Long-term Safety and Efficacy of Roflumilast Cream 0.15% in Adults and Children Aged ≥6 Years With Mild to Moderate Atopic Dermatitis:
A 52-week, Phase 3, Open-Label Safety Trial

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Introduction

Current topical AD treatments are limited by dosing frequency, tolerability issues, and restrictions on application to the face/eyelids, large body surface areas, and long-term use

- These limitations have driven reactive treatment of recurring AD flares rather than proactive use for long-term flare-free disease control

Roflumilast cream 0.15% is a once-daily nonsteroidal drug being investigated for AD

- Does not contain ethanol, propylene glycol, or fragrances that can irritate skin
- Roflumilast is a PDE4 inhibitor[1,2] with ~25 to >300-fold higher potency than apremilast and crisaborole,[3] with roflumilast more closely mimicking the 3 key binding sites of cAMP to PDE4[4]

In two phase 3 trials (INTEGUMENT-1 and -2), roflumilast cream 0.15% was well tolerated and demonstrated efficacy in patients ≥6 years of age with AD[5]

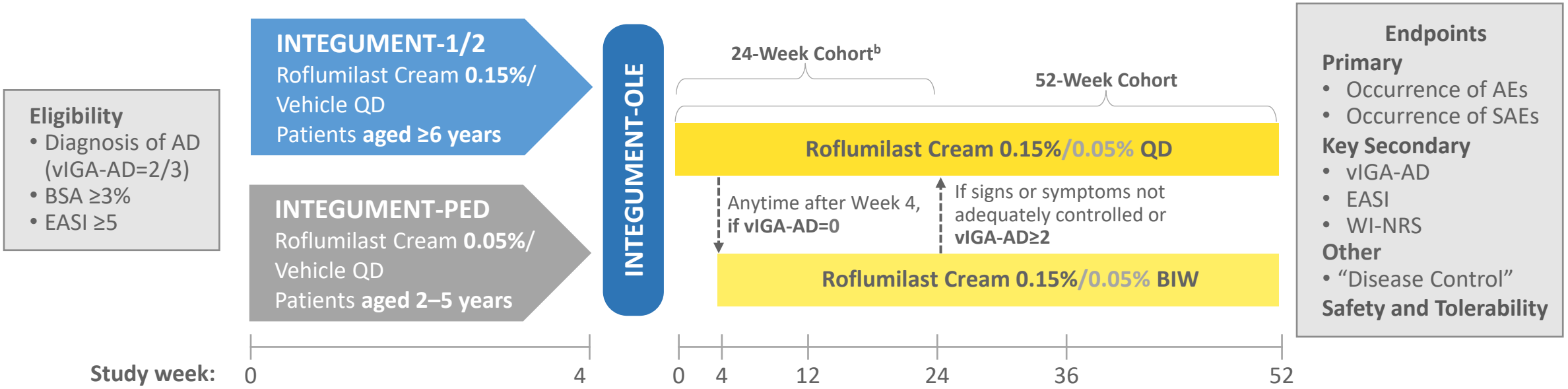
- Here we present results for patients ≥6 years of age from the phase 3 open-label extension trial (INTEGUMENT-OLE [NCT04804605]), including proactive twice-weekly (BIW) application for patients who achieved clear skin

AD: atopic dermatitis; cAMP: cyclic adenosine monophosphate; PDE4: phosphodiesterase 4 inhibitor.

1. ZORYVE (roflumilast) cream prescribing information. Arcutis Biotherapeutics, Inc, 2022. 2. ZORYVE (roflumilast) foam prescribing information. Arcutis Biotherapeutics, Inc, 2023. 3. Dong C, et al. *J Pharmacol Exp Ther* 2016;358:413–422. 4. Wang J, Bunick CG. *J Invest Dermatol* 2023;-143:S194. 5. Simpson E, et al. Presented at American Academy of Dermatology Annual Meeting 2023.

INTEGUMENT-OLE Study Design

- 52-week, phase 3, multicenter, open-label extension trial in adults and children ≥2 years of age with AD[a,b] (INTEGUMENT-OLE [NCT04804605])
  - Here we present results for patients who previously completed INTEGUMENT-1/2 (n=658; 299 in the 24-week cohort, 359 in the 52-week cohort)



Application of nonmedicated emollients or moisturizers was allowed as a part of the patient's stable regimen. "Disease Control" was defined as duration of vIGA-AD=0/1 with adequate control of signs and symptoms of AD on BIW dosing following achievement of vIGA-AD=0.

[a]This interim analysis included patients ≥6 years of age; analysis of patients aged 2-5 years is ongoing.

[b]After study enrollment commenced, the protocol was amended to allow patients (aged 2–5 years) who completed INTEGUMENT-PEDS to enroll as well as a 24-Week Cohort consisting of an additional ~550 patients aged 6–17 years.

AD: atopic dermatitis; AE: adverse event; BSA: body surface area; BIW: twice weekly; EASI: Eczema Area and Severity Index; OLE: open-label extension; QD, once daily; SAE: serious AE; vIGA-AD: Validated Investigator Global Assessment for AD; WI-NRS: Worst Itch-Numeric Rating Scale.

Demographics and Disease Characteristics

		Roflumilast 0.15% to Roflumilast 0.15% (n=439)	Vehicle to Roflumilast 0.15% (n=218)
Age, years, mean (SD) [range]		19.4 (16.4) [6–82]	20.5 (17.9) [6–84]
Age group, n (%)	6–11 years 12–17 years ≥18 years	183 (41.7) 140 (31.9) 116 (26.4)	79 (36.2) 79 (36.2) 60 (27.5)
Female at birth, n (%)		244 (55.6)	122 (56.0)
Not Hispanic or Latino, n (%)		361 (82.2)	182 (83.5)
Race, n (%)	White Asian Black or African-American American-Indian or Alaskan Native Native Hawaiian or Other Pacific Islander More than one race Other	272 (62.0) 63 (14.4) 58 (13.2) 6 (1.4) 1 (0.2) 20 (4.6) 19 (4.3)	139 (63.8) 35 (16.1) 31 (14.2) 0 0 7 (3.2) 6 (2.8)
Fitzpatrick Skin Type, n (%)	I to III IV to VI	245 (55.8) 194 (44.2)	120 (55.0) 98 (45.0)
Baseline vIGA-AD,[a] n (%)	2 (mild) 3 (moderate)	115 (26.2) 324 (73.8)	57 (26.0) 162 (74.0)
Disease characteristics,[a] mean (median) [range]	EASI BSA, % WI-NRS[b]	10.4 (8.8) [5.0–52.5] 14.4 (10.0) [3.0–88.0] 5.8 (6) [0–10]	10.6 (8.8) [5.0–37.9 15.6 (11.0) [3.0–86.0] 5.5 (6.0) [0.0–10.0]

Safety population, unless otherwise noted. At the start of the parent trial, unless otherwise noted.
aFAS (roflumilast 0.15% to roflumilast 0.15%, n=439; vehicle to roflumilast 0.15%, n=219). bIn patients ≥12 years of age.
BSA: body surface area; EASI: Eczema Area and Severity Index; FAS: full analysis set; SD: standard deviation; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis; WI-NRS: Worst Itch Numeric Rating Scale.

Long-Term Safety (Safety Population[a])

Patients, n (%)	Roflumilast cream 0.15% (n=657)
Patients with any TEAE	241 (36.7)
Patients with any treatment-related TEAE	31 (4.7)
Patients with any SAE[b]	8 (1.2)
Patients with any treatment-related SAE	0
Patients who discontinued trial because of AE[c]	20 (3.0)

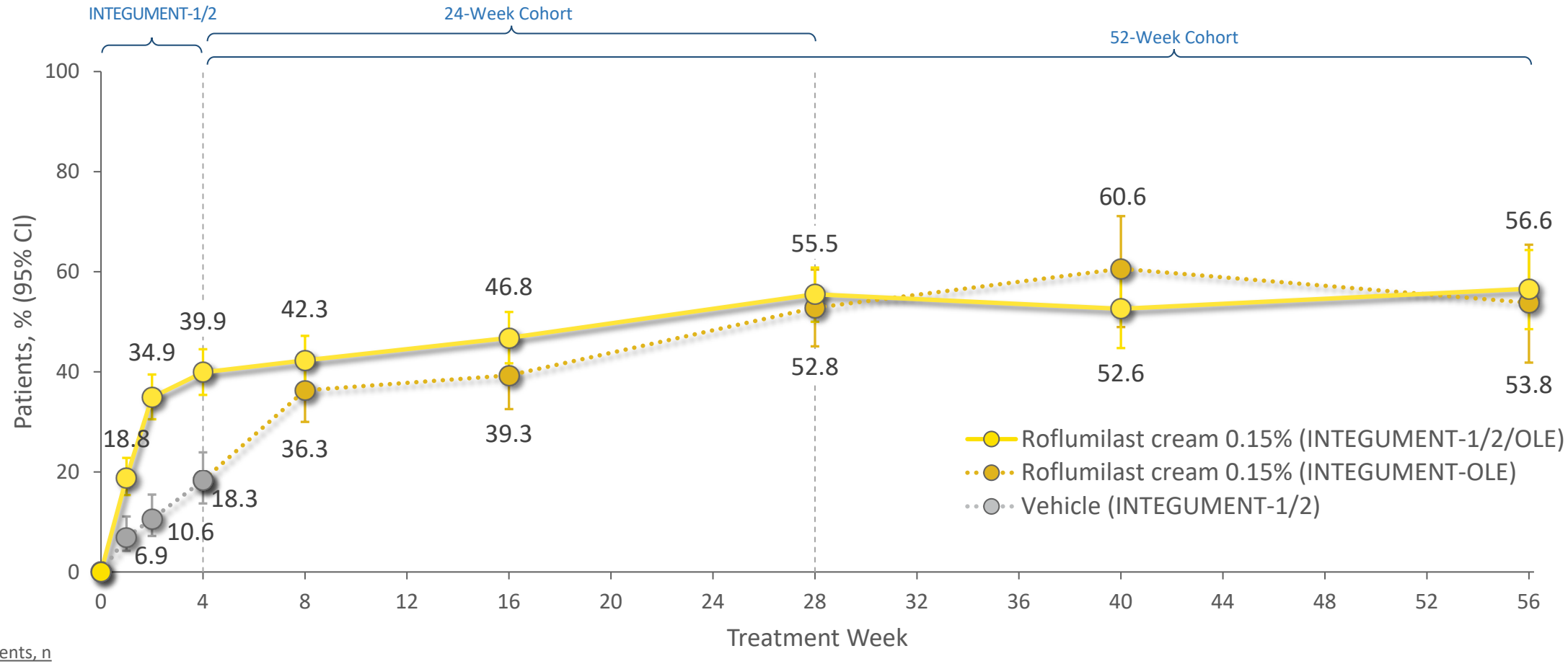
Most Common TEAEs
by Preferred Term (≥2% Overall)

Patients, n (%)	Roflumilast cream 0.15% (n=657)
COVID-19	30 (4.6)
Upper respiratory tract infection	21 (3.2)
Nasopharyngitis	20 (3.0)
Headache	18 (2.7)

- No new safety signals observed over up to 56 weeks of treatment
- 96.3% of patients who experienced TEAEs had AEs of mild or moderate severity
- At each visit, ≥98.1% of patients showed no evidence of irritation on investigator assessment of local tolerability
- Application site pain was reported in for 3 (0.5%) patients, and 0.4%–2.1% of patients reported severe stinging and/or burning at any visit

[a]Safety population was defined as all patients who enrolled and received ≥1 confirmed dose of trial medication.
[b]SAE preferred terms include diarrhea, vomiting, appendicitis, device-related infection, gastroenteritis, pneumonia, sepsis, headache, asthma, aortic aneurysm, and hypertension; all SAEs were deemed unrelated by the investigator.
[c]AEs leading to discontinuation: atopic dermatitis (n=5), nausea (n=2), application site dermatitis (n=2), other preferred term (n=11; 1 patient per preferred term).
AD: atopic dermatitis; AE: adverse event; TEAE: treatment-emergent adverse event; SAE: serious adverse event.

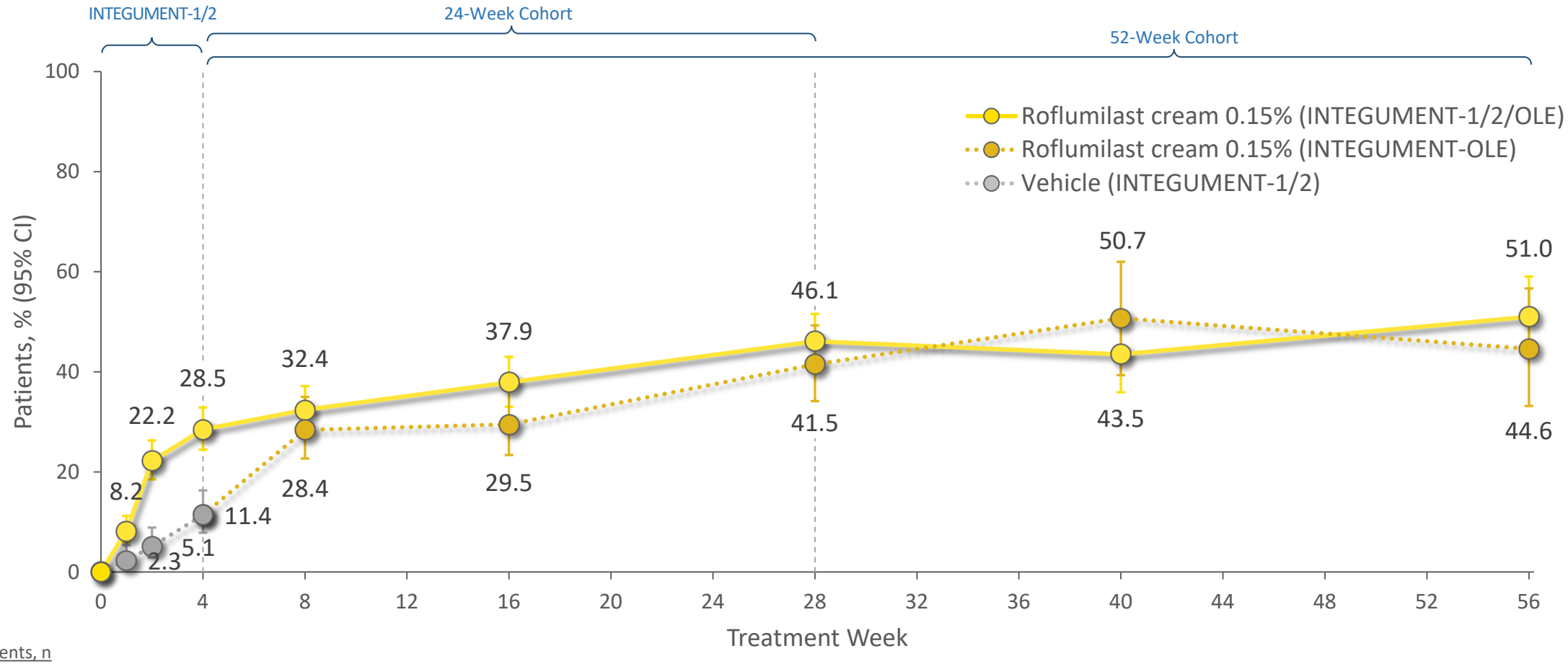
Proportion of Patients Achieving vIGA-AD of 0 (Clear) or 1 (Almost Clear) (FAS[a])



Patients, n							
Roflumilast to Roflumilast	439	439	404	359	319	154	145
Vehicle to Roflumilast	219	219	204	183	159	71	65

Observed cases, includes patients treated QD and BIW.
[a]FAS includes all enrolled patients.
BIW: twice weekly; FAS: full analysis set; OLE: open-label extension; QD: once daily; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis.

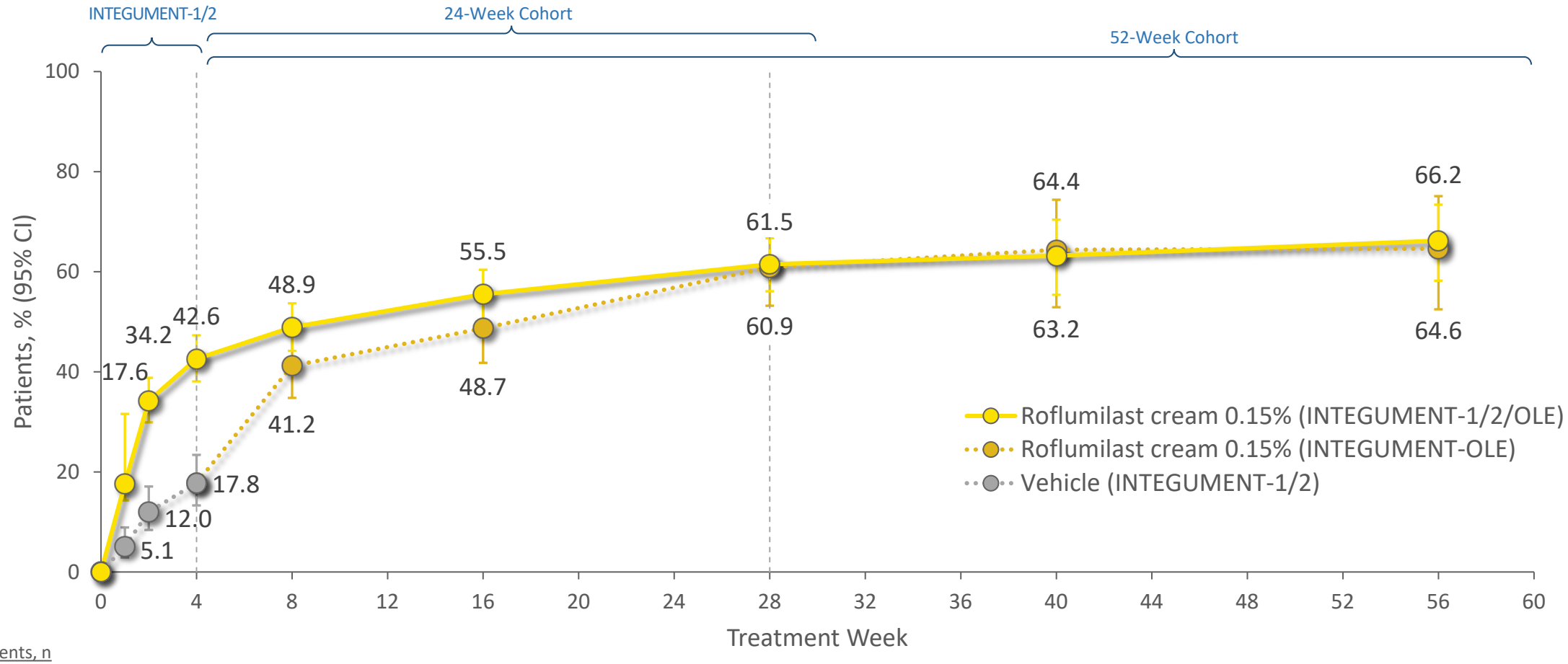
Proportion of Patients Achieving vIGA-AD Success (FAS[a])



Patients, n							
Roflumilast to Roflumilast	439	439	404	359	319	154	145
Vehicle to Roflumilast	219	219	204	183	159	71	65

Observed cases, includes patients treated QD and BIW.
vIGA-AD success = vIGA-AD 0/1 plus 2-grade improvement from parent trial baseline.
[a]FAS includes all enrolled patients.
BIW: twice weekly; FAS: full analysis set; OLE: open-label extension; QD: once daily; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis.

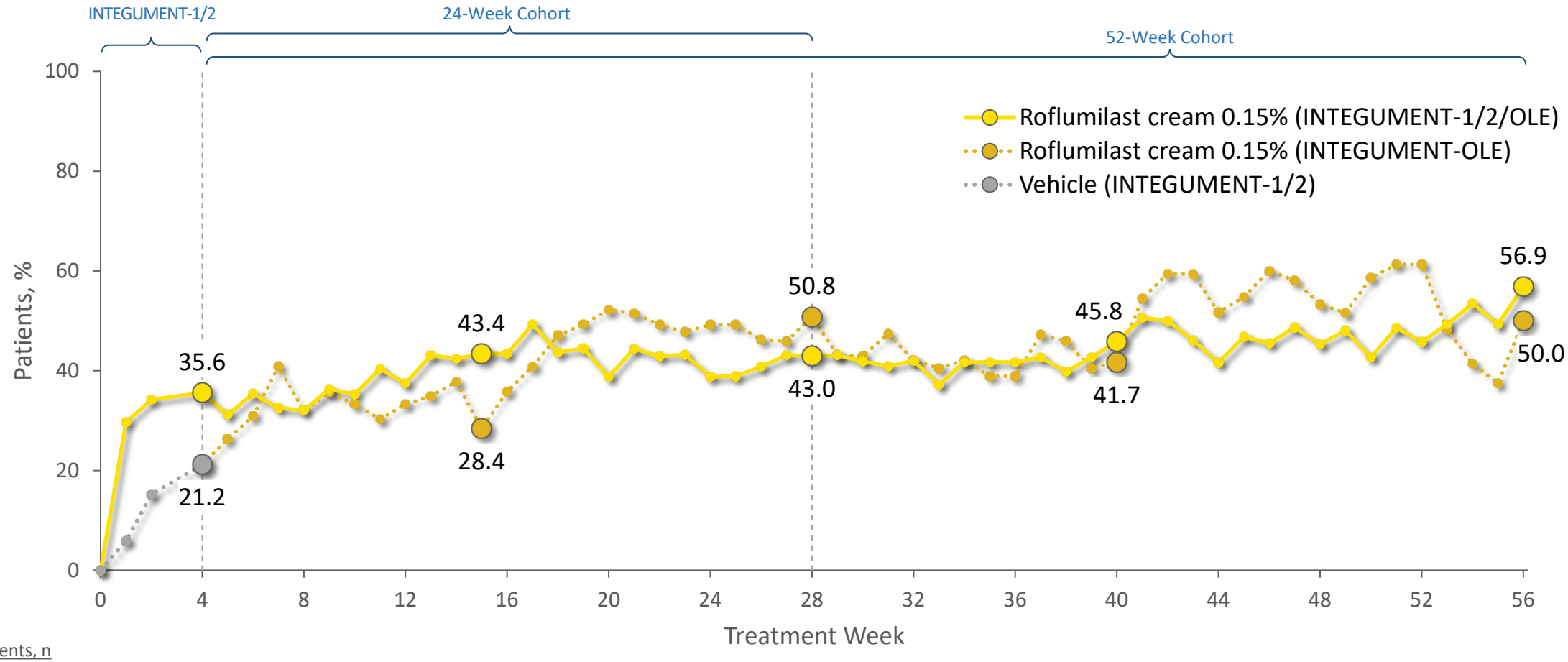
Proportion of Patients Achieving EASI-75 (FAS[a])



Patients, n							
Roflumilast to Roflumilast	439	439	417	375	325	155	145
Vehicle to Roflumilast	219	219	211	193	161	73	65

Observed cases, includes patients treated QD and BIW.
EASI-75 = ≥75% improvement in EASI from parent trial baseline.
[a]FAS includes all enrolled patients.
BIW: twice weekly; EASI: Eczema Area and Severity Index; FAS: full analysis set; OLE: open-label extension; QD: once daily.

Proportion of Patients Achieving WI-NRS Success (WI-NRS Population[a])



Patients, n						
Roflumilast to Roflumilast	206	177	152	121	77	58
Vehicle to Roflumilast	103	85	81	61	29	18

Observed cases, includes patients treated QD and BIW.
WI-NRS success = ≥4-point improvement in WI-NRS from parent trial baseline. Data from the OLE study are presented as weekly averages of daily assessments; for the parent trials, daily assessments on days 7, 14, and 28 are presented.
[a]WI-NRS population includes patients aged ≥12 years with baseline WI-NRS ≥4.
BIW: twice weekly; OLE: open-label extension; QD: once daily; WI-NRS: Worst Itch-Numeric Rating Scale

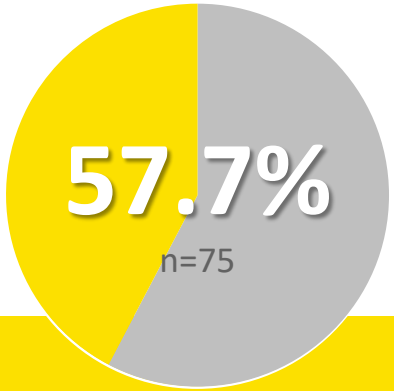
Duration of Disease Control with Proactive BIW Dosing in Patients Who Achieved vIGA-AD of 0

- **"Disease control"** was defined in the trial as the duration of vIGA-AD of 0/1 with adequate control of signs and symptoms of AD on BIW dosing following achievement of vIGA-AD of 0
- Among the 19.8% (n=130) of patients who achieved vIGA-AD of 0 and switched to proactive BIW application:

Median duration of "disease control" with BIW application

281 days

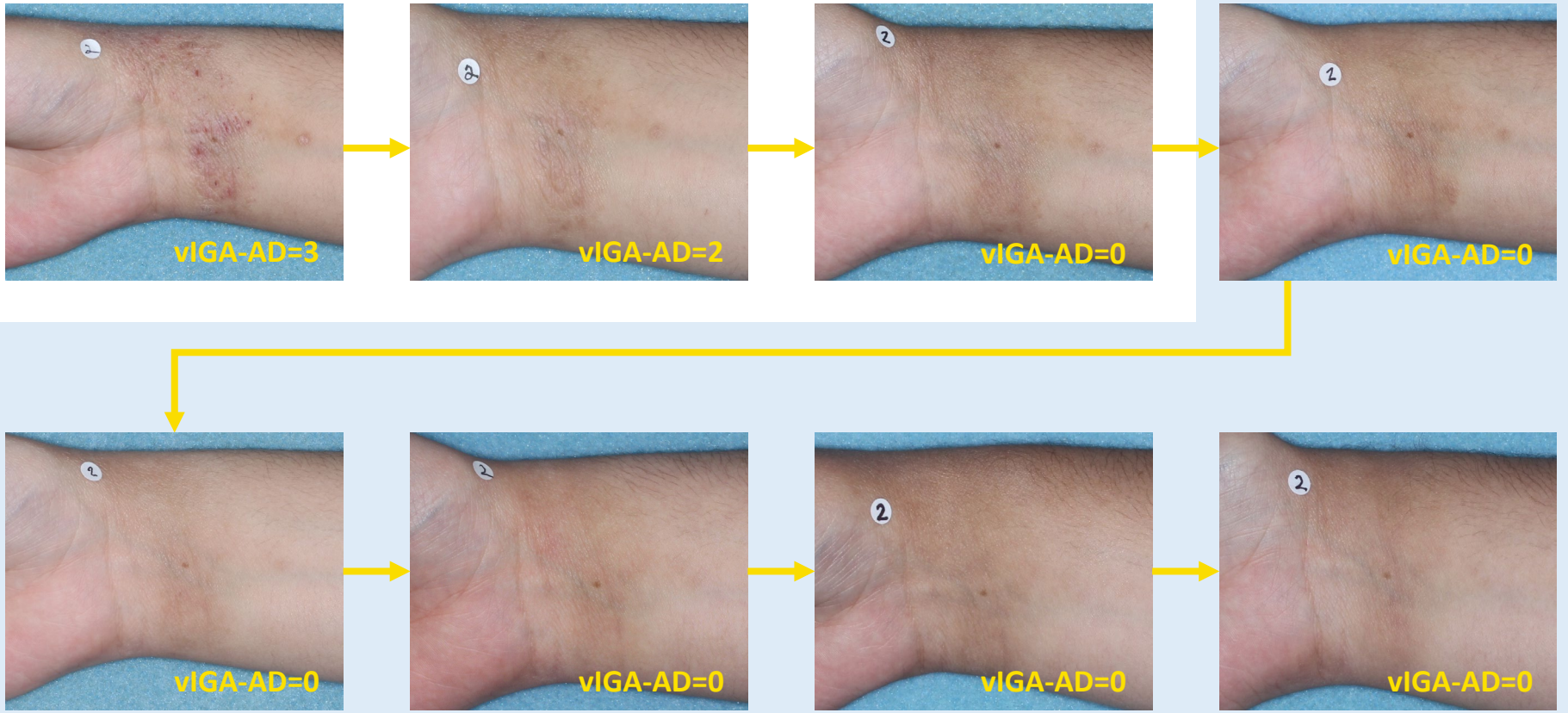
(95 CI%, 147–NE)



Maintained "disease control" through their final visit

BIW: twice-weekly; NE: not evaluable; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis.

Improvement in a Patient With AD Treated With Roflumilast Cream 0.15%



AD: atopic dermatitis; OLE: open-label extension.

Conclusions

Once-daily, nonsteroidal roflumilast cream 0.15% was well tolerated with no new safety signals for up to 56 weeks of treatment in patients ≥6 years of age with AD

- Roflumilast showed continued improvements in the signs and symptoms of AD, including pruritus through 56 weeks of treatment
- Of the subset of patients who were proactively managed with BIW application, the median duration of maintaining "disease control" for at least 281 days

Safety and efficacy are consistent with previous trials of roflumilast cream in patients with AD aged ≥2 years[1,2]

- Assessment of long-term safety and efficacy of roflumilast cream 0.05% in patients 2–5 years of age with AD is ongoing

This is the first clinical trial to assess scheduled proactive BIW treatment of previously active AD with roflumilast cream

- The results of this trial provide support for shifting from the reactive treatment of flares that often occurs in AD toward long-term flare-free disease control

AD: atopic dermatitis. BIW: twice weekly.

1. Simpson E, et al. Presented at American Academy of Dermatology Annual Meeting 2023. 2. Eichenfield L, et al. Presented at American Academy of Dermatology Annual Meeting 2024.

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