UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE

Biologics in Pediatric Atopic Dermatitis

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Disclosures

- Advisory Board Member – Incyte, Regeneron, Sanofi, Arcutis
- Consultant – Dermavant, Nobelpharma
- Speaker – Sanofi and Regeneron, Amgen

Dupilumab

Dupilumab

- Approved age 6 months and older for moderate to severe atopic dermatitis
- MOA: binding to alpha subunit of IL-4Ralpha blocking IL4 and IL13
- Dosing:
  - Weight based dosing of 200mg or 300mg every 2/4 weeks

Updates in Dupilumab- Vaccines

ORIGINAL ARTICLE

Pediatric Dermatology WILEY

A case series of live attenuated vaccine administration in dupilumab-treated children with atopic dermatitis

Elaine C. Siegfried MD[1,2] | Lara Wine Lee MD, PhD[3] | Jonathan M. Spergel MD, PhD[4] | Randy Prescilla MD[5] | Sumeet Uppal MS[6] | Anna Coleman MS[7] | Ashish Bansal MD, MBA[6] | Sonya L. Cyr PhD, MBA[6] | Brad Shumel MD[6]

- 9 children had protocol deviations and received MMR-V vaccine during phase 2/3 and open label extension
- Of these 9, 5 patients had an interval between last dupilumab and vaccination of 1–7 weeks, (during which serum dupilumab concentrations would still be detectable)
- Among these 5 patients, 1 resumed dupilumab treatment as early as 2 days and 4 resumed treatment 18–43 days after vaccination. No adverse events were reported

Dupilumab- Long term infections

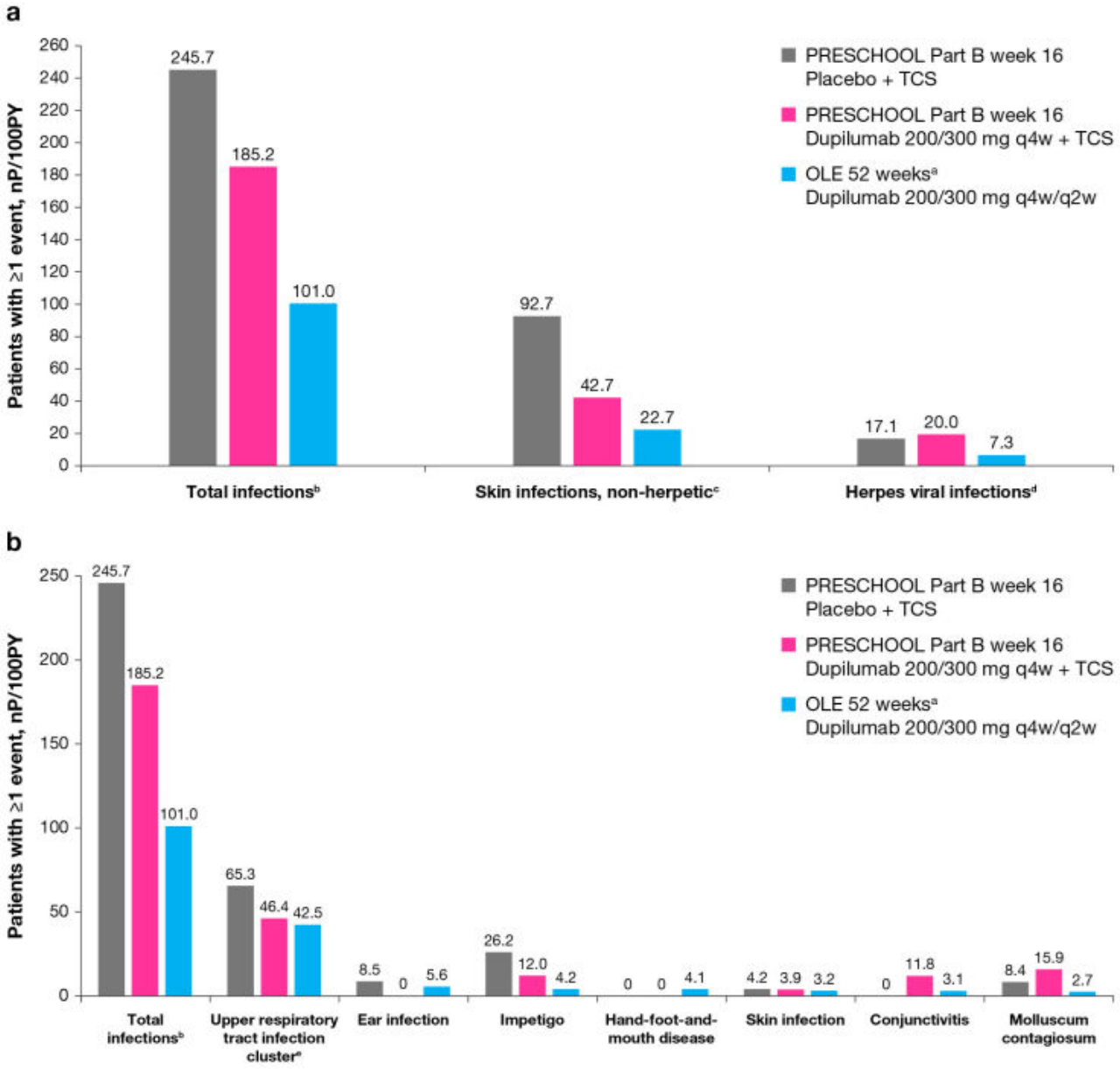
ORIGINAL ARTICLE OPEN ACCESS

Low Infection Rates With Long-Term Dupilumab Treatment in Patients Aged 6 Months to 5 Years: An Open-Label Extension Study

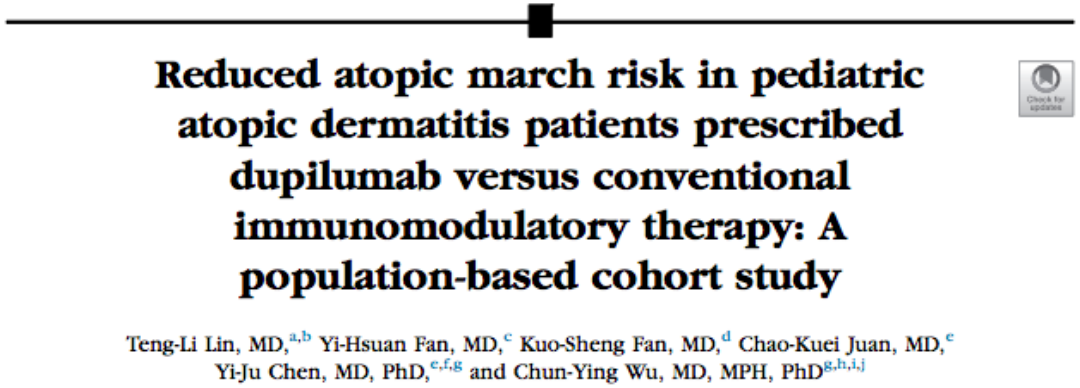
Amy S. Paller[1,2] | Michele Ramien[3,4] | Michael J. Cork[5,6] | Eric L. Simpson[7] | Lara Wine Lee[8] | Lawrence F. Eichenfield[9,10] | Faisal A. Khokhar[11] | Anna Coleman[12] | Guy Gherardi[13] | Zhen Chen[11] | Annie Zhang[14] | Sonya L. Cyr[11]

- Age 6 months to 5 years in trials who then subsequently enrolled in the open label extension
- Concomitant topical corticosteroids, antihistamines, and topical calcineurin inhibitors were permitted without restriction
- 180 patients

Dupilumab- Lower infection rates in long term use



Reduced atopic march with dupilumab



Reduced atopic march risk in pediatric atopic dermatitis patients prescribed dupilumab versus conventional immunomodulatory therapy: A population-based cohort study

Teng-Li Lin, MD,[a,b] Yi-Hsuan Fan, MD,[c] Kuo-Sheng Fan, MD,[d] Chao-Kuei Juan, MD,[e] Yi-Ju Chen, MD, PhD,[e,f,g] and Chun-Ying Wu, MD, MPH, PhD[g,h,i,j]

- The 3-year cumulative incidence of atopic march progression was lower in the dupilumab cohort than the conventional cohort (20.09% vs 27.22%; P<.001). Conventional cohort included MTX, CsA, steroids, azathioprine. Study excluded patients with prior h/o asthma or rhinitis.
- The DUPIcohort demonstrated significant risk reduction in atopic march progression (hazard ratio [HR] 0.68, 95% CI 0.55-0.83), individual asthma (HR 0.60, 0.45-0.81), and individual allergic rhinitis (HR 0.69, 0.54-0.88). **Younger patients on dupilumab exhibited a greater risk reduction**
- This suggests increased plasticity in type 2 immunity in younger AD patients

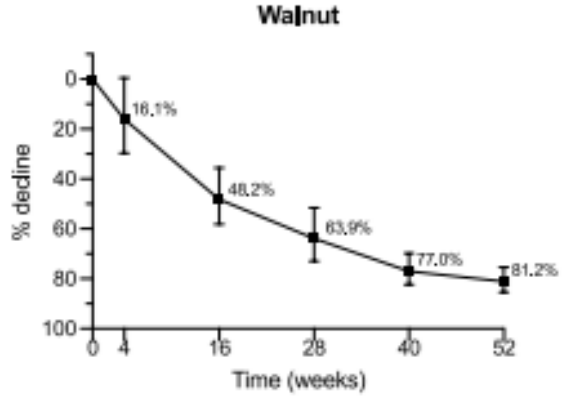
Dupilumab and food allergies?

LETTER

Dupilumab induces a significant decrease of food specific immunoglobulin E levels in pediatric atopic dermatitis patients

Lisa P. van der Rijst[1,2] | Michelle S. Hilbrands[2] | Nicolaas P. A. Zuithoff[3] | Marjolein S. de Bruin-Weller[2] | André C. Knulst[2] | Thuy-My Le[2] | Marlies de Graaf[1,2]

- Pediatric AD patients (aged 4–17 years) treated with dupilumab with a suggestive clinical history of food allergy for peanut, hazelnut, cashew nut, pistachio, almond, walnut, hen's egg, cow's milk, kiwi, and/or apple with a corresponding positive serum IgE (≥0.35 kU/L) at the start of treatment (baseline), were included. Serum IgE levels were measured at baseline and at least once during 1 year of follow- up
- Decrease of serum IgE levels in 10 common food allergens in food allergic pediatric patients with moderate to severe AD, ranging from 70.5% to 82.5% after 1 year of dupilumab treatment
- Still need further studies including oral food challenge before, during and after treatment to objectify whether dupilumab treatment leads to a higher threshold and/or less severe food allergy symptoms


Walnut
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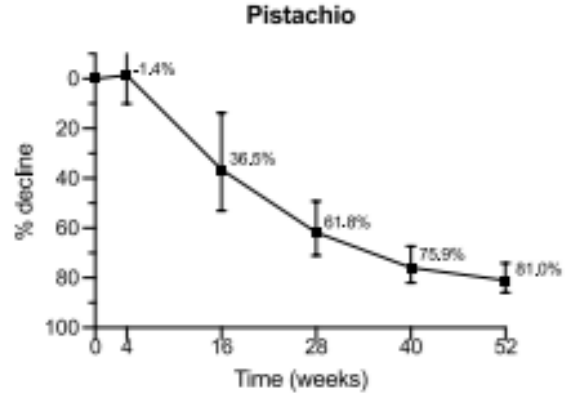
Time (weeks)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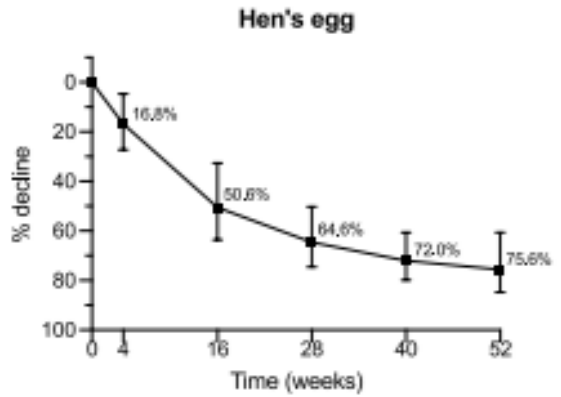
Hen's egg
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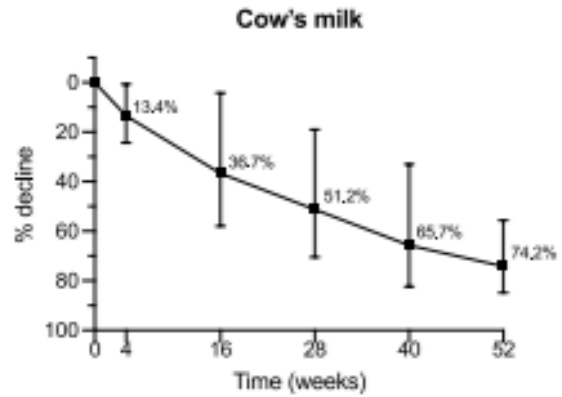
Time (weeks)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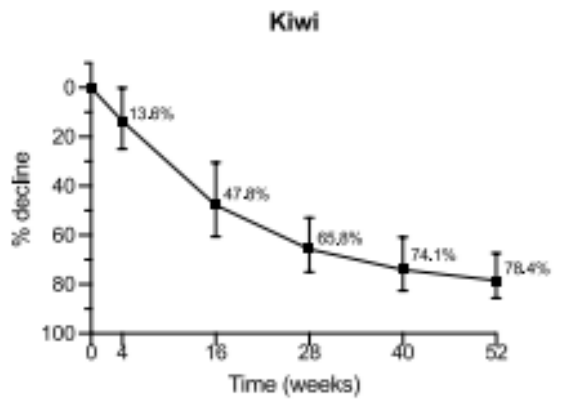
Time (weeks)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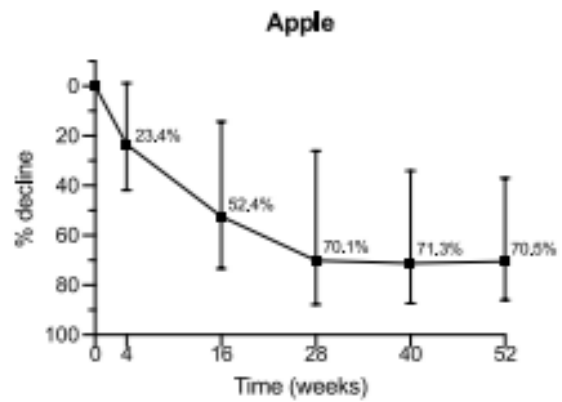
Apple
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52.4%
70.1%
71.3%
70.6%
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Time (weeks)

Lebrikizumab

Lebrikizumab

- Approved for moderate to severe atopic dermatitis in age 12 and older
- A monoclonal antibody that binds with high affinity and slow off-rate to interleukin (IL)-13
- Dosing: subcutaneous lebrikizumab 500 mg loading doses at baseline and Week 2, followed by 250 mg every 2 weeks thereafter
  - **If adequate clinical response is seen by week 16, can use maintenance dosing of 250mg every 4 weeks**

Lebrikizumab Efficacy

RESEARCH ARTICLE

OPEN ACCESS Check for updates

Efficacy of lebrikizumab in adolescent patients with moderate-to-severe atopic dermatitis: 16-week results from three randomized phase 3 clinical trials

Adelaide A. Hebert[a], Carsten Flohr[b], H. Chih-ho Hong[c], Alan D. Irvine[d], Evangeline Pierce[e], Hany Elmaraghy[e], Sreekumar Pillai[e], Zach Dawson[e], Sherry Chen[f], Clara Armengol[g], Elaine Siegfried[h] and Stephan Weidinger[i]

[a]UTHealth McGovern Medical School, Houston, Texas, USA; [b]St John's Institute of Dermatology, King's College London, London, UK; [c]University of British Columbia, and Probity Medical Research, Surrey, British Columbia, Canada; [d]Clinical Medicine, Trinity College Dublin, Dublin, Ireland; [e]Eli Lilly and Company, Indianapolis, Indiana, USA; [f]Tigermed, Somerset, New Jersey, USA; [g]Almirall S.A., Barcelona, Spain; [h]Saint Louis University, St. Louis, Missouri, USA; [i]University Hospital Schleswig-Holstein, Kiel, Germany

- ADhere allowed to use TCS and TCI during study

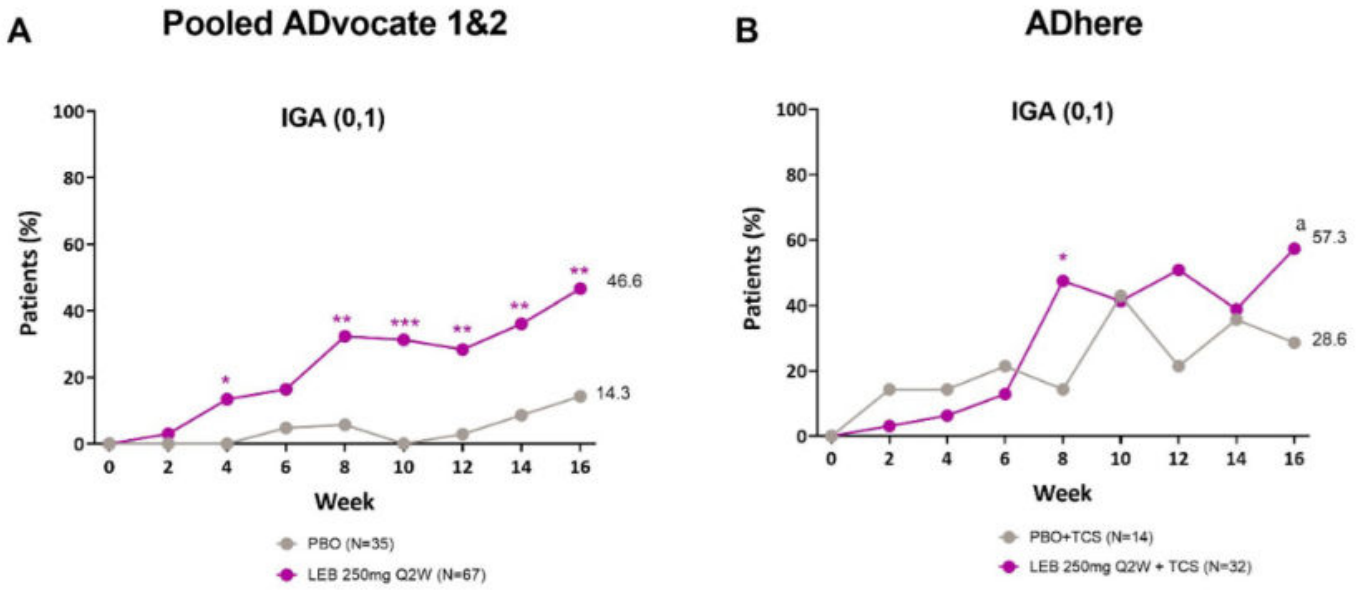
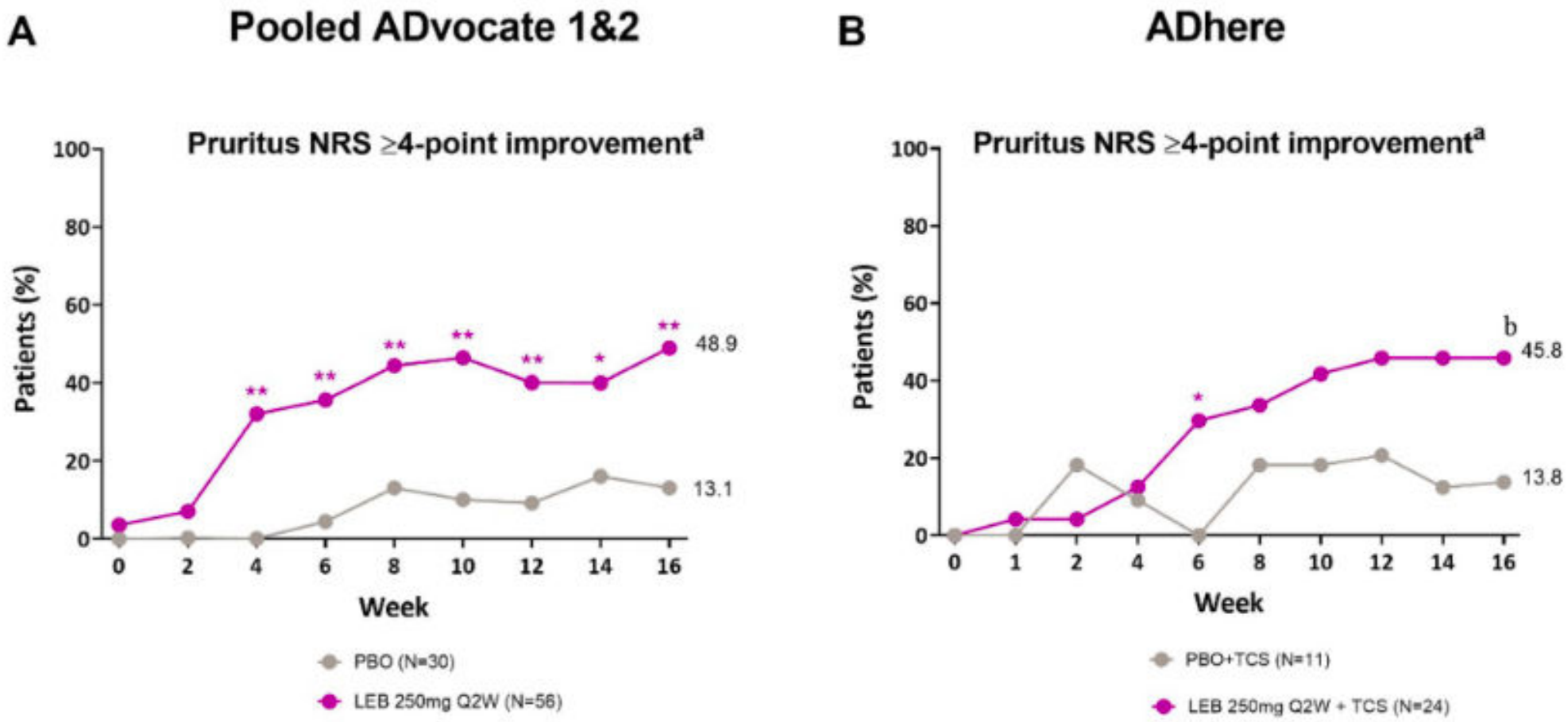


Figure 1. Adolescent time-course response for IGA (0, 1) with ≥2-point improvement from baseline.
Percentage of patients (%) with IGA (0, 1) and ≥2-point reduction from baseline to Week 16 in the ADvocate (A) and ADhere (B) studies. *$p<0.05$, **$p<0.01$, ***$p<0.001$, [a]$p=0.104$ vs PBO using the Cochran-Mantel-Haenszel test adjusted by study (only for pooled ADvocate1 and ADvocate2), geographic region, and disease severity. IGA = Investigator's Global Assessment; LEB = lebrikizumab; PBO = placebo; Q2W = every 2 weeks; TCS = topical corticosteroids.

Lebrikizumab Itch Reduction, significant by week 4



Lebrikizumab Safety

- Most common SE were nasopharyngitis (9.7%), COVID-19 infection (8.7%), upper respiratory tract infection (6.3%), headache (5.8%), and oral herpes (5.3%).
- AEs of special interest (AESIs) included conjunctivitis cluster (n = 14, 6.8%), herpes infection (n = 15, 7.3%), and parasitic infections (0%)

Lebrikizumab 52 week Open Label Extension

Safety and Efficacy of Lebrikizumab in Adolescent Patients with Moderate-to-Severe Atopic Dermatitis: A 52-Week, Open-Label, Phase 3 Study

Amy S. Paller · Carsten Flohr · Lawrence F. Eichenfield · Alan D. Irvine · Jamie Weisman · Jennifer Soung · Ana Pinto Correia · Chitra R. Natalie · Claudia Rodriguez Capriles · Evangeline Pierce · Sarah Reifeis · Renata Gontijo Lima · Clara Armengol Tubau · Vivian Laquer · Stephan Weidinger

- 62% achieving endpoint of IGA 0 or 1

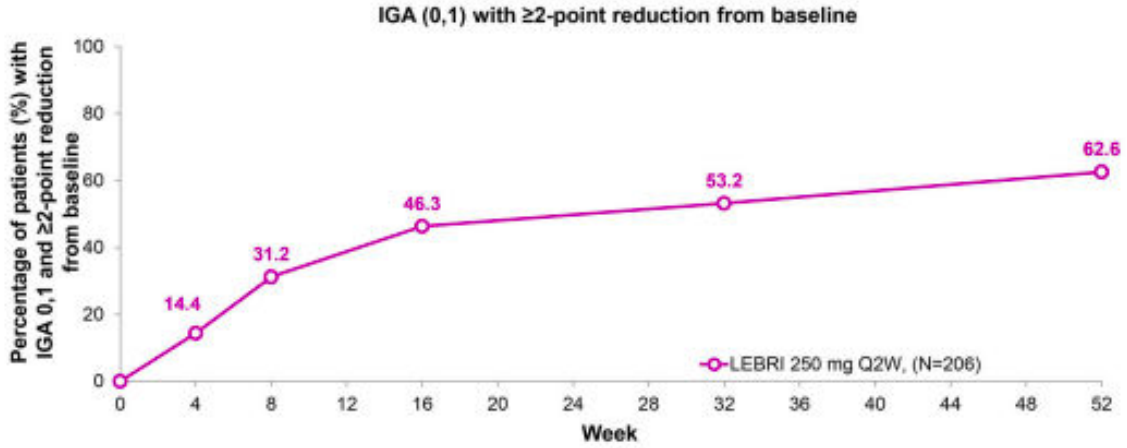


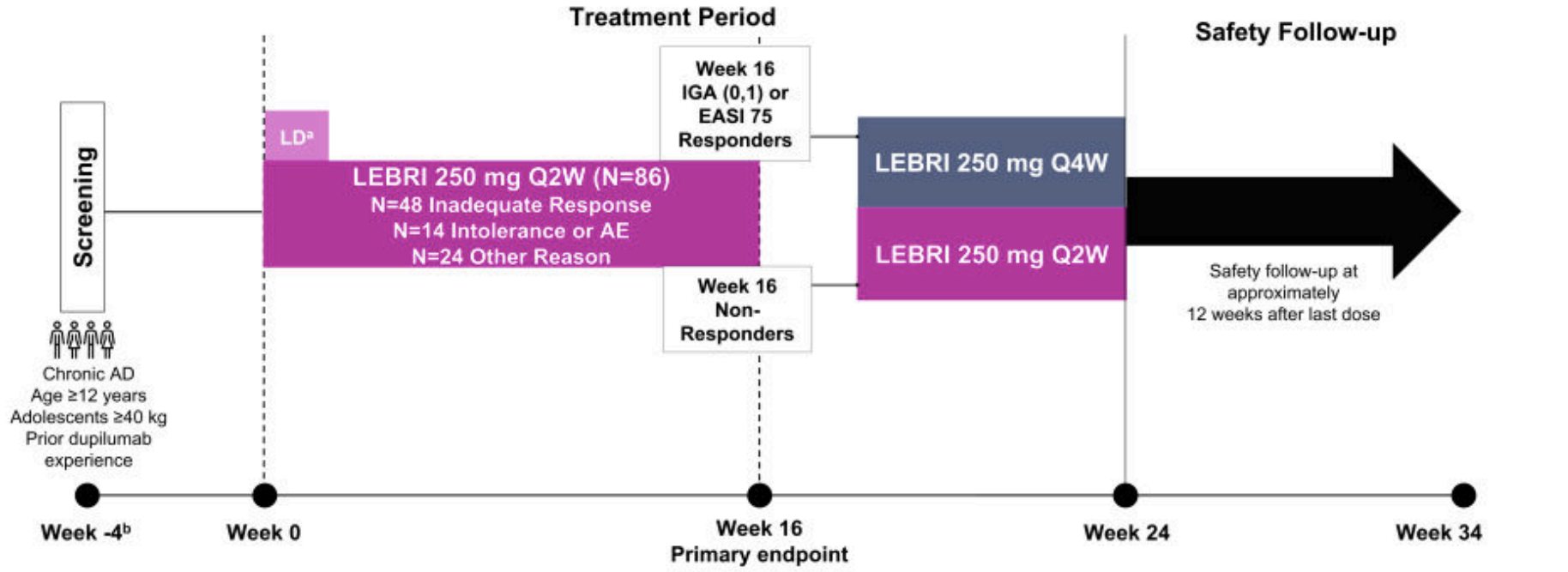
Fig. 3 Time course response for IGA (0,1) with ≥ 2-point reduction from baseline. Percentage of patients (%) with IGA 0,1 and ≥ 2-point reduction from baseline through 52 weeks. A total of 62.6% of patients (N = 129) achieved IGA 0 or 1 with ≥ 2-point reduction from baseline at Week 52. Missing data due to lack of efficacy were imputed with non-responder imputation. Other missing data were imputed with multiple imputation. Abbreviations: *IGA* Investigator's Global Assessment, *LEBRI* lebrikizumab, *Q2W* every 2 weeks

Lebrikizumab Use in Prior Dupilumab Patients

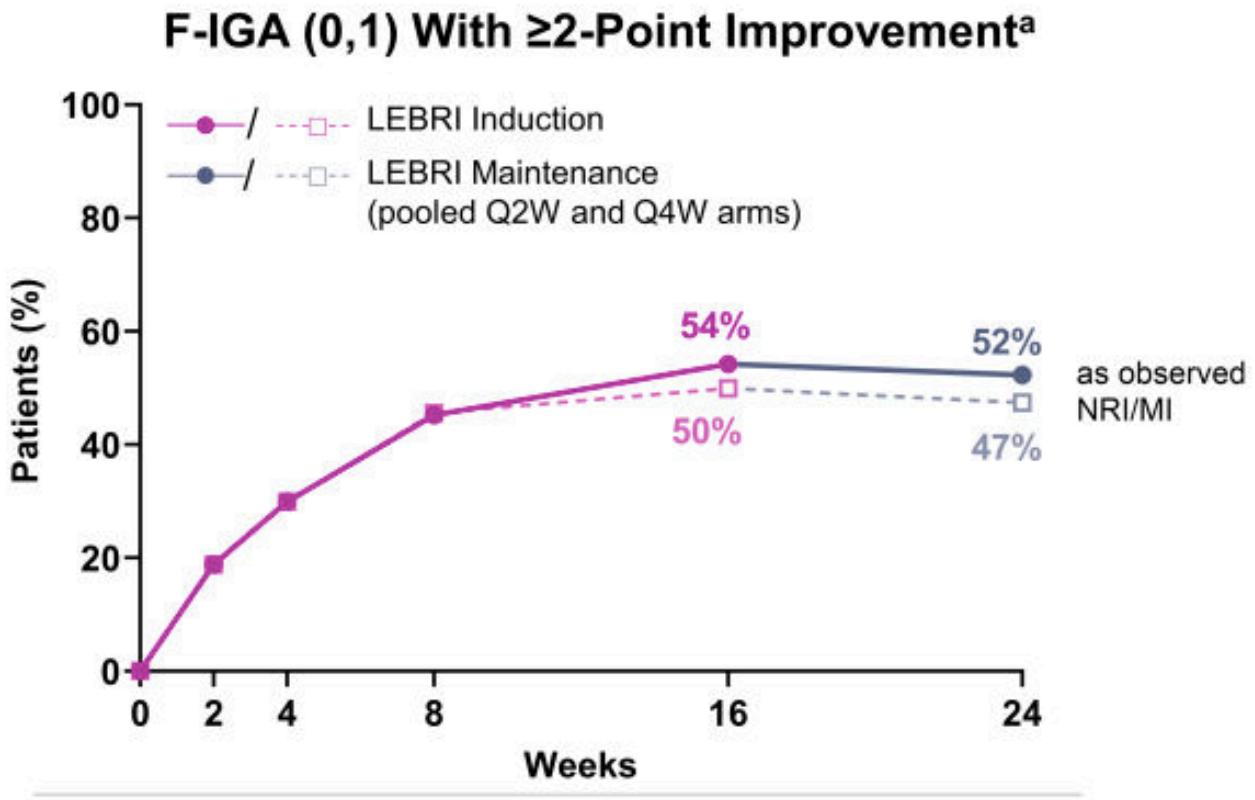
Lebrikizumab Improves Atopic Dermatitis and Quality of Life in Patients With Moderate-to-Severe Atopic Dermatitis Previously Treated With Dupilumab: Results From the ADapt Trial

Jonathan Silverberg[1], Lindsay Ackerman[2], Jerry Bagel[3], Linda Stein Gold[4], Andrew Blauvelt[5], David Rosmarin[6], Raj Chovatiya[7], Matthew Zirwas[8], Gil Yosipovitch[9], Jill Waibel[10], Jenny E. Murase[11], Ben Lockshin[12], Jamie Weisman[13], Amber Reck Atwater[14], Jennifer Proper[14], Maria Silk[14], Evangeline Pierce[14], Maria Lucia Buziqui Piruzeli[14], Sonia Montmayeur[14], Christopher Schuster[14], Jinglin Zhong[15], Maria Jose Rueda[14], Sreekumar Pillai[14], Eric Simpson[16]

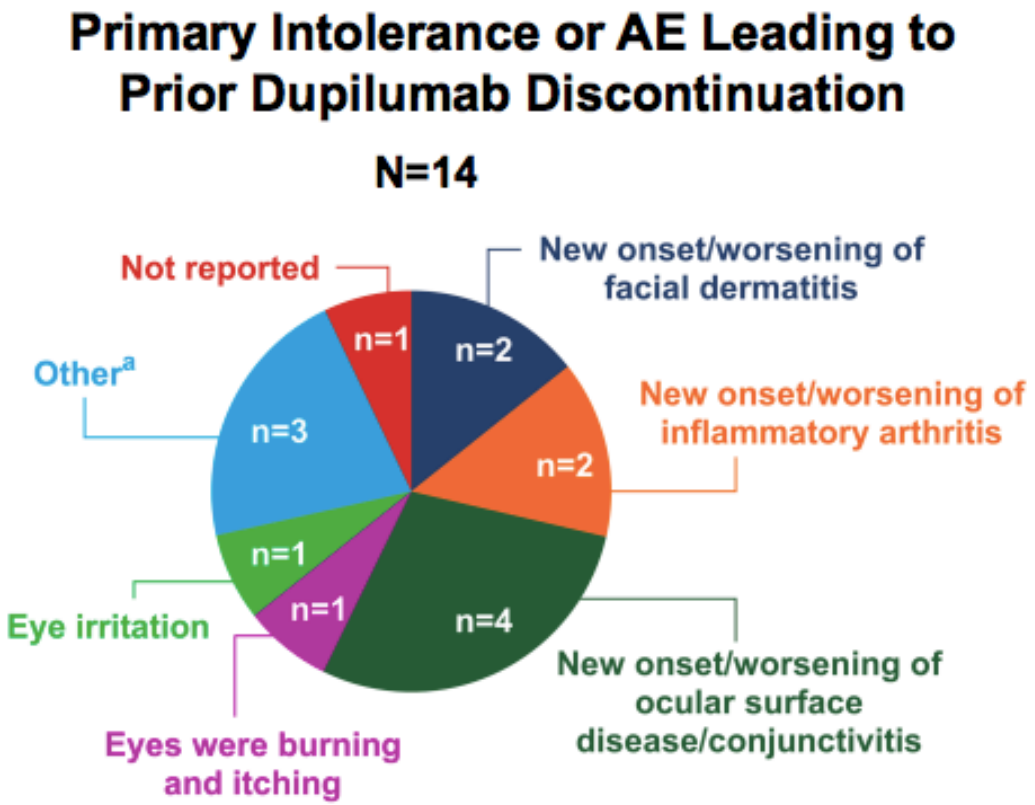
ADapt Study Design



Lebrikizumab



Lebrikizumab and Conjunctivitis



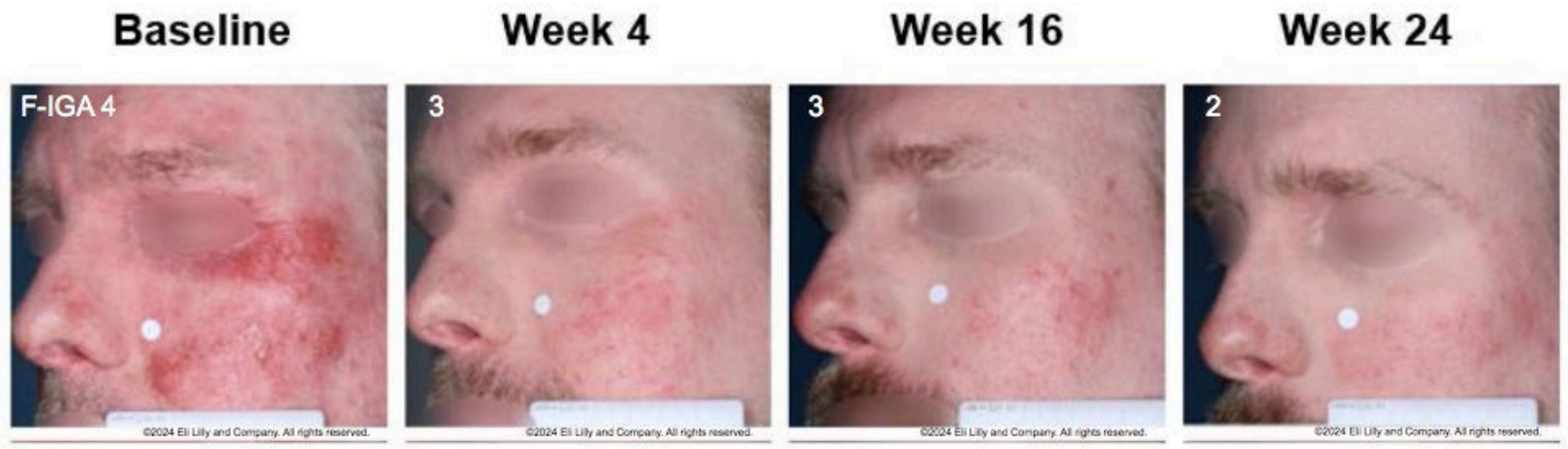
In the ADapt trial

- Of the 10 patients who reported eye-related events, facial dermatitis, or inflammatory arthritis as the reason for prior dupilumab discontinuation, none reported similar events with lebrikizumab
- Of the 14 patients with prior dupilumab discontinuation due to AEs
  - 2 discontinued treatment with lebrikizumab due to an AE:
    - Dermatitis atopic, n=1
    - Immune-mediated rash, n=1

[a]Other includes increased itching; weight gain and worsening of itch; hives, rash, pruritus, and swelling (n=1 each).
AE=adverse event.

Lebrikizumab and Facial Dermatitis

Photographs Showing Improvement in Facial Atopic Dermatitis With Lebrikizumab in a Patient Who Discontinued Dupilumab Due to Loss of Response

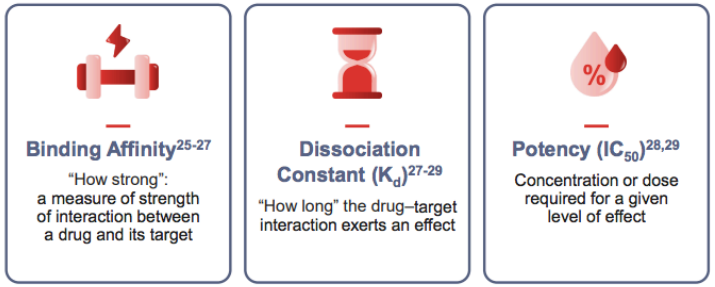


IL-13 binding affinity across biologics

	Lebrikizumab	Tralokinumab	
Binding Affinity (K_D)	6.3±0.9 pM	904±119 pM	Lebrikizumab has a ~140-fold **stronger affinity** for IL-13 than tralokinumab[a]
Dissociation Rate (k_{off} [± SD])	$(2.3±0.4)×10^{-5}$ s^{-1}	$(3.8±0.9)×10^{-3}$ s^{-1}	Lebrikizumab **stays bound** to IL-13 **longer** than tralokinumab[a]
Potency (IC_{50} [± SD])	13±1 pM	97±16 pM	Lebrikizumab demonstrated a ~7-fold **reduction of IC_{50}** value for IL-13 vs. tralokinumab[b]

The higher the Kd value, the weaker the binding and the lower the affinity

The IC_{50} value is correlated with drug potency, i.e., the amount of drug necessary to produce the effect—the lower the IC_{50} value, the more potent the drug



Tralokinumab

Tralokinumab

- Fully human IgG4 monoclonal antibody that binds to IL-13
- Approved for age 12 and older
- Dosing: 300 mg (two 150 mg injections) at week 0 followed by 150 mg (one 150 mg injection) every 2 weeks
  - **Currently no option for q4 dosing for peds, only available for adults <100kg after 16 weeks if IGA 0 or 1**

Tralokinumab Efficacy

JAMA Network — Click to view article >

JAMA Dermatol. 2023 Apr 19;159(6):596–605. doi: 10.1001/jamadermatol.2023.0627

Efficacy and Safety of Tralokinumab in Adolescents With Moderate to Severe Atopic Dermatitis

The Phase 3 ECZTRA 6 Randomized Clinical Trial

Amy S Paller [1,✉], Carsten Flohr [2], Michael Cork [3], Anthony Bewley [4], Andrew Blauvelt [5], H Chih-ho Hong [6], Shinichi Imafuku [7], Marie L A Schuttelaar [8], Eric L Simpson [9], Weily Soong [10], Petra Arlert [11], Katja Wendicke Lophaven [11], Azra Kurbasic [11], Lise Soldbro [11], Natacha Strange Vest [11], Andreas Wollenberg [12,13]

- More patients receiving tralokinumab, 150 mg, and tralokinumab, 300 mg achieved an IGA score of 0 or 1 without rescue medication at week 16 (21 [21.4%] and 17 [17.5%], respectively) vs placebo (n = 94; 4 [4.3%])
- Proportions of patients with Adolescent Worst Pruritus Numeric Rating Scale reduction of 4 or more from baseline were greater with tralokinumab, 150 mg (23.2%), and tralokinumab, 300 (25.0%), vs placebo (3.3%)

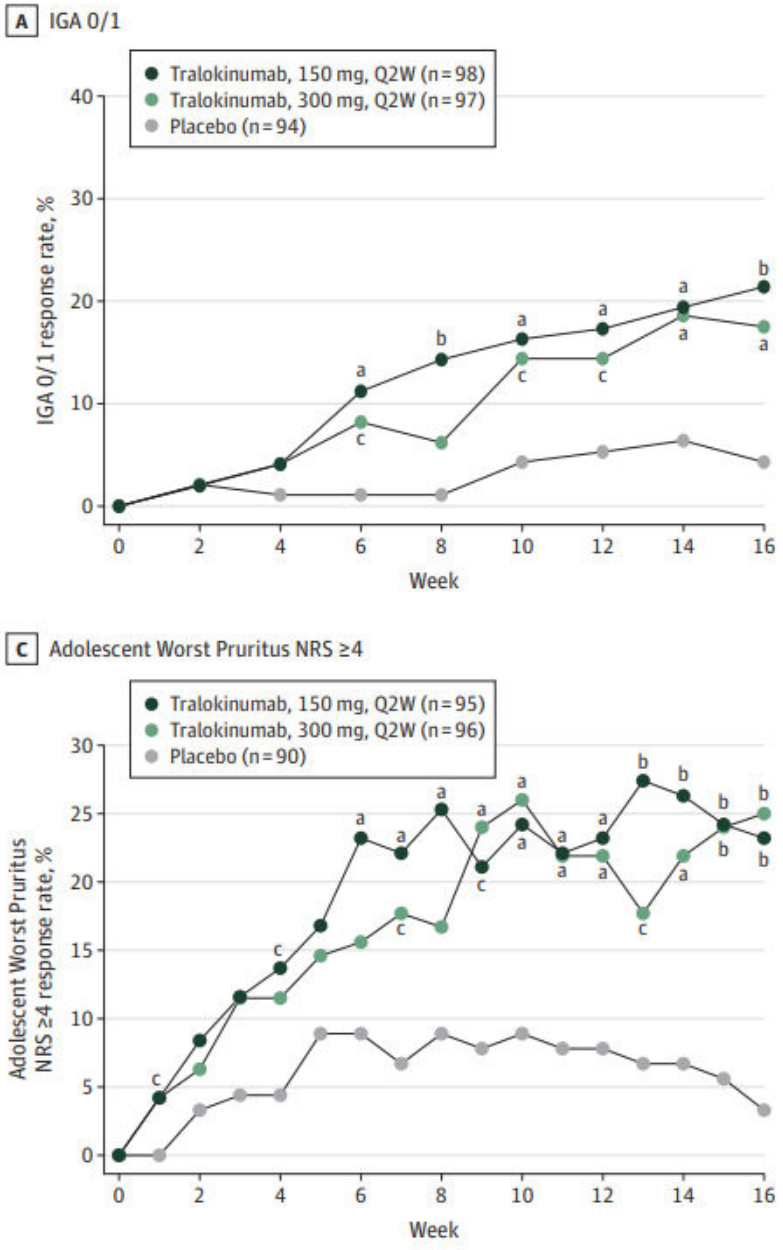
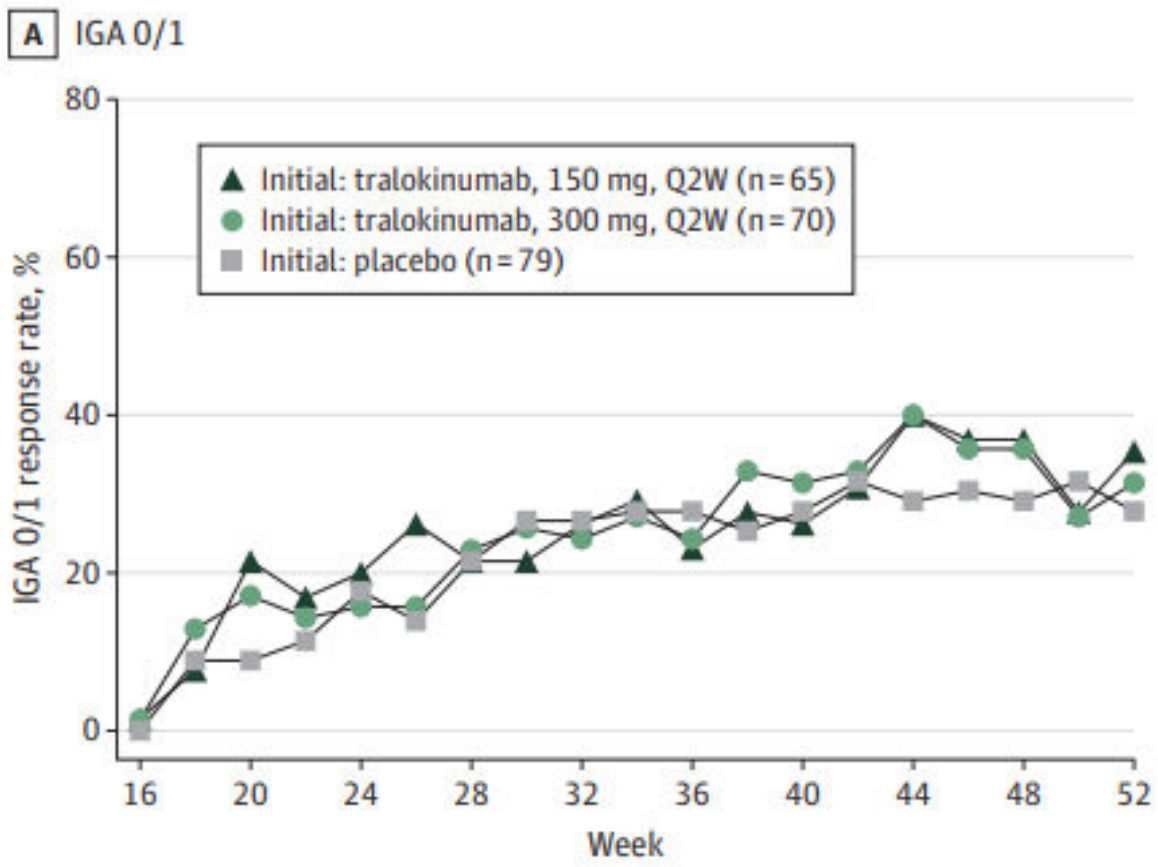


Figure 2. Tralokinumab Efficacy vs Placebo Across Primary and Key Secondary End Points up to Week 16 (Initial Treatment Period), Full Analysis Set.

Tralokinumab 52-week open label extension

- Could stay on topical corticosteroids and/or TCI
- At week 52, tralokinumab efficacy was maintained without rescue in more than 50% of patients meeting primary end point(s) at week 16.
- In the open-label phase, IGA score of 0 or 1 was achieved 33.3% of patients at week 52



Tralokinumab Safety

- Most frequent AEs were URI, dermatitis atopic (disease exacerbation), injection-site reaction, asthma, and headache
- Proportions of patients with conjunctivitis were low
- Frequencies of other AEs of special interest, including eczema herpeticum and skin infections requiring systemic treatment, were low across all treatment arms.

Table 2. Safety Outcomes in the Initial Treatment Phase, Safety Analysis Set (N = 289).

Outcome	No. (%)		
	Placebo (n = 94)	Tralokinumab every 2 wk	
		150 mg (n = 98)	300 mg (n = 97)
Adverse events (patients with ≥1)	58 (61.7)	66 (67.3)	63 (64.9)
Serious adverse events (patients with ≥1)[a]	5 (5.3)	3 (3.1)	1 (1.0)
Severity of adverse events			
Mild	40 (42.6)	48 (49.0)	47 (48.5)
Moderate	31 (33.0)	33 (33.7)	32 (33.0)
Severe	7 (7.4)	5 (5.1)	3 (3.1)
Adverse event related to investigational medicinal product	20 (21.3)	26 (26.5)	25 (25.8)
Adverse event leading to withdrawal	0	1 (1.0)[b]	0
Frequent adverse events (≥5% in any group)			
Viral upper respiratory tract infection	8 (8.5)	19 (19.4)	12 (12.4)
Upper respiratory tract infection	4 (4.3)	8 (8.2)	11 (11.3)
Dermatitis atopic	12 (12.8)	13 (13.3)	7 (7.2)
Injection-site reaction	0	6 (6.1)	2 (2.1)
Asthma	5 (5.3)	0	3 (3.1)
Headache	3 (3.2)	5 (5.1)	6 (6.2)
Adverse events of special interest			
Eye disorders	2 (2.1)	4 (4.1)	4 (4.1)
Conjunctivitis	2 (2.1)	4 (4.1)	3 (3.1)
Conjunctivitis (preferred term)	0	2 (2.0)	0
Conjunctivitis bacterial (preferred term)	0	0	1 (1.0)
Conjunctivitis allergic (preferred term)	2 (2.1)	2 (2.0)	2 (2.1)
Conjunctivitis viral (preferred term)	0	0	0
Keratitis	0	0	1 (1.0)

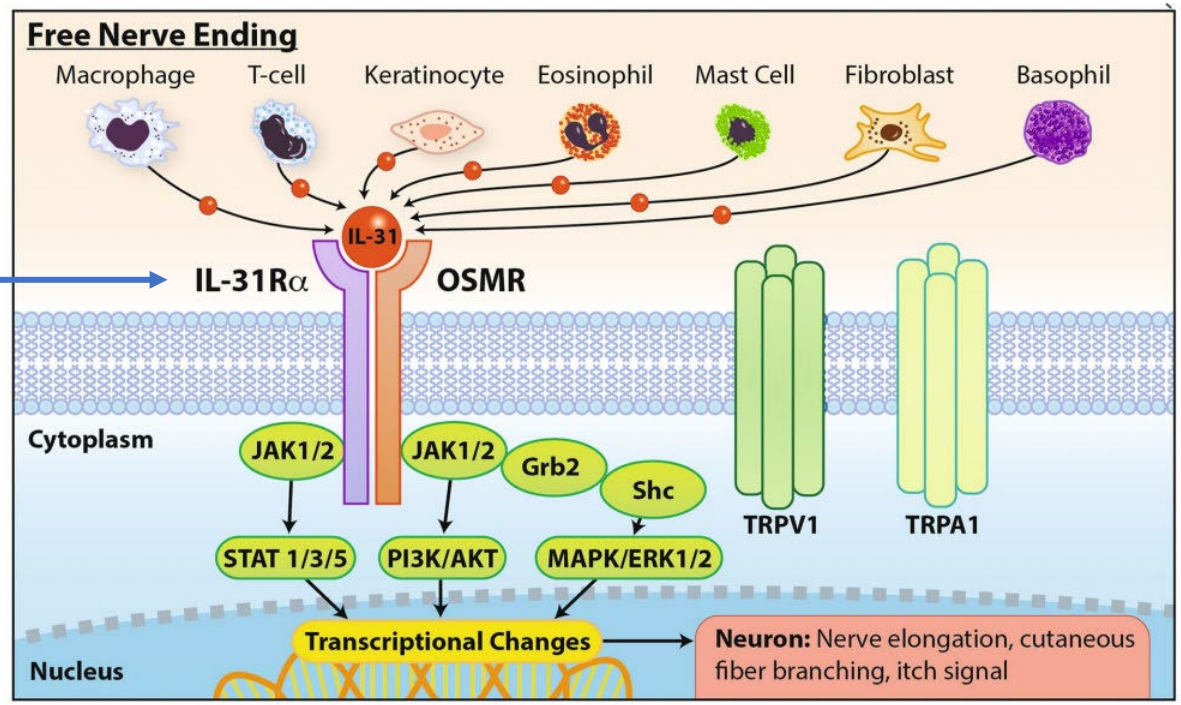
Nemolizumab

Nemolizumab

- Humanized IgG2 monoclonal antibody that inhibits IL-31 signaling by binding to IL-31 receptor antagonist
- Indicated for patients 12 and older for moderate to severe atopic dermatitis
- Dosing: 60mg (2 30mg injections) followed by 30mg every 4 weeks
  - **After 16 weeks if maintenance achieved, can lower dose to 30mg every 8 weeks**

IL-31 MOA

Nemolizumab



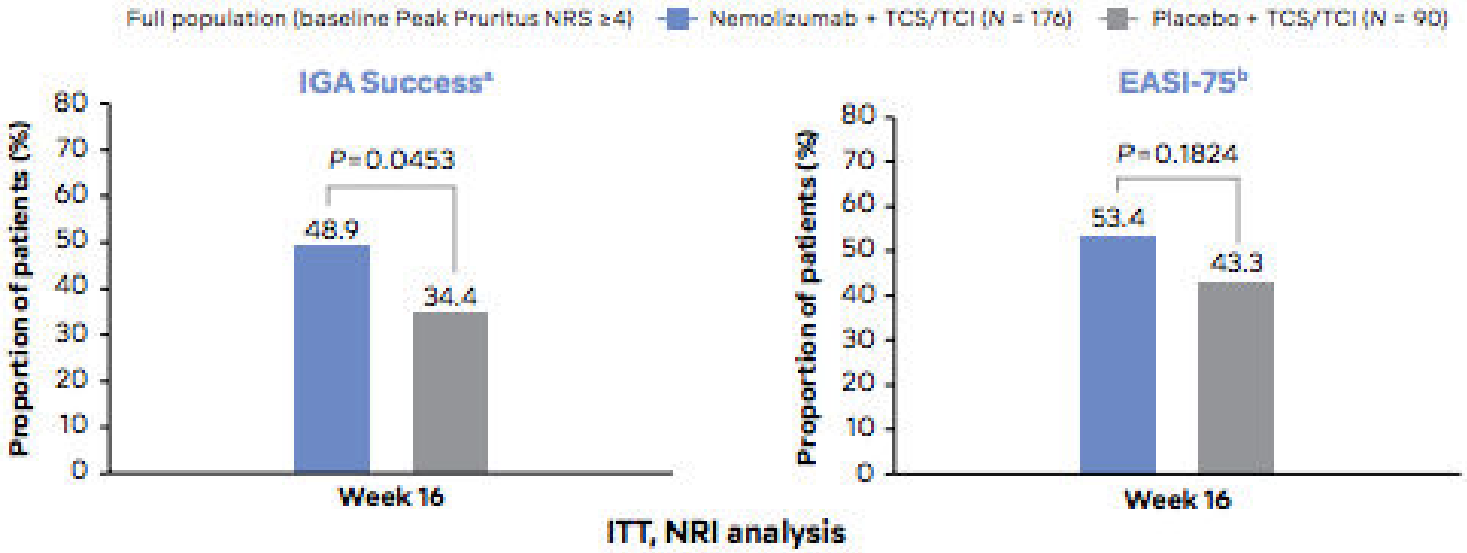
- Primarily produced by Th2 cells
- Binds to IL31Rα and OSMRβ on DRG
- One of the “master itch cytokines”

- Signals through JAK/STAT and MAPK/ERK
- Induces neurogenic inflammation and barrier dysfunction

Roh et al. *Drugs*. 2021.
Datsi et al. *Allergy. 2021.*
Cevikbas et al. J Allergy Clin Immunol. *2014.*

Nemolizumab Efficacy in Adolescent Subset

Figure 2. IGA Success and EASI-75 At Week 16



EASI-75, 75% improvement in the Eczema Area and Severity Index; IGA, Investigator's Global Assessment ; ITT, intent-to-treat; N, total number of patients in treatment group; NRI, non-responder imputation; NRS, Numerical Rating Scale; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids

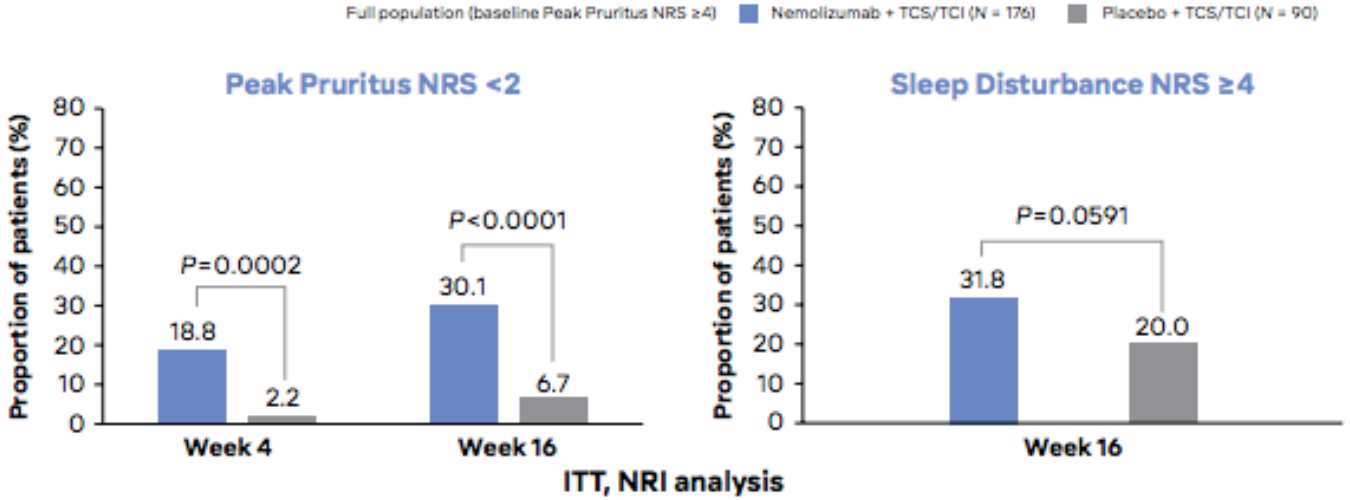
Percentages (%) are based on the number of patients in each treatment group (N).

For non-responder imputation, patients with data collected after use of rescue therapy or with missing data at a visit were considered non-responders. Strata adjusted *P*-values were from Cochran-Mantel-Haenszel test adjusting for the stratification variable study.

[a]IGA success was defined as IGA (0, 1) and ≥2 points improvement.
[b]EASI-75 was defined as ≥75% improvement in EASI from initial baseline.

Nemolizumab and Pruritus

Figure 4. Weekly Average Improvement in Peak Pruritus NRS Score <2 and Weekly Average Improvement in Sleep Disturbance NRS Score ≥4 at Week 4 and Week 16



ITT, intent-to-treat; *N*, total number of patients in treatment group; NRI, non-responder imputation; NRS, Numerical Rating Scale; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids

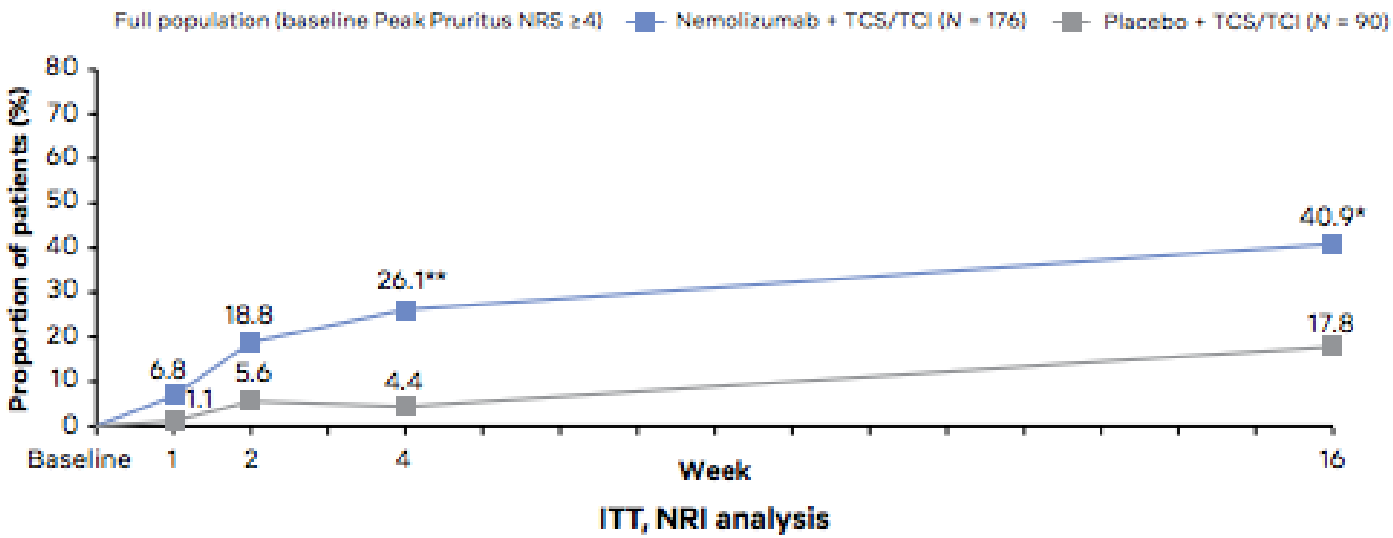
Weekly SD NRS and PP NRS score is calculated using 7 consecutive days diary data and set to missing if less than 4 days data available. Baseline value is the weekly score prior to first injection of study treatment of initial period.

For non-responder imputation, patients with data collected after use of rescue therapy or with missing data at a visit were considered non-responders. Strata adjusted *P*-values were from Cochran-Mantel-Haenszel test adjusting for the stratification variable study.

Percentages (%) are based on the number of patients in each treatment group (*N*).

Nemolizumab and Pruritus at Week 16

Figure 3. ≥4-Point Improvement from Baseline in Peak Pruritus NRS Score



Nemolizumab Safety

Table 2. Overall Summary of Treatment-Emergent Adverse Events

	Nemolizumab + TCS/TCI N=176	Placebo + TCS/TCI N=89
AEs or SAEs, *n* (%)		
Any TEAE	64 (36.4)	35 (39.3)
Any serious TEAE	3 (1.7)	1 (1.1)
Any serious TEAE related to study drug	1 (0.6)	0
Any TEAE leading to study discontinuation, *n* (%)	1 (0.6)	1 (1.1)
Any TEAE leading to death, *n* (%)	0	0
Any severe TEAE, *n* (%)	4 (2.3)	1 (1.1)
AESI, *n* (%)	16 (9.1)	3 (3.4)
Elevated ALT or AST (>3xULN) in combination with elevated bilirubin (>2xULN)	0	0
Peripheral edema: limbs, bilateral; facial edema	2 (1.1)	0
Infections	6 (3.4)	2 (2.2)
Newly diagnosed asthma or worsening of asthma	9 (5.1)	2 (2.2)
Injection-related reactions	0	0
TEAEs ≥5% (MedDRA Preferred Term), *n* (%)		
Dermatitis atopic	10 (5.7)	8 (9.0)

Table 3. Adverse Events of Interest in the Field of Atopic Dermatitis

	Nemolizumab + TCS/TCI N=176	Placebo + TCS/TCI N=89
Conjunctivitis allergic, *n* (%)	0	1 (1.1)
Nasopharyngitis, *n* (%)	9 (5.1)	2 (2.2)
COVID-19, *n* (%)	2 (1.1)	2 (2.2)
Upper respiratory tract infection, *n* (%)	5 (2.8)	3 (3.4)
Sinusitis, *n* (%)	2 (1.1)	1 (1.1)
Urinary tract infection, *n* (%)	0	0
Conjunctivitis, *n* (%)	1 (0.6)	0
Herpes infections, *n* (%)	2 (1.1)	0
Herpes zoster	1 (0.6)	0
Other Herpes infections*	1 (0.6)	3 (3.3)
Neoplasms benign, malignant and unspecified (including cysts and polyps), *n* (%)	0	0

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Thank you!