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Roflumilast Cream Provides Long-Term Improvements in Atopic Dermatitis: Subgroup Analysis of Patients With Other Atopic Conditions

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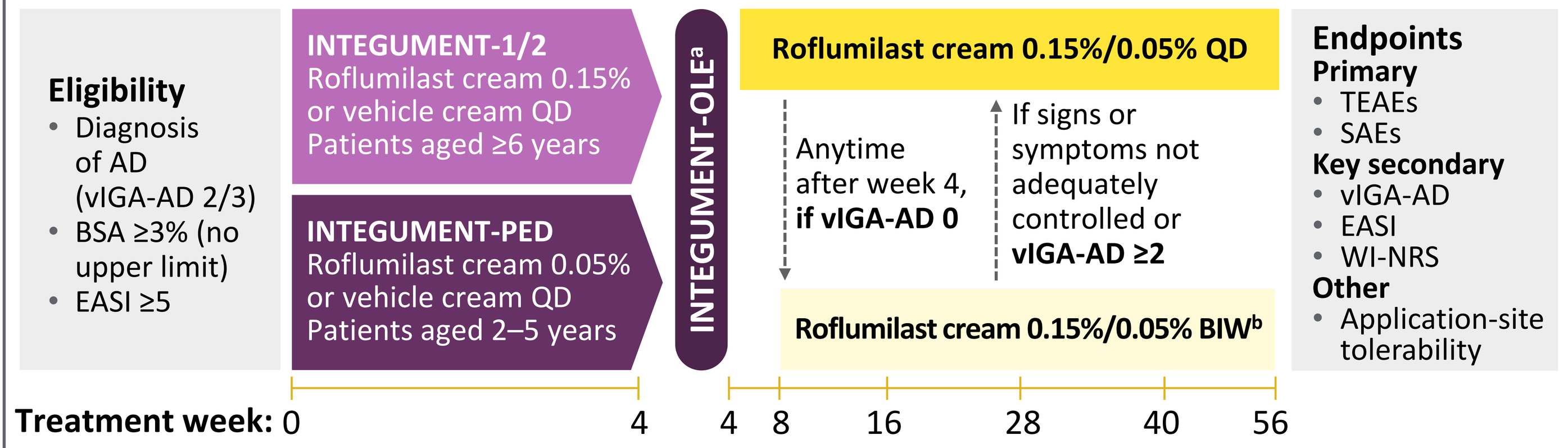
INTRODUCTION

- AD frequently occurs with other atopic conditions (eg, asthma, food allergy, hay fever)[1] that are commonly treated with corticosteroids[2,3]
  - This can lead to substantial overall corticosteroid burden and raises concerns over the cumulative effects of corticosteroid exposure across routes of administration[2]
- TCS are not approved for long-term use because of an increased risk of cutaneous and systemic AEs, and higher-potency TCS are not recommended for thin-skinned areas (eg, face, intertriginous areas, and genital region; overall thinner skin in infants and children) where systemic absorption is greater[4,5]
- Roflumilast cream is a PDE4 inhibitor–based advanced targeted topical therapy that is formulated without propylene glycol, formaldehyde, fragrances, or other potential irritating excipients[6]
  - Roflumilast cream 0.15% and 0.05% is approved for the treatment of mild-to-moderate AD in patients aged ≥6 years and 2–5 years, respectively[7]
  - Efficacy and safety of roflumilast cream were demonstrated in patients with AD in the INTEGUMENT-1 and -2[8] and INTEGUMENT-PED[9] phase 3, 4-week, randomized, vehicle-controlled trials
- Long-term maintenance and further improvements in AD signs and symptoms in patients from these parent trials were observed with up to 52 weeks of roflumilast cream application in the OLE study (INTEGUMENT-OLE/NCT04804605)[10,11]
  - Outcomes in patients enrolled in INTEGUMENT-OLE with other atopic conditions are reported here

METHODS

- INTEGUMENT-1/2 and INTEGUMENT-PED were 4-week, randomized, vehicle-controlled, phase 3 trials that enrolled patients aged ≥6 years and 2–5 years, respectively, with mild-to-moderate AD
- Patients who completed one of these parent trials could enroll in INTEGUMENT-OLE during which roflumilast cream 0.15% (≥6 years) or 0.05% (2–5 years) was applied once daily for ≤52 weeks
  - Patients could switch to BIW application any time at or 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)
- Parent-study baseline was used for the efficacy assessments, which included:
  - vIGA-AD 0/1 and vIGA-AD success (vIGA-AD 0/1 plus ≥2-point improvement)
  - WI-NRS no (0)/minimal (1) itch and WI-NRS success (≥4-point improvement in patients with baseline score ≥4)
  - ≥75% improvement in EASI (EASI-75)
- Outcomes were assessed in the overall population and in patients with additional atopic conditions: allergic upper airway/ocular disease, allergic lower airway disease, food/gastrointestinal allergic disease, or systemic hypersensitivity reactions
  - Patients were also assessed on the basis of the number of additional atopic conditions (0, 1, ≥2)

INTEGUMENT-OLE Study Design


Eligibility
Diagnosis of AD (vIGA-AD 2/3)
BSA ≥3% (no upper limit)
EASI ≥5
INTEGUMENT-1/2
Roflumilast cream 0.15% or vehicle cream QD
Patients aged ≥6 years
INTEGUMENT-PED
Roflumilast cream 0.05% or vehicle cream QD
Patients aged 2–5 years
INTEGUMENT-OLE[a]
Roflumilast cream 0.15%/0.05% QD
Anytime after week 4, if vIGA-AD 0
If signs or symptoms not adequately controlled or vIGA-AD ≥2
Roflumilast cream 0.15%/0.05% BIW[b]
Endpoints
Primary
TEAEs
SAEs
Key secondary
vIGA-AD
EASI
WI-NRS
Other
Application-site tolerability
Treatment week: 0 4 4 8 16 28 40 56

Application of nonmedicated emollients or moisturizers was allowed as a part of the patient's stable regimen

[a]After OLE study enrollment commenced, the protocol was amended to allow patients (aged 2–5 years) who completed INTEGUMENT-PED to enroll, as well as a 24-week cohort consisting of an additional ~550 patients aged 6-17 years. Patients must have completed 4 weeks in a parent trial with no safety concerns. [b]For BIW application, study medication was to be applied on 2 nonconsecutive days per week to areas commonly and/or most recently affected by AD, and any areas where AD was developing.

RESULTS

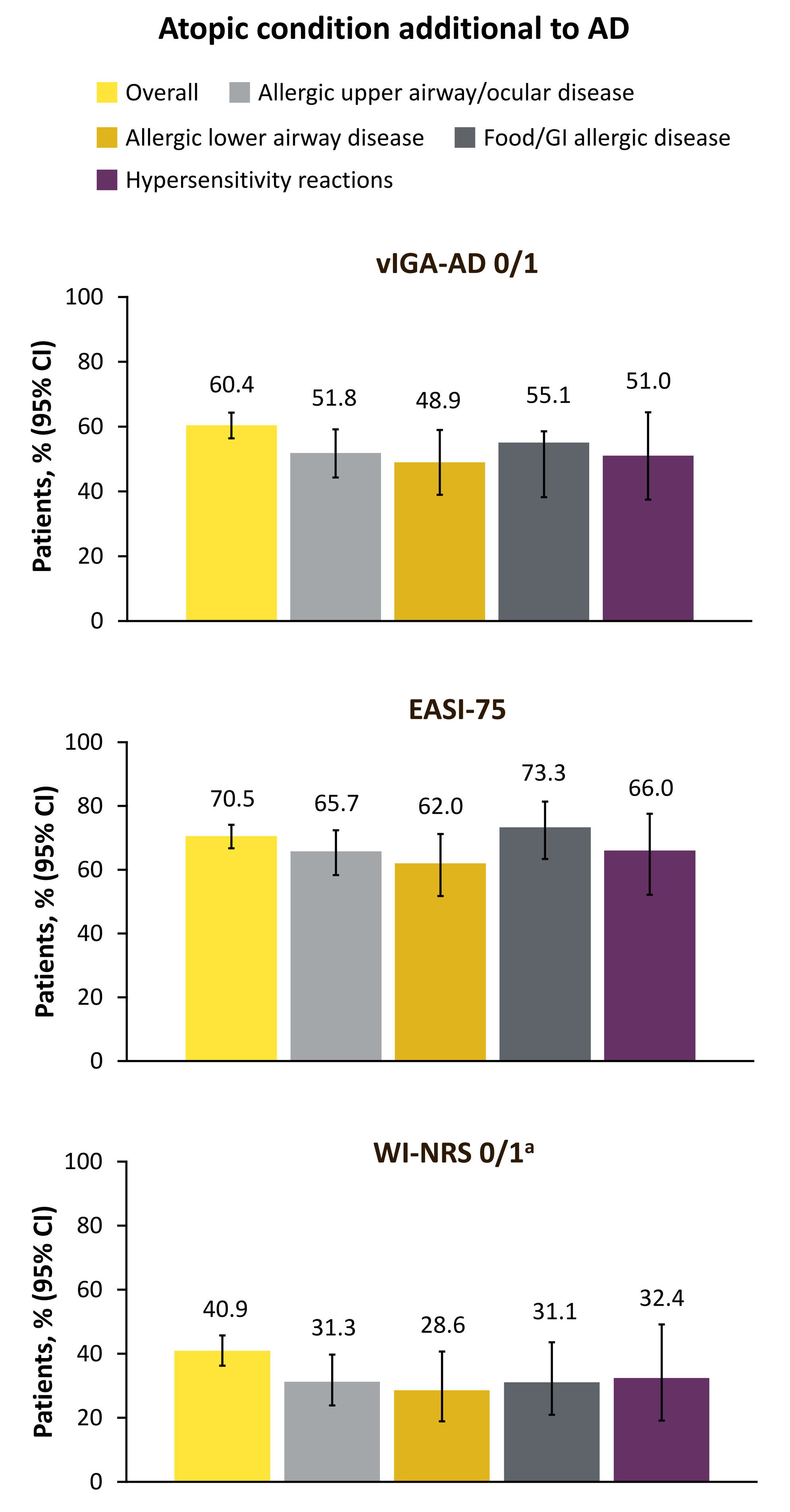
- Among 1219 patients enrolled in the INTEGUMENT-OLE trial, the mean age of patients rolling over from INTEGUMENT-1/2 was 19.7 years (range, 6–84) and from INTEGUMENT-PED was 3.3 years (range, 2–5); 52.7% of patients were female
  - The majority of patients were White (66.4%) and not Hispanic or Latino (82.7%)
  - Approximately 30% of patients had at least 1 additional atopic condition
  - 32.2% of patients had an allergic upper airway/ocular disease, 20.5% had allergic lower airway disease, 18.8% had food/gastrointestinal allergic disease, and 8.1% had systemic hypersensitivity reactions
- Improvements in AD signs and symptoms were observed in the overall population and across the other atopic conditions subgroups at OLE week 52
  - Roflumilast also improved signs and symptoms of AD in patients with 0, 1, or ≥2 additional atopic conditions
- Roflumilast cream 0.15% and 0.05% were well tolerated; throughout INTEGUMENT-OLE:
  - Application-site pain TEAEs were reported for 7 (0.6%) patients
  - ≥97.2% of patients had no evidence of irritation at the application site (as reported by investigators); ≤1.7% of patients reported a severe hot, tingling/stinging sensation that caused definite discomfort

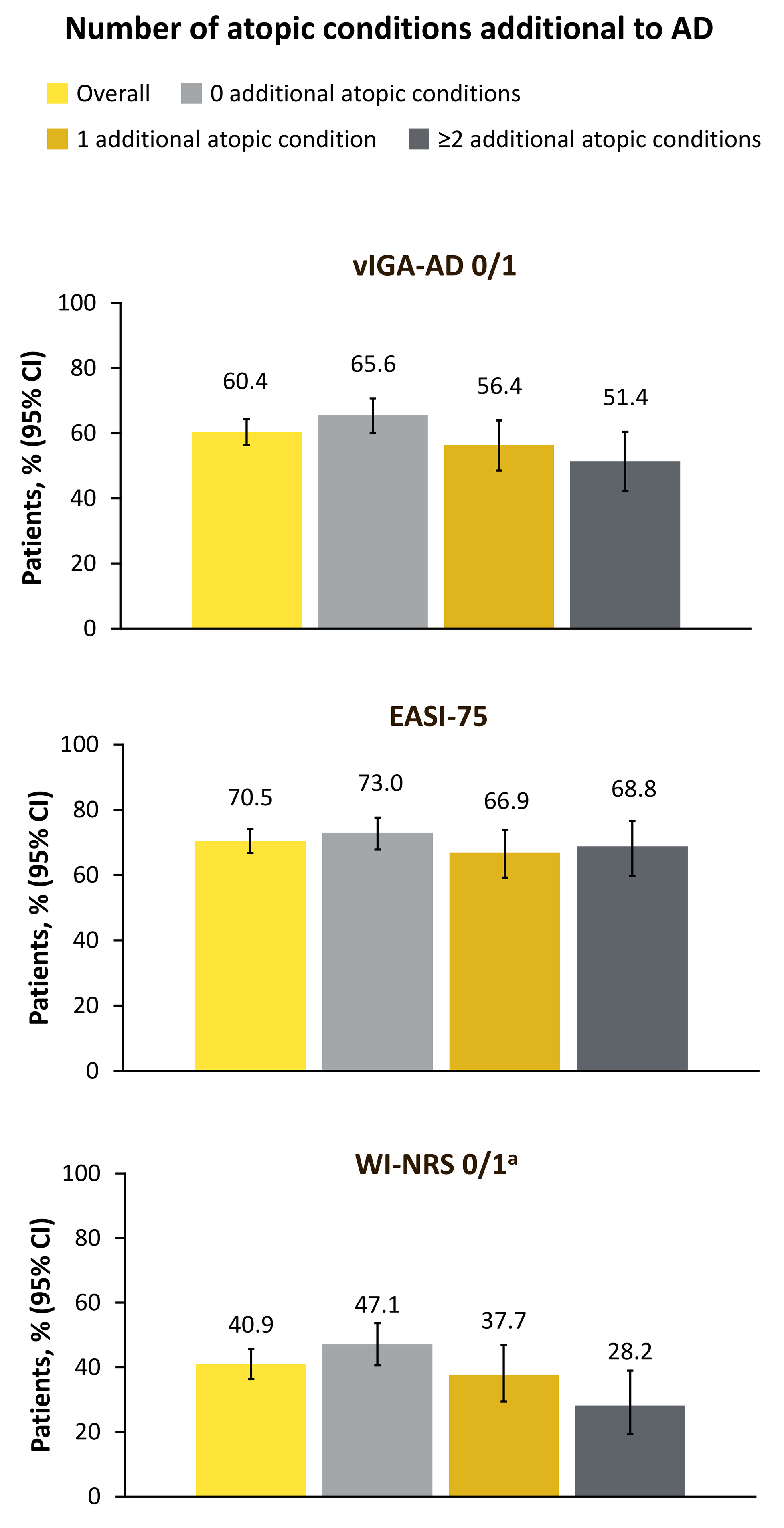
Baseline Clinical Characteristics

		Overall (N=1219)	Number of atopic conditions additional to AD: 0 (n=597)	1 (n=345)	≥2 (n=277)
BSA, %, mean (median) [range]		18.2 (14.0) [3.0–88.0]	17.4 (14.0) [3.0–75.8]	17.9 (13.0) [3.0–88.0]	20.5 (16.0) [3.2–86.0]
vIGA-AD, n (%)	Mild (2)	293 (24.0)	141 (23.6)	94 (27.2)	58 (20.9)
	Moderate (3)	926 (76.0)	456 (76.4)	251 (72.8)	219 (79.1)
WI-NRS, mean (median)[a]		5.9 (6.0)	5.7 (6.0)	5.8 (6.0)	6.2 (6.0)
EASI, mean (median) [range]		11.2 (9.3) [4.6–52.5]	10.7 (8.8) [4.6–39.6]	11.1 (9.0) [5.0–45.0]	12.6 (11.2) [5.0–52.5]
Atopic condition additional to AD, n (%)	Allergic upper airway/ocular disease	392 (32.2)	NA	NA	NA
	Allergic lower airway disease	250 (20.5)			
	Food/GI allergic disease	229 (18.8)			
	Systemic hypersensitivity reactions	99 (8.1)			

Safety population. [a]Range of WI-NRS was 0–10 in all groups.

Long-Term Improvement in Signs and Symptoms of AD (Treatment Week 56)

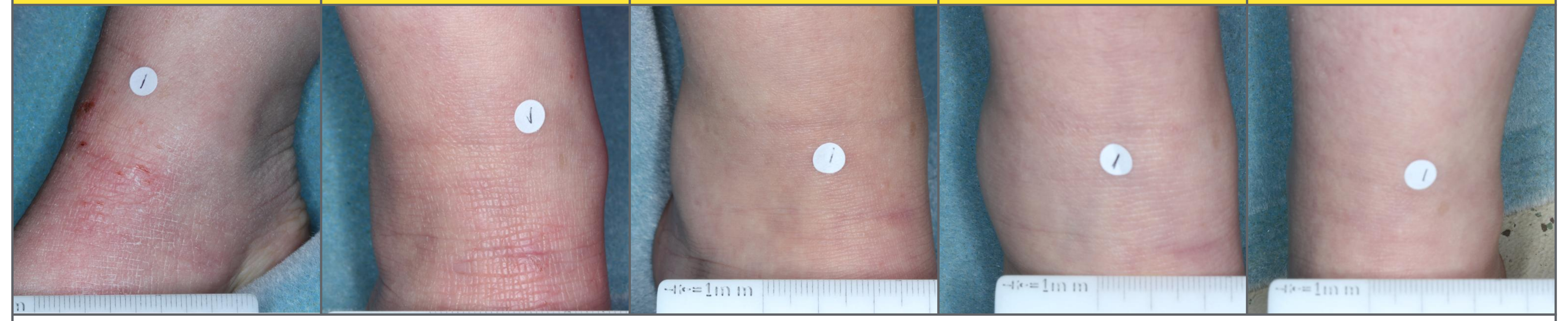

Atopic condition additional to AD
Overall
Allergic upper airway/ocular disease
Allergic lower airway disease
Food/GI allergic disease
Hypersensitivity reactions
vIGA-AD 0/1
60.4 51.8 48.9 55.1 51.0
EASI-75
70.5 65.7 62.0 73.3 66.0
WI-NRS 0/1[a]
40.9 31.3 28.6 31.1 32.4
Patients, % (95% CI)
0 20 40 60 80 100


Number of atopic conditions additional to AD
Overall
0 additional atopic conditions
1 additional atopic condition
≥2 additional atopic conditions
vIGA-AD 0/1
60.4 65.6 56.4 51.4
EASI-75
70.5 73.0 66.9 68.8
WI-NRS 0/1[a]
40.9 47.1 37.7 28.2
Patients, % (95% CI)
0 20 40 60 80 100

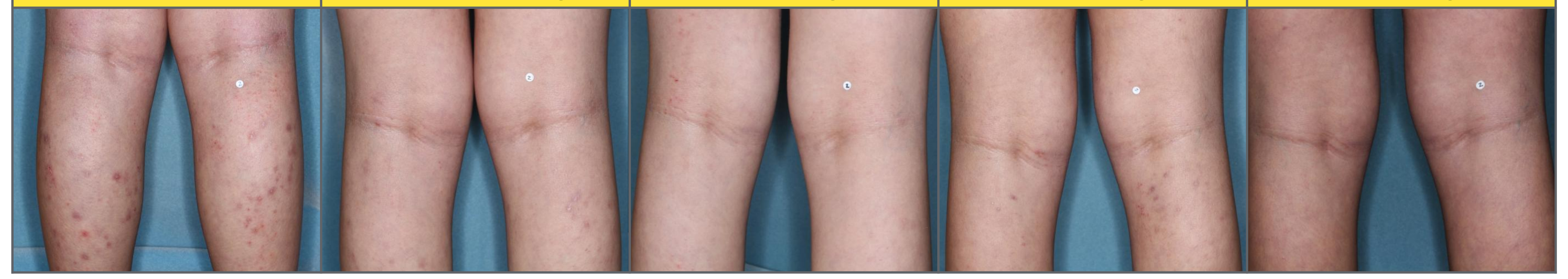
FAS; observed data. [a]Patients with WI-NRS ≥2 at parent-study baseline overall (n=1137), with allergic upper airway/ocular disease (n=368), allergic lower airway disease (n=238), food/GI allergic disease (n=219), hypersensitivity reactions (n=94), or 0 (n=549), 1 (n=324), or ≥2 (n=264) conditions additional to AD.

Improvements With Roflumilast Cream 0.15%/0.05% by Treatment Week

Baseline	Week 8	Week 28	Week 40	Week 56
4-year-old multiracial[a] female with a history of inadequate response, intolerance, and/or contraindications to TCS, a 4-year history of AD, and a 7-month history of allergic upper airway disease				
vIGA-AD 3	vIGA-AD 2	vIGA-AD 1	vIGA-AD 0 *Started BIW dosing*[b]	vIGA-AD 0 *BIW dosing*



Baseline	Week 8	Week 28	Week 40	Week 56
11-year-old Black/African American, Hispanic female with a 4-year history of both AD and environmental allergies				
vIGA-AD 3	vIGA-AD 0 *Started BIW dosing*[c]	vIGA-AD 0 *BIW dosing*	vIGA-AD 0 *BIW dosing*	vIGA-AD 0 *BIW dosing*



Note: The white sticker is placed by the investigator for reference; vIGA-AD is a global measure. [a]American Indian or Alaskan Native and White. [b]Patient started BIW dosing at treatment week 40 and did not switch back to QD dosing. [c]Patient started BIW dosing at treatment week 8 and did not switch back to QD dosing.

Safety Summary[a]

Patients, n (%)		Roflumilast cream 0.15%/0.05% (n=1219)
≥1 TEAE		522 (42.8)
≥1 treatment-related AE		45 (3.7)
≥1 SAE		26 (2.1)
≥1 treatment-related SAE		0
≥1 TEAE leading to discontinuation of study/study drug		37 (3.0)/39 (3.2)
Most common (≥2% of patients overall) TEAEs	Upper respiratory tract infection	70 (5.7)
	COVID-19	49 (4.0)
	Nasopharyngitis	48 (3.9)
	Pyrexia	33 (2.7)
	Influenza	32 (2.6)

Safety population. [a]Summary of TEAEs occurring during INTEGUMENT-OLE.

CONCLUSIONS

- Roflumilast cream 0.15% and 0.05% demonstrated long-term improvements in signs and symptoms of AD across a variety of efficacy endpoints (ie, vIGA-AD, WI-NRS, and EASI-75)
  - Outcomes were consistent among the total population and in patients with individual or multiple additional atopic conditions
- Roflumilast cream 0.15% and 0.05% were both well tolerated with an application-site pain TEAE reported for <1% of patients during the trial
- Roflumilast cream 0.15% and 0.05% improved signs and symptoms of AD in subgroups of patients with other atopic conditions, providing an opportunity to reduce overall corticosteroid burden

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; GI, gastrointestinal; NA, not applicable; OLE, open-label extension; PDE4, phosphodiesterase 4; QD, once daily; SAE, serious AE; 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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