UPDATES IN THE TREATMENT OF *ATOPIC DERMATITIS*

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CHICAGO INTEGRATIVE ECZEMA CENTER

DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

Relationship	Manufacturer
Speaker	Regeneron/Sanofi Genzyme, Pfizer, Eli Lilly, LEO, Galderma, Incyte, L'Oreal
Advisory Board	Almirall, ASLAN Pharmaceuticals, Dermavant, Regeneron/Sanofi Genzyme, Pfizer, LEO Pharmaceuticals, AbbVie, Eli Lilly, Micreos, L'Oreal, Pierre-Fabre, Johnson & Johnson, Level Ex, KPAway, Unilever, Menlo Therapeutics, Theraplex, IntraDerm, Exeltis, AOBiome, Realm Therapeutics, Altus Labs, Galderma, Verrica, Arbonne, Amyris, Bodewell, YobeeCare, Burt's Bees, My-Or Diagnostics, Kimberly-Clark
Research	AOBiome, Regeneron/Sanofi Genzyme, and AbbVie
Patent Holder	Theraplex AIM (Patent Pending)
Stockholder	Micreos, YobeeCare, and Altus Labs, KPAway, LearnSkin

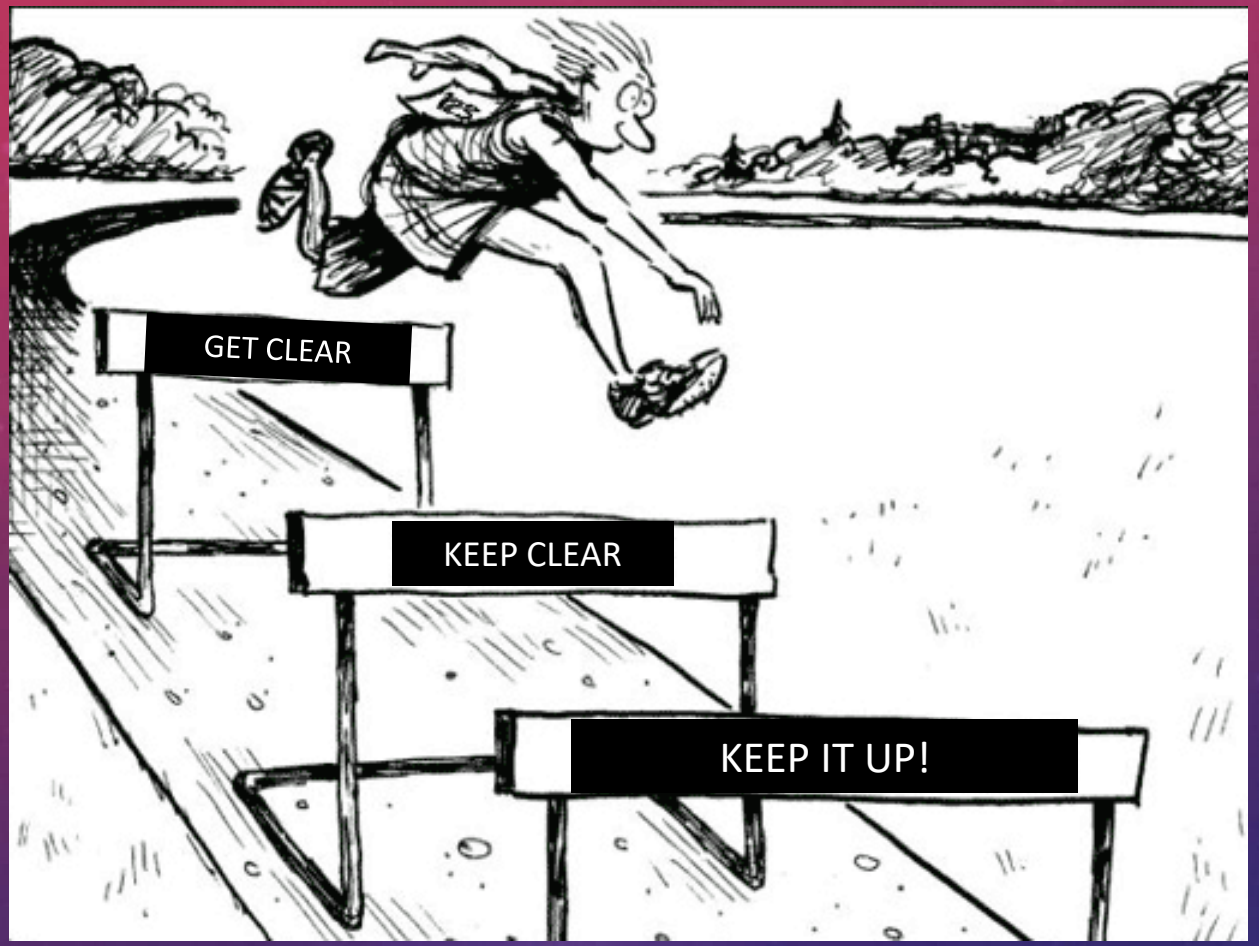
LEARNING OBJECTIVES

- Review the diagnosis and clinical management of atopic dermatitis with a focus on new treatment options.
- Become familiar with the role of biologics in the treatment of atopic dermatitis.
- Discuss the importance of a shared decision making approach to selection and evaluation of therapies with patients.

“Eczema has been rightly called the keystone of dermatology, and he who fully masters its management is not only skilled in regard to treating one of the most common and distressing of all cutaneous diseases, but has acquired a knowledge of the principles of dermatologic practice which will assist in the treatment of many, if not all, other maladies of the skin.”

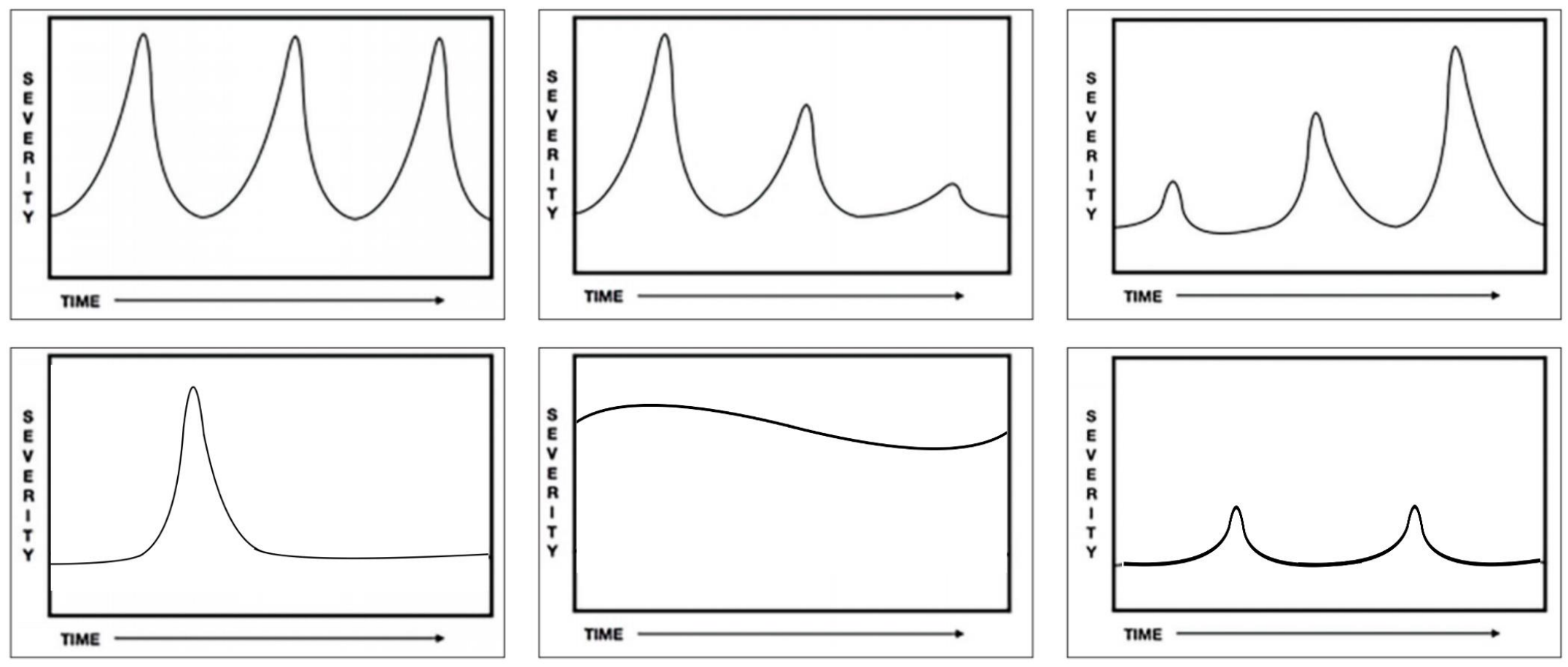
-L. Duncan Bulkley

Eczema and Its Management: A Practical Treatise Based on the Study of Three Thousand Cases of the Disease, 1881

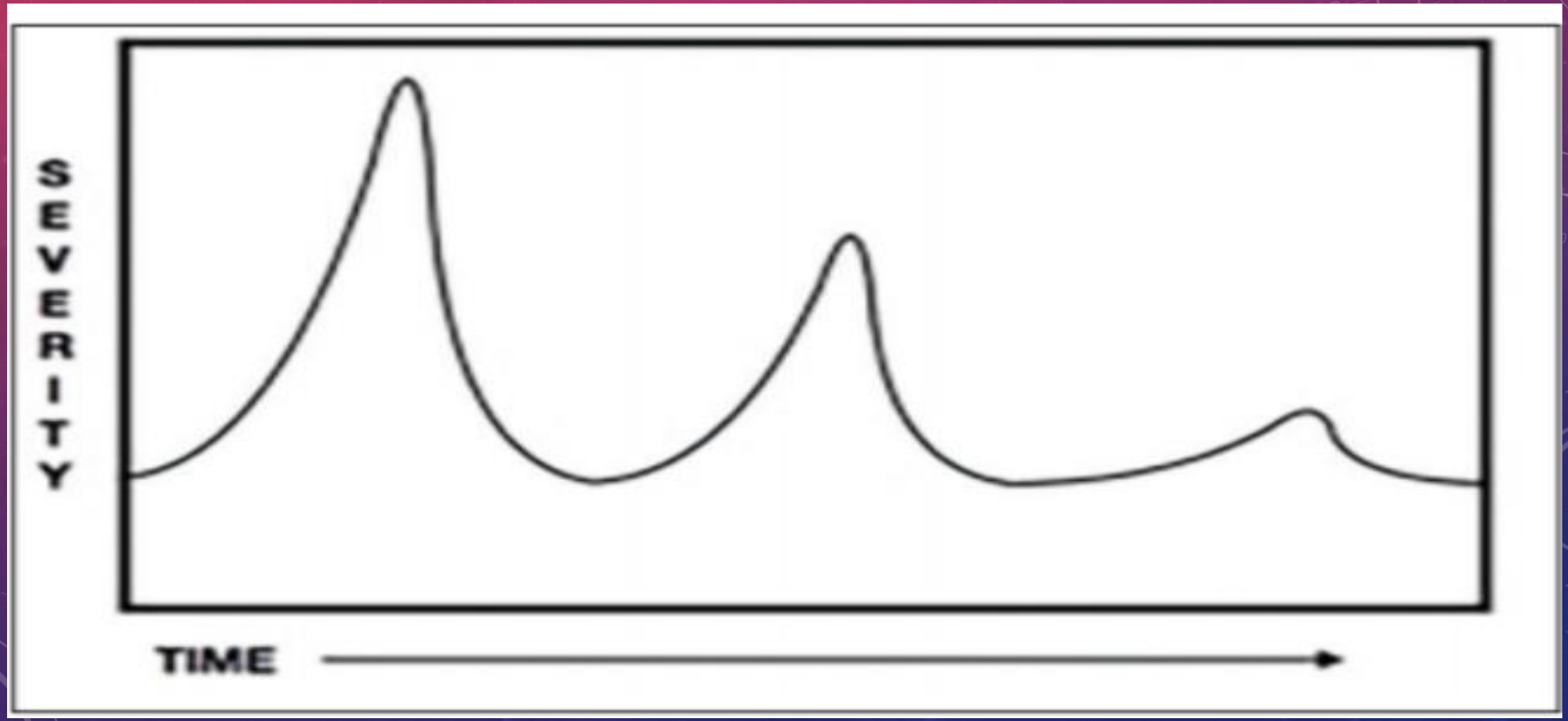


1) Get Clear
2) Keep Clear—Safely
3) Keep It Up

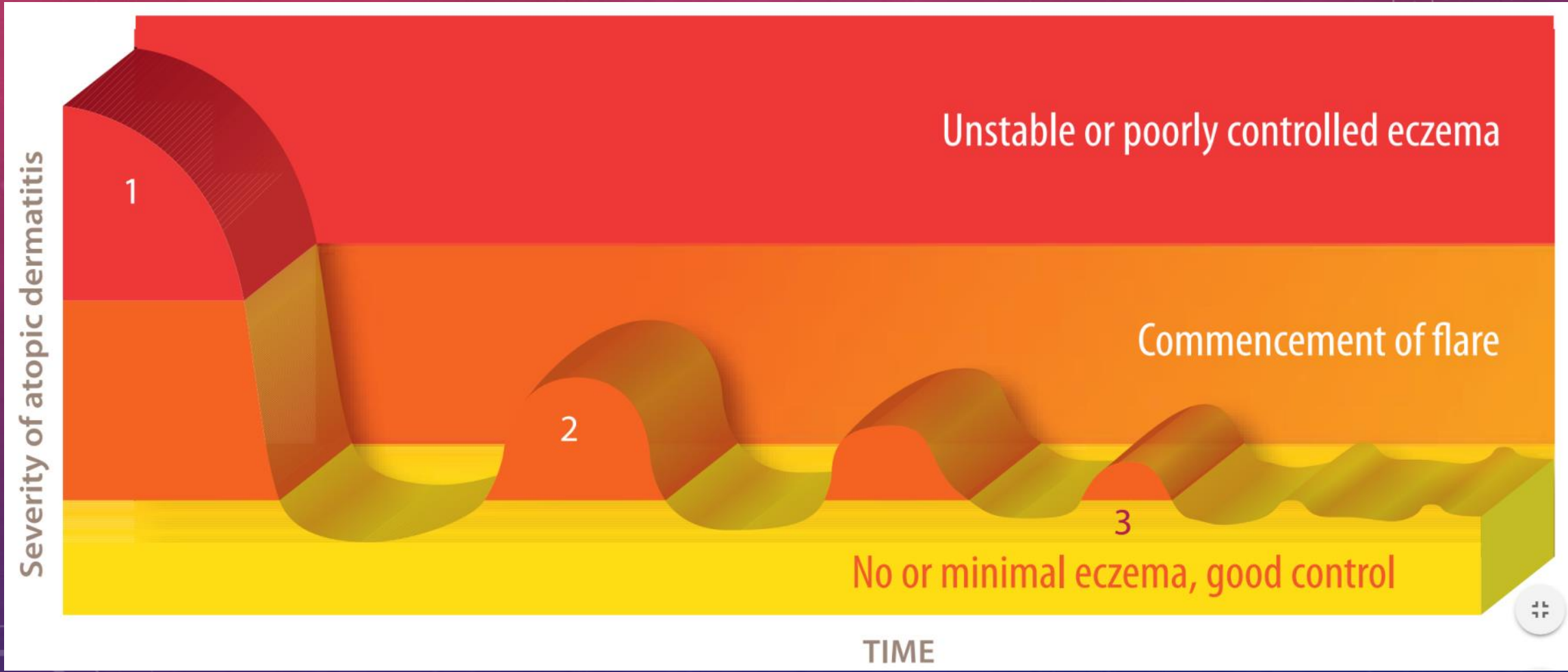
DIFFERENT PATTERNS



DIFFERENT PATTERNS

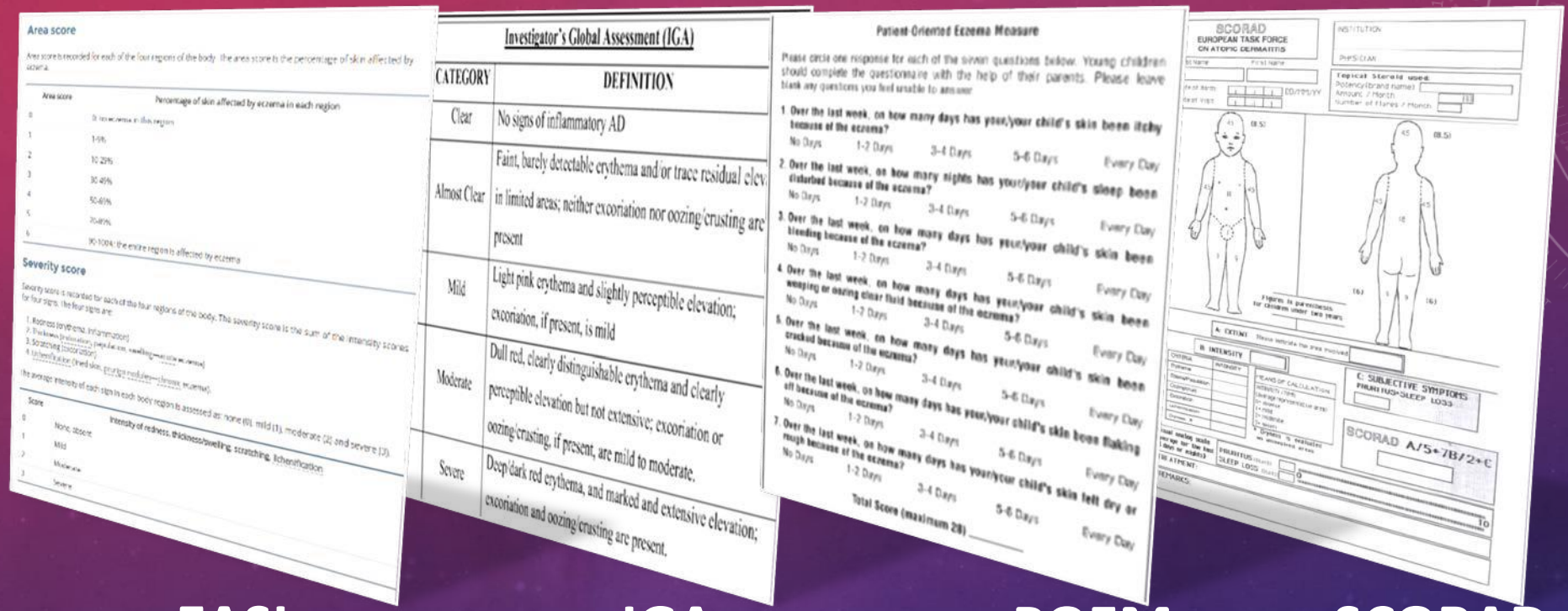


TREATMENT GOAL



Consensus guidelines for the management of atopic dermatitis: an Asia-Pacific perspective. Rubel D, Thirumoorthy T, Soebaryo RW, Weng SC, Gabriel TM, Villafuerte LL, Chu CY, Dhar S, Parikh D, Wong LC, Lo KK; Asia-Pacific Consensus Group for Atopic Dermatitis. J Dermatol. 2013 Mar;40(3):160-71.

VALIDATED SEVERITY ASSESSMENT TOOLS USED IN CLINICAL TRIALS



EASI
Eczema Area and Severity Index

IGA
Investigator's Global Assessment

POEM
Patient Oriented Eczema Measure

SCORAD
Scoring Atopic Dermatitis

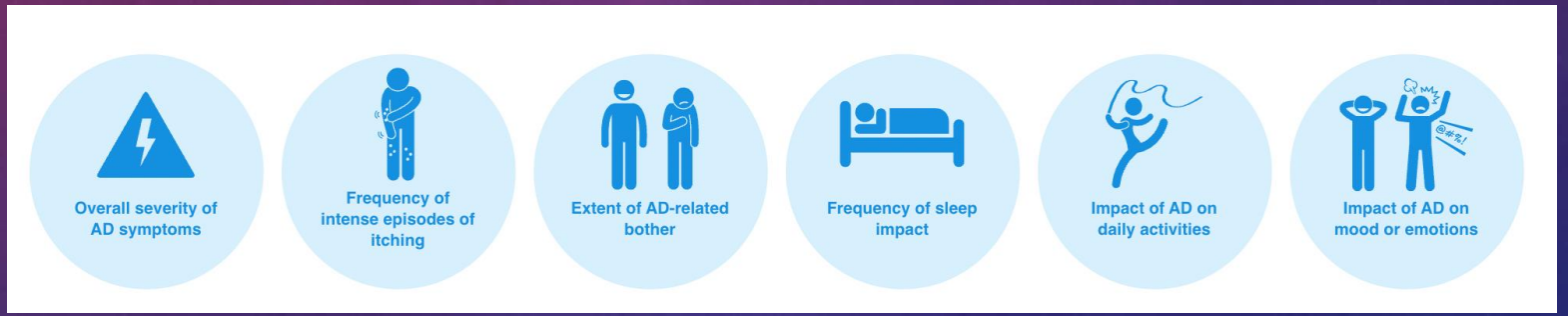
Hanifin JM, et al. *Exp Dermatol*. 2001;10:11-18.

Futamura M, et al. *J Am Acad Dermatol*. 2016;74:288-294.

Charman CR, et al. *Arch Dermatol*. 2004;140:1513-1519. Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. *Dermatology*. 1993;186:23-31.

VALIDATED IMPACT ASSESSMENT TOOL

- Atopic Dermatitis Control Tool (ADCT) – a validated, brief and easily scored patient self-assessment tool
- Six questions to evaluate the different dimensions of atopic dermatitis (AD) control identified as relevant by patients and clinicians
- ADCT can be self-administered by patients or used in routine consultations
- ADCT is designed to help facilitate meaningful patient-physician discussion on control of AD in every day clinical practice



https://www.adcontroltool.com/

Pariser DM, et al. Evaluating patient-perceived control of atopic dermatitis: design, validation, and scoring of the Atopic Dermatitis Control Tool (ADCT). Curr Med Res Opin (2019) doi:10.1080/03007995.2019.1699516

Simpson E, et al. Validation of the Atopic Dermatitis Control Tool (ADCT©) using a longitudinal survey of biologic-treated patients with atopic dermatitis. BMC Dermatol 19, 15 (2019) doi:10.1186/s12895-019-0095-3

ADCT

1. Over the last week, how would you rate your eczema-related symptoms?	(None) **0 points**	(Mild) **1 point**	(Moderate) **2 points**	(Severe) **3 points**	(Very Severe) **4 points**
2. Over the last week, how many days did you have intense episodes of itching because of your eczema?	(Not at all) **0 points**	(1-2 days) **1 point**	(3-4 days) **2 points**	(5-6 days) **3 points**	(Every day) **4 points**
3. Over the last week, how bothered have you been by your eczema?	(Not at all) **0 points**	(A little) **1 point**	(Moderately) **2 points**	(Very) **3 points**	(Extremely) **4 points**
4. Over the last week, how many nights did you have trouble falling or staying asleep because of your eczema?	(No nights) **0 points**	(1-2 nights) **1 point**	(3-4 nights) **2 points**	(5-6 nights) **3 points**	(Every night) **4 points**
5. Over the last week, how much did your eczema affect your daily activities?	(Not at all) **0 points**	(A little) **1 point**	(Moderately) **2 points**	(A lot) **3 points**	(Extremely) **4 points**
6. Over the last week, how much did your eczema affect your mood or emotions?	(Not at all) **0 points**	(A little) **1 point**	(Moderately) **2 points**	(A lot) **3 points**	(Extremely) **4 points**

Step 3: Speak to your doctor about how your AD affects your day-to-day life

Your AD may not be well controlled if:

- **Your ADCT total score is at least 7 points**
  OR
- **One of your answers falls in a blue coloured box of the ADCT table above**
  OR
- **Your ADCT total score has increased by 5 points or more since you last used ADCT**

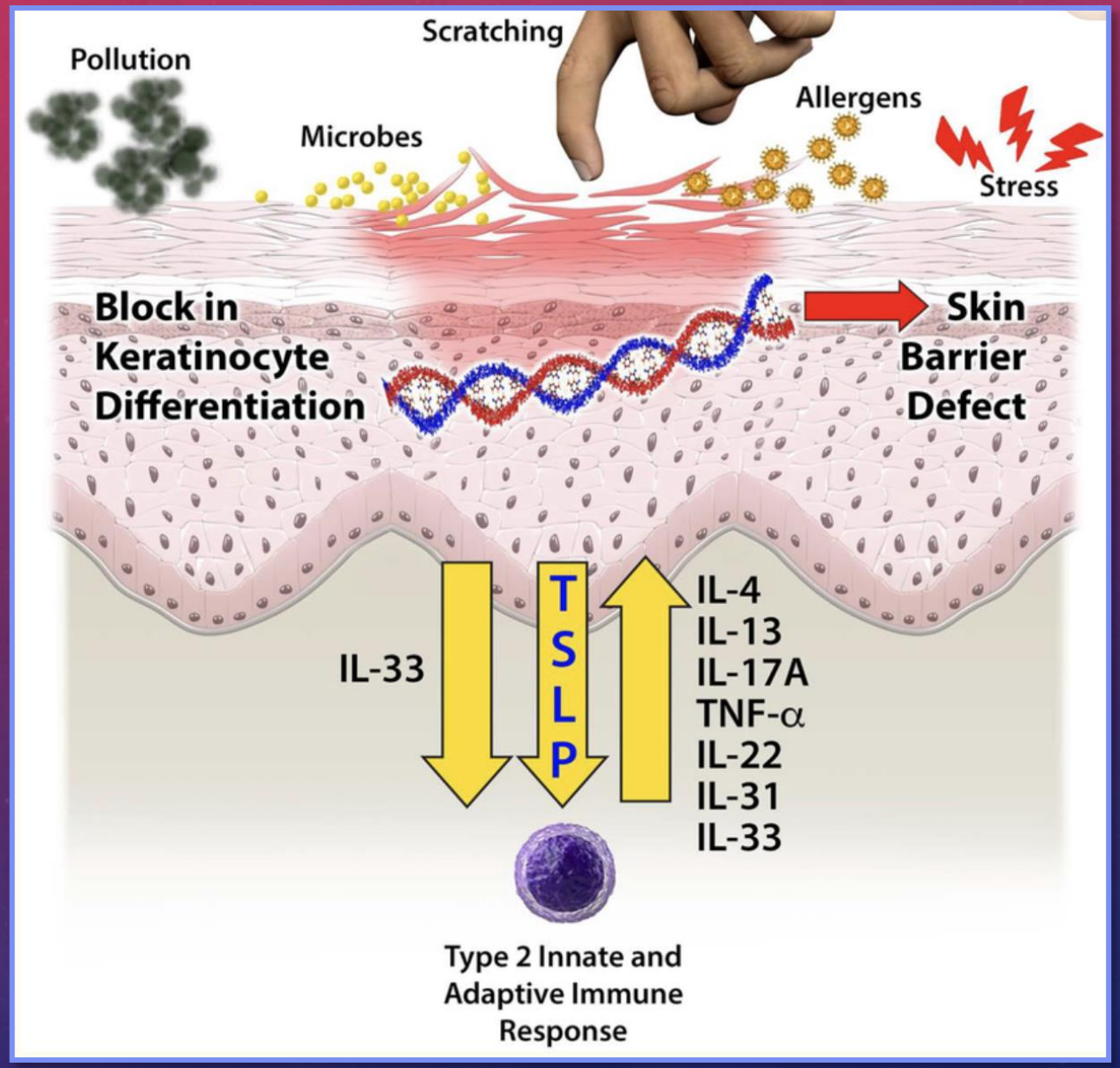
✓ If you are concerned that your AD may not be well controlled, you should seek medical advice
✓ Bring your completed ADCT with you for your next scheduled consultation
✓ Speak to your doctor about your responses to the ADCT questions and how your AD is affecting you

https://www.adcontroltool.com/

Pariser DM, et al. Evaluating patient-perceived control of atopic dermatitis: design, validation, and scoring of the Atopic Dermatitis Control Tool (ADCT). Curr Med Res Opin (2019) doi:10.1080/03007995.2019.1699516

Simpson E, et al. Validation of the Atopic Dermatitis Control Tool (ADCT©) using a longitudinal survey of biologic-treated patients with atopic dermatitis. BMC Dermatol 19, 15 (2019) doi:10.1186/s12895-019-0095-3

FACTORS CONTRIBUTING TO AD



Leung DYM, et al. *J Allergy Clin Immunol.* 2020;145:1485-1497.

The New European (EADV/EDF) Guidelines for the Management of AD

Treatment recommendation for atopic eczema: adult

- For every phase, *additional* therapeutic options should be considered
- Add antiseptics / antibiotics in cases of superinfection
- Consider compliance and diagnosis, if therapy has insufficient effect
- Refer to guideline text for restrictions, especially for treatment marked with [1]
- Licensed indication are marked with [2], off-label treatment options are marked with [3]

SEVERE: SCORAD >50 / or persistent eczema	Hospitalization; systemic immunosuppression: cyclosporine A [2], short course of oral glucocorticosteroids [2], dupilumab [1,2], methotrexate [3], azathioprin [3], mycophenolate mofetil [3]; PUVA [1]; alitretinoin [1,3]
MODERATE: SCORAD 25-50 / or recurrent eczema	Proactive therapy with topical tacrolimus [2] or class II or class III topical glucocorticosteroids [3], wet wrap therapy, UV therapy (UVB 311 nm, medium dose UVA1), psychosomatic counseling, climate therapy
MILD: SCORAD <25 / or transient eczema	Reactive therapy with topical glucocorticosteroids class II [2] or depending on local cofactors: topical calcineurin inhibitors [2], antiseptics incl. silver [2], silver coated textiles [1]
BASELINE: Basic therapy	Educational programmes, emollients, bath oils, avoidance of clinically relevant allergens (encasings, if diagnosed by allergy tests)

Wollenberg A, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. Journal of the European Academy of Dermatology and Venereology. 2018 Jun;32(6):850-78.

ECZEMA ACTION PLAN

<u>When flaring (itchy, red, oozing)</u>

AM
1. Apply mometasone to the eczema areas
2. Apply moisturizer liberally

PM
1. Wash with gentle cleanser
2. Apply mometasone to the eczema areas
3. Apply moisturizer liberally
4. Apply damp layer, then dry layer (“wet wrap”)

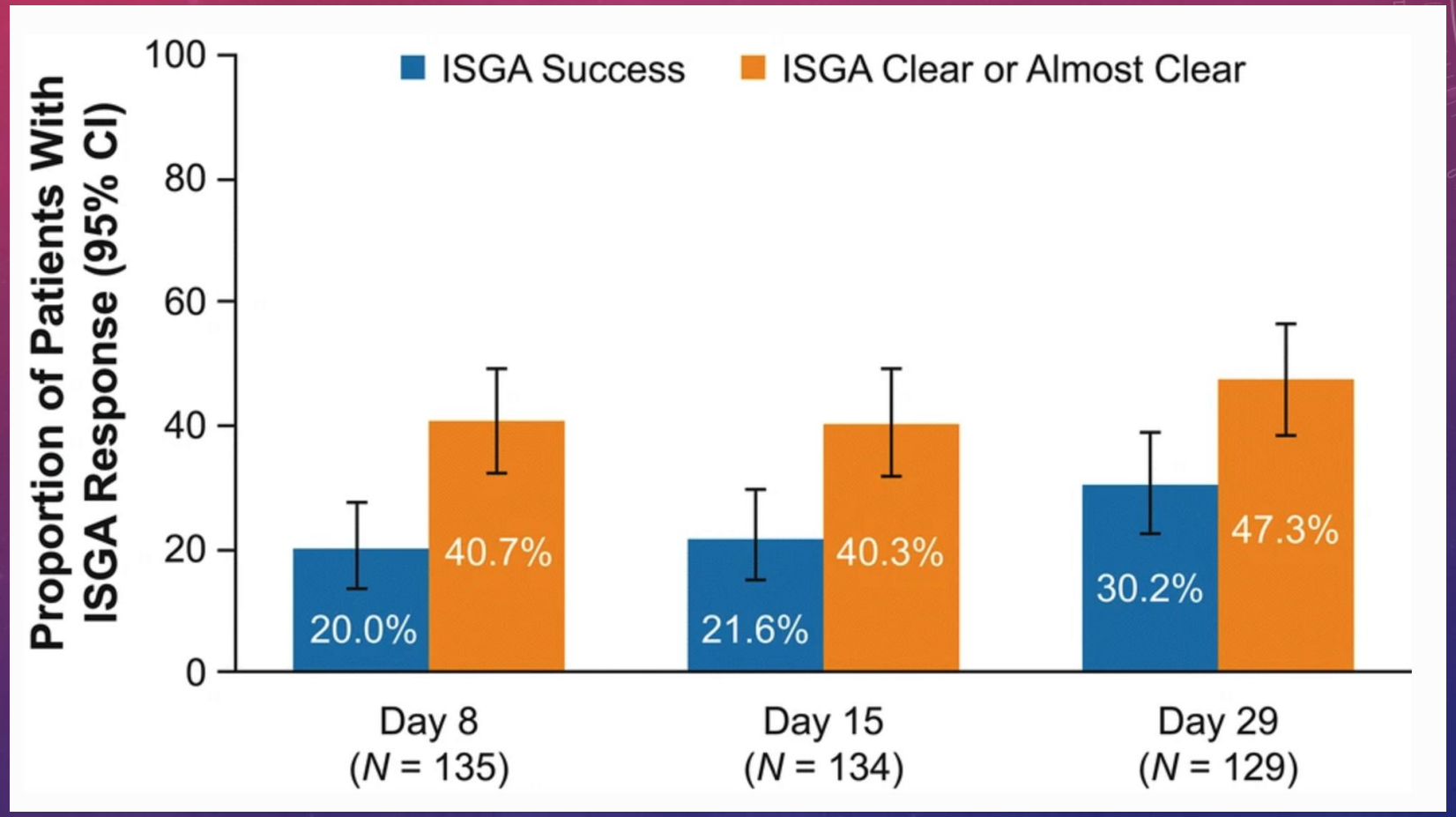
****Do this for several days (up to 1 week) until better…****

<u>Once better</u>

AM
1. Apply tacrolimus ointment to remaining areas/trouble spots
2. Apply moisturizer liberally

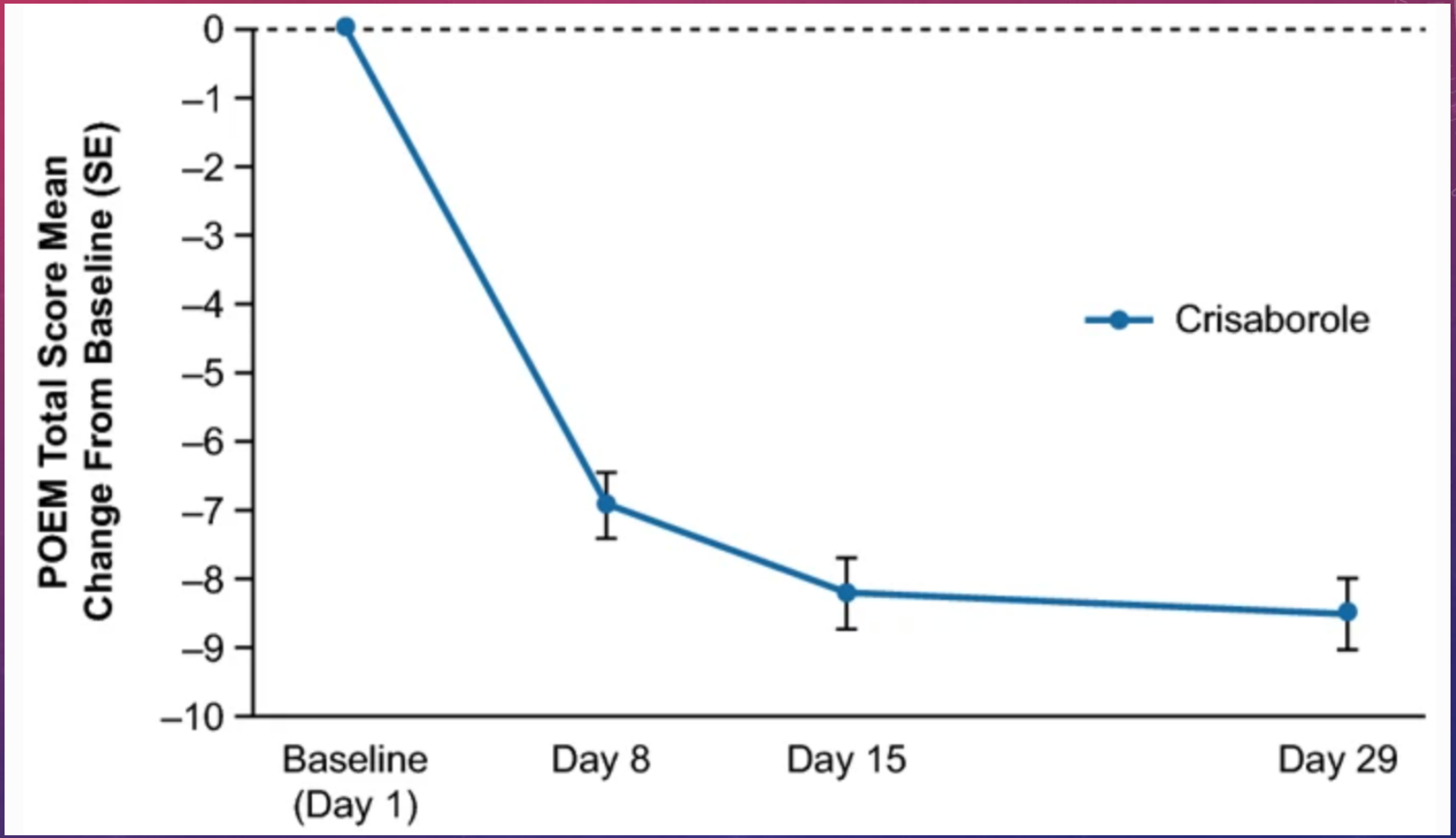
PM
1. Wash with gentle cleanser
2. Apply tacrolimus ointment to remaining areas/trouble spots
3. Apply moisturizer liberally

2020: CRISABOROLE APPROVED DOWN TO 3 MONTHS OF AGE



Schlessinger J, Shepard JS, Gower R, et al. Safety, Effectiveness, and Pharmacokinetics of Crisaborole in Infants Aged 3 to < 24 Months with Mild-to-Moderate Atopic Dermatitis: A Phase IV Open-Label Study (CrisADe CARE 1). *Am J Clin Dermatol*. 2020;21(2):275-284. [15]

2020: CRISABOROLE APPROVED DOWN TO 3 MONTHS OF AGE



Schlessinger J, Shepard JS, Gower R, et al. Safety, Effectiveness, and Pharmacokinetics of Crisaborole in Infants Aged 3 to < 24 Months with Mild-to-Moderate Atopic Dermatitis: A Phase IV Open-Label Study (CrisADe CARE 1). Am J Clin Dermatol. 2020;21(2):275-284.

WHEN TO USE SYSTEMIC THERAPY
INTERNATIONAL ECZEMA COUNCIL PANEL RECOMMENDATIONS

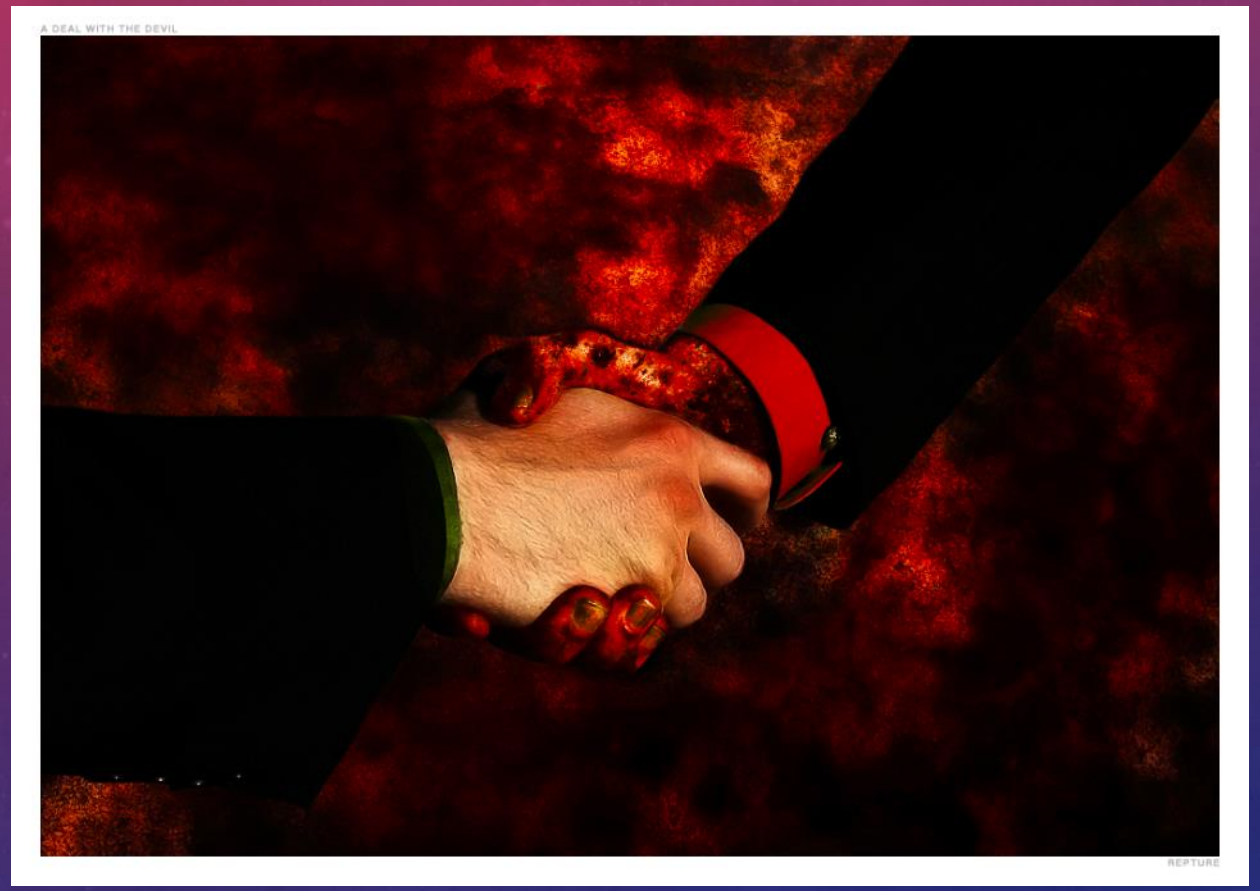
If aggressive topical therapy is not achieving adequate control of the disease

AND

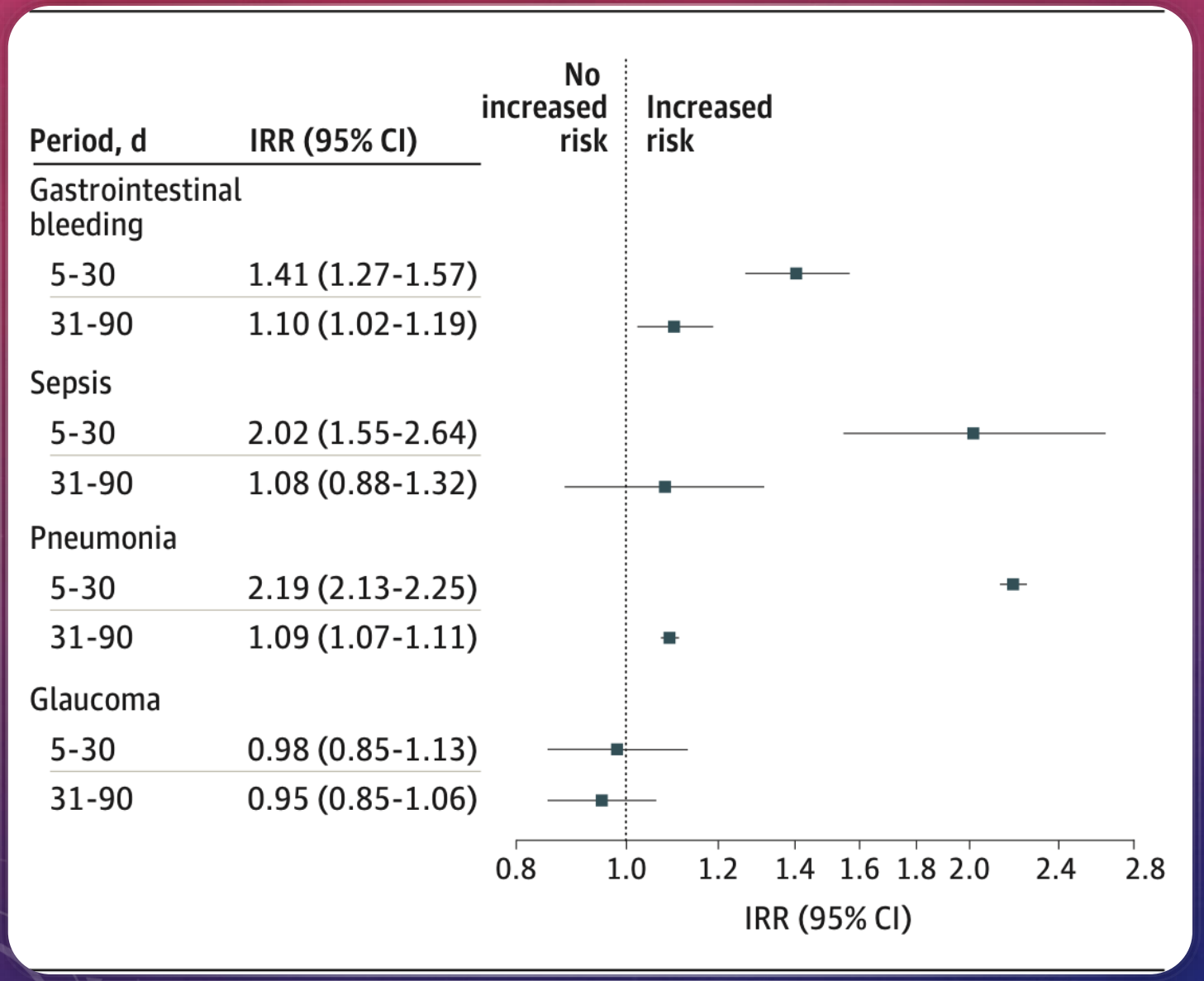
- Adequate education delivered
- Infection addressed
- Large impact on QoL
- Diagnosis *reconsidered*, eg, cutaneous T-cell lymphoma or allergic contact dermatitis
- Phototherapy considered

Simpson EL, et al. *J Am Acad Dermatol*. 2017;77:623-633.

PREDNISONE?



ASSOCIATION BETWEEN EXPOSURE TO CORTICOSTEROID BURSTS AND ADVERSE OUTCOMES



Yao TC, Wang JY, Chang SM, Chang YC, Tsai YF, Wu AC, Huang JL, Tsai HJ. Association of Oral Corticosteroid Bursts With Severe Adverse Events in Children. JAMA pediatrics. 2021 Apr 19.

ASSOCIATION BETWEEN EXPOSURE TO CORTICOSTEROID BURSTS AND ADVERSE OUTCOMES

"Treatment with corticosteroid bursts is associated with a 1.4- to 2.2-fold increased risk of GI bleeding, sepsis, and pneumonia within the first month after initiation of corticosteroid therapy among children.

Clinicians should be aware of these rare but potentially serious adverse events associated with use of corticosteroid bursts for children, particularly during the first month after corticosteroid initiation."

Yao TC, Wang JY, Chang SM, Chang YC, Tsai YF, Wu AC, Huang JL, Tsai HJ. Association of Oral Corticosteroid Bursts With Severe Adverse Events in Children. JAMA pediatrics. 2021 Apr 19.

SYSTEMIC TREATMENT OPTIONS

- Dupilumab/Tralokinumab
- Cyclosporine*
- Phototherapy
- Methotrexate*
- Mycophenolate mofetil*
- Azathioprine*

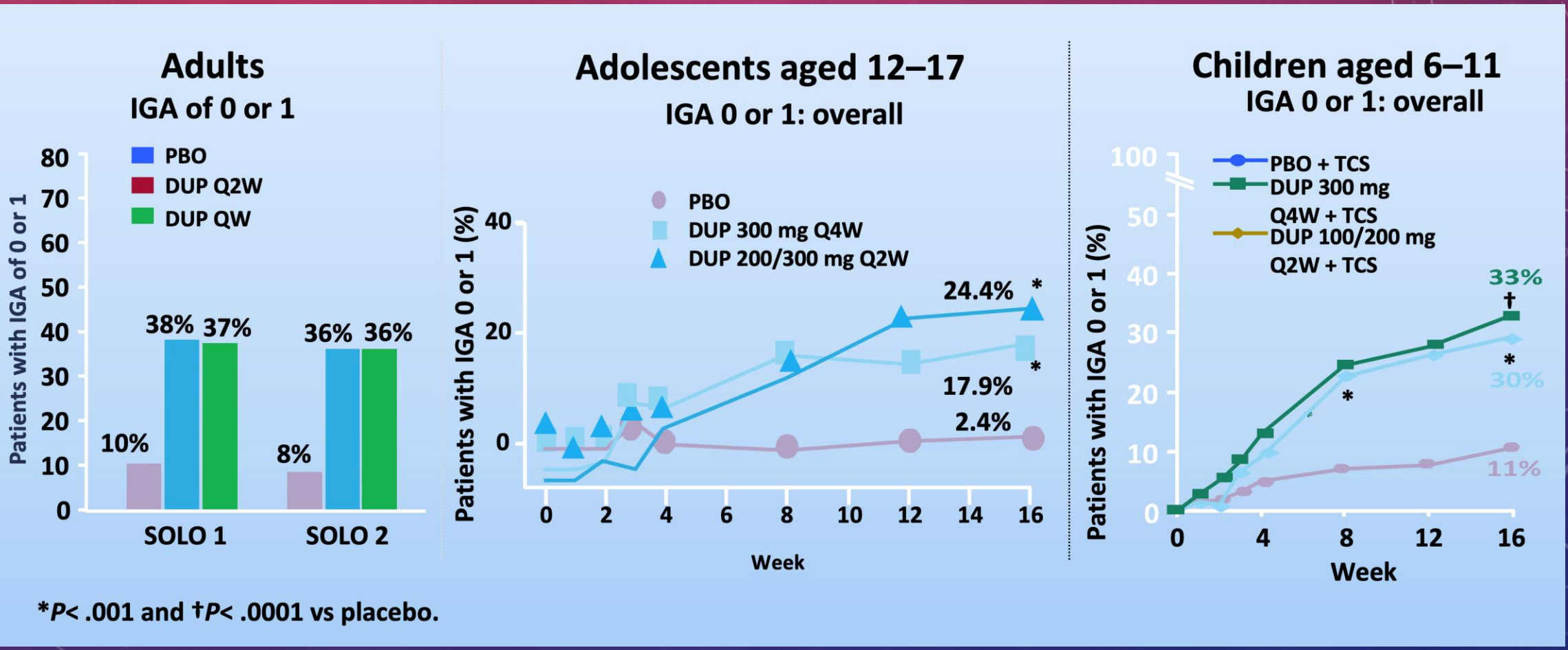
Dupilumab is FDA-approved for AD in patients aged ≥6 years; Tralokinumab is approved for ≥18

Sidbury R, et al. *J Am Acad Dermatol*. 2014;71:327-349. Boguniewicz M, et al. *Ann Allergy Asthma Immunol*. 2018;120:10-22.e2. Dupilumab (Dupixent®) PI 2021 (www.accessdata.fda.gov/drugsatfda_docs/label/2020/761055s020lbl.pdf). Accessed 10/27/2021.

DUPILUMAB

- A human monoclonal antibody against IL-4 receptor alpha
- Inhibits signaling of IL-4 and IL-13
- FDA approved for moderate-severe AD in ages 6 and up
- Injected SC every 2-4 weeks

DUPILUMAB: IGA IMPROVEMENTS IN 3 AGE COHORTS



1. Simpson EL, et al. *N Engl J Med*. 2016;375:2335-2348. 2. Simpson EL, et al. *JAMA Dermatol*. 2020;156:44-56. 3. Paller AS, et al. *J Am Acad Dermatol*. 2020;83:1282-1293.

SAFETY IN 6-12 AGE GROUP

n (%)	Placebo + TCS (n = 120)	Dupilumab 300 mg q4w + TCS (n = 120)	Dupilumab 100 mg or 200 mg q2w + TCS (n = 122)
Patients with ≥ 1 TEAE	88 (73.3)	78 (65.0)	82 (67.2)
Patients with ≥ 1 serious TEAE	2 (1.7)	2 (1.7)	0
Patients with ≥ 1 TEAE leading to permanent treatment discontinuation	2 (1.7)	0	2 (1.6)
Deaths	0	0	0
TEAEs (PT) reported in ≥ 5% of patients			
Dermatitis atopic, exacerbation	17 (14.2)	8 (6.7)	10 (8.2)
Asthma	12 (10.0)	2 (1.7)	4 (3.3)
Nasopharyngitis	8 (6.7)	15 (12.5)	8 (6.6)
Upper respiratory tract infection	12 (10.0)	13 (10.8)	10 (8.2)
Viral upper respiratory tract infection	6 (5.0)	2 (1.7)	1 (0.8)
Vomiting	8 (6.7)	6 (5.0)	6 (4.9)
Cough	9 (7.5)	3 (2.5)	5 (4.1)
Headache	10 (8.3)	6 (5.0)	7 (5.7)

Baseline weight < 30 kg	Placebo + TCS (n = 60)	Dupilumab 300 mg q4w + TCS (n = 60)	Dupilumab 100 mg q2w + TCS (n = 63)
Patients with ≥ 1 TEAE, n (%)	43 (71.7)	39 (65.0)	46 (73.0)
TEAEs (PT), n (%)			
Dermatitis atopic	7 (11.7)	4 (6.7)	8 (12.7)
Asthma	7 (11.7)	0	4 (6.3)
Rhinitis allergic	2 (3.3)	1 (1.7)	3 (4.8)
Food allergy	0	1 (1.7)	3 (4.8)
Conjunctivitis cluster[a]	2 (3.3)	4 (6.7)	13 (20.6)
Herpes infections (HLT)	3 (5.0)	0	3 (4.8)
Baseline weight ≥ 30 kg	**Placebo + TCS (n = 60)**	**Dupilumab 300 mg q4w + TCS (n = 60)**	**Dupilumab 200 mg q2w + TCS (n = 59)**
Patients with ≥ 1 TEAE, n (%)	45 (75.0)	39 (65.0)	36 (61.0)
TEAEs (PT), n (%)			
Dermatitis atopic	10 (16.7)	4 (6.7)	2 (3.4)
Asthma	5 (8.3)	2 (3.3)	0
Rhinitis allergic	3 (5.0)	2 (3.3)	1 (1.7)
Food allergy	0	0	0
Conjunctivitis cluster[a]	3 (5.0)	4 (6.7)	5 (8.5)
Herpes infections (HLT)	3 (5.0)	2 (3.3)	1 (1.7)

Paller AS, et al. Poster 215. Presented at the Revolutionizing Atopic Dermatitis (RAD) Conference 2020.

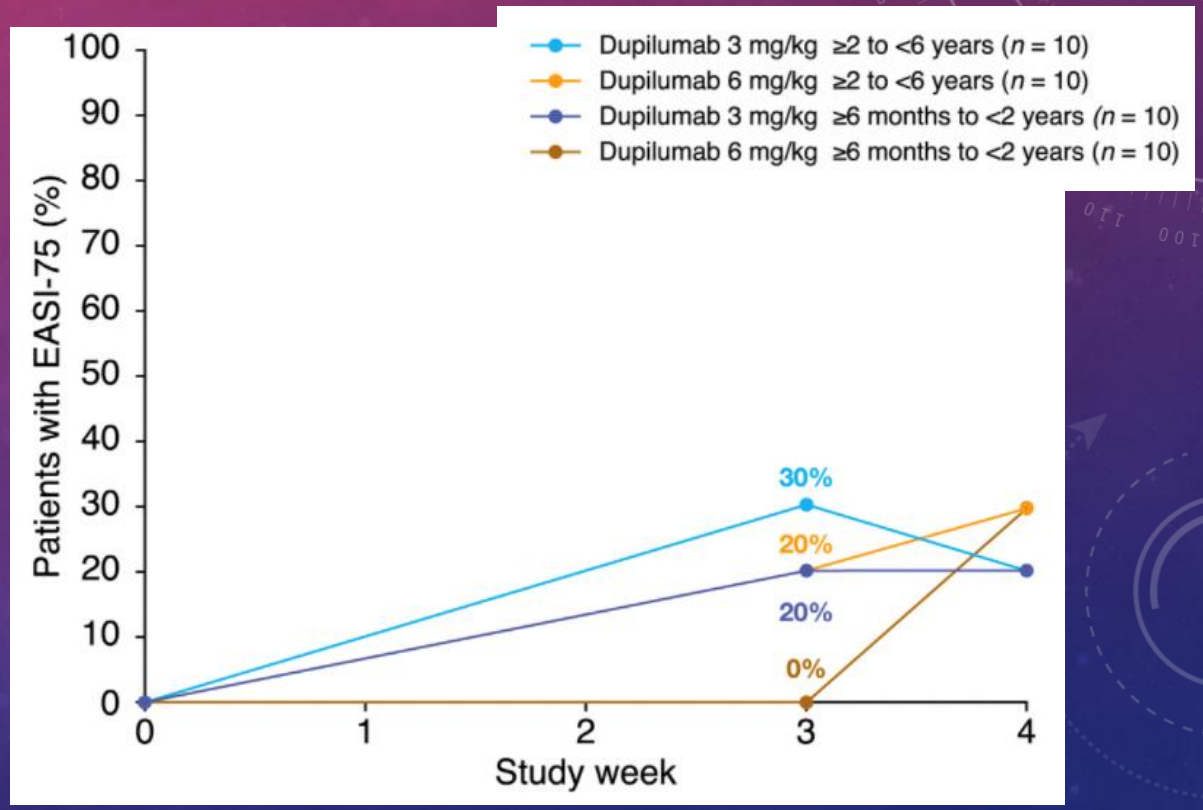
LIBERTY AD PRESCHOOL

- Phase 2, open-label study of single-dose dupilumab in 40 children aged 6 months to <6 years with severe AD

At week 3:

Reduced mean **EASI score** by **−44.6%** & **−49.7%** *(older cohort)* and **−42.7%** & **−38.8%** *(younger cohort)*

Reduced mean **PP-NRS scores** by **−22.9%** & **−44.7%** *(older cohort)* and **−11.1%** & **−18.2%** *(younger cohort)*

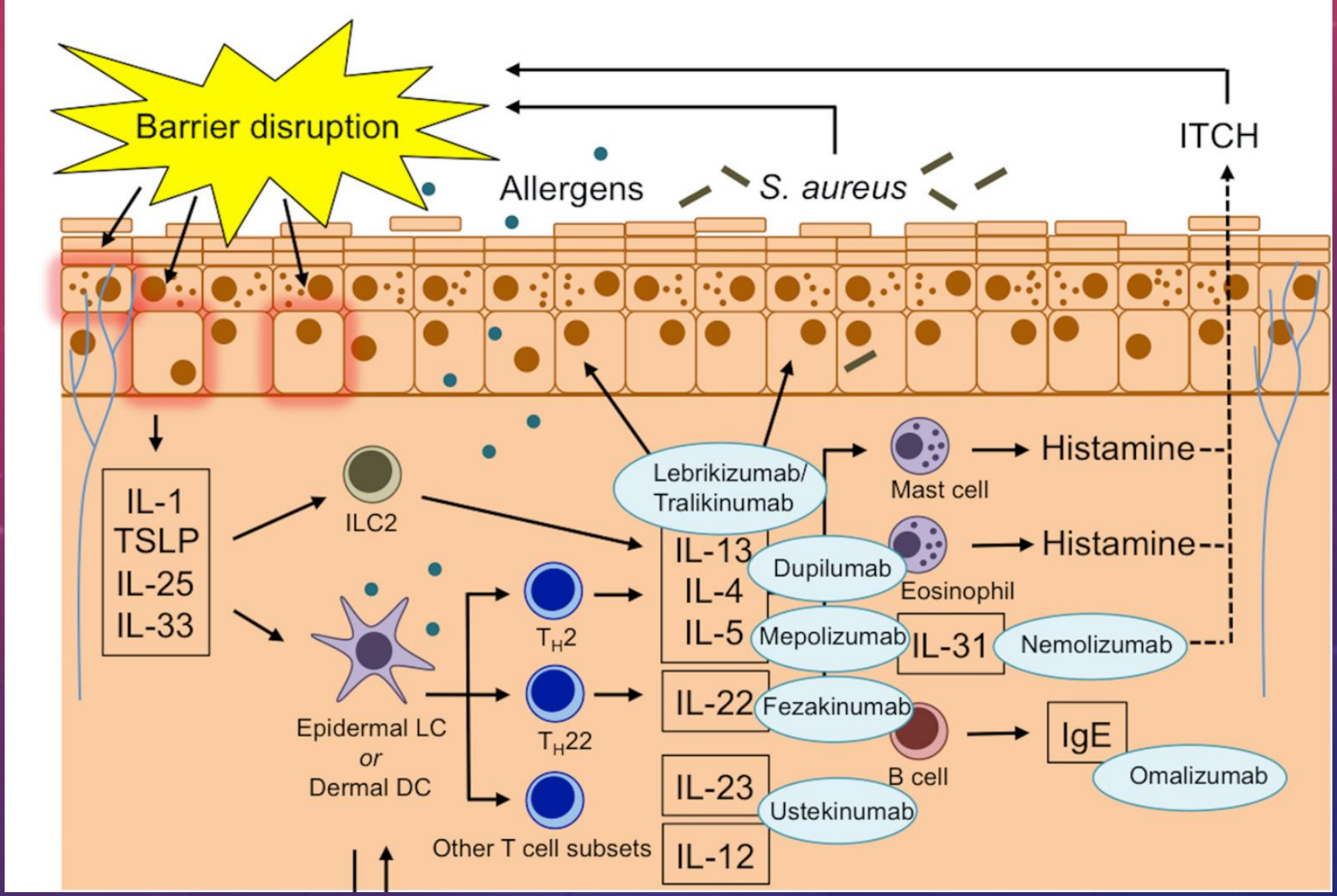


Paller AS, Siegfried EC, Simpson EL, et al. A phase 2, open-label study of single-dose dupilumab in children aged 6 months to< 6 years with severe uncontrolled atopic dermatitis: pharmacokinetics, safety and efficacy. Journal of the European Academy of Dermatology and Venereology. 2021 Feb;35(2):464-75.

LIBERTY AD PRESCHOOL

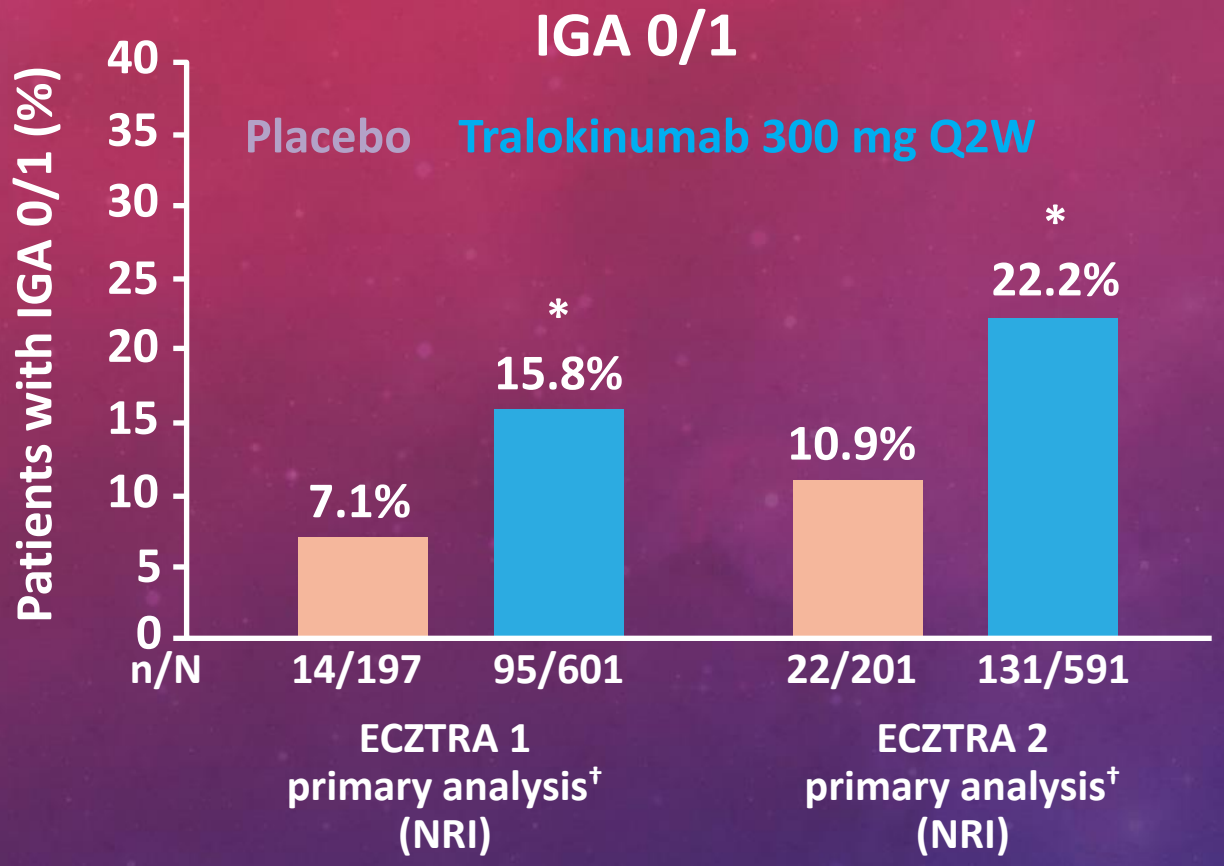
- *“The safety profile of dupilumab in children aged ≥6 months to <6 years was comparable to that seen in adults, adolescents and children >6 years. There were no dupilumab-related events of serious infection or systemic hypersensitivity.”*

Paller AS, Siegfried EC, Simpson EL, et al. A phase 2, open-label study of single-dose dupilumab in children aged 6 months to< 6 years with severe uncontrolled atopic dermatitis: pharmacokinetics, safety and efficacy. Journal of the European Academy of Dermatology and Venereology. 2021 Feb;35(2):464-75.



Alexander H, Patton T, Jabbar-Lopez ZK, Manca A, Flohr C. Novel systemic therapies in atopic dermatitis: what do we need to fulfil the promise of a treatment revolution? F1000Res. 2019 Jan 31;8:F1000 Faculty Rev-132. doi: 10.12688/f1000research.17039.1. PMID: 30774935

TRALOKINUMAB (ANTI–IL-13): IGA 0/1 AT WEEK 16



Approved on 12/28/21 in the US

- Blocks IL-13 cytokine
- Q2W Dosing
- Common AE: conjunctivitis
- Improved efficacy beyond week 16 with Q4W dosing possible for some patients

****P*< .01 vs placebo. †Use of rescue medication considered as nonresponse; missing data imputed as nonresponse.**

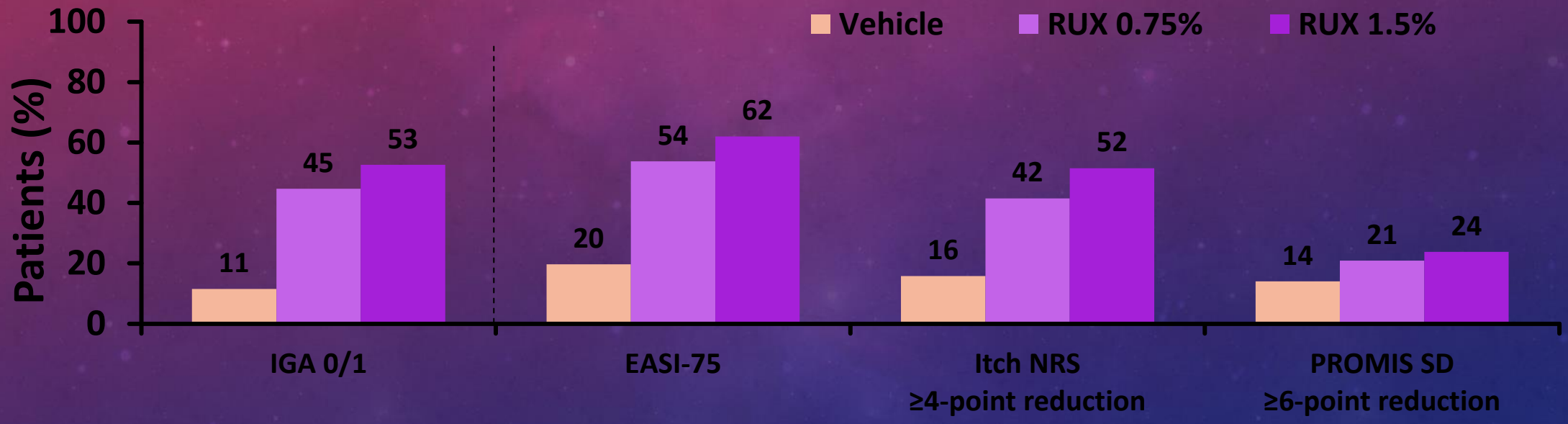
NRI = non-responder imputation.

- 1. Simpson E, et al. AAD virtual meeting experience (VMX). 2020 (https://jofskin.org/index.php/skin/article/view/1066/pdf).
- 2. Weidinger S, et al. AAD VMX. 2020 (https://jofskin.org/index.php/skin/article/view/ 1079/pdf). Accessed 10/27/2021.

TOPICAL JAK INHIBITOR: RUXOLITINIB

Approved on 9/21/21 in the US

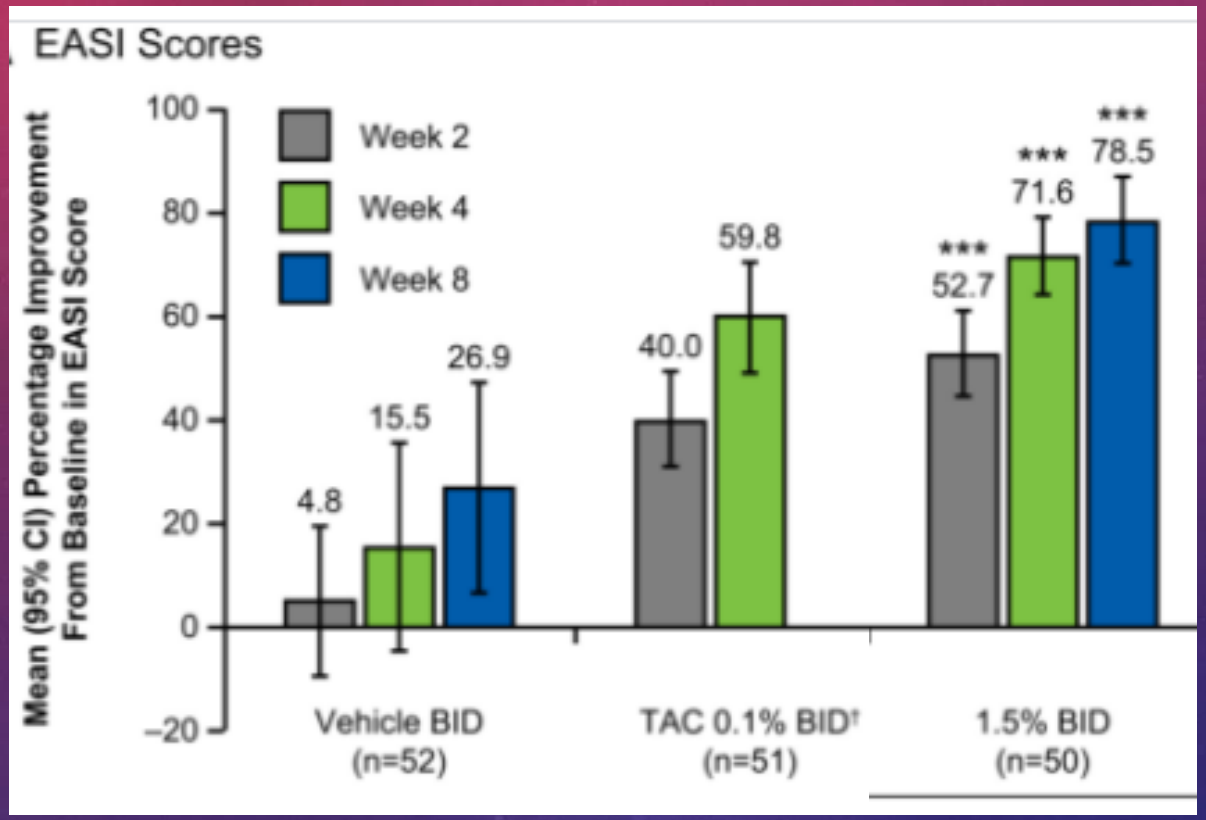
- Well tolerated with minimal application-site reactions in phase 3 study
- No treatment-related AEs (and all TEAEs mild-to-moderate)
- Itch reduction within 1st day of use



AE = adverse event; JAK = Janus kinase; NRS = numerical rating scale; PROMIS SD = Patient-Reported Outcomes Measurement Information System Sleep Disturbance; RUX = ruxolitinib.

Papp K, et al. *J Am Acad Dermatol*. 2021;85:863-872. Ruxolitinib (Opzelura™) PI 9/2021 (www.opzelura.com/prescribing-information.pdf). Accessed 10/27/2021.

TREATMENT OF AD WITH RUXOLITINIB CREAM OR TRIAMCINOLONE CREAM



Kim BS, Howell MD, Sun K, et al. *J Allergy Clin Immunol*. 2020;145(2):572-582. doi:10.1016/j.jaci.2019.08.042

RUXOLITINIB SAFETY

INDICATIONS AND USAGE

OPZELURA is a Janus kinase (JAK) inhibitor indicated for the topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. (1)

Limitation of Use

Use of OPZELURA in combination with therapeutic biologics, other JAK inhibitors or potent immunosuppressants such as azathioprine or cyclosporine is not recommended. (1)

DOSAGE AND ADMINISTRATION

- Apply a thin layer twice daily to affected areas of up to 20% body surface area. Do not use more than 60 grams per week. (2)
- For topical use only. (2)
- Not for ophthalmic, oral, or intravaginal use. (2)

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE), AND THROMBOSIS

See full prescribing information for complete boxed warning.

- **Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving Janus kinase inhibitors for inflammatory conditions. (5.1)**
- **Higher rate of all-cause mortality, including sudden cardiovascular death have been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. (5.2)**
- **Lymphoma and other malignancies have been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. (5.3)**
- **Higher rate of MACE (including cardiovascular death, myocardial infarction, and stroke) has been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. (5.4)**
- **Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis, some fatal, have occurred in patients treated with Janus kinase inhibitors for inflammatory conditions. (5.5)**

WARNINGS AND PRECAUTIONS

- *Serious Infections:* Serious bacterial, mycobacterial, fungal and viral infections have occurred. Regularly monitor patients for infection and manage it promptly. (5.1)
- *Non-melanoma Skin Cancers.* Basal cell and squamous cell carcinoma have occurred. Perform periodic skin examinations during treatment and following treatment as appropriate. (5.3)
- *Thrombosis.* Thromboembolic events have occurred. (5.5)
- *Thrombocytopenia, Anemia and Neutropenia:* Thrombocytopenia, anemia and neutropenia have occurred. Perform CBC monitoring as clinically indicated (5.6).

ADVERSE REACTIONS

- The most common adverse reactions (incidence ≥1%) are nasopharyngitis, diarrhea, bronchitis, ear infection, eosinophil count increased, urticaria, folliculitis, tonsillitis, and rhinorrhea. (6)

DRUGS IN THE PIPELINE

RECENT DRUGS AND PIPELINE: SELECTED AGENTS

	Drug Name	Target	Status
Topicals	Crisaborole (Eucrisa)	PDE4	FDA approved for ages 2 years and up (2016) FDA approved for ages 3 months and up (2020)
	Roflumilast	PDE4	Phase 2a
	Tofacitinib	JAK1, JAK3	Phase 2a
	Delgocitinib	JAK1, JAK2, JAK3 and tyrosine kinase 2	Phase 1 in USA, Phase 3 in Japan
	Ruxolitinib	JAK1, JAK2	Phase 3
	Tapinarof	Aryl hydrocarbon receptor (AhR)	Phase 2b
Systemic small molecules	Upadacitinib	JAK1	Phase 3
	Abrocitinib	JAK1	Phase 3
	Baricitinib	JAK1, JAK2	Phase 3
Biologics	Dupilumab (Dupixent)	IL-4/IL-13 Receptors	FDA approved for ages 18 years and up (2017) FDA approved for ages 12-17 years (2019) FDA approved for ages 6-11 years (2020)
	Lebrikizumab	IL-13	Phase 3
	Tralokinumab	IL-13	Phase 3
	Nemolizumab	IL-31 Receptor A	Phase 3

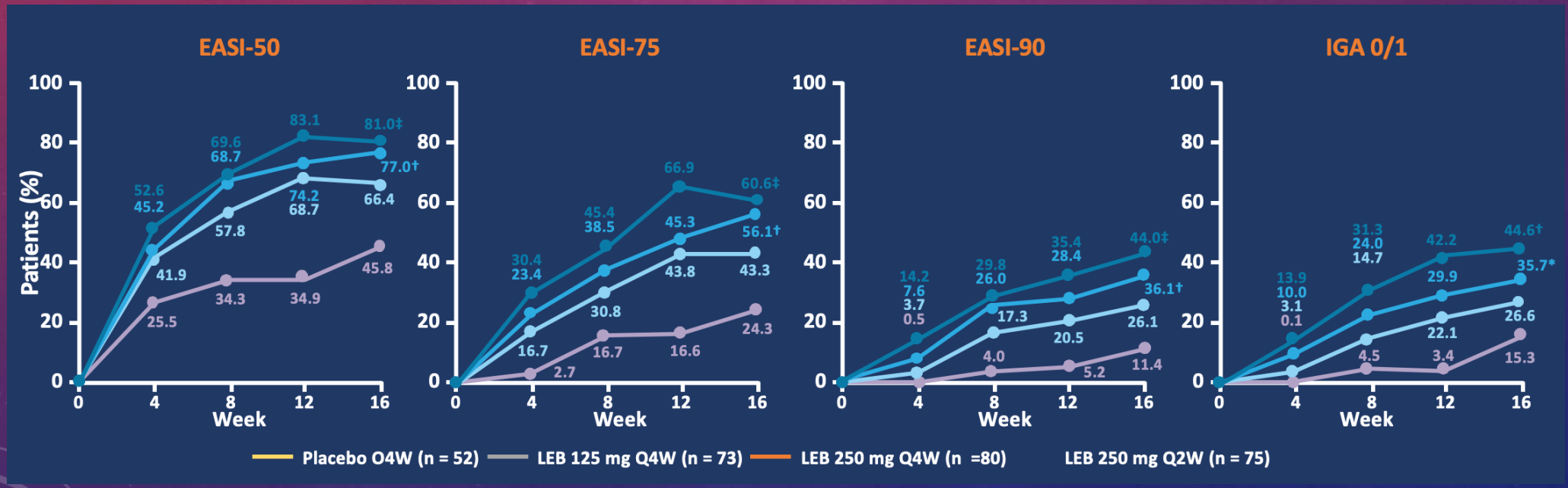
From: Lio P, Rangwani S. Look to the EAST: Shared Decision Making in the Era of New Therapies. Practical Dermatology, 2020, October: 24-30.

WHY IT IS IMPOSSIBLE TO COMPARE ACROSS TRIALS

- Silverberg, J.I., Simpson, E.L., Armstrong, A.W. *et al.* Expert Perspectives on Key Parameters that Impact Interpretation of Randomized Clinical Trials in Moderate-to-Severe Atopic Dermatitis.*Am J Clin Dermatol* (2021). https://doi.org/10.1007/s40257-021-00639-y

LEBRIKIZUMAB (IL-13)

- Phase 2, RCT monotherapy trial in 280 adults with moderate-to-severe AD inadequately controlled with topical corticosteroids (TCS)
- At week 12, significantly more patients achieved EASI-50/75/90 with lebrikizumab (LEB) 250 mg Q2W or Q4W than with placebo.



Guttman-Yassky E, et al. 38th Annual Fall Clinical Dermatology Conference; Oct 17-20, 2019; Las Vegas, NV.

NEMOLIZUMAB (IL-31)

- 24-week, DB-RCT multicenter study of nemolizumab (10, 30, and 90 mg) subcutaneous injections every 4 weeks vs placebo, with topical corticosteroids in adults with moderate-to-severe AD, severe pruritus, and inadequate control with topical treatments

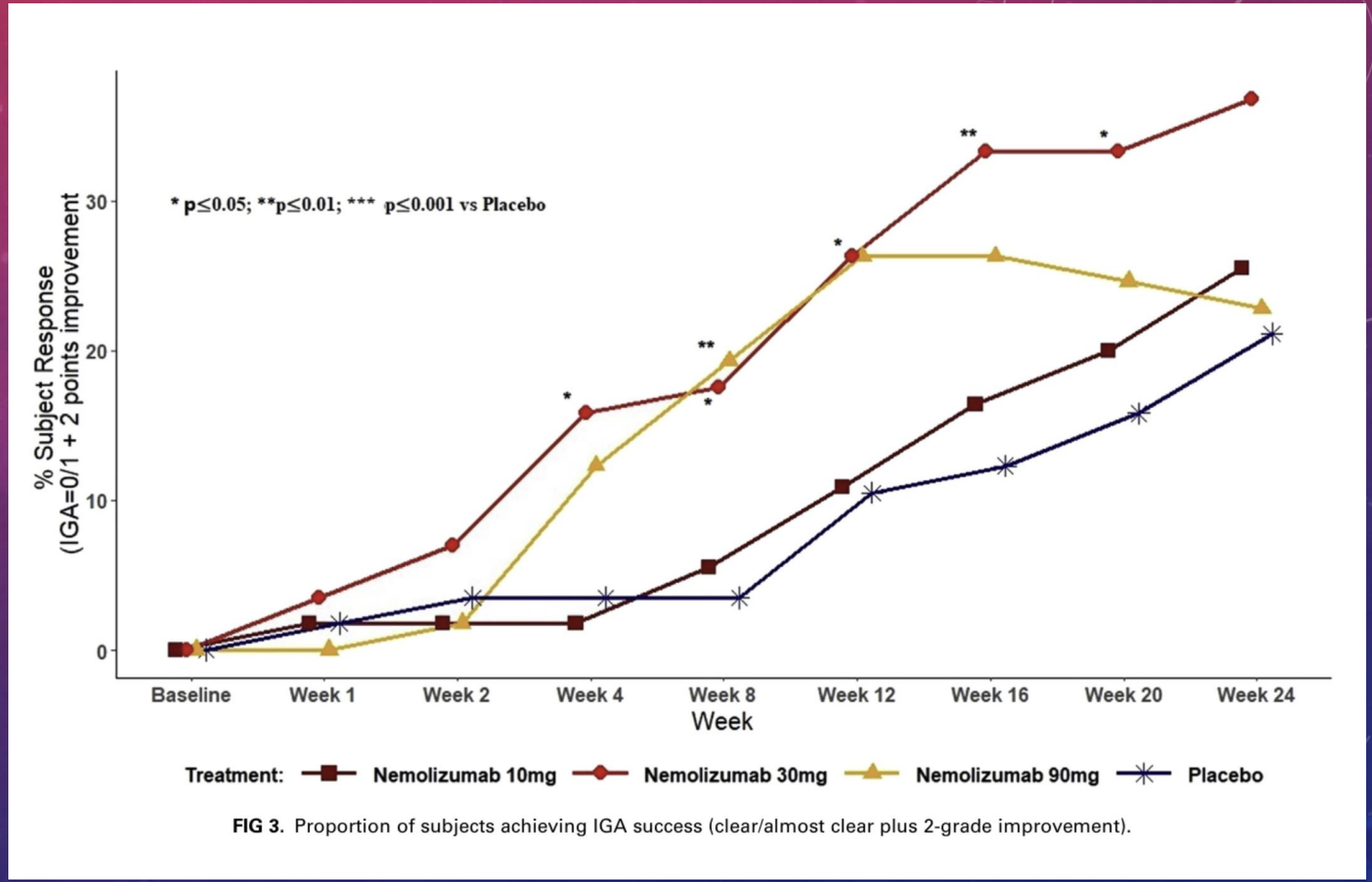


FIG 3. Proportion of subjects achieving IGA success (clear/almost clear plus 2-grade improvement).

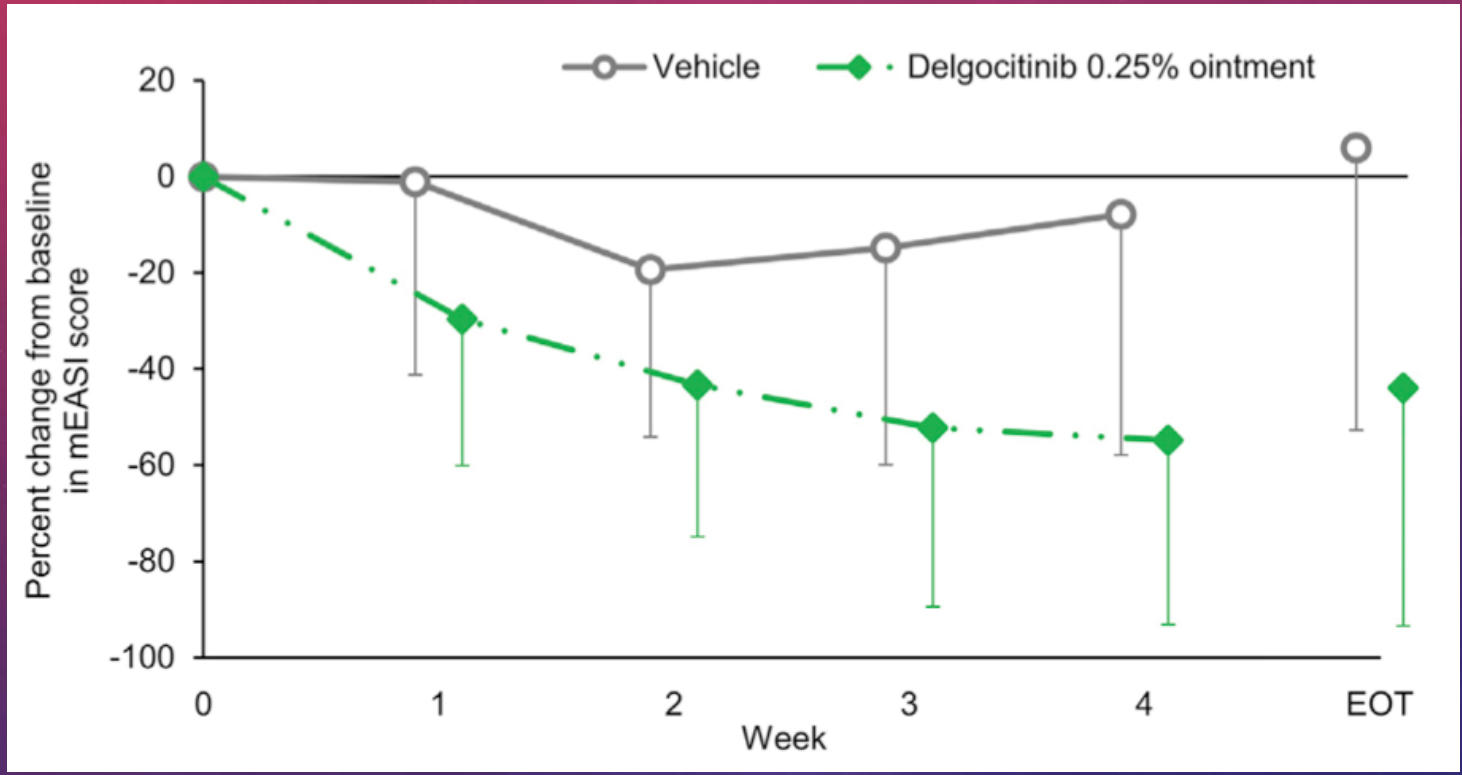
Silverberg JI, et al. *J Allergy Clin Immunol*. 2020;145(1):173-182.

DELGOCITINIB OINTMENT IN PEDIATRIC PATIENTS WITH ATOPIC DERMATITIS

- Delgocitinib (pan-JAK inhibitor) broadly inhibits signaling of inflammatory cytokines involved in the pathophysiology of AD
- It may also improve the skin barrier via promoting the production of terminal differentiation proteins, such as filaggrin
- 4-week double-blind period in which Japanese patients age 2-15 years were randomized in a 1:1 ratio to delgocitinib 0.25% ointment or vehicle ointment
- Then a 52- week extension period was continued

Nakagawa H, Nemoto O, Igarashi A, Saeki H, Kabashima K, Oda M, Nagata T. Delgocitinib ointment in pediatric patients with atopic dermatitis: a phase 3, randomized, double-blind, vehicle-controlled study and a subsequent open-label, long-term study. Journal of the American Academy of Dermatology. 2021 Jun 10.

DELGOCITINIB OINTMENT IN PEDIATRIC PATIENTS WITH ATOPIC DERMATITIS



Nakagawa H, Nemoto O, Igarashi A, Saeki H, Kabashima K, Oda M, Nagata T. Delgocitinib ointment in pediatric patients with atopic dermatitis: a phase 3, randomized, double-blind, vehicle-controlled study and a subsequent open-label, long-term study. Journal of the American Academy of Dermatology. 2021 Jun 10.

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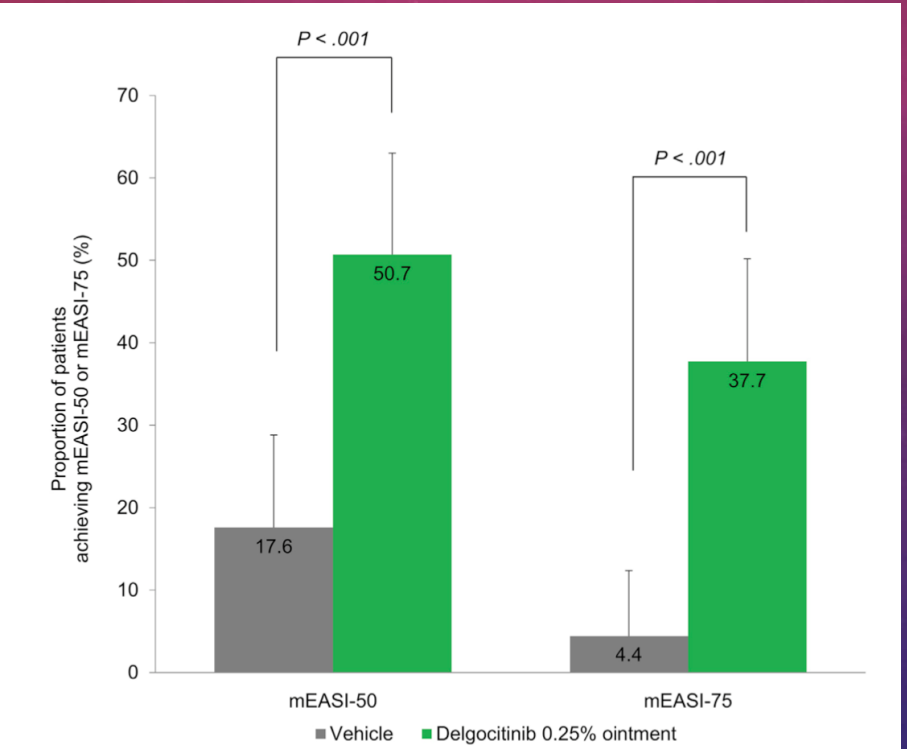


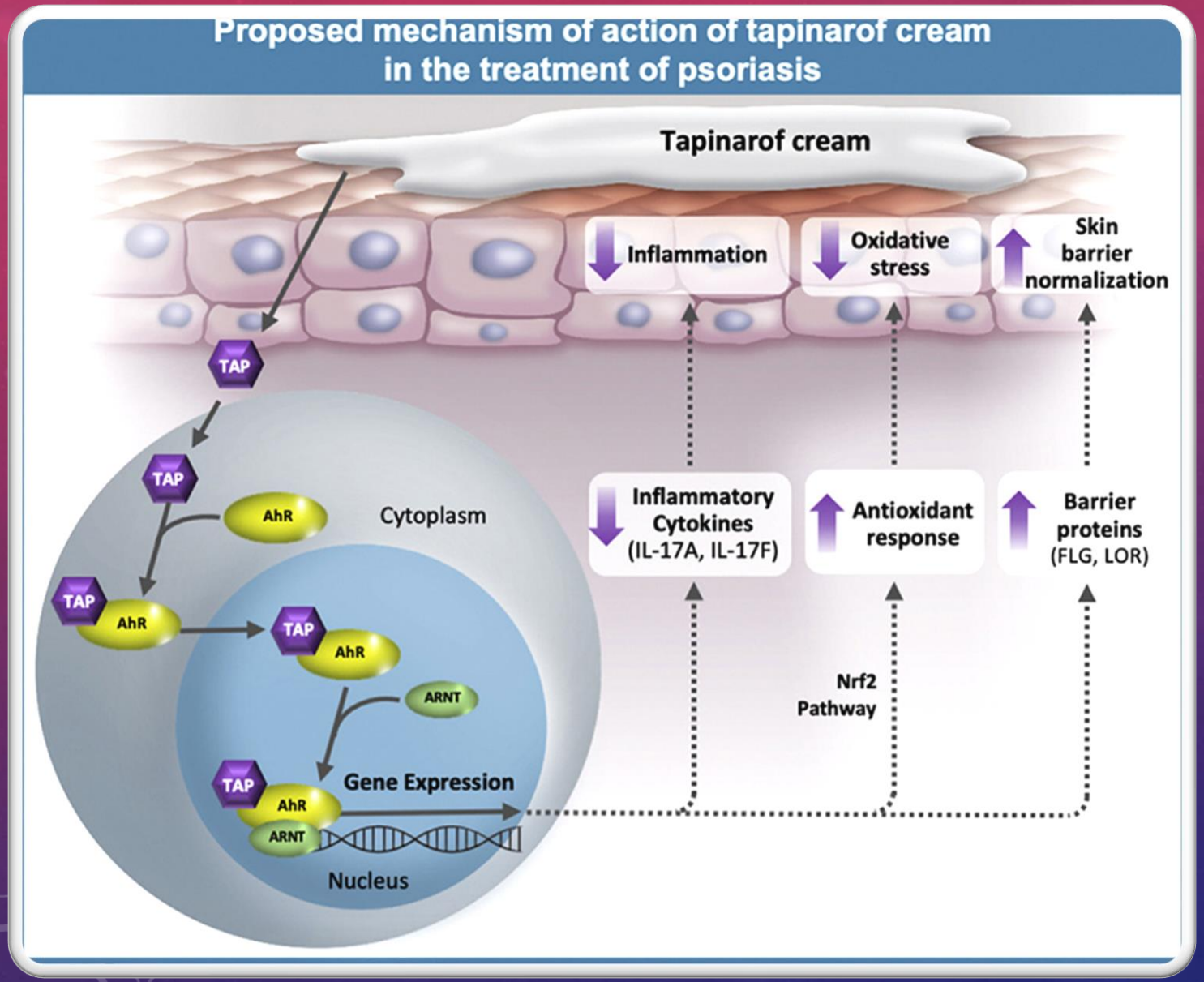
Fig 3. Proportion of patients achieving at least 50% or at least 75% improvement in mEASI score at the end of treatment. The error bars represent 95% confidence intervals. *mEASI,* Modified Eczema Area and Severity Index; *mEASI-50,* at least 50% improvement from baseline in mEASI score; *mEASI-75,* at least 75% improvement from baseline in mEASI score.

Nakagawa H, Nemoto O, Igarashi A, Saeki H, Kabashima K, Oda M, Nagata T. Delgocitinib ointment in pediatric patients with atopic dermatitis: a phase 3, randomized, double-blind, vehicle-controlled study and a subsequent open-label, long-term study. Journal of the American Academy of Dermatology. 2021 Jun 10.

TOPICAL AHR RECEPTOR LIGAND (TAPINAROF)

- Activates epidermal aryl hydrocarbon receptors
- Improves barrier function and ceramide production
- Coal tar may work through a similar mechanism
- Randomized, vehicle-controlled, double-blind phase 2b dose-finding adolescents and adults with moderate to severe AD
  - IGA 0 or 1 with ≥2-point reduction
  - 1% BID vs. vehicle 53% vs. 24%
  - Itch reduction at 1 week
  - AE: Stinging/burning

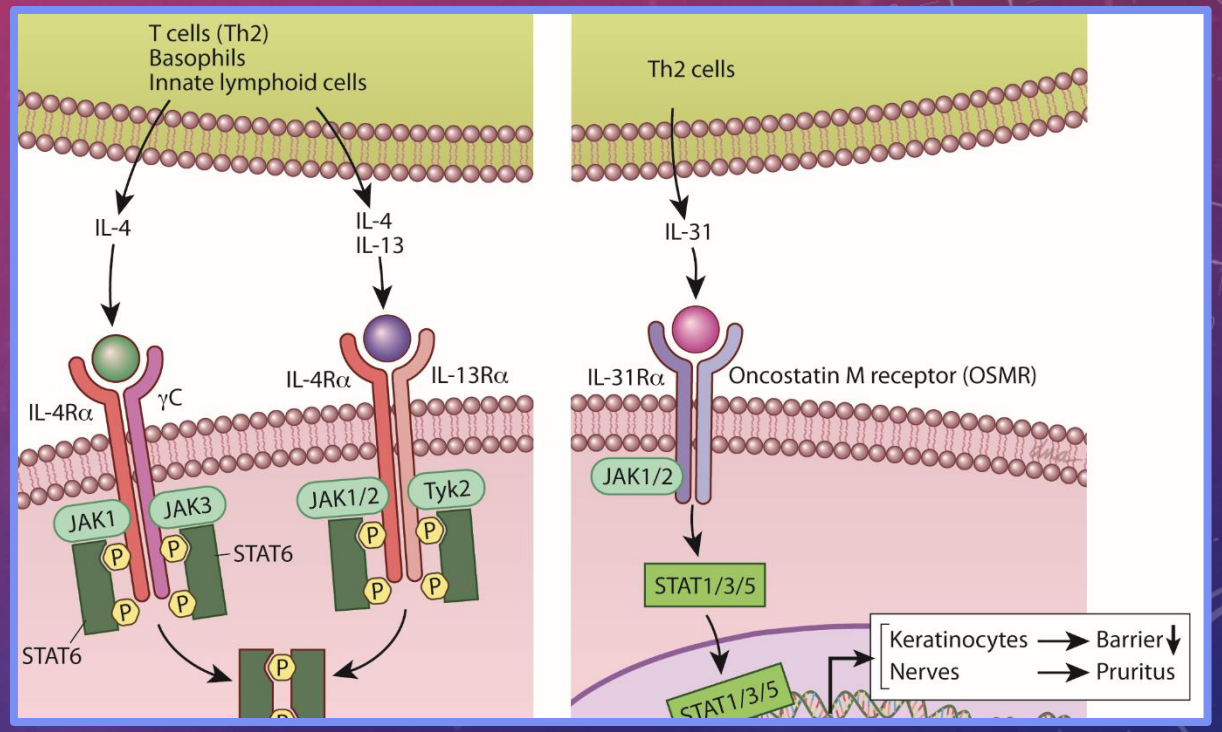
Peppers J, et al. *J Am Acad Dermatol*. 2019;80(1):89-98.



BISSONNETTE R, GOLD LS, RUBENSTEIN DS, TALLMAN AM, ARMSTRONG A. TAPINAROF IN THE TREATMENT OF PSORIASIS: A REVIEW OF THE UNIQUE MECHANISM OF ACTION OF A NOVEL THERAPEUTIC AHR MODULATING AGENT (TAMA). JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY. 2020 NOV 3.

JANUS ASSOCIATED KINASE

- The JAK-STAT pathway is a conserved master regulator of immunity and myeloproliferation.
- JAK inhibitors are used to treat several hematologic and inflammatory diseases.
- Small molecules (including JAK inhibitors) show improvement in AD disease scores, patient-reported outcomes, and QoL.

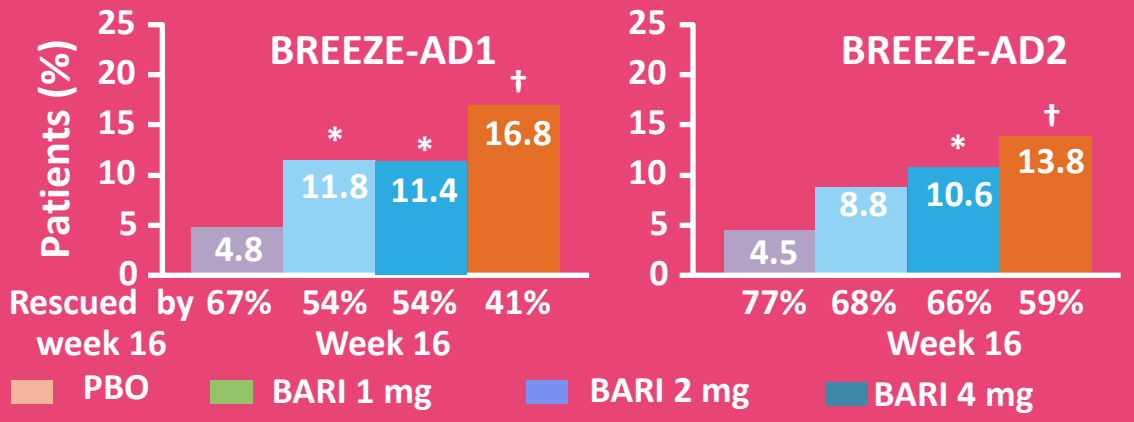


Cotter DG, et al. *J Am Acad Dermatol*. 2018;78(suppl 1):S53-S62. Mobasher P, et al. *J Dermatolog Treat*. 2019;30:550-557. Paller AS, et al. *J Allergy Clin Immunol*. 2017;140:633-643.

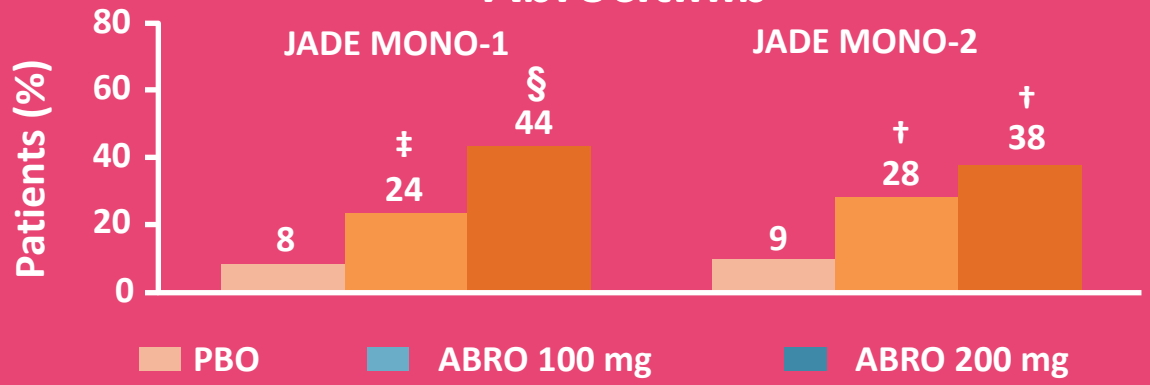
JAK INHIBITORS IN AD

Proportion of clear/almost clear at week 12/16 (monotherapy)

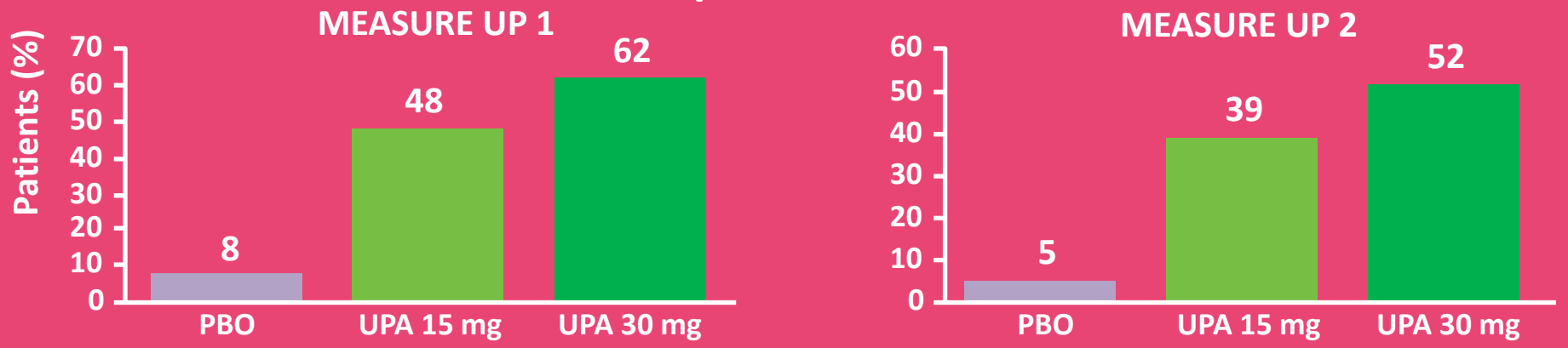
Baricitinib[1]



Abrocitinib[2,3]



Upadacitinib[4]



*P <.05; †P <.001; ‡P = .0037; §P <.0001 vs PBO.

BARI = baricitinib; ABRO= abrocitinib; UPA = upadacitinib.

1. Simpson EL, et al. *Br J Dermatol*. 2020;183:242-255 and supplement. 2. Simpson EL, et al. *Lancet*. 2020;396:255-266. 3. Silverberg JI, et al. *JAMA Dermatol*. 2020;156:863-873. 4. Guttman-Yassky E, et al. *Lancet*. 2021;397:2151-2168.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Abrocitinib versus Placebo or Dupilumab for Atopic Dermatitis

T. Bieber, E.L. Simpson, J.I. Silverberg, D. Thaçi, C. Paul, A.E. Pink, Y. Kataoka, C.-Y. Chu, M. DiBonaventura, R. Rojo, J. Antinew, I. Ionita, R. Sinclair, S. Forman, J. Zdybski, P. Biswas, B. Malhotra, F. Zhang, and H. Valdez, for the JADE COMPARE Investigators*

- 12 WEEK STUDY OF ABROCITINIB 200MG, 100MG, DUPILUMAB 300MG Q2WKS AND PLACEBO
- 838 PATIENTS RANDOMIZED
- “THE 200-MG DOSE, BUT NOT THE 100-MG DOSE, OF ABROCITINIB WAS SUPERIOR TO DUPILUMAB WITH RESPECT TO ITCH RESPONSE AT WEEK 2”

Bieber T, Simpson EL, Silverberg JI, Thaçi D, Paul C, Pink AE, Kataoka Y, Chu CY, DiBonaventura M, Rojo R, Antinew J. Abrocitinib versus placebo or dupilumab for atopic dermatitis. New England Journal of Medicine. 2021 Mar 25;384(12):1101-12.

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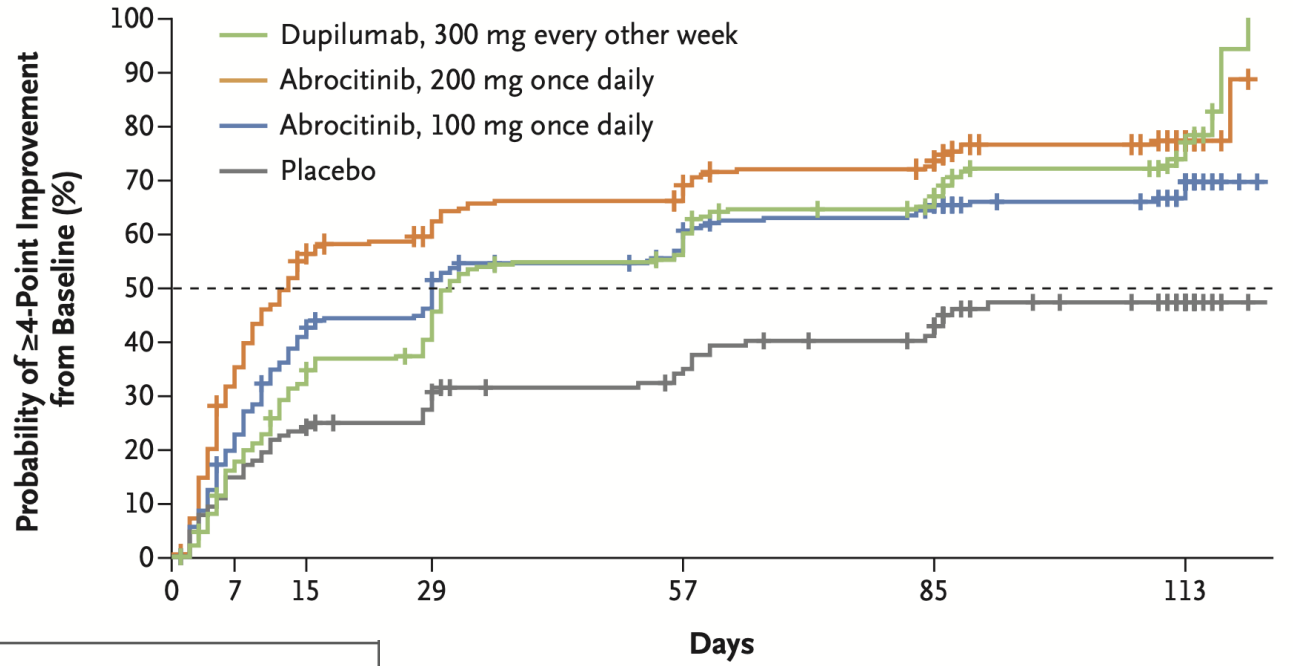
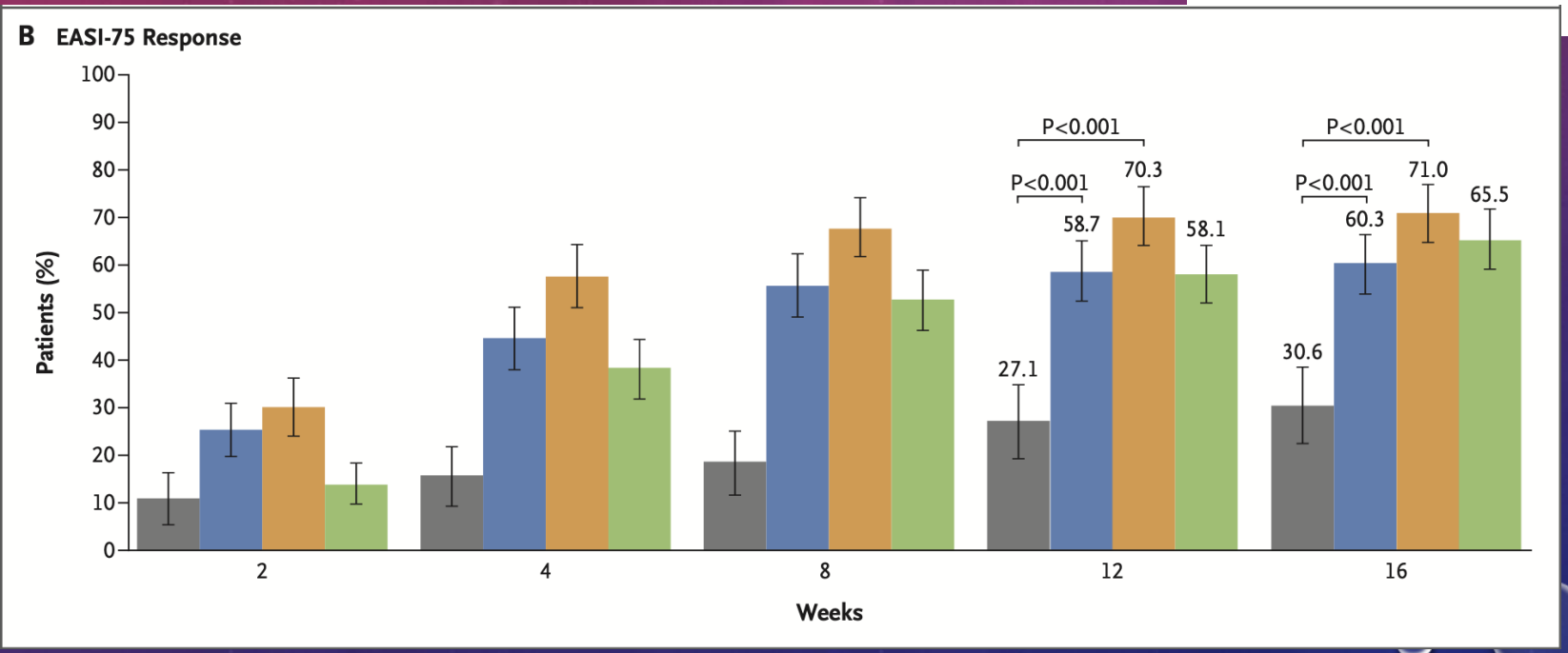




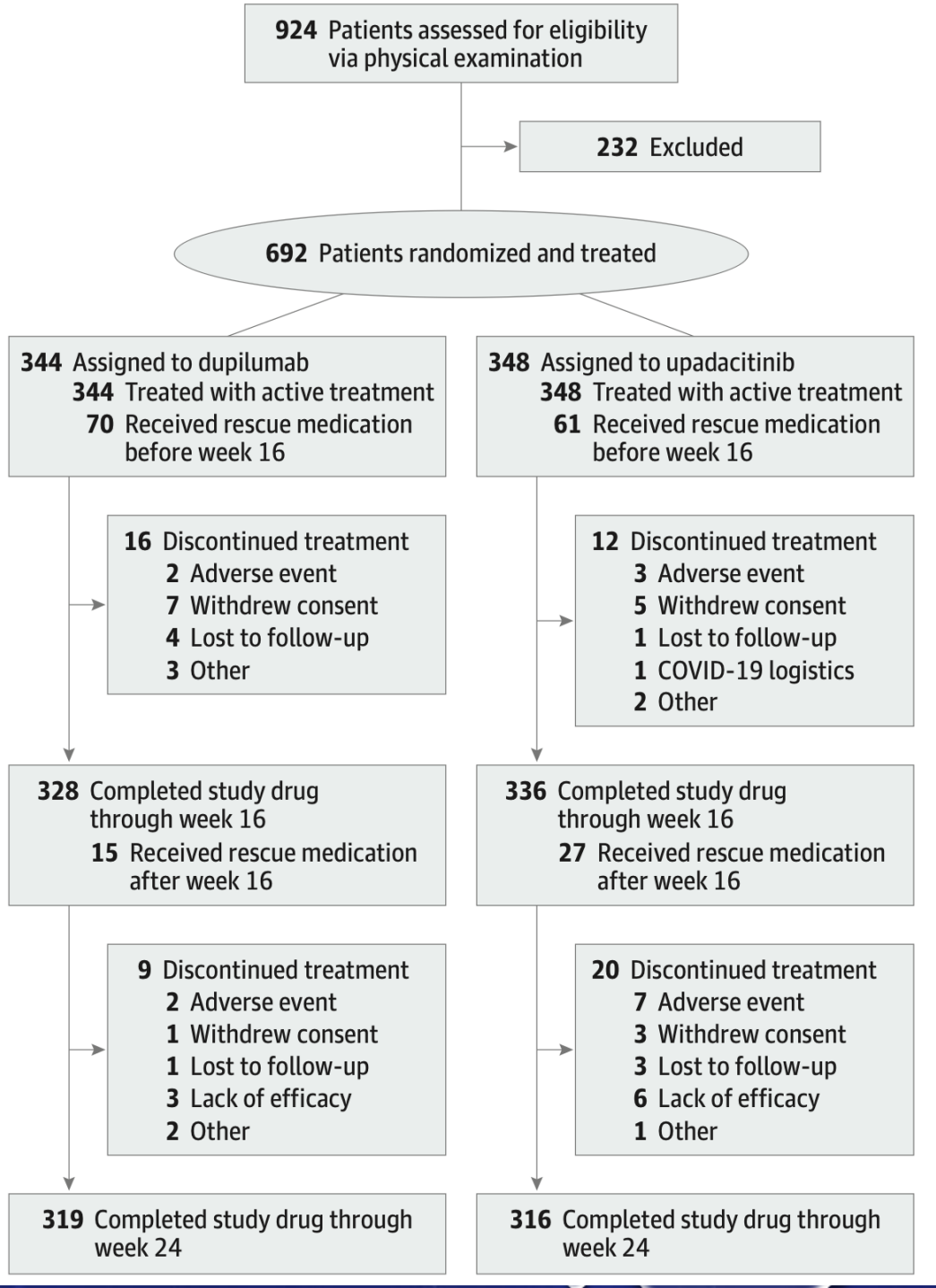
Bieber T, Simpson EL, Silverberg JI, Thaçi D, Paul C, Pink AE, Kataoka Y, Chu CY, DiBonaventura M, Rojo R, Antinew J. Abrocitinib versus placebo or dupilumab for atopic dermatitis. New England Journal of Medicine. 2021 Mar 25;384(12):1101-12.

JAMA Dermatology | Original Investigation

Efficacy and Safety of Upadacitinib vs Dupilumab in Adults With Moderate-to-Severe Atopic Dermatitis

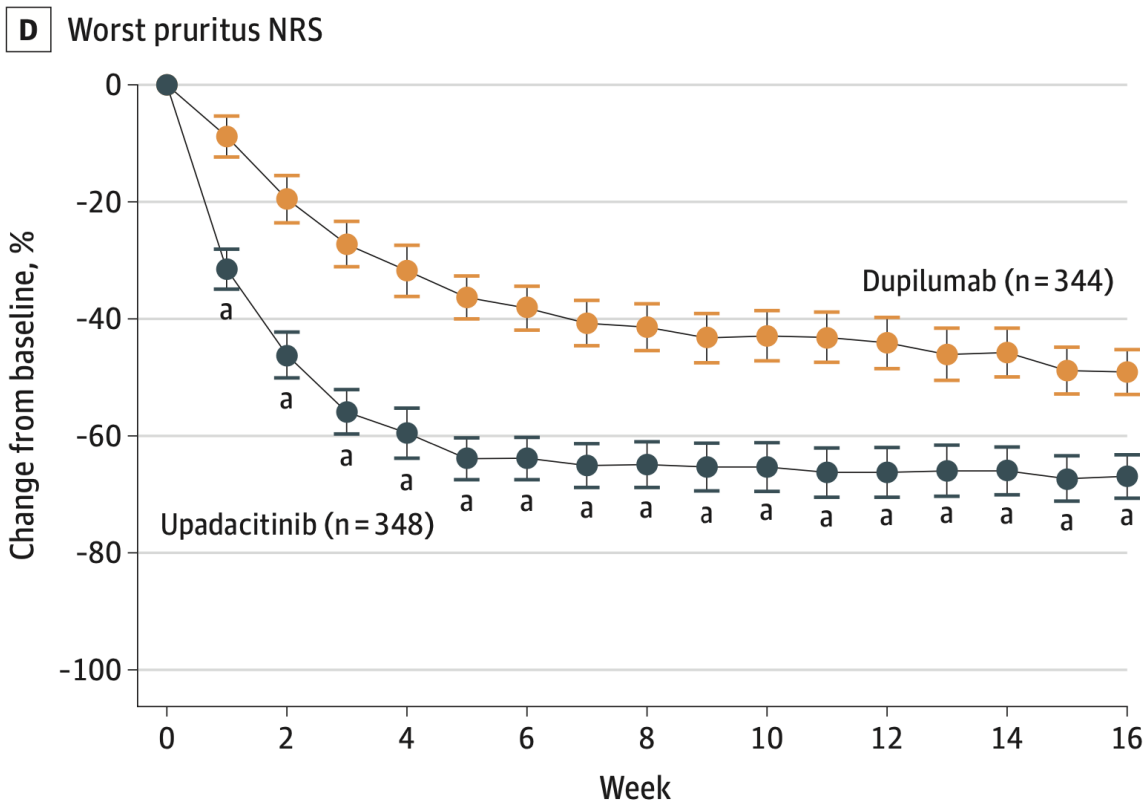
A Randomized Clinical Trial

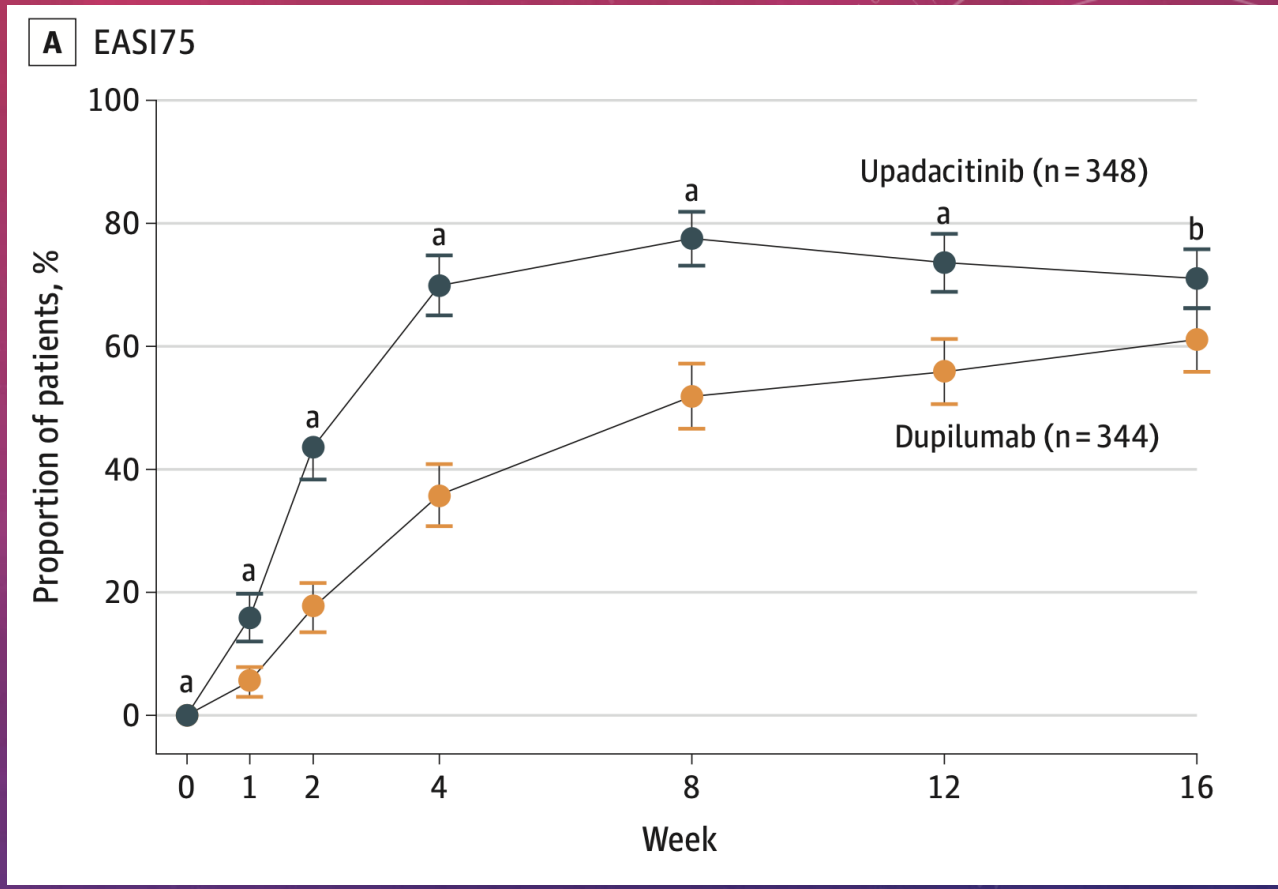
Andrew Blauvelt, MD, MBA; Henrique D. Teixeira, PhD, MBA; Eric L. Simpson, MD, MCR; Antonio Costanzo, MD; Marjolein De Bruin-Weller, MD; Sebastien Barbarot, MD, PhD; Vimal H. Prajapati, MD; Peter Lio, MD; Xiaofei Hu, PhD; Tianshuang Wu, PhD; John Liu, MD, MS; Barry Ladizinski, MD, MPH, MBA; Alvina D. Chu, MD; Kilian Eyerich, MD



Blauvelt A, Teixeira HD, Simpson EL, et al. Efficacy and Safety of Upadacitinib vs Dupilumab in Adults With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial. *JAMA Dermatol.* Published online August 04, 2021. doi:10.1001/jamadermatol.2021.3023

COMPARISON

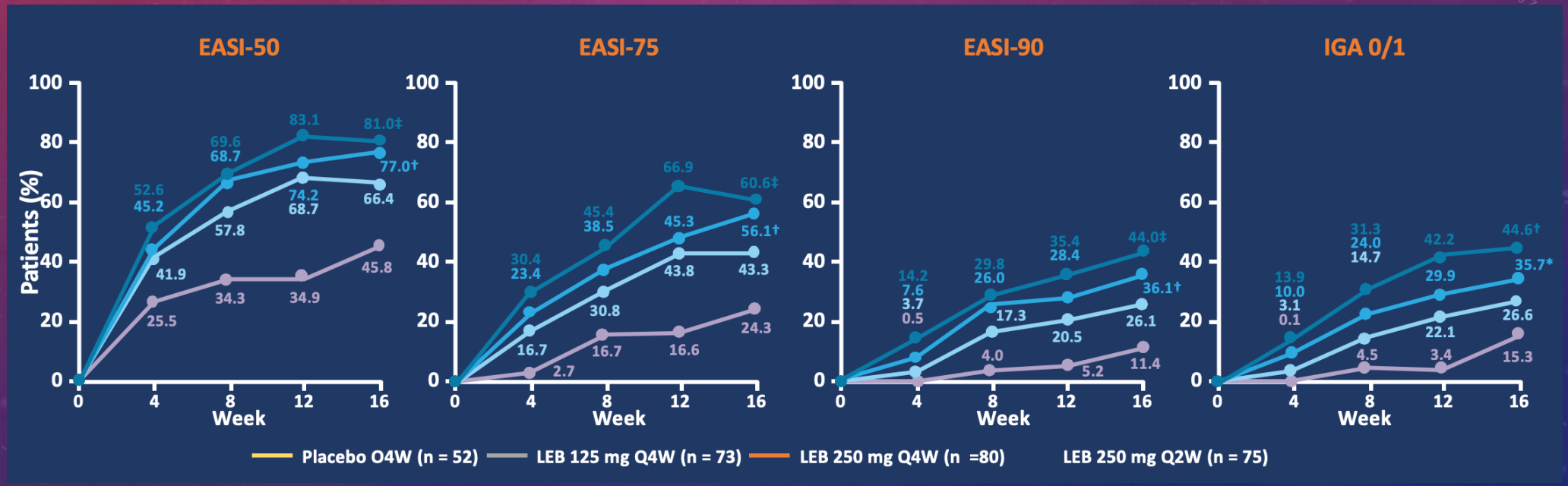




Blauvelt A, Teixeira HD, Simpson EL, et al. Efficacy and Safety of Upadacitinib vs Dupilumab in Adults With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial. *JAMA Dermatol.* Published online August 04, 2021. doi:10.1001/jamadermatol.2021.3023

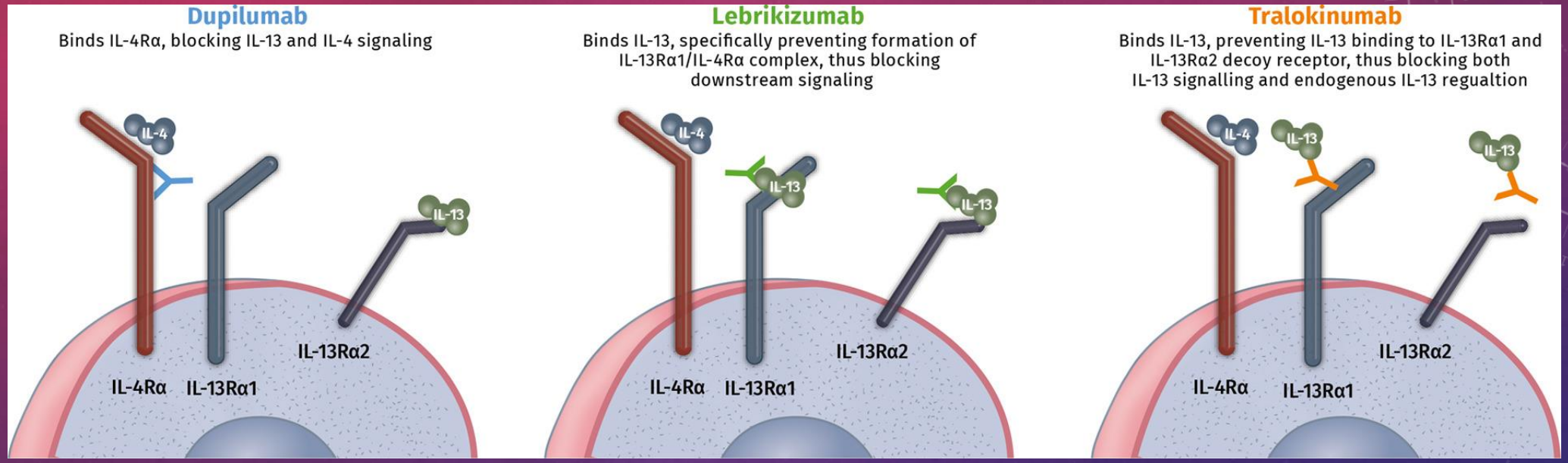
EMERGING AGENT: LEBRIKIZUMAB (ANTI-IL-13)

- Phase 2, RCT monotherapy trial in 280 adults with moderate-to-severe AD inadequately controlled with topical corticosteroids (TCS)
- At week 12, significantly more patients achieved EASI-50/75/90 with lebrikizumab (LEB) 250 mg Q2W or Q4W than with placebo.



Guttman-Yassky E, et al. 38th Annual Fall Clinical Dermatology Conference; Oct 17-20, 2019; Las Vegas, NV.

NOT IDENTICAL



Lebrikizumab does not prevent binding to Ra2 → no increased levels of IL-13

Tralokinumab prevents the binding to Ra2 → thus increased total IL-13 levels

What does this mean?

We don't know!

Experimental Dermatology, Volume: 28, Issue: 7, Pages: 756-768, First published: 02 March 2019, DOI: (10.1111/exd.13911)

EMERGING AGENT: NEMOLIZUMAB (ANTI-IL-31)

- 24-week, DB-RCT multicenter study of nemolizumab (10, 30, and 90 mg) subcutaneous injections every 4 weeks versus placebo, with topical corticosteroids in adults with moderate-to-severe AD,severe pruritus, and inadequate control with topical treatments

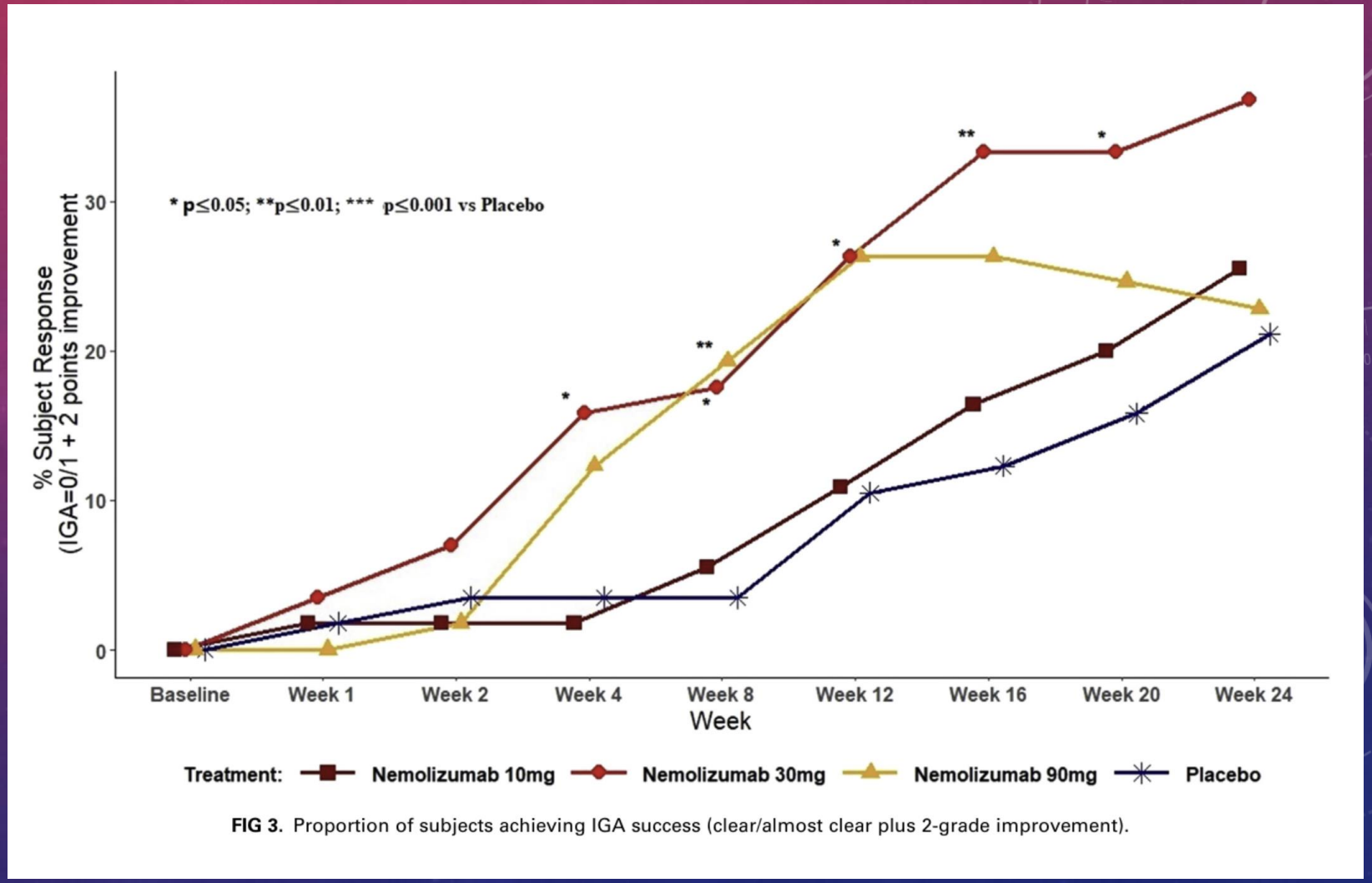


FIG 3. Proportion of subjects achieving IGA success (clear/almost clear plus 2-grade improvement).

Silverberg JI et al. Phase 2B randomized study of nemolizumab in adults with moderate-to-severe atopic dermatitis and severe pruritus. Journal of Allergy and Clinical Immunology. 2020 Jan 1;145(1):173-82.

EMERGING AGENT: NEMOLIZUMAB (ANTI-IL-31)

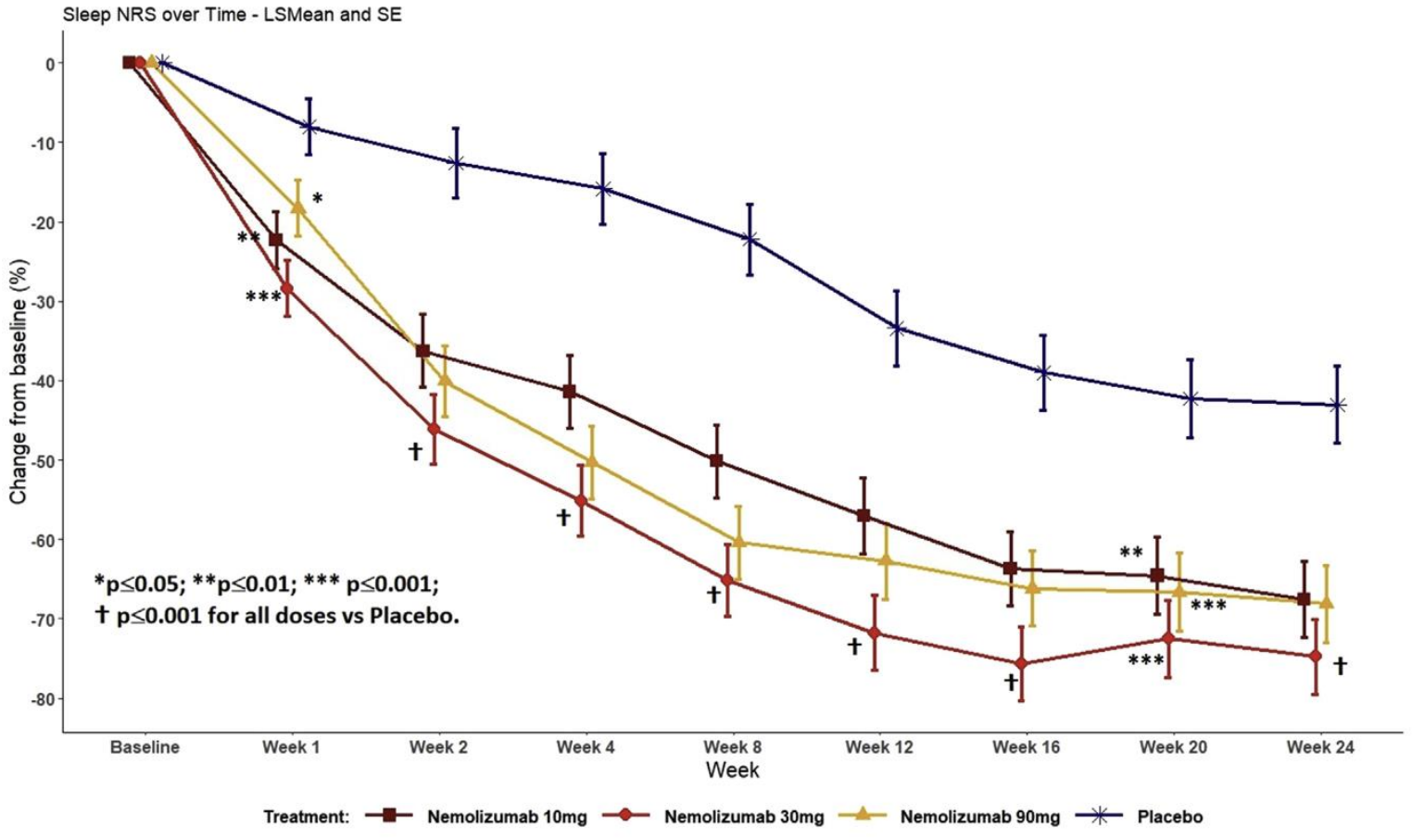


FIG 5. Change in sleep NRS scores over time.

Silverberg JI et al. Phase 2B randomized study of nemolizumab in adults with moderate-to-severe atopic dermatitis and severe pruritus. Journal of Allergy and Clinical Immunology. 2020 Jan 1;145(1):173-82.

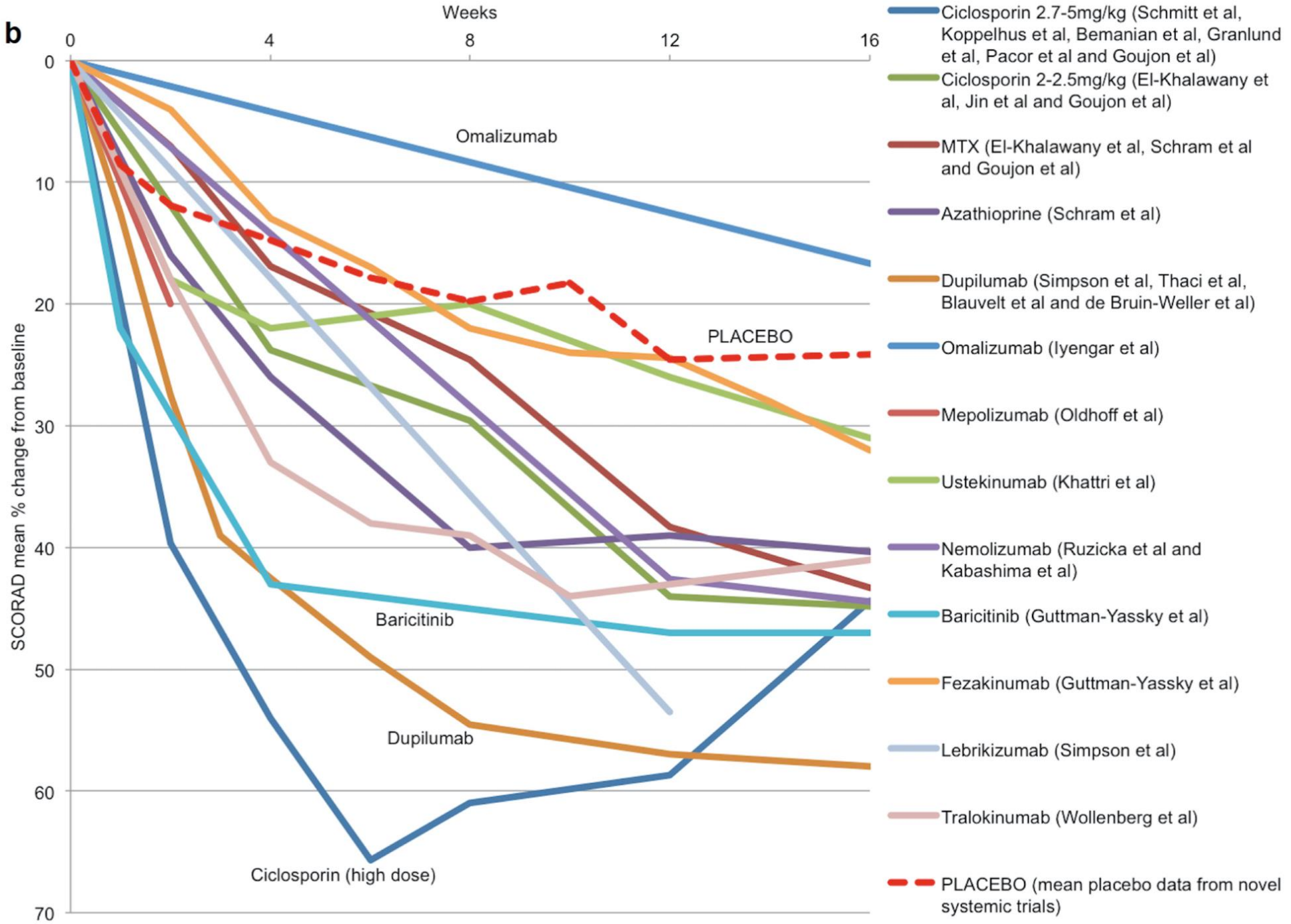
EMERGING AGENT: NEMOLIZUMAB (ANTI-IL-31)

TABLE III. TEAEs occurring in 5% or greater by system organ class and preferred term, all causes (safety population)

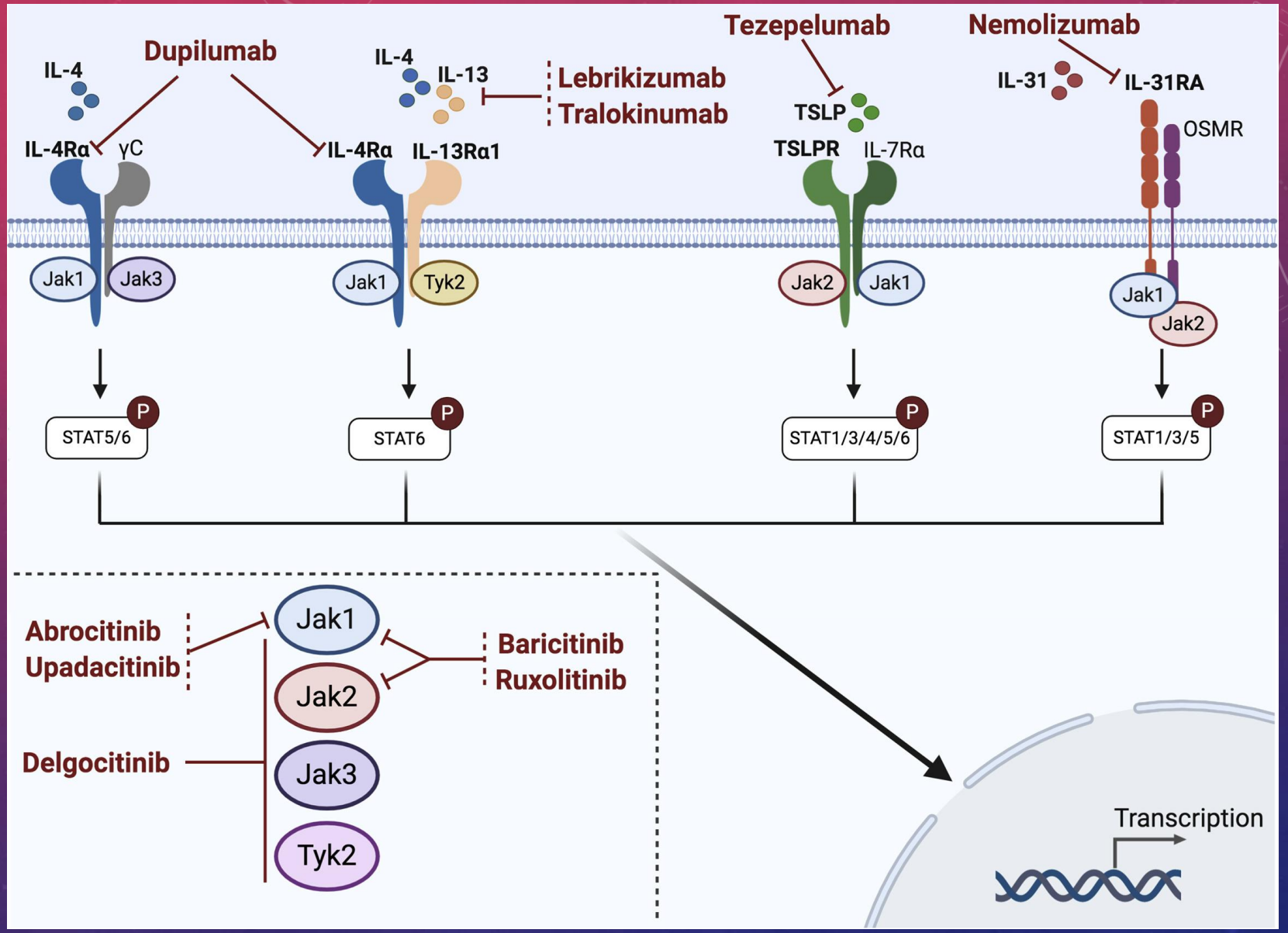
		Nemolizumab			
	Placebo (n = 56)	10 mg (n = 55)	30 mg (n = 57)	90 mg (n = 57)	All (n = 169)
≥1 TEAE	43 (76.8%)	47 (85.5%)	47 (82.5%)	48 (84.2%)	142 (84%)
Infection and infestation	23 (41.4%)	34 (61.8%)	34 (59.6%)	34 (59.6)	102 (60.4%)
Nasopharyngitis	12 (21.4%)	18 (32.7%)	14 (24.6%)	13 (22.8%)	45 (26.6%)
URTI	1 (1.8%)	4 (7.3%)	6 (10.5%)	4 (7%)	14 (8.3%)
Gastroenteritis	0	0	3 (5.3%)	4 (7%)	7 (4.1%)
Sinusitis	0	3 (5.5%)	3 (5.3%)	1 (1.8%)	7 (4.1%)
Oral herpes	1 (1.8%)	2 (3.6%)	1 (1.8%)	3 (5.3%)	6 (3.6%)
UTI	3 (5.4%)	3 (5.5%)	1 (1.8%)	2 (3.5%)	6 (3.6%)
Rhinitis	3 (5.4%)	0	3 (5.3%)	1 (1.8%)	4 (2.4%)
Herpes infection	5 (8.9%)	4 (7.3%)	3 (5.3%)	5 (8.7%)	12 (7.1%)
Skin and subcutaneous tissue disorders	20 (35.7%)	18 (32.7%)	23 (40.4%)	23 (40.4%)	64 (37.9%)
Atopic dermatitis	18 (32.1%)	12 (21.8%)	14 (24.6%)	16 (28.1%)	42 (24.9%)
Dry skin	0	0	3 (5.3%)	0	3 (1.8%)
Respiratory, thoracic, and mediastinal disorders	7 (12.5%)	6 (10.9%)	13 (22.8%)	12 (21.1%)	31 (18.3%)
Asthma event	1 (1.8%)	2 (3.6%)	7 (12.3%)	10 (17.5%)	19 (11.2%)
Cough	2 (3.6%)	1 (1.8%)	3 (5.3%)	2 (3.5%)	6 (3.6%)

UTI, Urinary tract infection; *URTI*, upper respiratory tract infection.

Silverberg JI et al. Phase 2B randomized study of nemolizumab in adults with moderate-to-severe atopic dermatitis and severe pruritus. Journal of Allergy and Clinical Immunology. 2020 Jan 1;145(1):173-82.



Alexander H, Patton T, Jabbar-Lopez ZK, Manca A, Flohr C. Novel systemic therapies in atopic dermatitis: what do we need to fulfil the promise of a treatment revolution? F1000Res. 2019 Jan 31;8:F1000 Faculty Rev-132. doi: 10.12688/f1000research.17039.1. PMID: 30774935



Abreu D and Kim BS. Innate Immune Regulation of Dermatitis. Immunology and Allergy Clinics of North America. 2021. DOI: https://doi.org/10.1016/j.iac.2021.04.011

Table 2. Summary of adverse events.

Systemic agent	SAE incidence rate per patient week (%)	AE incidence rate per patient week (%)	Common AEs (clinical trial incidence of ≥1/100)
Ciclosporin	0–2.2	0–20.8	Serum creatinine increase, hypertension, GI upset, infections, skin infections, headache, fatigue, cramps, paraesthesia, lower limb oedema, hypertrichosis, gingival hyperplasia, anaemia, leukopenia, pancytopenia, thrombocytopenia, ESR increase, liver enzyme increase, magnesium decrease, fever, malaise, AD exacerbation, dyslipidaemia, tremor, flushing, metallic taste
Methotrexate	0.19	9.8–23.5	GI upset, infections, liver enzyme increase, skin infections, AD exacerbation, anaemia, leukopenia, pancytopenia, fatigue, headache, renal impairment, fever, malaise
Azathioprine	0.03	3–22.9	GI upset, URTI, LRTI, fatigue, light-headedness, malaise, headache, folliculitis, skin infections, lymphopenia, neutropenia, liver enzyme increase, AD exacerbation
Mycophenolate mofetil	0	4.2	Nausea, headache, fatigue, paraesthesia, muscle ache, infections, serum creatinine increase, leukopenia, liver enzyme increase, magnesium decrease
Dupilumab	0–0.55	6.4–21.6	Nasopharyngitis, headache, URTI, injection site reactions, conjunctivitis, AD exacerbation, skin infections, herpes viral infections
Nemolizumab	0.18	6.6	Nasopharyngitis, AD exacerbation, serum CK increase, URTI, headache, peripheral oedema, impetigo, injection-site reactions
Ustekinumab	0	2.3–2.4	Nasopharyngitis, AD exacerbation
Fezakinumab	0.42	2.25	Viral URTI
Lebrikizumab	Not reported (3.2% of patients had ≥1 SAE over 20-week study)	Not reported (67% of patients had ≥1 AE over 20-week study)	Infections, skin infections, HSV and HZV infections, conjunctivitis, injection site reactions
Baricitinib	0.08%	Not reported (59% of patients had ≥1 AE over 16-week study)	Headache, serum CK increase, AD exacerbation, nasopharyngitis, cellulitis, infections
Tralokinumab	Not reported (3.3% of patients had ≥1 SAE over 12-week study)	Not reported (66% of patients had ≥1 AE over 12-week study)	Nasopharyngitis, URTI, headache, AD exacerbation, injection site reactions, arthralgia, syncope

AD, atopic dermatitis; AE, adverse event; CK, creatine kinase; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; HSV, herpes simplex virus; HZV, herpes zoster virus; LRTI, lower respiratory tract infection; SAE, serious adverse event; URTI, upper respiratory tract infection.

Alexander H, Patton T, Jabbar-Lopez ZK, Manca A, Flohr C. Novel systemic therapies in atopic dermatitis: what do we need to fulfil the promise of a treatment revolution? F1000Res. 2019 Jan 31;8:F1000 Faculty Rev-132. doi: 10.12688/f1000research.17039.1. PMID: 30774935

ICER REVIEW—HOT OFF THE PRESS!

TABLE 1 Proportions of Patients Achieving EASI Thresholds as Estimated From Bayesian Network Meta-Analysis

Treatment	EASI 50 (95% CrI)[a]	EASI 75 (95% CrI)[b]	EASI 90 (95% CrI)[c]
Placebo	0.21 (0.20-0.23)	0.12 (0.1-0.13)	0.05 (0.04-0.06)
Dupilumab 300 mg Q2W	0.64 (0.58-0.70)	0.49 (0.42-0.55)	0.32 (0.27-0.38)
Abrocitinib 100 mg	0.55 (0.45-0.65)	0.40 (0.30-0.50)	0.24 (0.17-0.33)
Abrocitinib 200 mg	0.73 (0.64-0.81)	0.58 (0.49-0.68)	0.41 (0.32-0.52)
Baricitinib 1 mg	0.31 (0.25-0.39)	0.19 (0.14-0.25)	0.09 (0.07-0.14)
Baricitinib 2 mg	0.44 (0.36-0.52)	0.29 (0.23-0.37)	0.16 (0.12-0.22)
Tralokinumab 300 mg	0.46 (0.38-0.53)	0.31 (0.24-0.38)	0.17 (0.13-0.23)
Upadacitinib 15 mg	0.70 (0.64-0.76)	0.55 (0.48-0.61)	0.38 (0.31-0.45)
Upadacitinib 30 mg	0.80 (0.75-0.84)	0.67 (0.61-0.73)	0.50 (0.44-0.57)

[a]*EASI 50: a percentage improvement of EASI score from baseline that is ≥50%.*

[b]*EASI 75: a percentage improvement of EASI score from baseline that is ≥75%.*

[c]*EASI 90: a percentage improvement of EASI score from baseline that is ≥90%.*

CrI = credible interval; EASI = Eczema Area Severity Index; Q2W = once every 2 weeks.

Agboola F, Atlas SJ, Brouwer E, Carlson JJ, Hansen RN, Herron-Smith S, Nhan E, Rind DM, Pearson SD. JAK inhibitors and monoclonal antibodies for the treatment of atopic dermatitis: effectiveness and value: A summary from the Institute for Clinical and Economic Review's New England Comparative Effectiveness Public Advisory Council. Journal of Managed Care & Specialty Pharmacy. 2022;28(1):108-14.

ICER REVIEW—HOT OFF THE PRESS!

TABLE 2 Health Care Perspective

Treatment	Comparator	Incremental cost-effectiveness ratios	
		Cost per QALY[b]	Cost per evLYG[b]
Abrocitinib[a]	Standard of care	$148,300	$148,300
Baricitinib		$71,600	$71,600
Tralokinumab[a]		$129,400	$129,400
Upadacitinib		$248,400	$248,400
Dupilumab		$110,300	$110,300
Abrocitinib[a]	Dupilumab	$303,400	$303,400
Baricitinib		Less costly, less effective	Less costly, less effective
Tralokinumab[a]		Less costly, less effective	Less costly, less effective
Upadacitinib		$1,912,200	$1,912,200

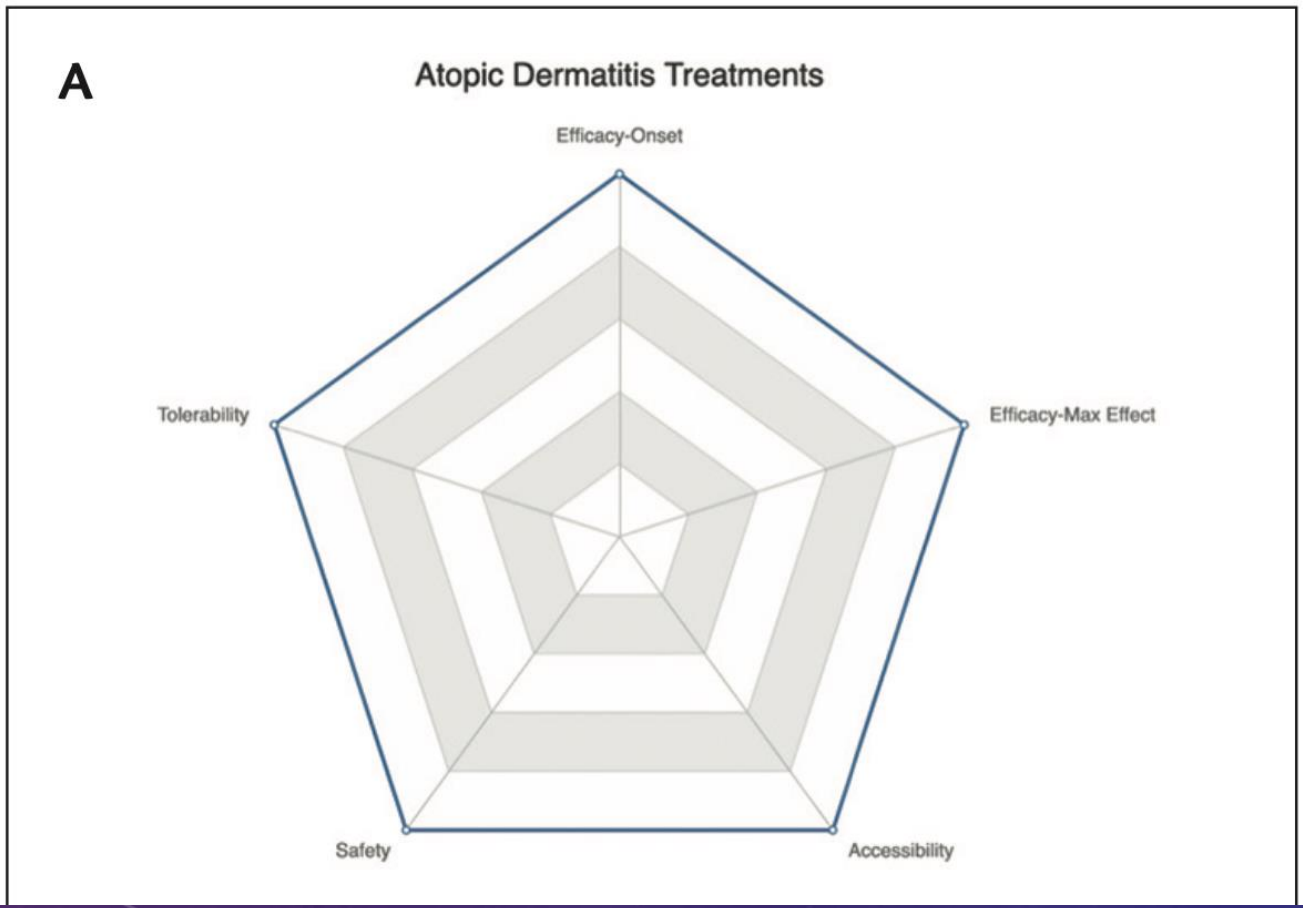
[a]*Using placeholder price.*

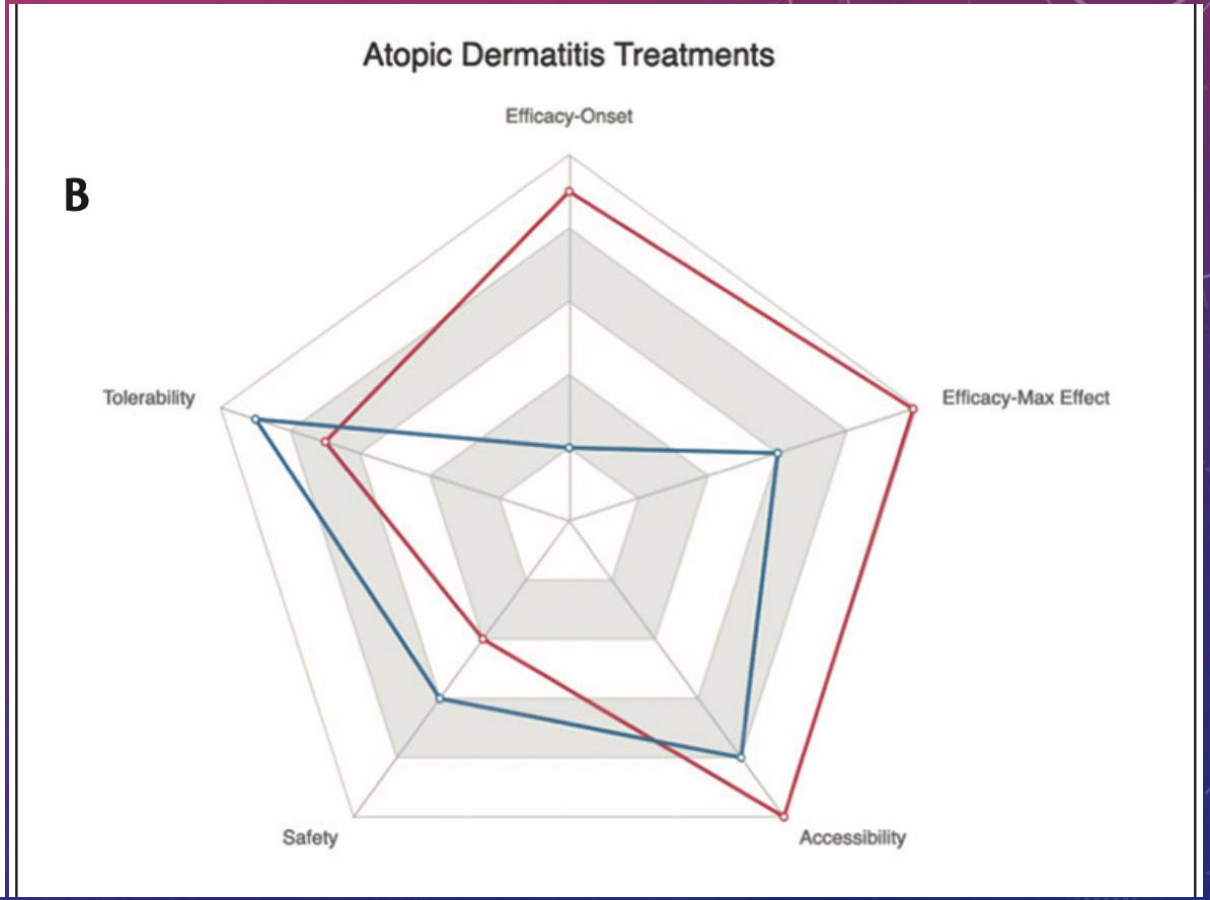
[b]*The cost per QALY and cost per evLYG ratios were the same, given that the treatments have not been shown to lengthen life.*

evLYG = equal value life-year gained; QALY = quality-adjusted life-year.

Agboola F, Atlas SJ, Brouwer E, Carlson JJ, Hansen RN, Herron-Smith S, Nhan E, Rind DM, Pearson SD. JAK inhibitors and monoclonal antibodies for the treatment of atopic dermatitis: effectiveness and value: A summary from the Institute for Clinical and Economic Review's New England Comparative Effectiveness Public Advisory Council. Journal of Managed Care & Specialty Pharmacy. 2022;28(1):108-14.

Shared Decision Making…
EAST: Prednisone Red and Mycophenolate Blue





From: Lio P, Rangwani S. Look to the EAST: Shared Decision Making in the Era of New Therapies. Practical Dermatology, 2020, October: 24-30.

CONCLUSIONS

- The past 50 years have been relatively quiet for AD… but that does not seem to be predictive of the next 5-10!
- We are on the verge of a giant leap in understanding AD
- With new understanding comes new treatment approaches with more promise than ever before!


THANK YOU!