Latest Updates and Expert Recommendations in Treating Atopic Dermatitis

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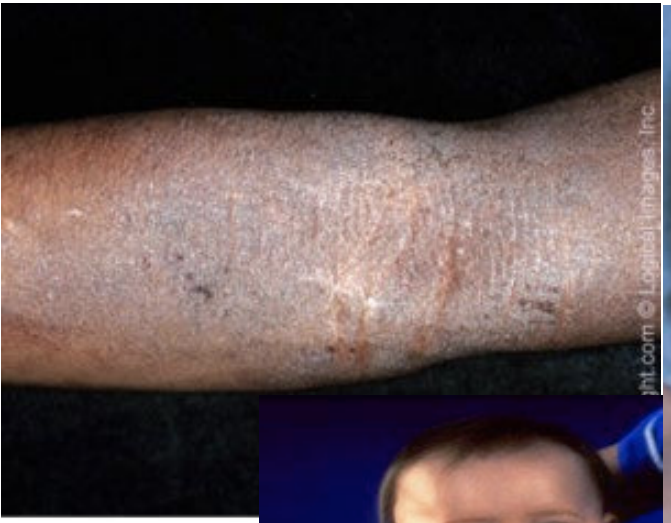
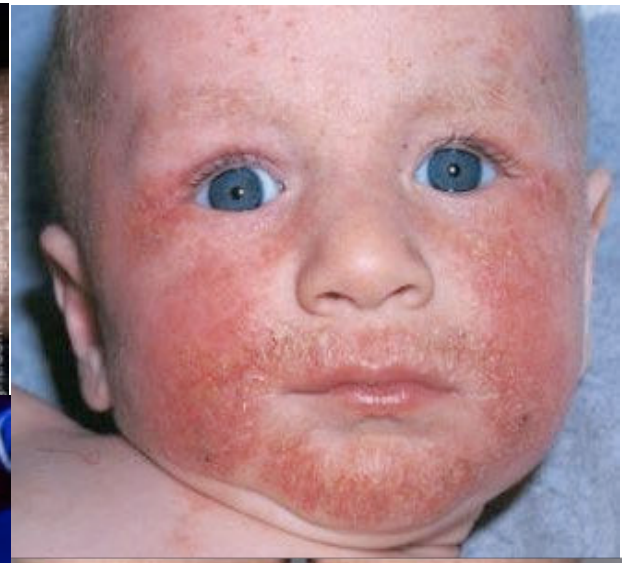
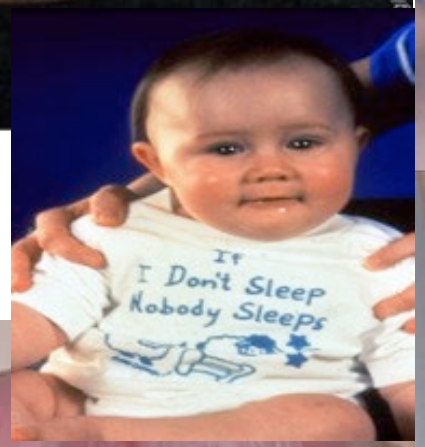
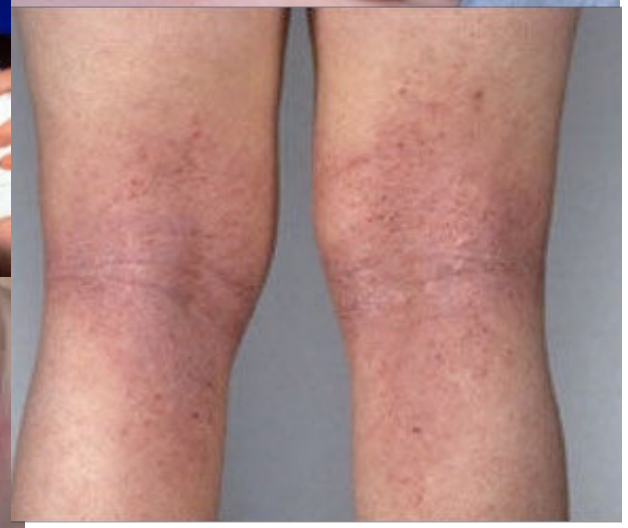
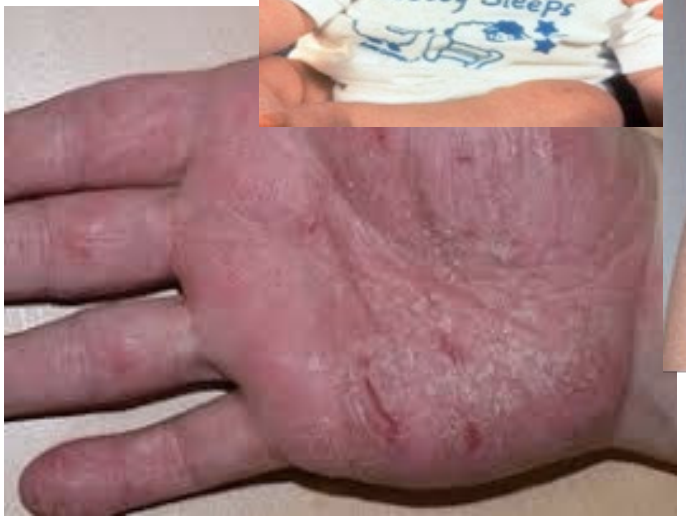
Atopic Dermatitis







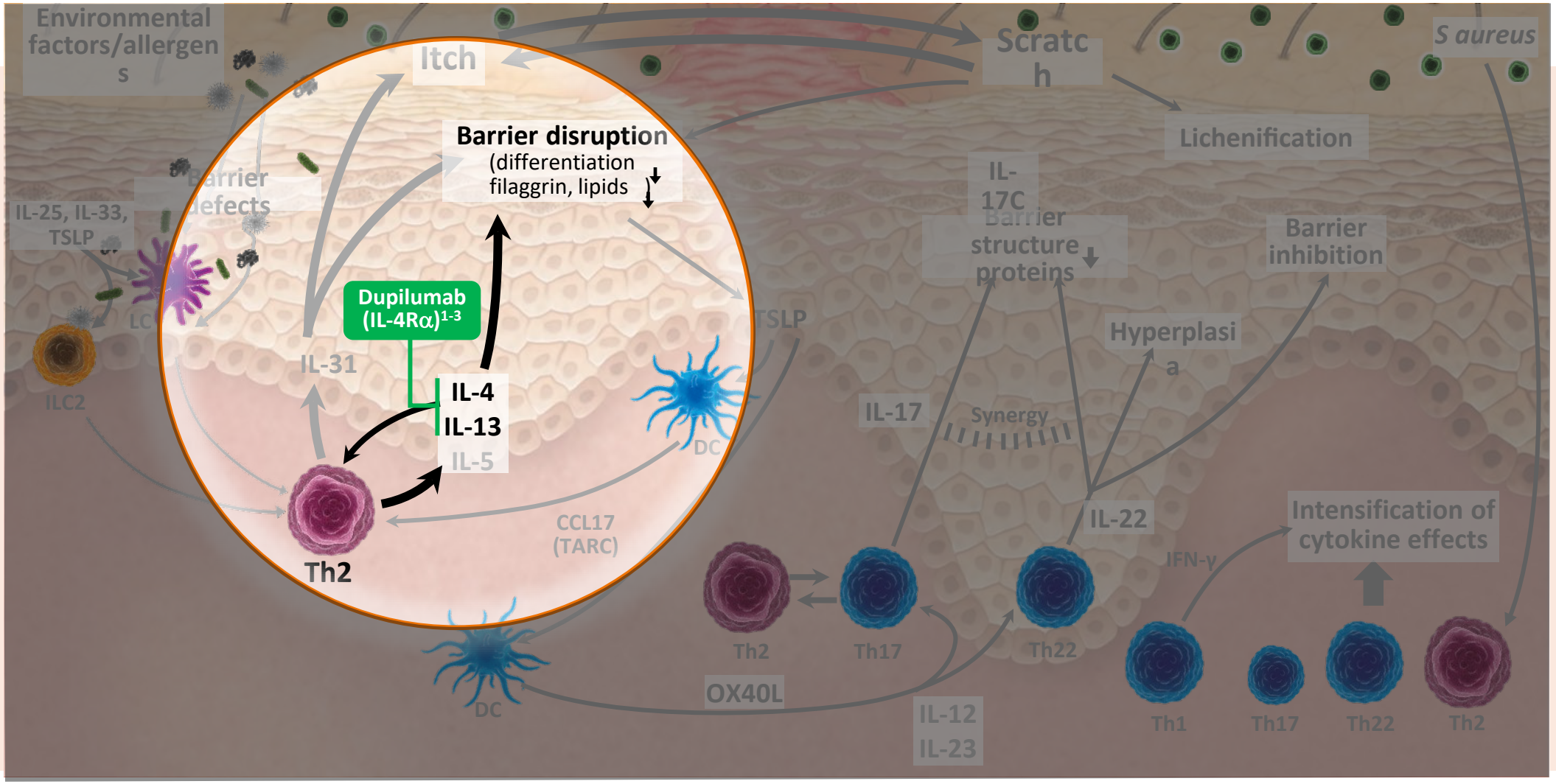




- Most common inflammatory skin disease (~7% of adults in US, 15% of children)
- 20-30% of patients have moderate-to severe disease
- Large Unmet Need for long-term disease control

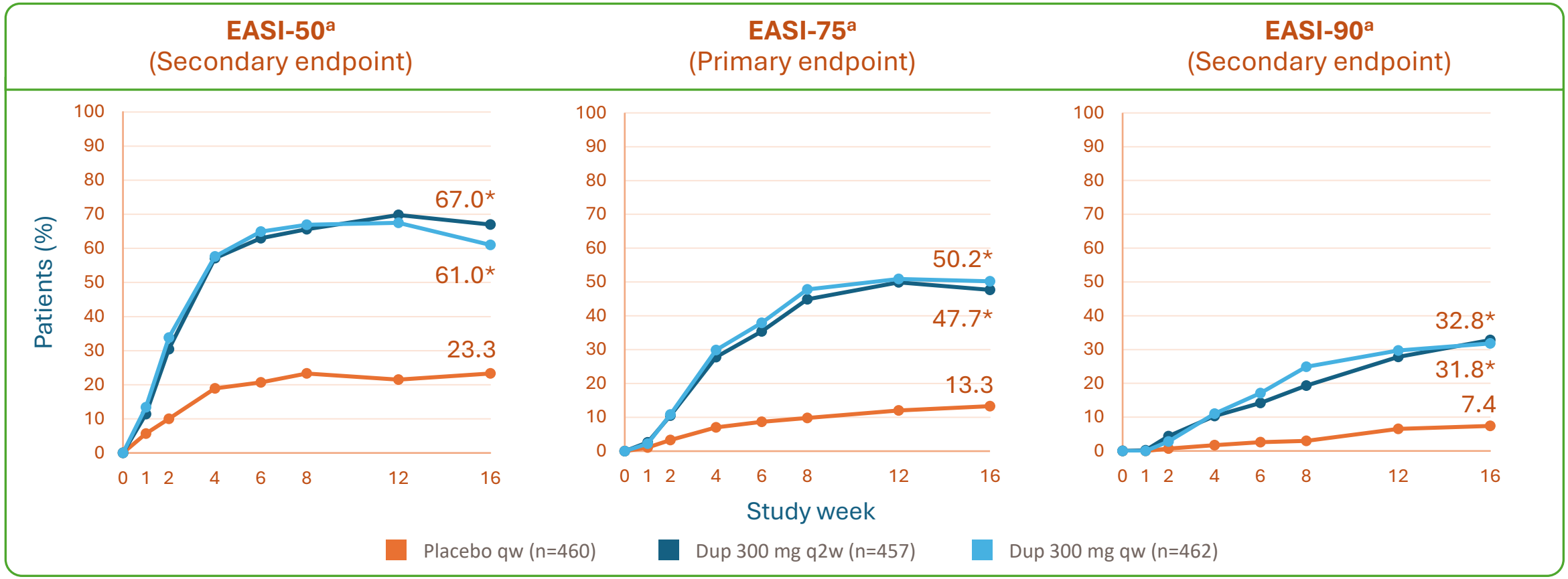
The therapeutic drought is finally ending!

Specific Th2 Targeting: Dupilumab



- 1. Paller AS, et al. *J Allergy Clin Immunol*. 2017;140(3):633-643. 2. European Medicines Agency. Dupixent. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR__Summary_for_the_public/human/004390/WC500236510.pdf. Accessed March 20, 2018. 3. Dupilumab [summary of product characteristics]. Paris, France: sanofi-aventis groupe; 2017.

EASI-50/75/90 in POOLED SOLO 1 & 2 MONOTHERAPY 16 WEEKS STUDIES



*P<0.0001 vs placebo.

The only licensed dose for dupilumab in moderate-tosevere AD patients is 300 mg Q2W.

- [a]Baseline EASI mean scores (SD): placebo, dupilumab 300 mg q2w, and dupilumab 300 mg qw were 34.0 (14.4), 32.4 (13.3), and 32.5 (13.3), respectively.
- Dup=dupilumab; EASI=Eczema Area and Severity Index; EASI-50/75/90=proportion of patients with ≥ 50%/75%/90% improvement in EASI score from baseline; q2w=every 2 weeks; qw=weekly; SD=standard deviation.
- 1. Ferrándiz C, et al. Dupilumab in moderate-to-severe atopic dermatitis: pooled efficacy results from two identically designed randomized phase 3 trials (SOLO 1 & 2). Presented at: EADV 2017; September 13-17, 2017; Geneva, Switzerland.

Dupilumab Long Term Safety for up to 172 Weeks in Adults

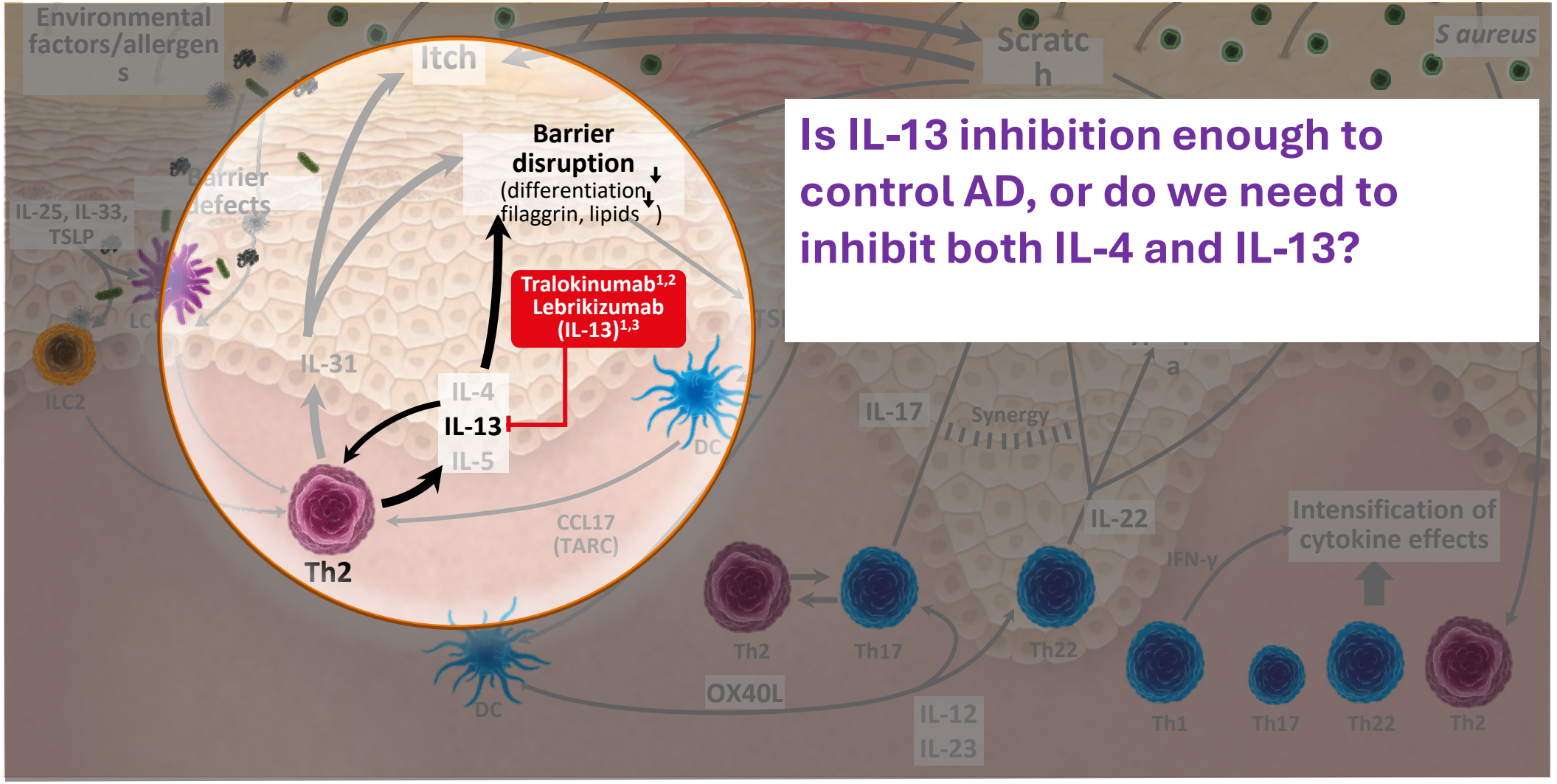
	OLE (AD-1225) **Week 172**		**CHRONOS** (AD-1224) **Week 52, final data set**			
	Dupilumab 300 mg qw		**Placebo + TCS**		**Dupilumab 300 mg qw + TCS**	
	n=2677		n=315		n=315	
		PY				
TEAE						
Severe TEAE						
SAE						
SAE related to						
TEAE leading t drug discontin						
PT (≥5% of pa OLE)						
Nasopharyng						
Atopic dermatitis	528 (19.7%)	**11.6**	147 (46.7%)	**80.97**	55 (17.5%)	**35.82**
Upper respiratory tract infection	358 (13.4%)	**7.4**	32 (10.2%)	**11.56**	43 (13.7%)	**15.41**
Headache	217 (8.1%)	**4.3**	19 (6.0%)	**6.11**	25 (7.9%)	**7.87**
Conjunctivitis (narrow)	528 (19.7%)	**11.6**	25 (7.9%)	**9.24**	61 (19.4%)	**23.37**
Injection-site reaction	138 (5.2%)	**2.7**	25 (7.9%)	**8.24**	61 (19.4%)	**20.72**

In the pediatric Population: the risk of infections and the conjunctivitis rates were comparable to that in adults

nP, number of patients; OLE, open label extension; PT, MedDRA Preferred Term; Pts, patients; PY, patient years; qw, weekly; SAE, serious adverse event; TCS, topical corticosteroid; TEAE, treatment emergent adverse event.

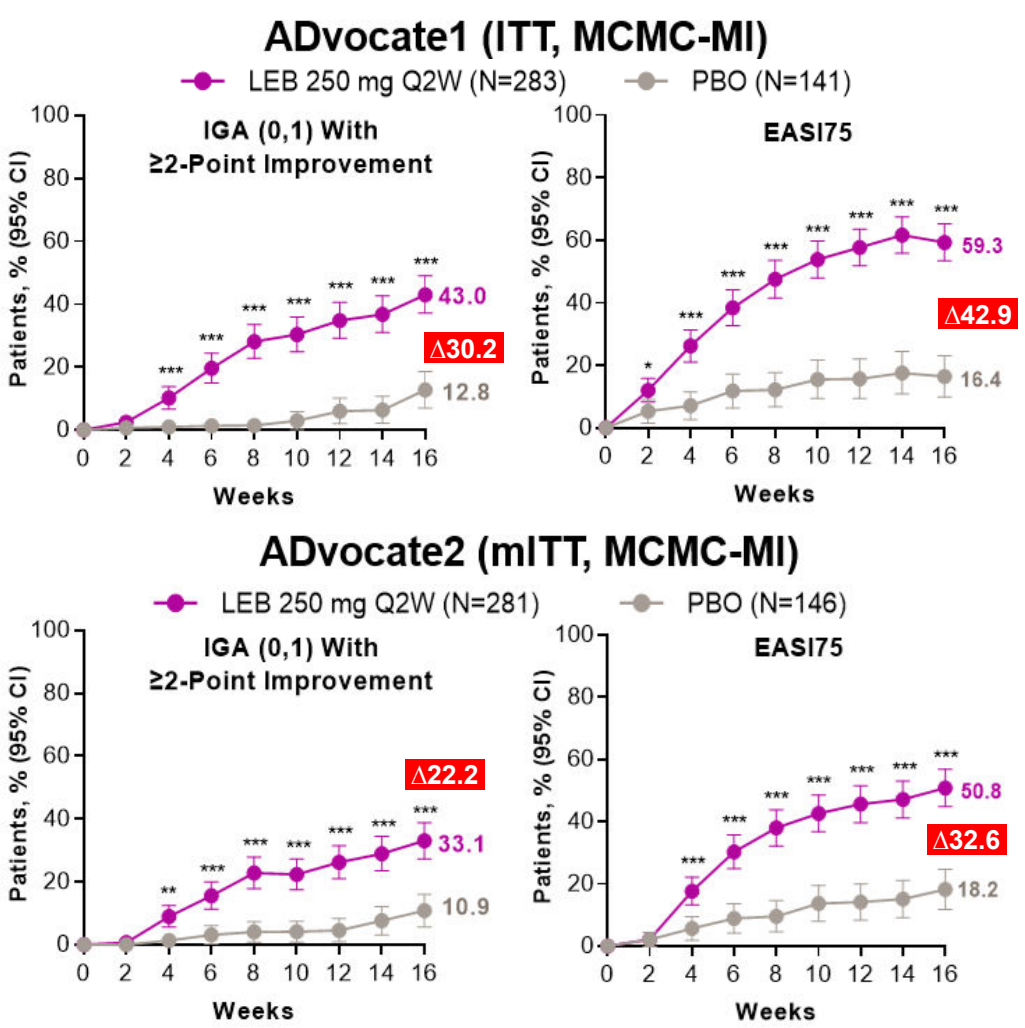
Wollenberg A, et al. Presented at 30th EADV Virtual Congress, September 29–October 2, 2021. Poster P0726.

TRALOKINUMAB and LEBRIKIZUMAB TARGET IL-13



Is IL-13 inhibition enough to control AD, or do we need to inhibit both IL-4 and IL-13?

ADvocate1 and 2: Primary/coprimary endpoint results with 16 weeks lebrikizumab among patients with moderate to severe AD



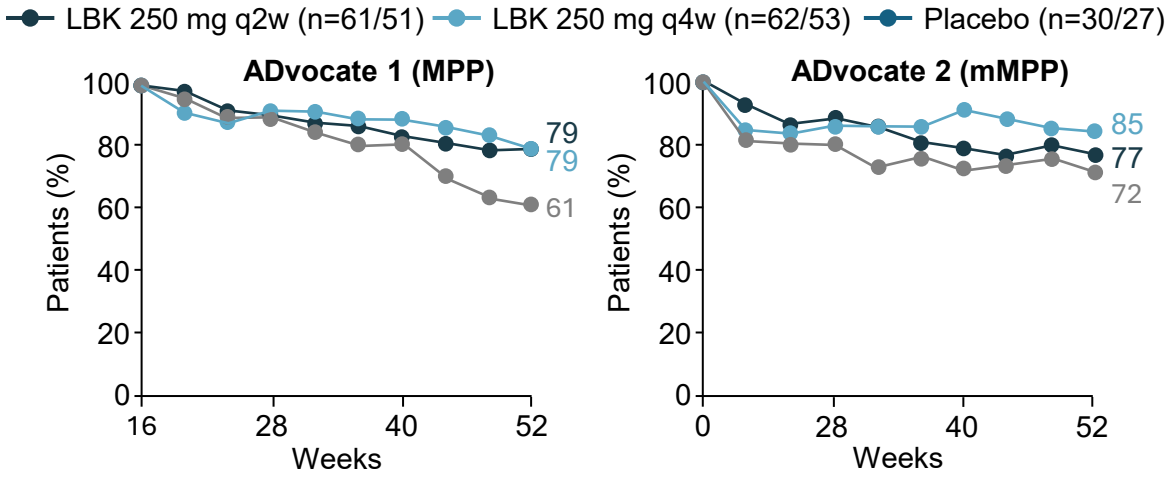
	ADvocate1 (Safety Population)		ADvocate2 (Modified Safety Population)	
	PBO Q2W (N=141)	LEB 250 mg Q2W (N=282)	PBO Q2W (N=145)	LEB 250 mg Q2W (N=281)
Any TEAE	72 (51.5)	128 (45.4)	96 (66.2)	149 (53.0)
Mild	34 (24.1)	78 (27.7)	40 (27.6)	73 (26.0)
Moderate	31 (22.0)	44 (15.6)	49 (33.8)	69 (24.6)
Severe	7 (5.0)	6 (2.1)	7 (4.8)	7 (2.5)
Most common TEAEs (≥5% in either LEB group)				
Conjunctivitis[a]	4 (2.8)	21 (7.4)	3 (2.1)	22 (7.8)
Exacerbation of AD	28 (19.9)	15 (5.3)	37 (25.5)	28 (10.0)
Nasopharyngitis	3 (2.1)	11 (3.9)	3 (2.1)	14 (5.0)
Headache	2 (1.4)	9 (3.2)	6 (4.1)	14 (5.0)
Serious AE[b]	1 (0.7)	6 (2.1)	4 (2.8)	2 (0.7)
Death	0	0	1 (0.7)	0
AEs leading to treatment discontinuation[b]	1 (0.7)	3 (1.1)	4 (2.8)	8 (2.8)
Injection site reactions	3 (2.1)	3 (1.1)	1 (0.7)	7 (2.5)
Herpes infections	6 (4.3)	9 (3.2)	6 (4.1)	8 (2.8)

- Overall good safety

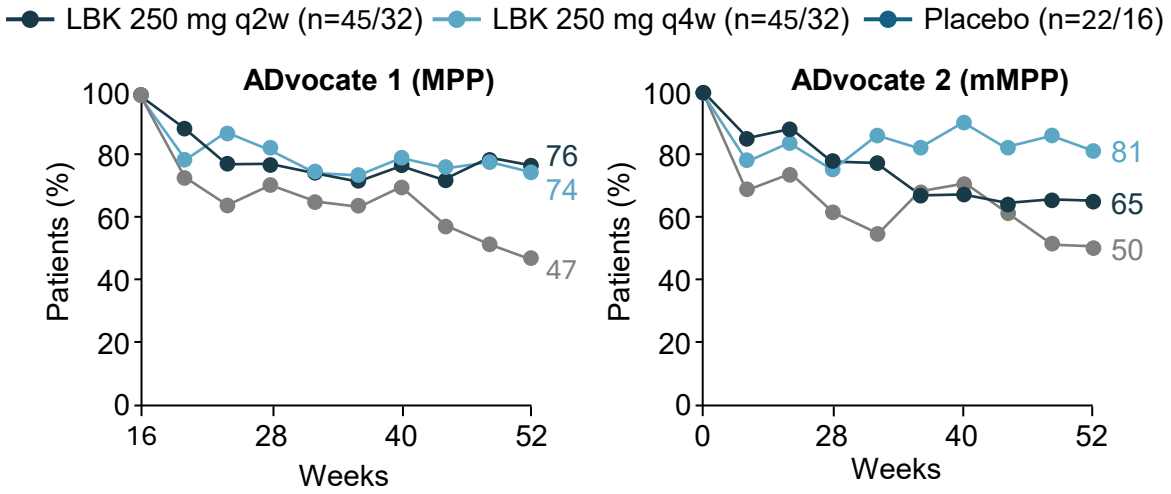
- * p<0.05; ** p<0.01; *** p<0.001 vs. PBO; Missing data as a result of rescue medication or treatment discontinuation due to lack of efficacy were imputed with baseline values; missing data due to other reasons were imputed with MCMC-MI within treatment arms
- *Silverberg JI, et al. AAD 2022, late-breaking abstract. Sponsored by Eli Lilly and Company; Silverberg JI, Guttman-Yassky et al. NEJM 2023*

ADvocate 1 and 2: 52-week efficacy and safety of lebrikizumab monotherapy among patients with moderate-to-severe atopic dermatitis (responder analysis)

Maintenance of EASI 75 through Week 52 (MCMC-MI)[a]



Maintenance of IGA 0/1 through Week 52 (MCMC-MI)[a]



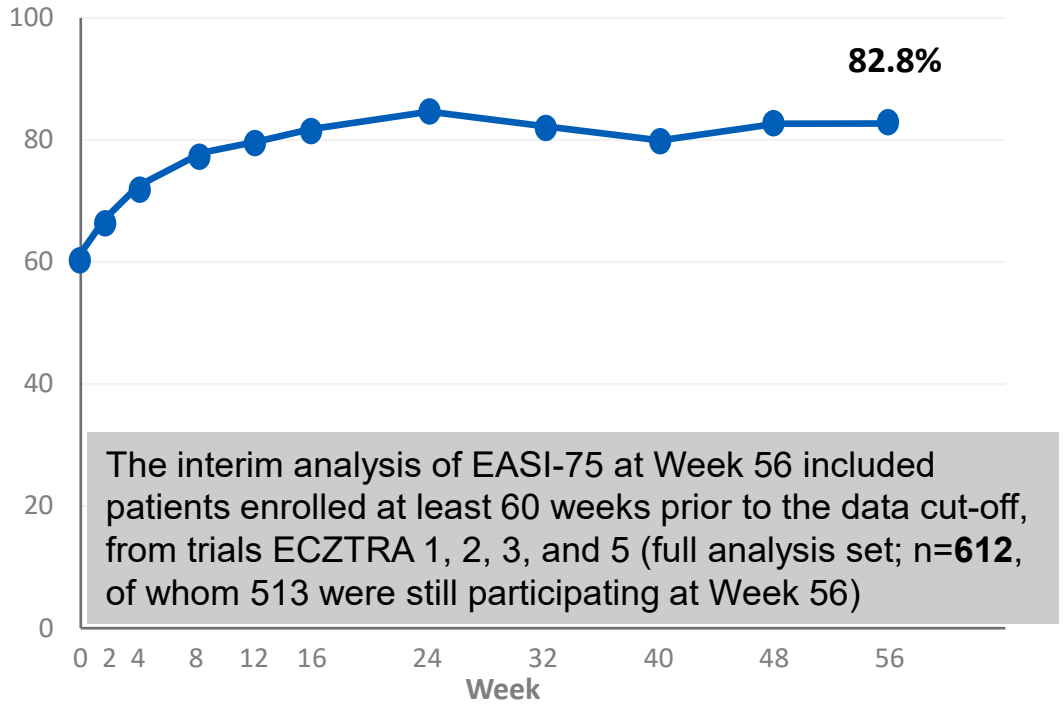
Safety through Week 52, n (%)	ADvocate 1 (N=399)	ADvocate2 (N=407)[a]
Any TEAE	232 (58)	276 (68)
Mild	124 (31)	112 (28)
Moderate	91 (23)	146 (36)
Severe	17 (4)	18 (4)
Serious AE	17 (4)	11 (3)
Death[b]	0	1 (0.2)
AE leading to discontinuation	9 (2)	16 (4)
Common TEAEs[c] (≥5% in either study)		
AD	31 (8)	41 (10)
Nasopharyngitis	27 (7)	39 (10)
Conjunctivitis	33 (8)	33 (8)
Conjunctivitis allergic	22 (6)	26 (6)
Headache	13 (3)	23 (6)
COVID-19	24 (6)	14 (3)
AEs of special interest		
Conjunctivitis cluster[d]	54 (14)	60 (15)
Keratitis cluster	2 (1)	4 (1)
Herpes infection	20 (5)	20 (5)
Skin infection	12 (3)	20 (5)
Potential opportunistic infections	3 (1)	6 (2)
Injection-site reactions	7 (2)	12 (3)
Eosinophilia	5 (1)	7 (2)

[a]Modified safety population excluding 18 patients from a single site; [b]Investigator-assessed as not related to the study drug; [c]Based on individual preferred term; [d]Defined using MedDRA preferred terms conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral, and giant papillary conjunctivitis

- Blauvelt A, et al. EADV 2022, D1T01.3D. Funded by Dermira, a wholly-owned subsidiary of Eli Lilly and Company

Tralokinumab: Long-term Efficacy through 56 Weeks: Interim Analysis of the ECZTEND OLE Study

Sustained EASI-75 response at Week 56[1,†]

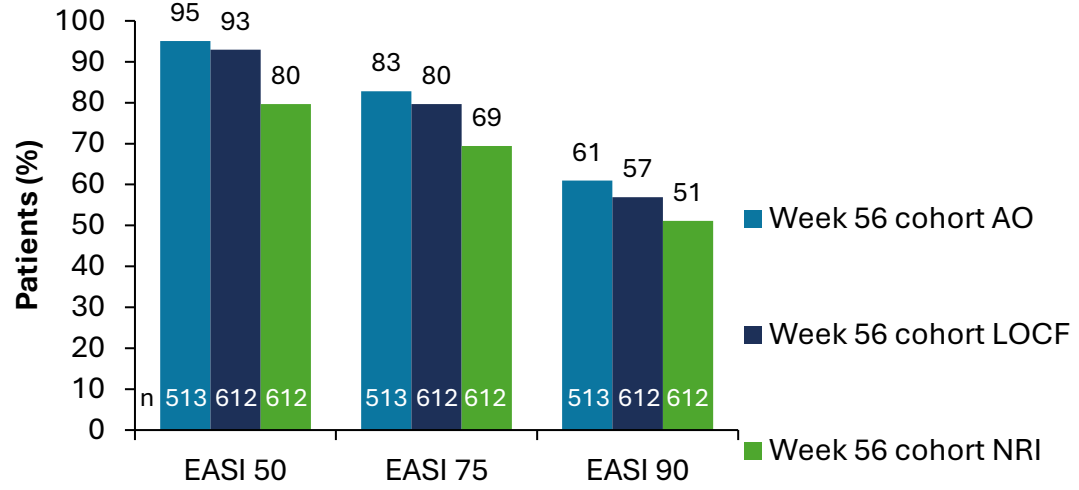


The interim analysis of EASI-75 at Week 56 included patients enrolled at least 60 weeks prior to the data cut-off, from trials ECZTRA 1, 2, 3, and 5 (full analysis set; n=**612**, of whom 513 were still participating at Week 56)

- Good safety profile, with rates of conjunctivitis lower than expected

EASI 50, 75 and 90 responses at Week 56 of ECZTEND (Week 56 cohort)

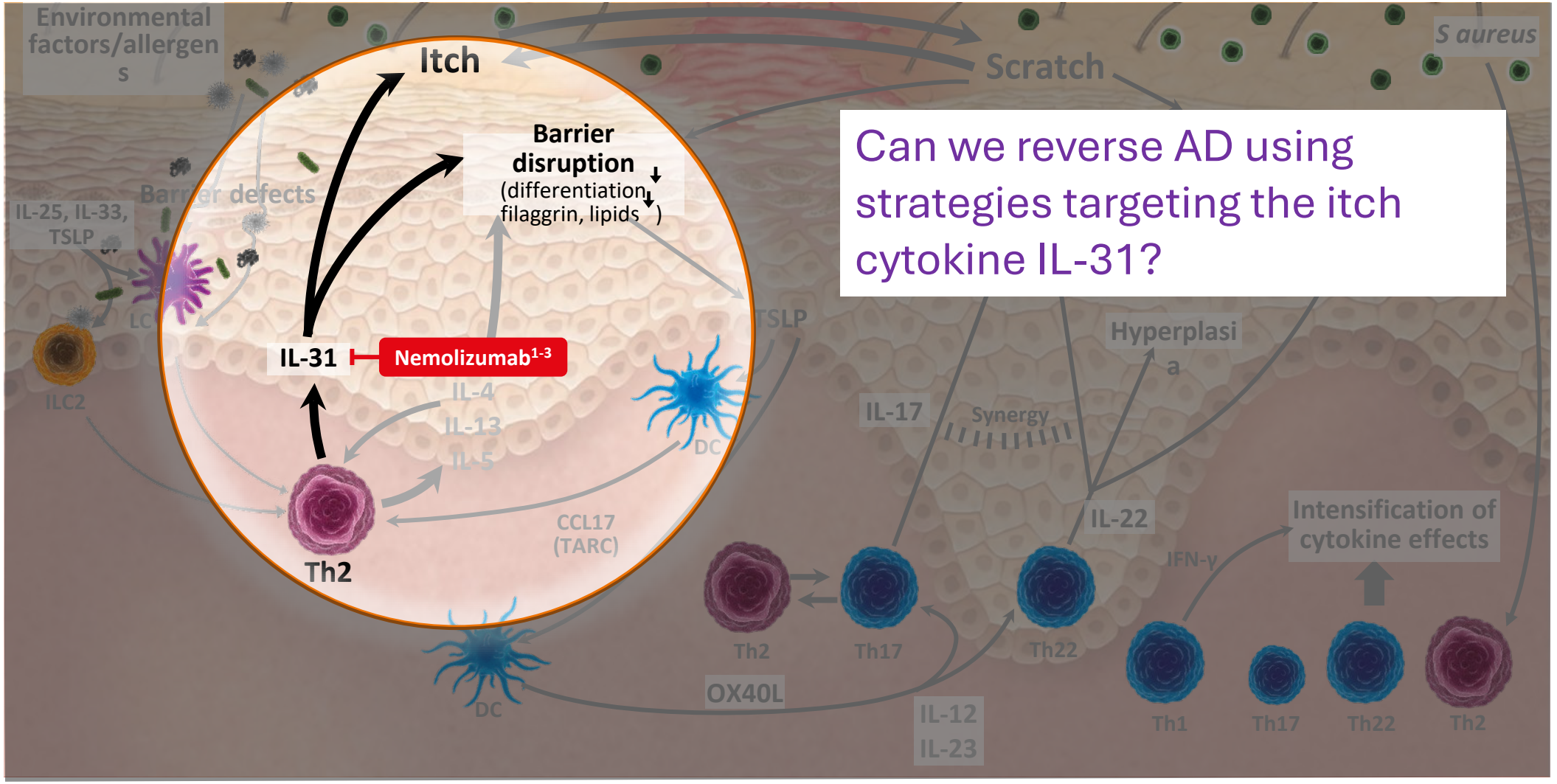
All patients from ECZTRA 1, 2, 3 and 5



- Tralokinumab demonstrates high levels of efficacy, with maintenance of effect at 56 weeks (and 2 years (data not shown)

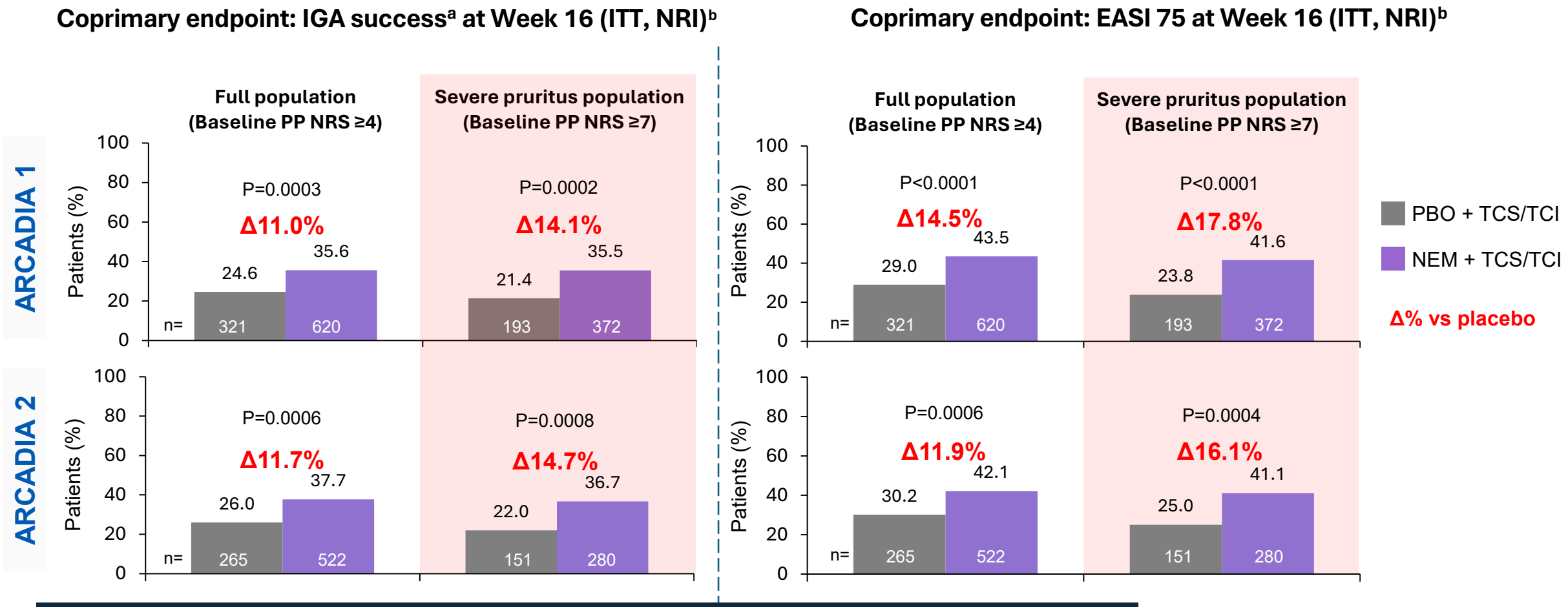
- The ECZTEND open-label extension trial enrolled patients with AD who completed previous tralokinumab trials (ECZTRA 1-8 or TraSki) without any safety concerns. The interim Week 56 analysis included all patients (n=612) who reached this timepoint or would have reached it had they not discontinued earlier.
- EASI, Eczema Area and Severity Index; EASI-50/75/90, ≥50/75/90% reduction in Eczema Area and Severity Index; NRS, numeric rating scale; OLE, open-label extension.
- Blauvelt A, et al. Oral presentation at American Academy of Dermatology Virtual Meeting Experience, 23–25 April 2021. Oral S033.

NEMOLIZUMAB TARGETS IL-31



Can we reverse AD using strategies targeting the itch cytokine IL-31?

ARCADIA 1 and 2: Phase 3, randomized, double-blind, placebo-controlled trials of nemolizumab plus topicals for adults and adolescents with moderate to severe AD

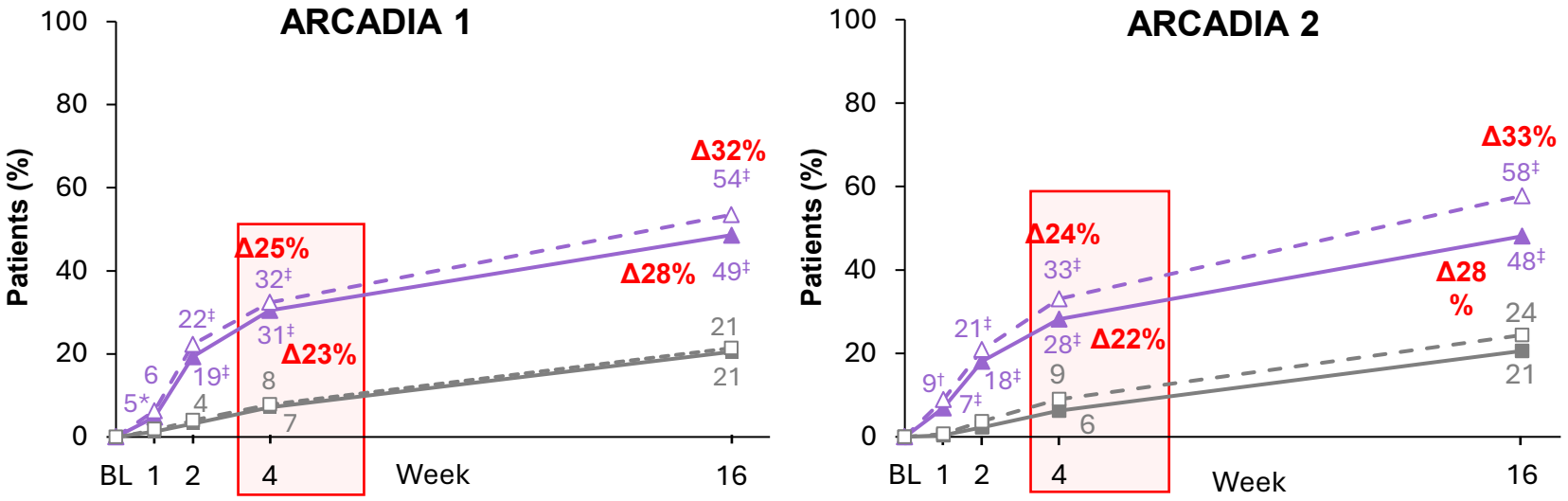


- More severe pruritus at baseline shows some trend for better efficacy vs placebo

- *P≤0.01; †P≤0.001; ‡P≤0.0001 vs respective placebo + TCS/TCI; MAR, missing at random; [a]Weekly PP NRS calculated using data of 7 consecutive days and set to missing if data for <4 days available; [b]Patients receiving rescue therapy were considered treatment failures; Strata adjusted P-values are presented derived from a CMH test adjusting for randomized stratification variables (full population: IGA and PP NRS [≥7/<7]. Baseline PP NRS ≥7 population: IGA only)
- Silverberg JI, et al. EADV 2023, D1T01.1C. Sponsored by Galderma

ARCADIA 1 and 2: Effect of nemolizumab with concomitant TCS/TCI on pruritus among adults and adolescents with moderate to severe AD

Key secondary endpoint: ≥4-point improvement in PP NRS score[a] (ITT, MI MAR[b])



Data are not based on head-to-head trials and cannot be directly compared	
	DUP 300 mg q2w + TCS (CHRONOS)
PP NRS4 at Wk 4, % (Δ vs PBO)	37 (Δ21)

Blauvelt A, et al. Lancet 2017;389:2287–303

Full population (BL PP NRS ≥4) (n ARCADIA 1/2)

- NEM + TCS/TCI (n=620/522)
- PBO + TCS/TCI (n=321/265)

Severe pruritus population (BL PP NRS ≥7)

- NEM + TCS/TCI (n=372/280)
- PBO + TCS/TCI (n=193/151)

Δ = Δ% vs placebo

- Slightly more effective for itch in the severe pruritus at baseline population

- *P≤0.01; †P≤0.001; ‡P≤0.0001 vs respective placebo + TCS/TCI; MAR, missing at random; [a]Weekly PP NRS calculated using data of 7 consecutive days and set to missing if data for <4 days available; [b]Patients receiving rescue therapy were considered treatment failures; Strata adjusted P-values are presented derived from a CMH test adjusting for randomized stratification variables (full population: IGA and PP NRS [≥7/<7]. Baseline PP NRS ≥7 population: IGA only)
- Silverberg JI, et al. EADV 2023, D1T01.1C. Sponsored by Galderma

ARCADIA 1 and 2: 16-week safety of nemolizumab with concomitant TCS/TCI among adults and adolescents with moderate to severe AD

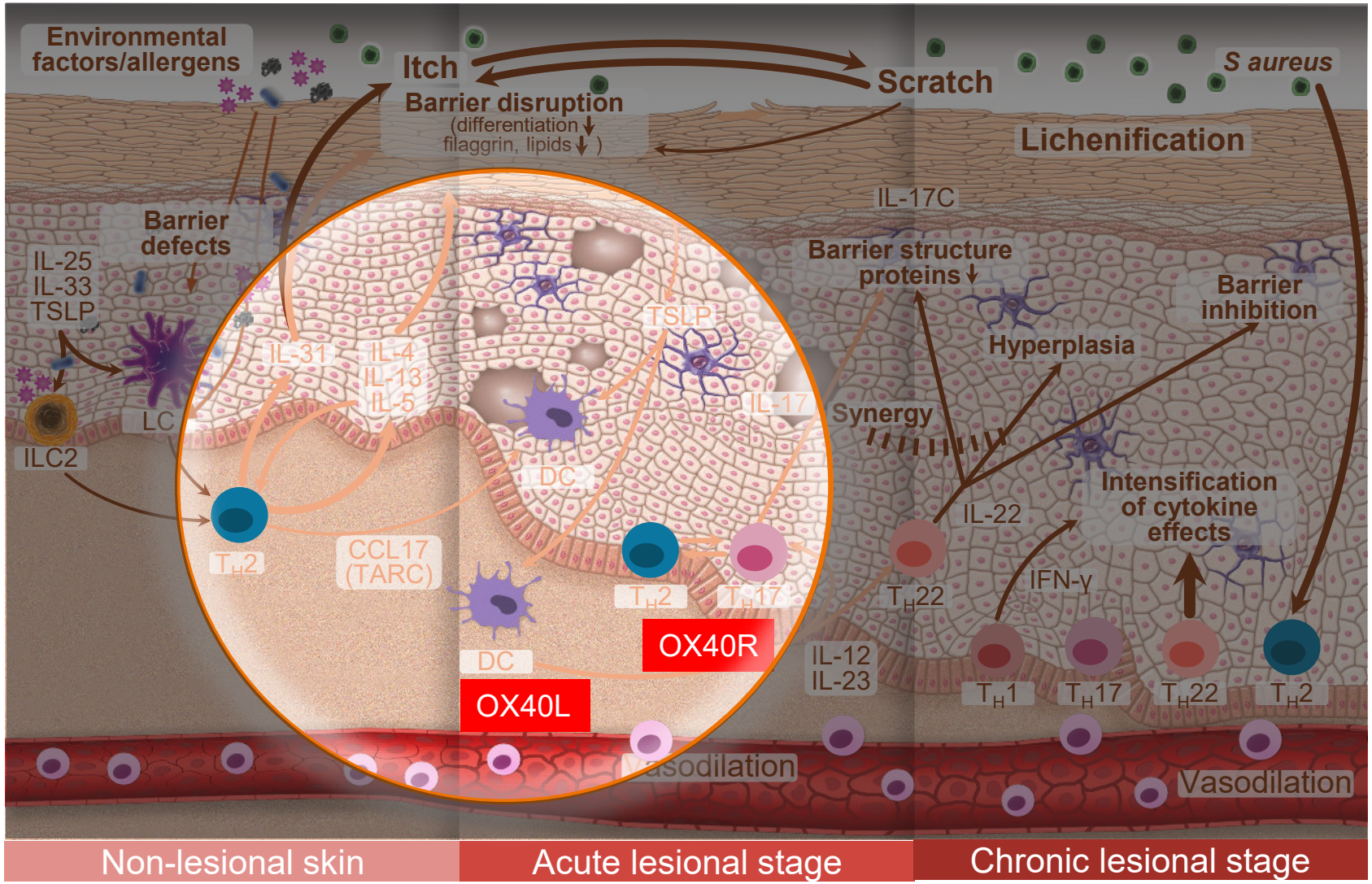
Safety through Week 16

Data are n (%)	ARCADIA 1		ARCADIA 2	
	Placebo + TCS/TCI (n=321)	NEM 30 mg + TCS/TCI (n=616)	Placebo + TCS/TCI (n=263)	NEM 30 mg + TCS/TCI (n=519)
AEs or SAEs				
Any AE	146 (45.5)	306 (49.7)	117 (44.5)	215 (41.4)
Any serious AE	4 (1.2)	6 (1.0)	3 (1.1)	13 (2.5)
Any serious AE related to study drug	0	0	0	5 (1.0)
Any AE leading to study discontinuation	3 (0.9)	9 (1.5)	3 (1.1)	15 (2.9)
Any severe AE	8 (2.5)	18 (2.9)	7 (2.7)	21 (4.0)
AESI	20 (6.2)	56 (9.1)	21 (8.0)	47 (9.1)
Infections	10 (3.1)	20 (3.2)	12 (4.6)	20 (3.9)
Injection-related reactions	0	1 (0.2)	0	0
Peripheral edema: limbs, bilateral; facial edema	1 (0.3)	7 (1.1)	1 (0.4)	12 (2.3)
Worsening of asthma (post-adjudication)	13 (4.0)	32 (5.2)	6 (2.3)	7 (1.3)
TEAEs ≥5% (MedDRA Preferred Term)				
Asthma	13 (4.0)	33 (5.4)	7 (2.7)	11 (2.1)
Dermatitis atopic	34 (10.6)	75 (12.2)	15 (5.7)	37 (7.1)
Adverse events of interest in the field of AD				
Conjunctivitis allergic	4 (1.2)	6 (1.0)	2 (0.8)	1 (0.2)
Nasopharyngitis	8 (2.5)	9 (1.5)	12 (4.6)	19 (3.7)
Conjunctivitis	0	2 (0.3)	3 (1.1)	3 (0.6)
Herpes infections	9 (2.8)	16 (2.6)	7 (2.7)	10 (1.9)
Herpes zoster	0	4 (0.6)	0	1 (0.2)
Other Herpes infections	9 (2.8)	12 (1.9)	7 (2.7)	9 (1.7)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	3 (0.9)	3 (0.5)	2 (0.8)	2 (0.4)

- No AEs leading to death

- Does not appear to be a signal for conjunctivitis
- Mechanism of edema unclear

OX40R/OX40L: A new pathway to explore in AD

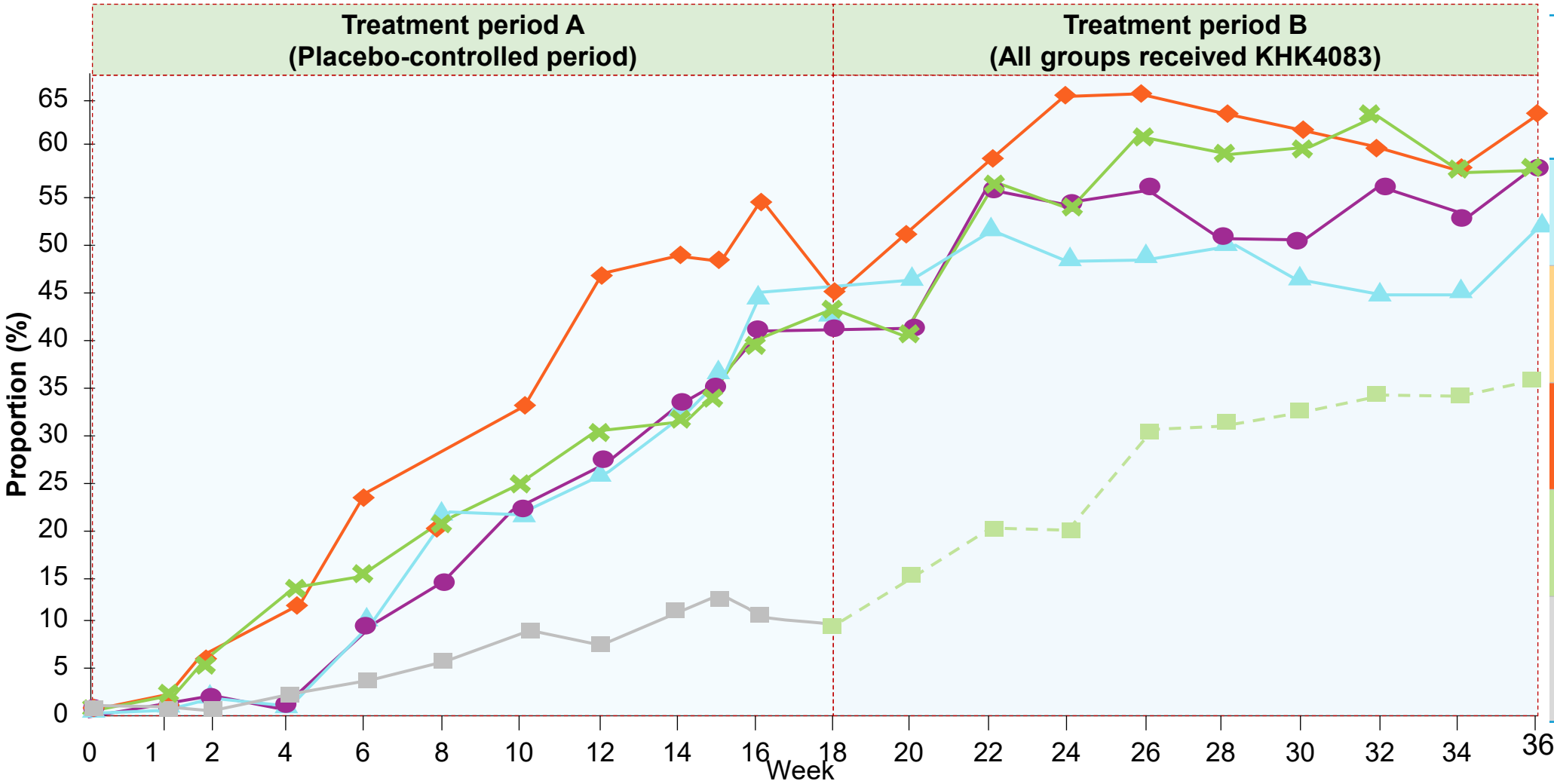


- The OX40 receptor is primarily expressed by activated T cells and binds OX40L on APCs
- Rocatinlimab is a fully human, anti-OX40 monoclonal antibody
- Amlitelimab targets OX40L on dendritic and other cells

AD, atopic dermatitis; APC, antigen-presenting cell; CCL, C-C motif chemokine ligand; DC, dendritic cell; IFN, interferon; IL, interleukin; ILC2, innate lymphoid type-2 cell; LC, lymphoid cell; OX40L, OX40 ligand; OX40R, OX40 receptor; TARC, thymus and activation-regulated chemokine; T_H, T helper; TSLP, thymic stromal lymphopoietin.

1. Guttman-Yassky E, et al. Lancet 2023;401:204–214; 2. Guttman-Yassky E, et al. J Allergy Clin Immunol 2019;144:482–493; 3. Nakagawa H, et al. J Dermatol Sci 2020;99:82–89; 4. Furue M, et al. J Clin Med 2021;10:2578.

OX40 Antagonism with KHK4083/Rocatinlimab Showed Significantly Higher Proportions EASI-75 responders at Week 16 in all drug cohorts versus placebo



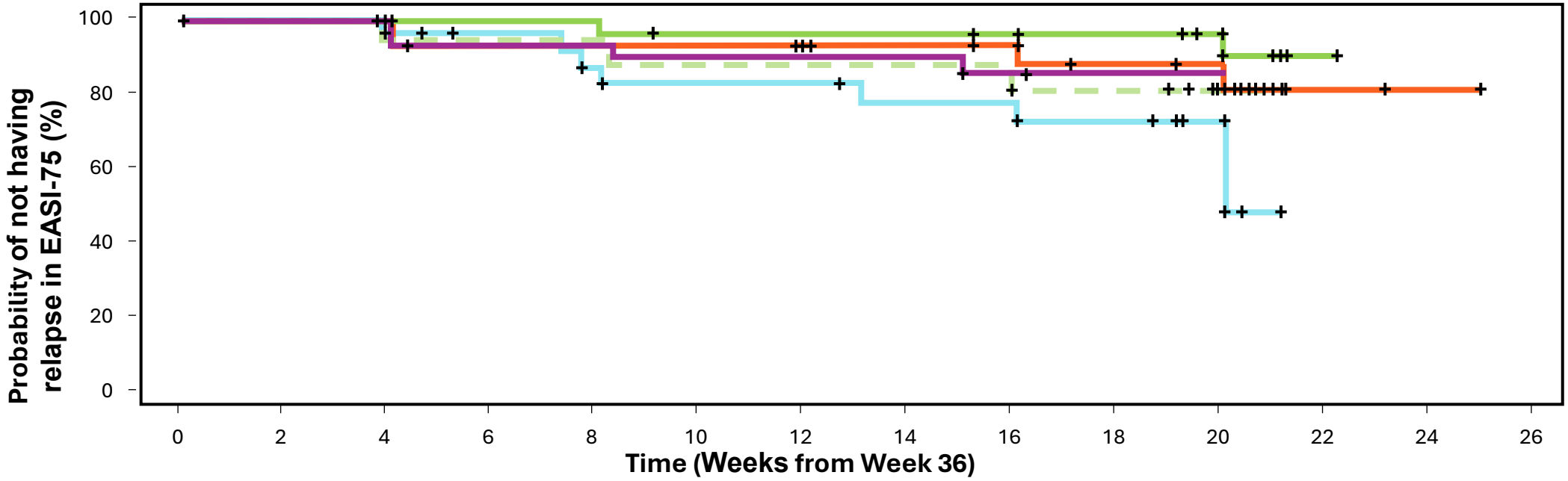
	Wk 16	Wk 24	Wk 36
KHK4083 150 mg Q4W, %	44.2**	48.1	51.9
KHK4083 600 mg Q4W, %	40.4**	53.8	57.7
KHK4083 300 mg Q2W, %	53.8**	65.4	63.5
KHK4083 600 mg Q2W, %	38.9**	53.7	57.4
Placebo/ KHK4083 600 mg Q2W, %	10.5	19.3	35.1

Guttman-Yassky E EADV 2021 Late Breaking Presentation; Guttman-Yassky E et al. Lancet 2021.

**p<0.001 vs placebo, assessed at Week 16

Durability of EASI-75 Response After Treatment Discontinuation (Full Analysis Set)

EASI-75 response was durable even after discontinuation of KHK4083 at Week 36



KHK4083 150 mg Q4W	27	26	26	22	19	17	17	15	15	13	9	0	0	0
KHK4083 600 mg Q4W	30	29	29	27	27	26	26	26	24	22	16	0	0	0
KHK4083 300 mg Q2W	33	30	29	25	25	25	24	22	21	18	13	2	1	0
KHK4083 600 mg Q2W	31	27	27	25	25	21	21	21	20	19	17	1	0	0
Placebo/KHK4083 600 mg Q2W	20	18	18	16	16	13	13	13	13	11	7	0	0	0

+Censored. EASI: Eczema Area and Severity Index; Q2W, every 2 weeks; Q4W, every 4 weeks.

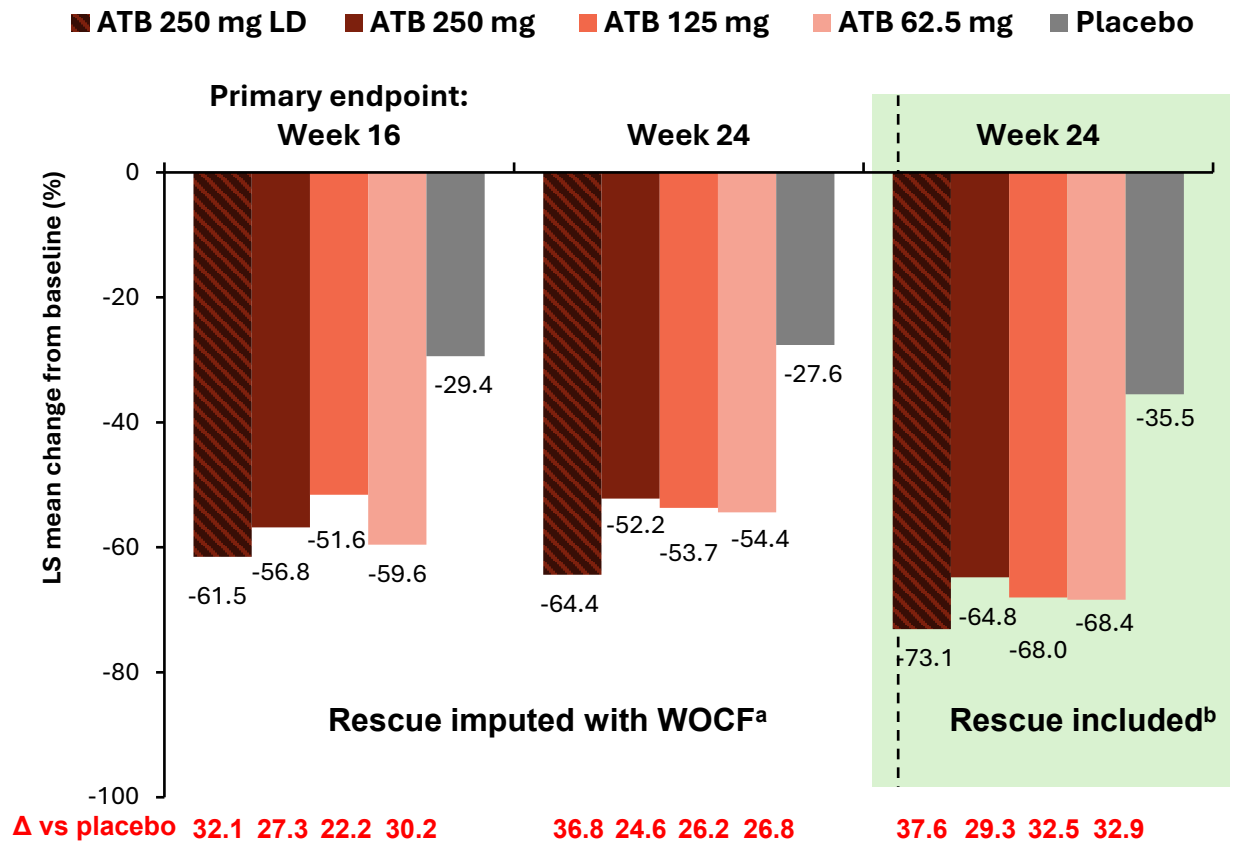
Subjects in the placebo group were switched to KHK4083 600 mg Q2W after Treatment A period. The numbers below the figure represent the number of remaining subjects at each visit.

Relapse is the loss of EASI-75 after achieving EASI-75 at Week 36. Censored cases are prohibited concomitant medications and/or therapies including rescue treatment started before the event confirmed, study completion without confirmed, and early termination of the study without the event confirmed. Time to relapse for EASI-75 is defined only for the subjects who achieve EASI-75 at Week 36.

Guttman-Yassky E EADV 2021 Late Breaking Presentation; Guttman-Yassky E et al. Lancet 2021.

STREAM-AD: Phase 2b trial of amlitelimab, an anti-OX40L for patients with moderate to severe AD: Change in EASI score through Week 24 of treatment

Change from baseline in EASI score at Weeks 16 and 24



- *WOCF, worst observation carried forward; [a]Data collected after early discontinuation due to reasons other than lack of efficacy prior to endpoint timepoint are included. Data on or after rescue medication impacting efficacy start date or after the date of treatment discontinuation due to lack of efficacy prior to endpoint timepoint, were set to missing and imputed by WOCF. Any other missing data imputed by multiple imputation; [b]All data used for analysis, regardless of treatment discontinuation or rescue/prohibited concomitant medications use. Missing data imputed by multiple imputation based on all patient's data*

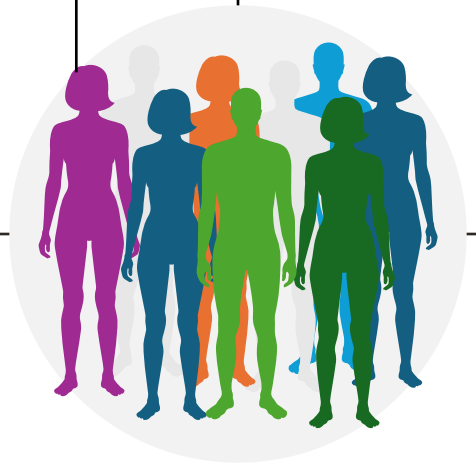
- *Weidinger S, et al. EADV 2023, D3T01.3G. Funded by Kymab LTD, a Sanofi company*

AD is highly heterogeneous and involves mutiple Immune Cytokines (e.g IL-4, IL-13, IL-22, IFN-γ)

AD exhibits variable patterns

- **Disease activity[1]**
- **Disease severity[2,6]**
- **Location (eg, face, genitals)[2]**

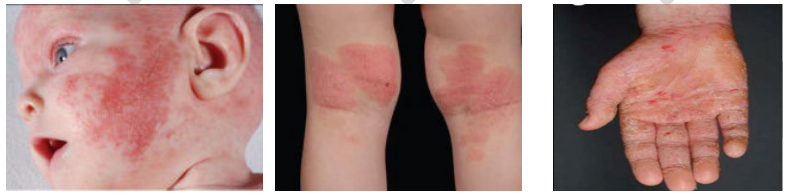
Immune activation may vary between age of onset[2], disease duration, and ethnicity, resulting in heterogeneous presentation



Immune Pathway Skewing

Morphology and distribution of AD lesions differ between age groups

Infantile phase | **Childhood phase** | **Adult phase**



Other factors varying between patients

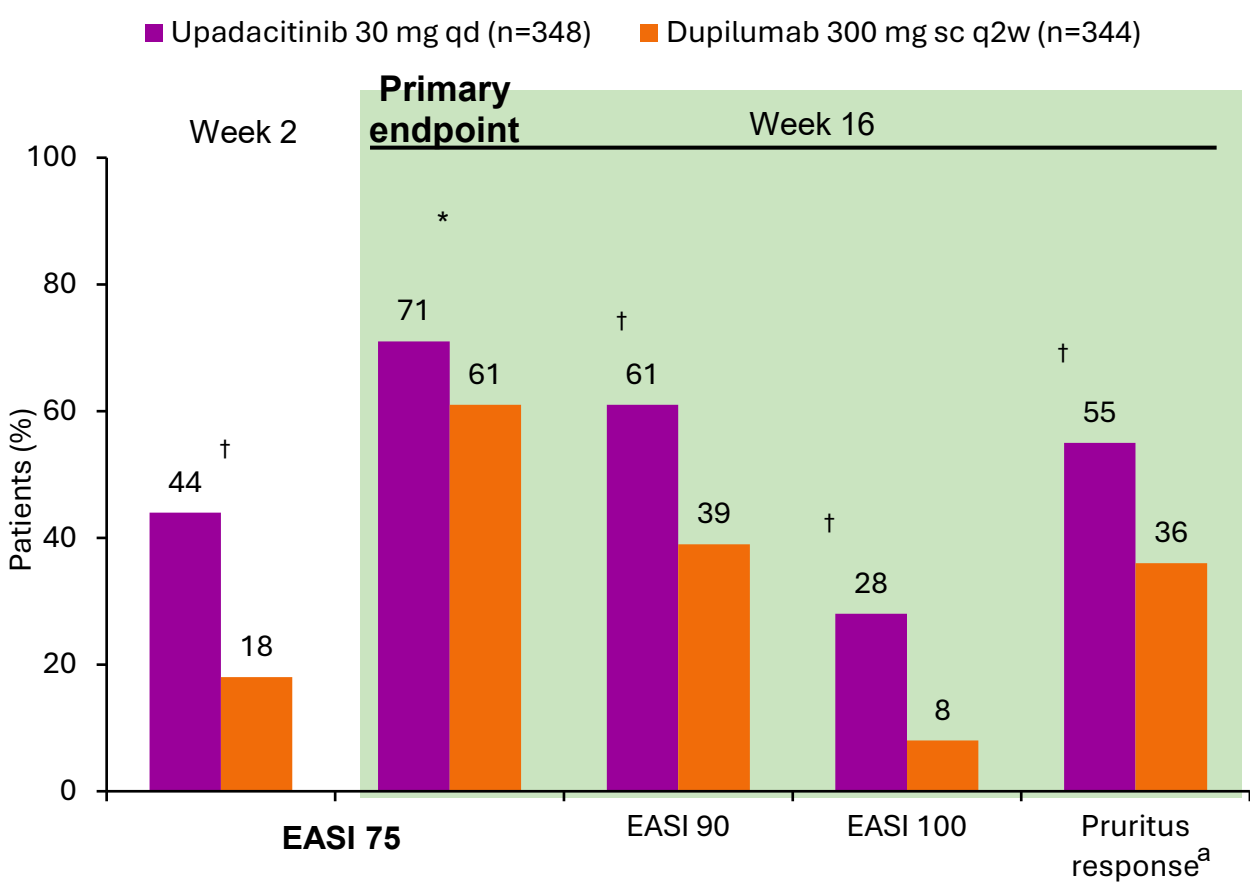
- **Response to therapy[2,6,7]**
- **IgE status[7]**
- **Trigger-induced events[2,3]**
- **Impact on itch, sleep, and QoL[3]**

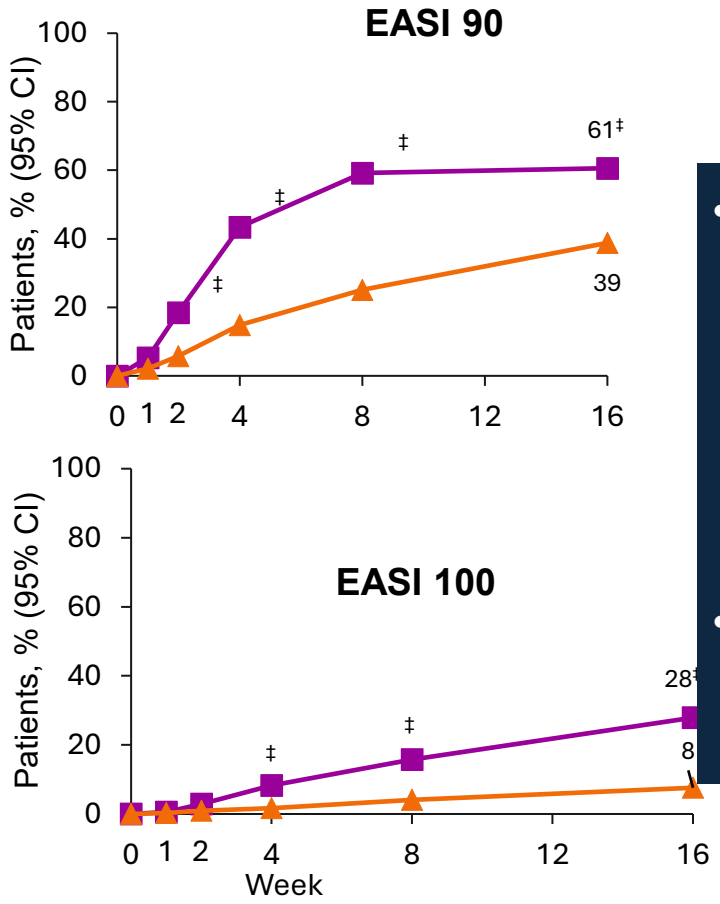
AD, atopic dermatitis; IgE, immunoglobulin E; QoL, quality of life; Th, T helper cell

1. Chovatiya R, Silverberg JI. Am J Clin Dermatol 2022. Online ahead of print; 2. Weidinger S, et al. Lancet 2016;387:1109–22; 3. Spergel JM, et al. J Allergy Clin Immunol 2003;112:S118–27; 4. Renert-Yuval Y, et al. Ann Allergy Asthma Immunol 2020;124:28–35; 5. Czarnowicki T, et al. J Allergy Clin Immunol 2019;143:1–11; 6. Weidinger S, et al. Nat Rev Dis Primers 2018;4:1; 7. Bieber T. Ann Dermatol 2010;22:125–37

Heads Up: Key efficacy outcomes among adults with moderate to severe AD treated with upadacitinib versus dupilumab (monotherapy) for 16 weeks

Patients achieving EASI and pruritus responses at Week 16

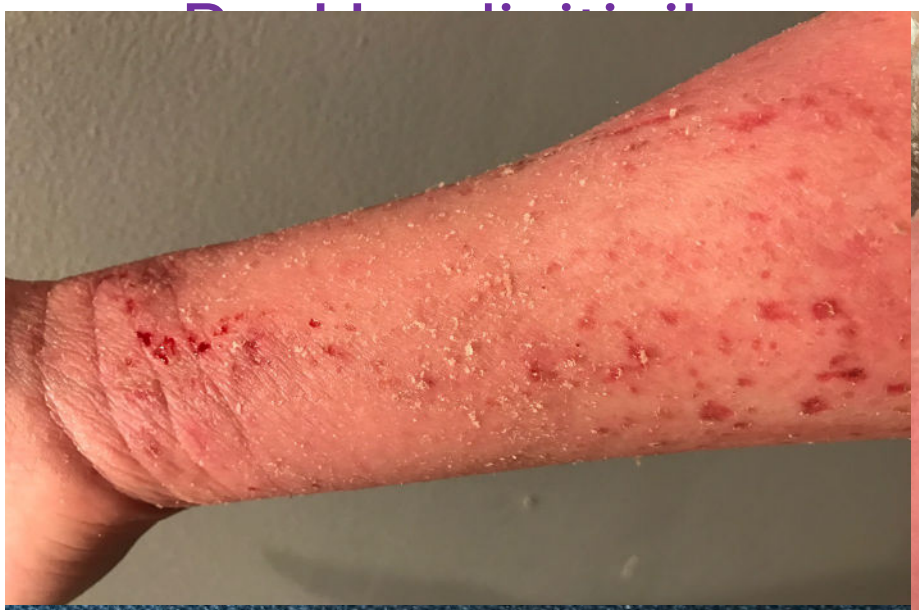


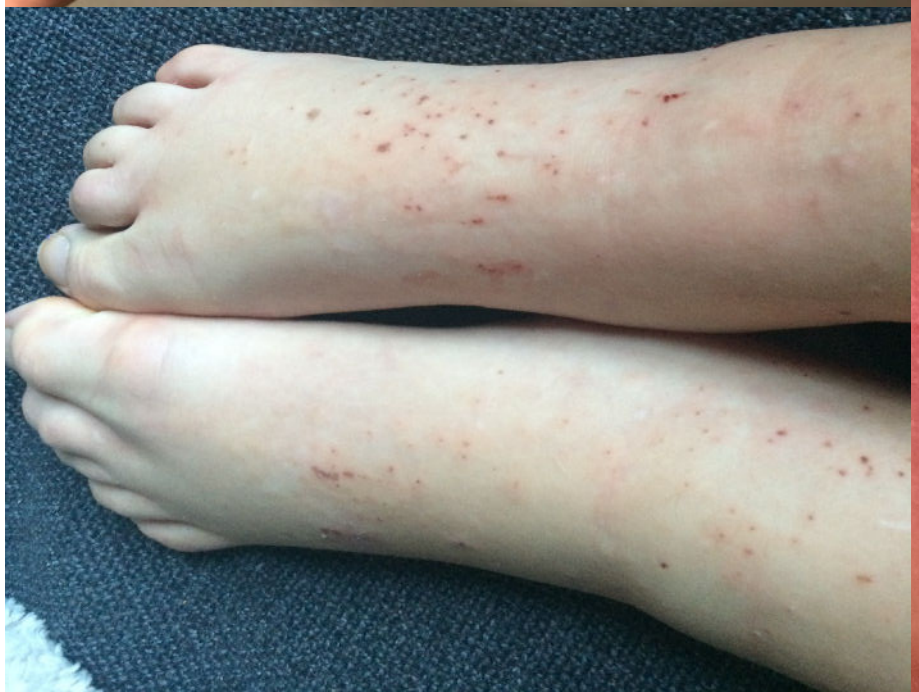


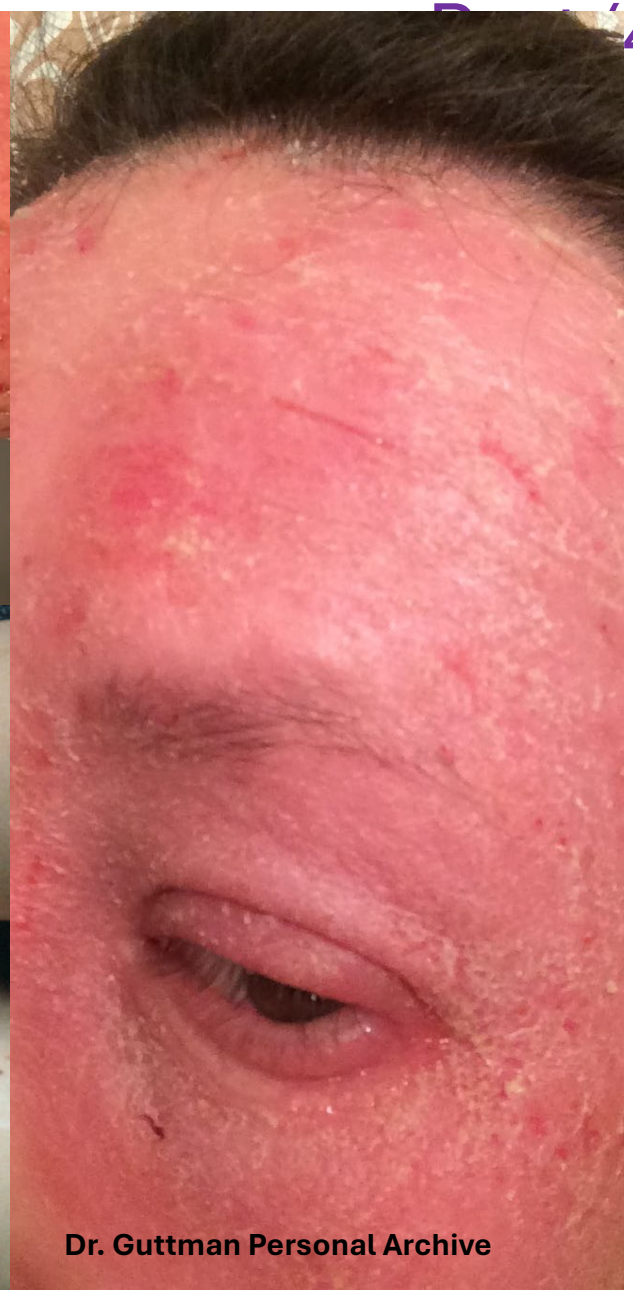
- For patients to rapidly achieve clearance (EASI 90/100), upadacitinib provides significant benefit over dupilumab
- Sprinters (JAKs) vs marathon runners (biologics)

- *P=0.006, †P<0.001 vs dupilumab; [a]≥4-point improvement in worst pruritus NRS. For pruritus,
- upadacitinib 30 mg qd: n=340, dupilumab 300 mg sc q2w: n=336

- Guttman-Yassky E et al Lancet 2021







Dr. Guttman Personal Archive

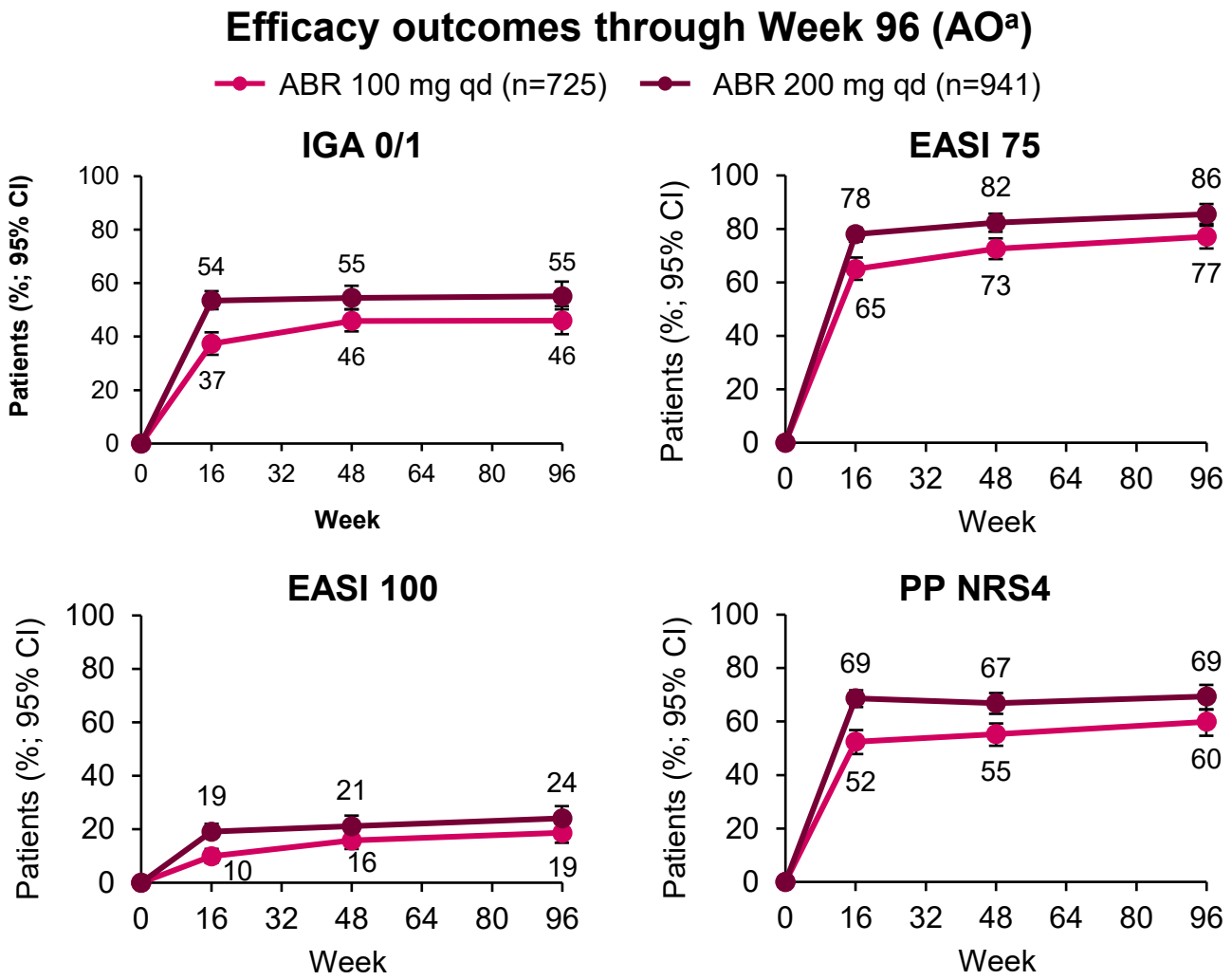
Upadacitinib and Dupilumab: Heads Up: Safety through Week 24

Overall TEAEs and TEAEs of special interest through Week 24, n (%)	**Dupilumab 300 mg q2w** (n=344)	**Upadacitinib 30 mg** (n=348)
Adverse event (AE)	230 (66.9)	270 (77.6)
AE with reasonable possibility of being drug related	129 (37.5)	170 (48.9)
Herpes zoster	4 (1.2)	12 (3.4)
Serious infections	2 (0.6)	4 (1.1)
Opportunistic infections (eczema herpeticum, non-serious)	0	3 (0.9)
Creatinine phosphokinase elevation	11 (3.2)	26 (7.5)
Hepatic disorder (including transaminase elevation)	5 (1.5)	12 (3.4)
Neutropenia	2 (0.6)	6 (1.7)
Lymphopenia	0	2 (0.6)
Adjudicated major adverse cardiovascular events	0	0
Adjudicated venous thromboembolic events	0	0
Conjunctivitis	35 (10.2)	5 (1.4)

- **Caution**: for JAK inhibitors **after 65 yo, smokers and OCP**: **Higher AEs:**
- **Herpes Zoster, VTEs, PEs, and malignancy**

- *As assessed by investigator; †40-year old woman deceased at home on Day 70 who had influenza A-associated bronchopneumonia.
- AE, adverse event; q2w, every 2 weeks; SAE, serious adverse event; Q2w, every 2 weeks; TEAE, treatment-emergent adverse event; 2w, every 2 weeks.
- *Blauvelt A, et al. Presented at ISAD 2021. PT29.*

JADE EXTEND: Efficacy of up to 96 weeks of abrocitinib treatment among patients with moderate to severe AD

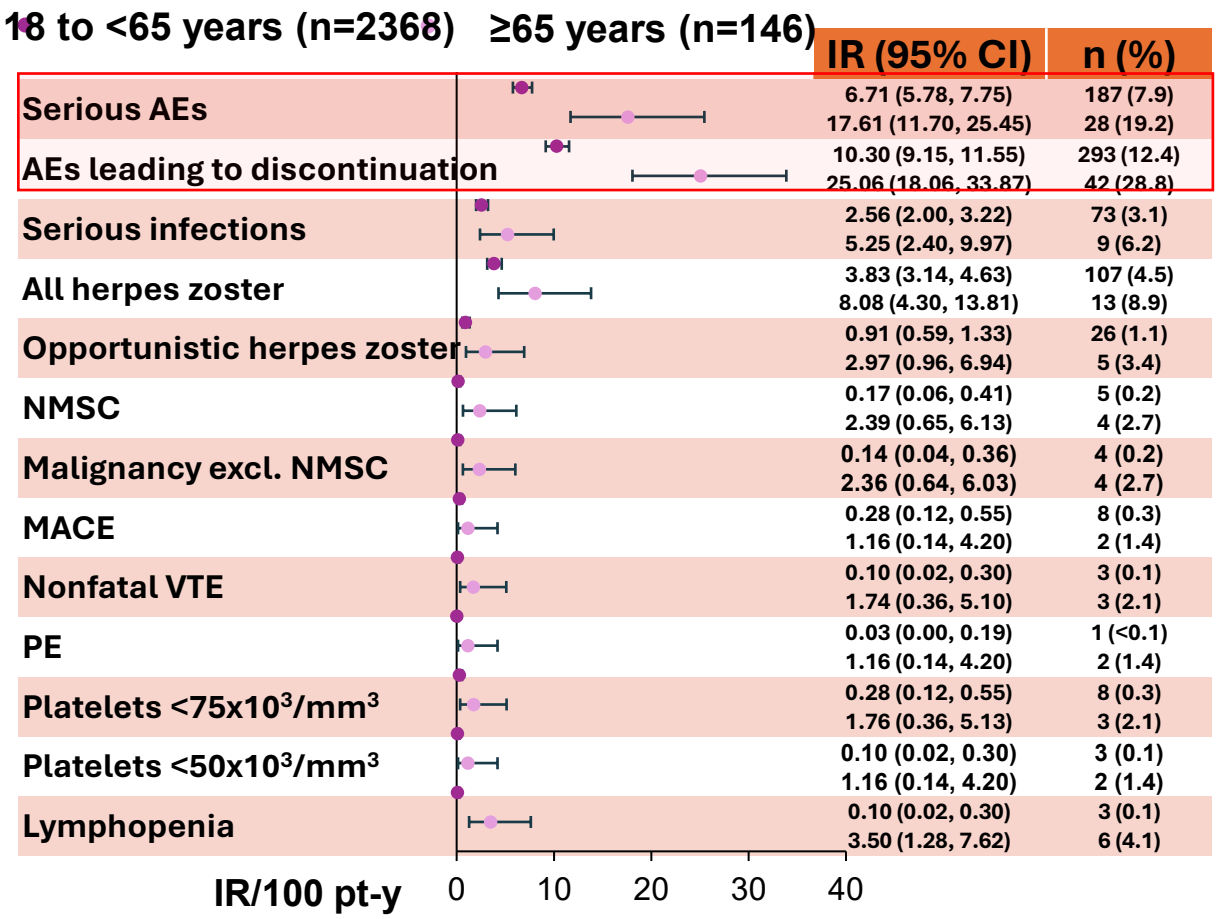


- EASI 100 achieved by ~25% patients with 200 mg
- Efficacy is not only maintained but even continues to increase to Week 96 with both doses and dose response preserved

[a]JADE EXTEND is ongoing and some patients have not reach Week 96 yet;

Integrated long-term safety of abrocitinib among patients with moderate to severe AD by age and smoking status

Incidence of AEs by age (consistent dose cohort)



Incidence of select AEs by smoking status

	Current/former smoker	Never-smoker
VTE	0.38 (0.10, 0.96)	0.11 (0.02, 0.32)
Malignancy (excluding NMSC)	0.38 (0.10, 0.96)	0.15 (0.04, 0.38)

Data are number of events per patient year (95% CI)

- Higher incidence of herpes zoster **for patients ≥65**
- **Some safety signals for older patients** (rates of serious AEs and infection) and smoker/former smoker (rate of VTE, malignancy)
- Disclaimer: number of patients ≥65 was small; larger numbers and further characterization of patients at risk for serious events (ie comorbidities, comedications) is necessary to understand the long-term safety profile

- *Simpson E, et al. AAD 2023, P44115.*