 (41.8)	98 (44.3)	189 (41.9)	99 (42.7)
Eyelid	84 (19.4)	43 (19.5)	94 (20.8)	56 (24.1)
WI-NRS[g] — no.	423	217	435	224
Mean (SD)	5.9 (2.1)	5.9 (2.4)	6.2 (2.2)	5.9 (2.1)
Median (Range)	6.1 (0, 10)	6.0 (0, 10)	6.4 (0, 10)	6.1 (0, 10)
Average weekly baseline WI-NRS ≥ — no. (%)	350 (80.8)	168 (76.0)	359 (79.6)	181 (78.0)

Abbreviations: BSA, body surface area; EASI, Eczema Area and Severity Index; SD, standard deviation; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis; WI-NRS, Worst Itch-Numeric Rating Scale.
[a]Patient demographics and baseline characteristics are for the intent-to-treat population, defined as all patients who were randomized to treatment.

[b]Percentages may not add up to 100% due to rounding.
[c]The other category includes patients who chose to describe their race rather than select one of the provided options as well as patients who did not report their race.
[d]Fitzpatrick Skin Type at screening: I. Always burns easily; never tans. II. Always burns easily; tans minimally. III. Burns moderately; tans gradually. IV. Burns minimally; always tans well. V. Rarely burns; tans profusely. VI. Never burns; deeply pigmented.
[e]The Validated Investigator Global Assessment for Atopic Dermatitis is a five-point scale for assessing inflammatory signs of atopic dermatitis.
[f]EASI is a measurement that combines disease severity and the area affected into one score; scores range from 0 (no disease) to 72 (maximal disease); however, due to the exclusion of the scalp, the maximum score was 70.8.
[g]WI-NRS score is a patient-reported assessment of itch in the preceding 24 hours; scores range from 0 (no itch) to 10 (worst itch imaginable).

eTable 3. vIGA-AD Success at Week 4

Baseline Characteristic, %	INTEGUMENT-1		INTEGUMENT-2	
	Roflumilast Cream 0.15% (n = 433)	Vehicle Cream (n = 221)	Roflumilast Cream 0.15% (n = 451)	Vehicle Cream (n = 232)
6–11 y of age	n = 88	n = 42	n = 126	n = 61
%	26.4	10.3	26.7	7.0
12–17 y of age	n = 113	n = 54	n = 80	n = 52
%	32.7	5.6	27.7	15.5
≥18 y of age	n = 233	n = 125	n = 245	n = 119
%	33.9	21.1	30.5	13.0
vIGA-AD of 3	n = 328	n = 164	n = 342	n = 179
%	35.0[a]	17.5	32.9[b]	13.1

vIGA-AD Success = vIGA-AD score of 0 (Clear) or 1 (Almost Clear) plus ≥2-grade improvement from baseline.
Abbreviations: ITT, intent-to-treat; vIGA-AD, Validated Global Assessment for Atopic Dermatitis; vIGA-AD Success.
[a]Difference, 17.4%; $P < 0.001$.
[b]Difference 19.1%, $P < 0.001$.

References

1. Otezla (apremilast) tablets prescribing information. Thousand Oaks, CA: Amgen; 2020.

2. Daliresp (roflumilast) tablets prescribing information. Wilmington, DE: AstraZeneca Pharmaceuticals; 2020.

3. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. *Exp Dermatol.* 2001;10:11-18.