Current & Emerging Therapies for Atopic Dermatitis

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Disclosures

- Investigator, Regeneron, Incyte
- Advisory Boards, Regeneron, Sanofi-Genzyme, Abbvie, Leo, Lilly, Pfizer, Janssen

Learning Objectives

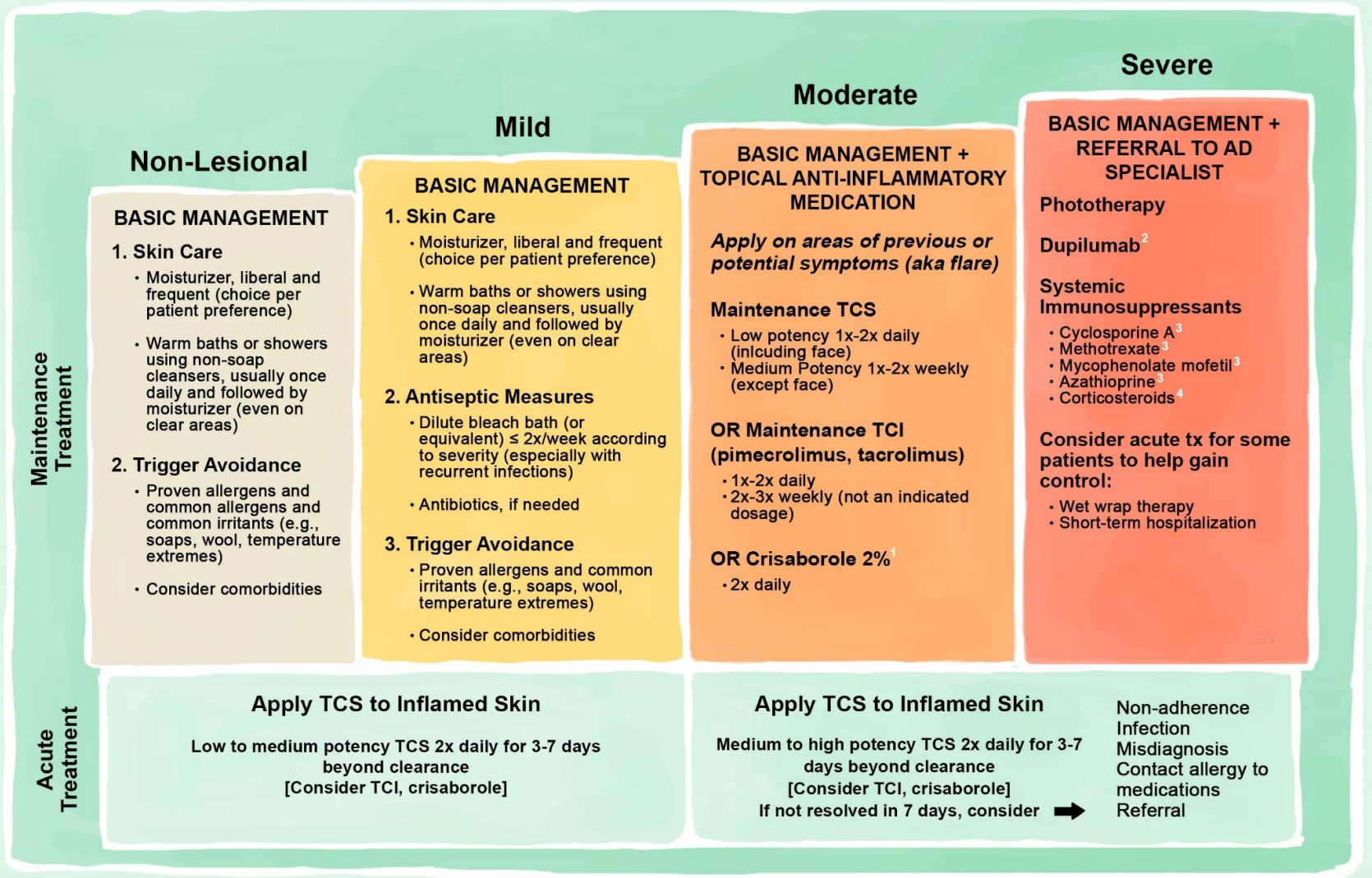
Upon completion of this learning activity, participants should be able to:

1. Describe current indications for biologic therapy in atopic dermatitis as well as potential adverse events
2. Recognize potential benefits and risks of new biologics and small molecules in atopic dermatitis

Clinical vignette…You remember the patient from 6/3 talk?

- You are asked to see Noel, a 22 year old college student with a history of chronic pruritic eczematous rash present since infancy involves his face, trunk and all 4 extremities including flexural aspects
- Course complicated by superficial skin infections including with MRSA as well as past history of localized HSV infection, but no recurrence; no history of deep seated abscesses or PNAs, no warts or molluscum
- Intermittent asthma treated with prn ICS & SABA and SAR treated with prn antihistamines
- He wants to understand his illness…what lies beneath, not just here for another Rx!
- Today, he wants to discuss current & emerging therapies for his AD…

ATOPIC DERMATITIS YARDSTICK



Boguniewicz M, et al. Ann Allergy Asthma Immunol 2018;120:10

UPDATES TO THE YARDSTICK

[1] Indicated for patients with mild to moderate AD, ages 3 months and older

[2] Indicated for patients with moderate to severe AD, ages 12 years and older

[3] Not FDA approved to treat AD

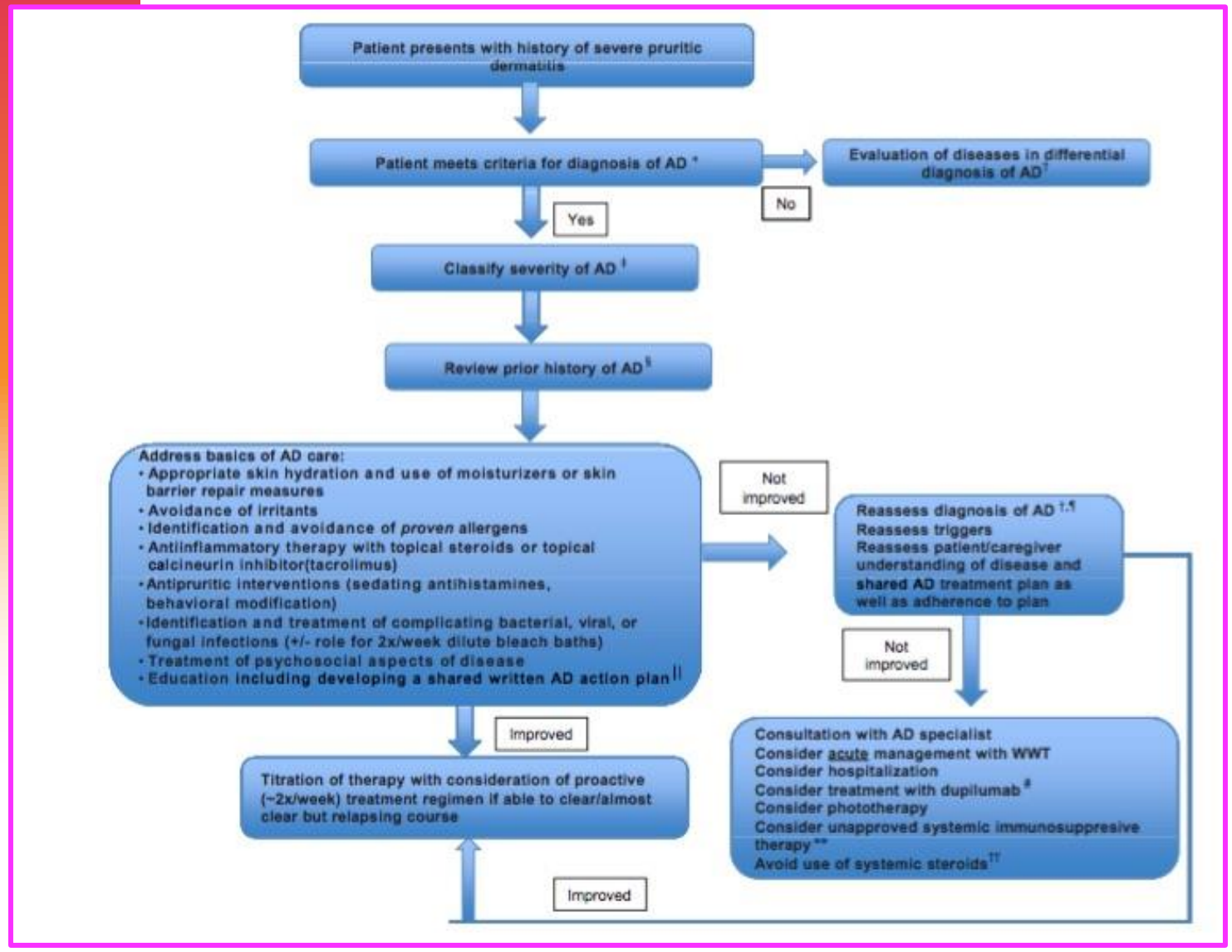
[4] FDA approved to treat AD, but not recommended for long term maintenance

Update to the Updates!

[2] Indicated for pts with moderate to severe AD, ages 6 years and older

(May 26, 2020)

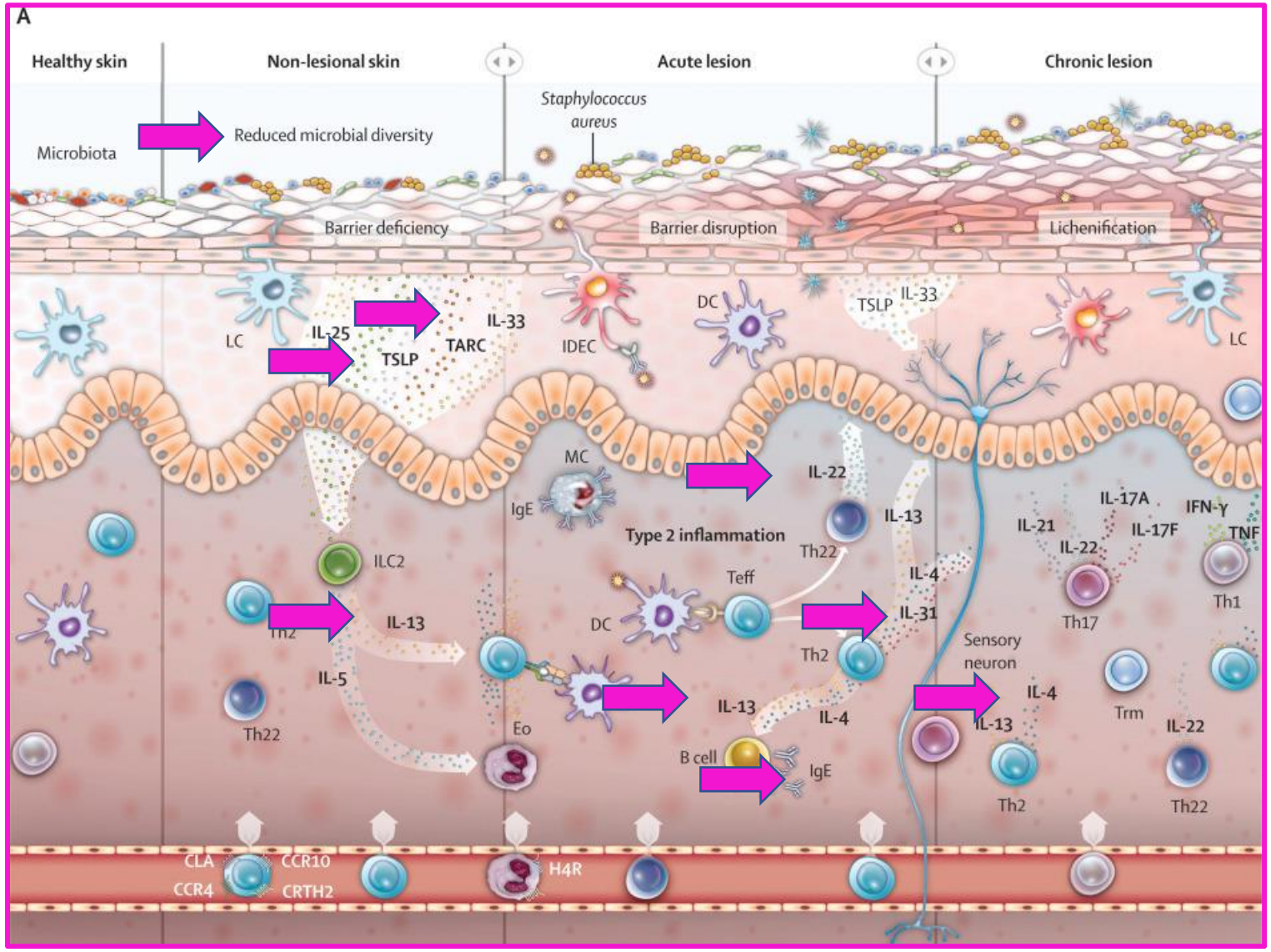
Annotated approach to the patient with severe AD



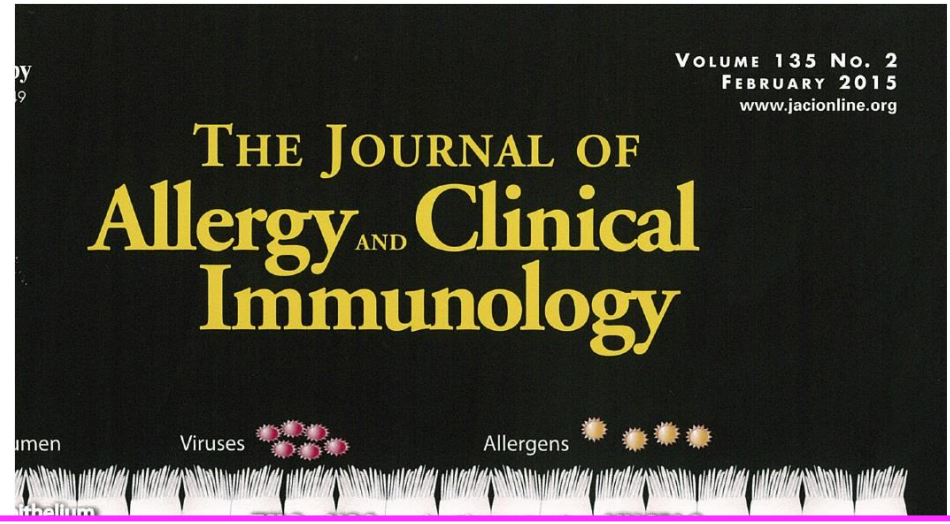
*e.g., Hanifin & Rajka, UK Working Party, AAD Consensus. †See Table II. ₸e.g., clinician evaluation (IGA, SCORAD, EASI) and/or patient-reported (AD global assessment, PO- SCORAD) (see Table I). § Onset, course, area involved, suspected triggers, complications (eg, infections), hospitalizations, associated atopic and nonatopic comorbidities, previous treatment including What? How much? and Where? IISee Fig. 2. (NJH AD Action Plan). {Consider biopsy, patch testing, genetic testing. #FDA approved for patients 18 years or older with moderate-to-severe AD not adequately controlled with topical steroid or when topical steroid not indicated. Document severe AD, body surface area greater than 10%, previous therapies. **CSA, MTX, MMF, AZA. ††While FDA approved, systemic corticosteroids should be avoided or used for shortest course possible, usually while transitioning to a systemic therapy with slower onset of action

J Allergy Clin Immunol Pract 2019;7:1-16 #FDA approved for pts 6 years or older…

Therapeutic targets



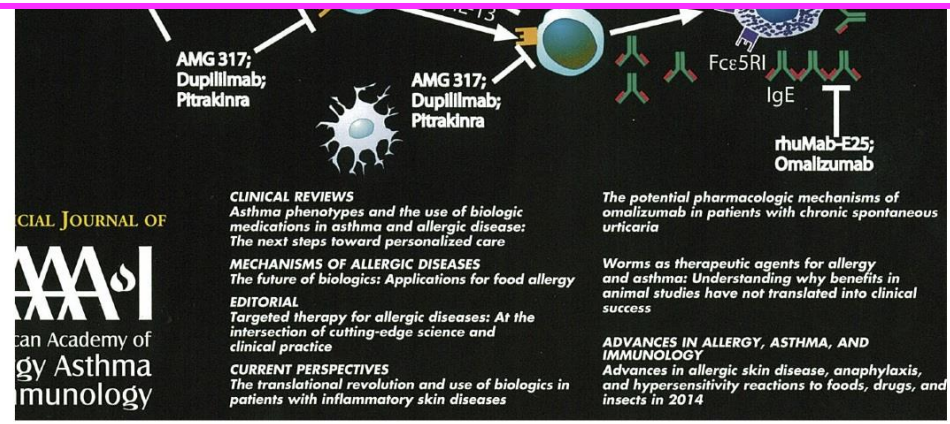
Lancet 2020;396:345-60



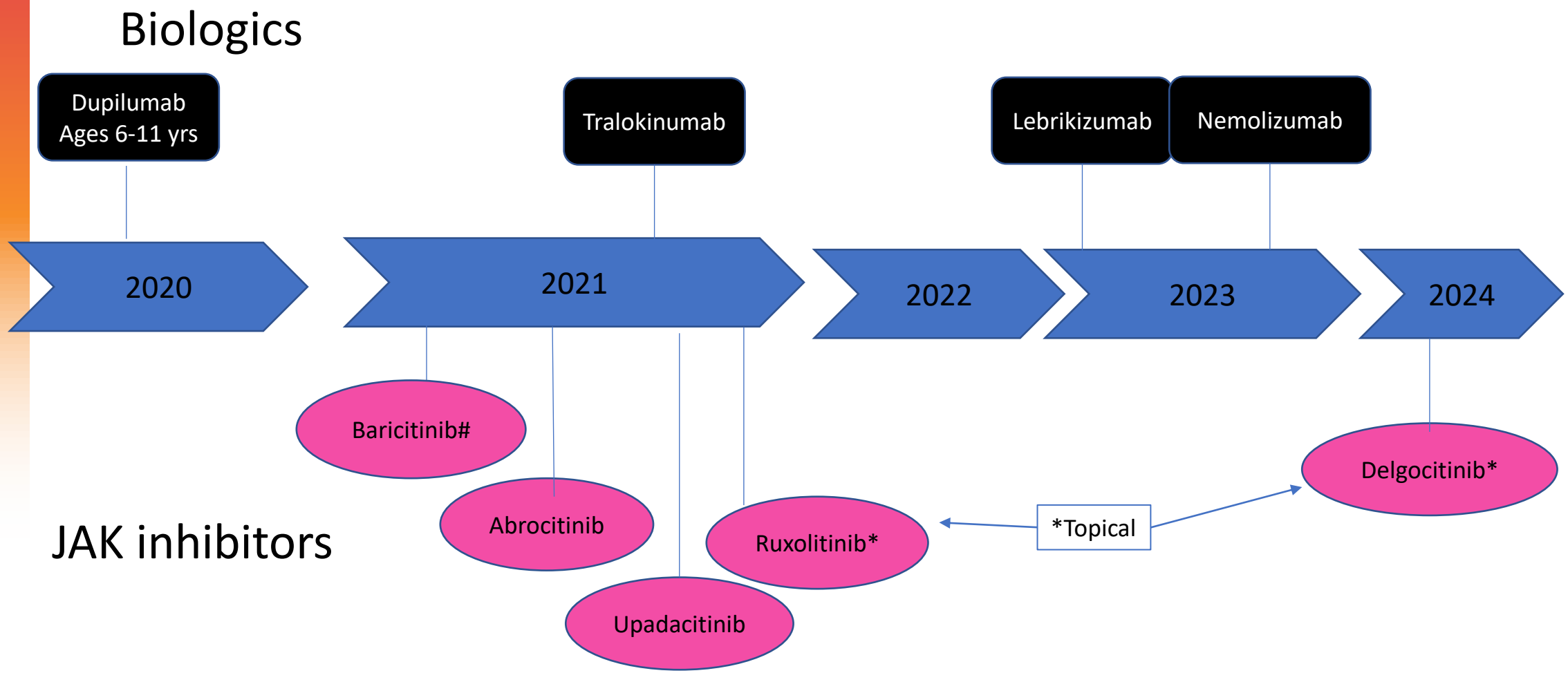
Editorial

Targeted therapy for allergic diseases: At the intersection of cutting-edge science and clinical practice

Mark Boguniewicz, MD, and Donald Y. M. Leung, MD, PhD *Denver, Colo*



Therapeutic landscape in atopic dermatitis



#Approved in EU for adults with moderate-severe AD who are candidates for systemic therapy

Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: A randomized, double-blinded, placebo-controlled phase 3 trial

Objective

- To report the efficacy and safety of dupilumab and concomitant TCS in children aged ≥ 6 to < 12 years with severe AD

Primary endpoint

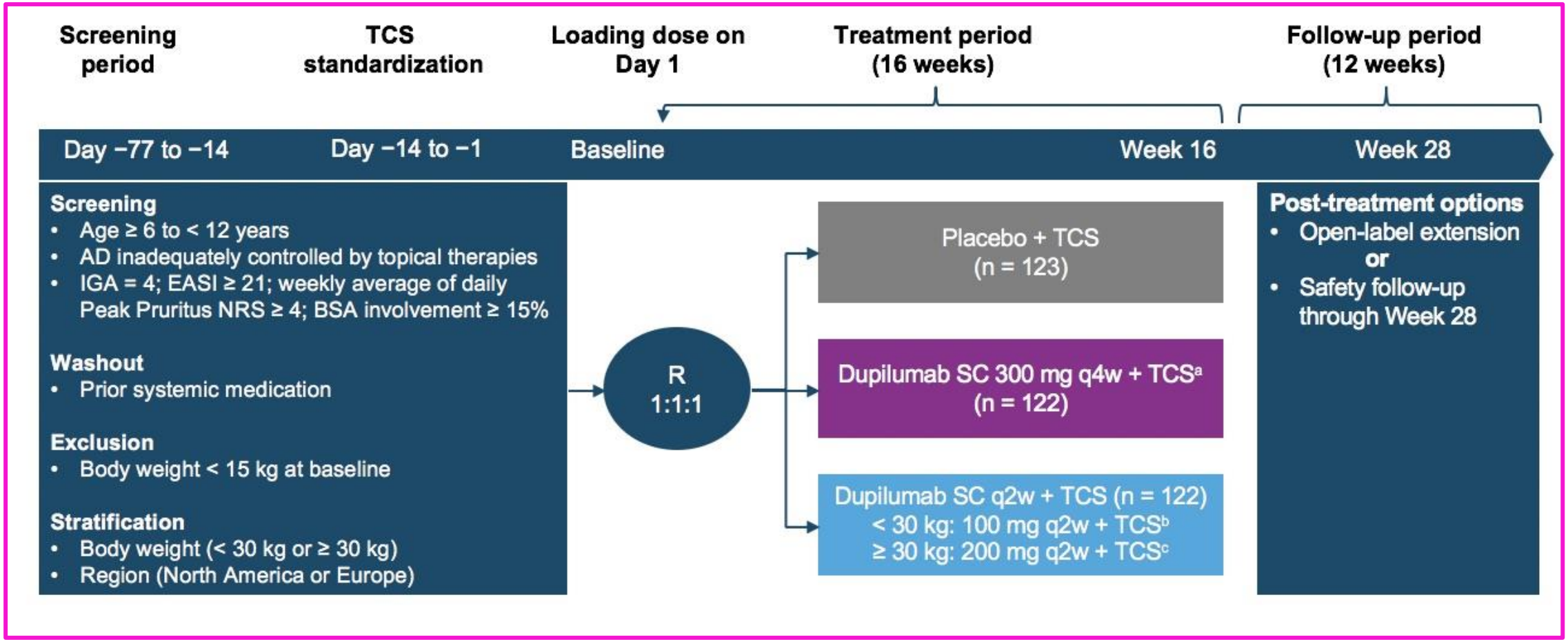
- Proportion of patients with IGA 0 or 1 at Week 16

Co-primary endpoints for EMA and EMA Reference Market Countries

- Proportion of patients with IGA 0 or 1 at Week 16
- Proportion of patients with EASI-75 at Week 16

J Am Acad Dermatol 2020;83:1282-93

Study design



[a]600 mg loading dose; [b]200 mg loading dose; [c]400 mg loading dose.

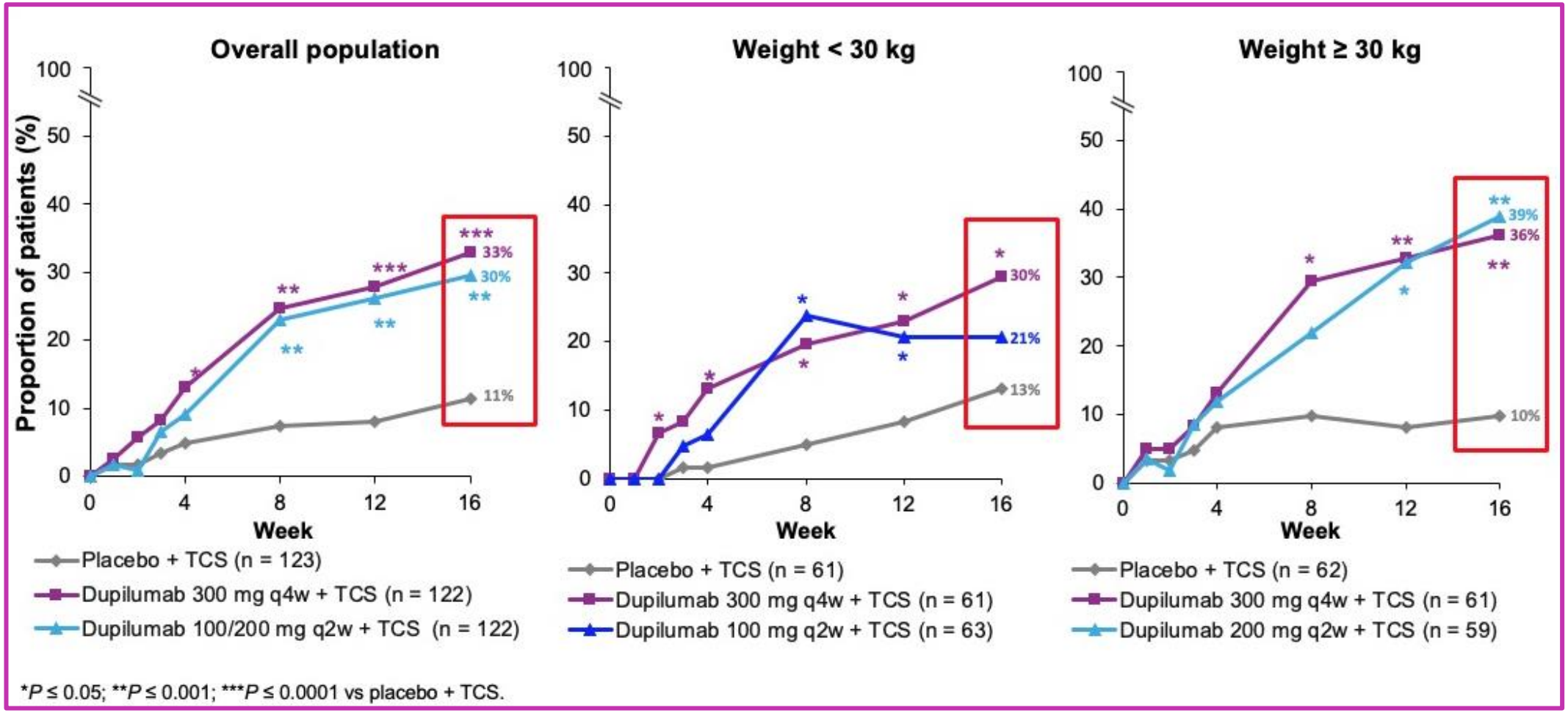
J Am Acad Dermatol 2020;83:1282-93

Baseline disease characteristics

	Placebo + TCS (n = 123)	Dupilumab 300 mg q4w + TCS (n = 122)	Dupilumab 100 mg or 200 mg q2w + TCS (n = 122)
Duration of AD, mean (SD), years	7.2 (2.2)	7.4 (2.4)	7.2 (2.3)
Patients with IGA score = 4, n (%)	123 (100.0)	121 (99.2)	122 (100.0)
EASI score, mean (SD)	39.0 (12.0)	37.4 (12.5)	37.3 (10.9)
Weekly average of daily Peak Pruritus NRS, mean (SD)	7.7 (1.5)	7.8 (1.6)	7.8 (1.5)
BSA, mean (SD), %	60.2 (21.5)	54.8 (21.6)	57.8 (20.0)
SCORAD, mean (SD)	72.9 (12.0)	75.6 (11.7)	72.3 (10.8)
CDLQI, mean (SD)	14.6 (7.4)	16.2 (7.9)	14.5 (6.8)
POEM, mean (SD)	20.7 (5.5)	21.3 (5.5)	20.5 (5.5)
DFI, mean (SD)	15.0 (7.5)	16.9 (8.7)	14.9 (7.1)
PROMIS anxiety, mean (SD)	57.3 (11.6)	59.8 (13.7)	58.6 (11.3)
PROMIS depression, mean (SD)	55.0 (12.1)	58.1 (12.8)	56.3 (11.2)
History of atopic morbidities not including AD, n/N1 (%)	111/120 (92.5)	107/120 (89.2)	114/122 (93.4)

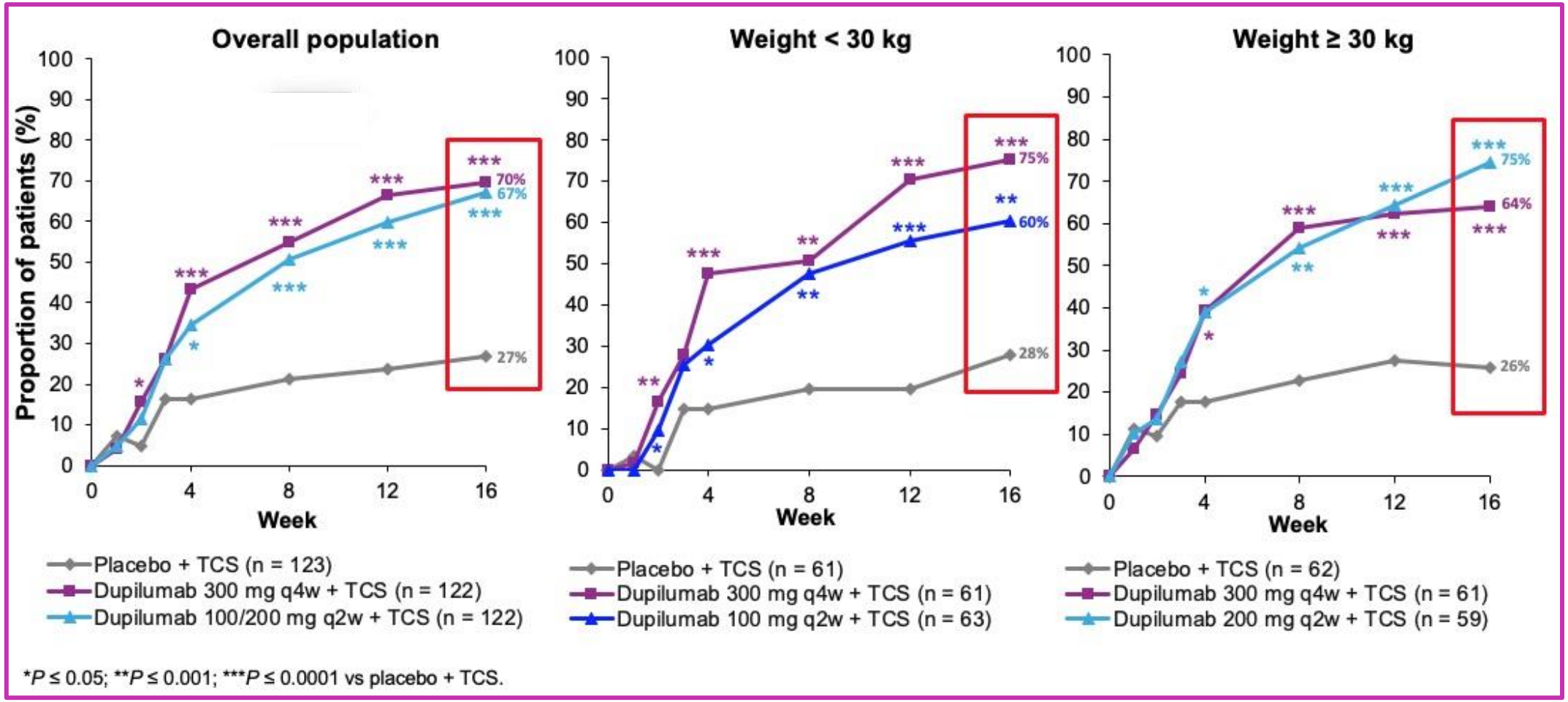
J Am Acad Dermatol 2020;83:1282-93

Proportion of patients achieving co-primary endpoint of IGA 0/1



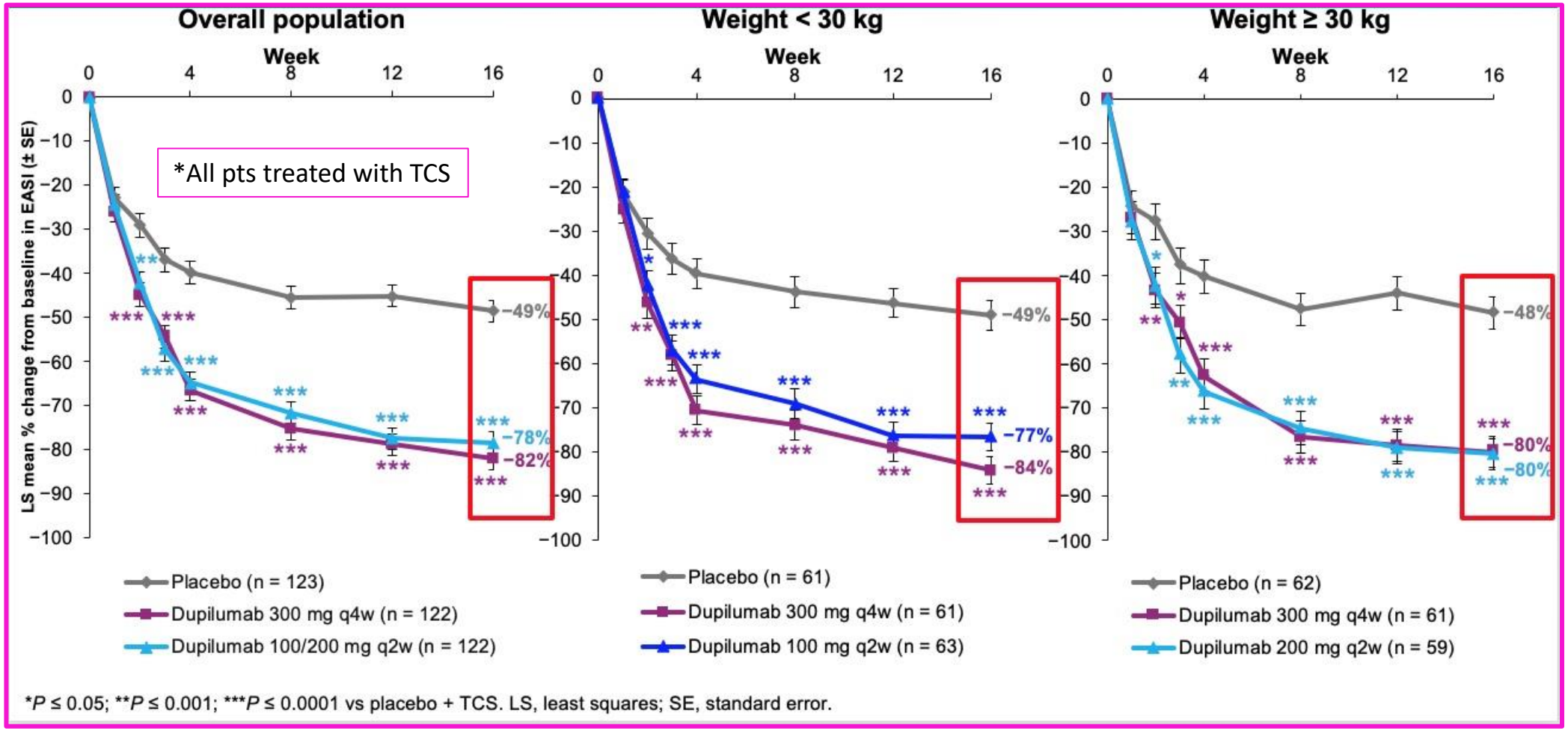
J Am Acad Dermatol 2020;83:1282-93

Proportion of patients achieving co-primary endpoint of EASI-75



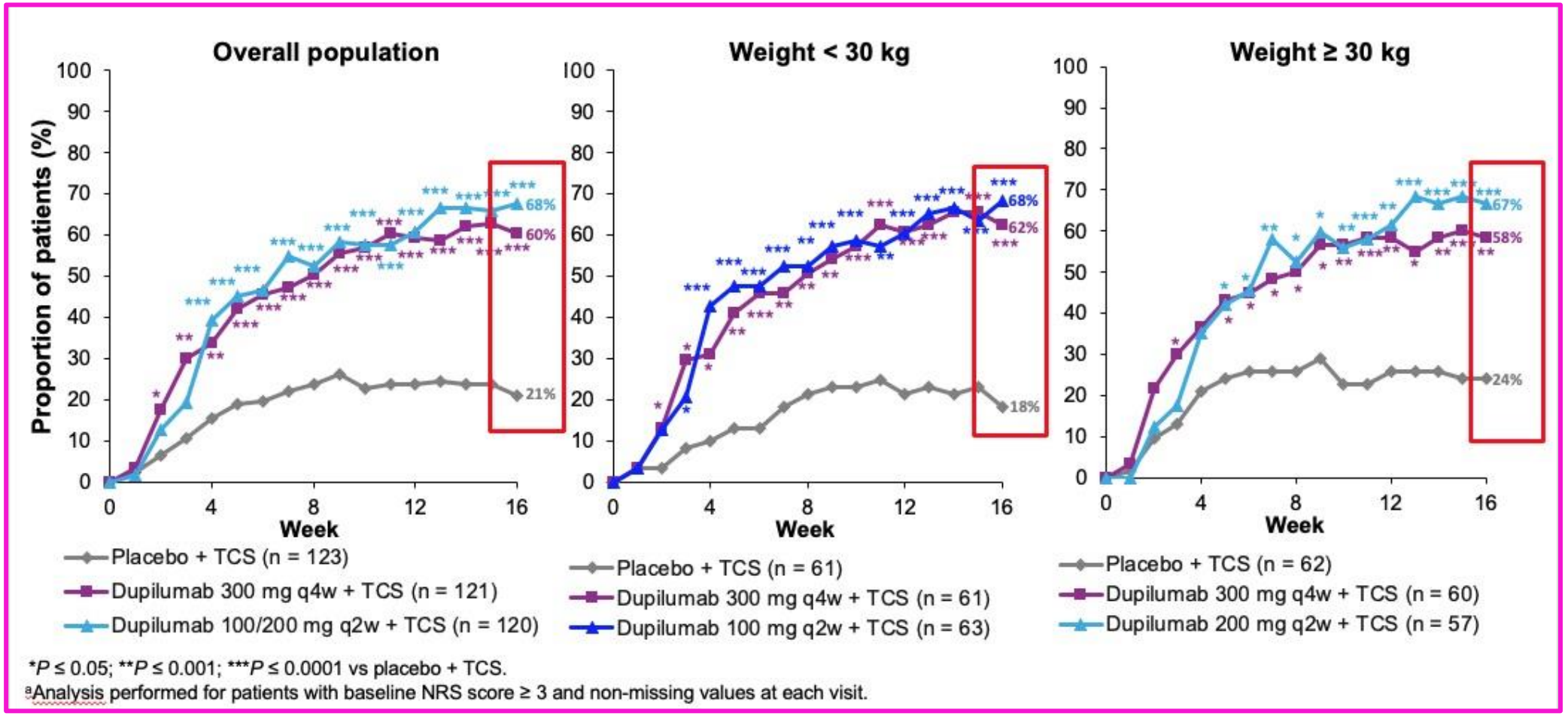
J Am Acad Dermatol 2020;83:1282-93

Percent change from baseline in EASI



J Am Acad Dermatol 2020;83:1282-93

Proportion of patients with ≥3 point improvement in weekly average of Peak Pruritus NRS



*$P \leq 0.05$; **$P \leq 0.001$; ***$P \leq 0.0001$ vs placebo + TCS.

[a]Analysis performed for patients with baseline NRS score ≥ 3 and non-missing values at each visit.

J Am Acad Dermatol 2020;83:1282-93

Safety assessment: other adverse events

	Placebo + TCS (n = 120)	Dupilumab 300 mg q4w + TCS (n = 120)	Dupilumab 100 mg or 200 mg q2w + TCS (n = 122)
Infections and infestations (SOC) , n (%)	61 (50.8)	52 (43.3)	49 (40.2)
Conjunctivitis cluster,[a,1] n (%)	5 (4.2)	8 (6.7)	18 (14.8)
Keratitis cluster,[b] n (%)	0	0	1 (0.8)
Skin infection (adjudicated),[c] n (%)	16 (13.3)	7 (5.8)	10 (8.2)
Injection-site reactions (HLT), n (%)	7 (5.8)	12 (10.0)	13 (10.7)
Herpes viral infections (HLT), n (%)	6 (5.0)	2 (1.7)	4 (3.3)

J Am Acad Dermatol 2020;83:1282-93

Conclusions

- Dupilumab + TCS showed clinically meaningful and statistically significant improvement in AD signs and symptoms in children aged ≥ 6 to < 12 years with severe AD
- Differences were observed in key efficacy parameters between the 300 mg q4w + TCS and 100 mg + TCS q2w in children weighing < 30 kg groups, and 200 mg q2w + TCS and 300 mg + TCS q4w in children ≥ 30 kg groups
- Dupilumab + TCS was well tolerated, and data were consistent with the known dupilumab safety profile observed in adults and adolescents

J Am Acad Dermatol 2020;83:1282-93

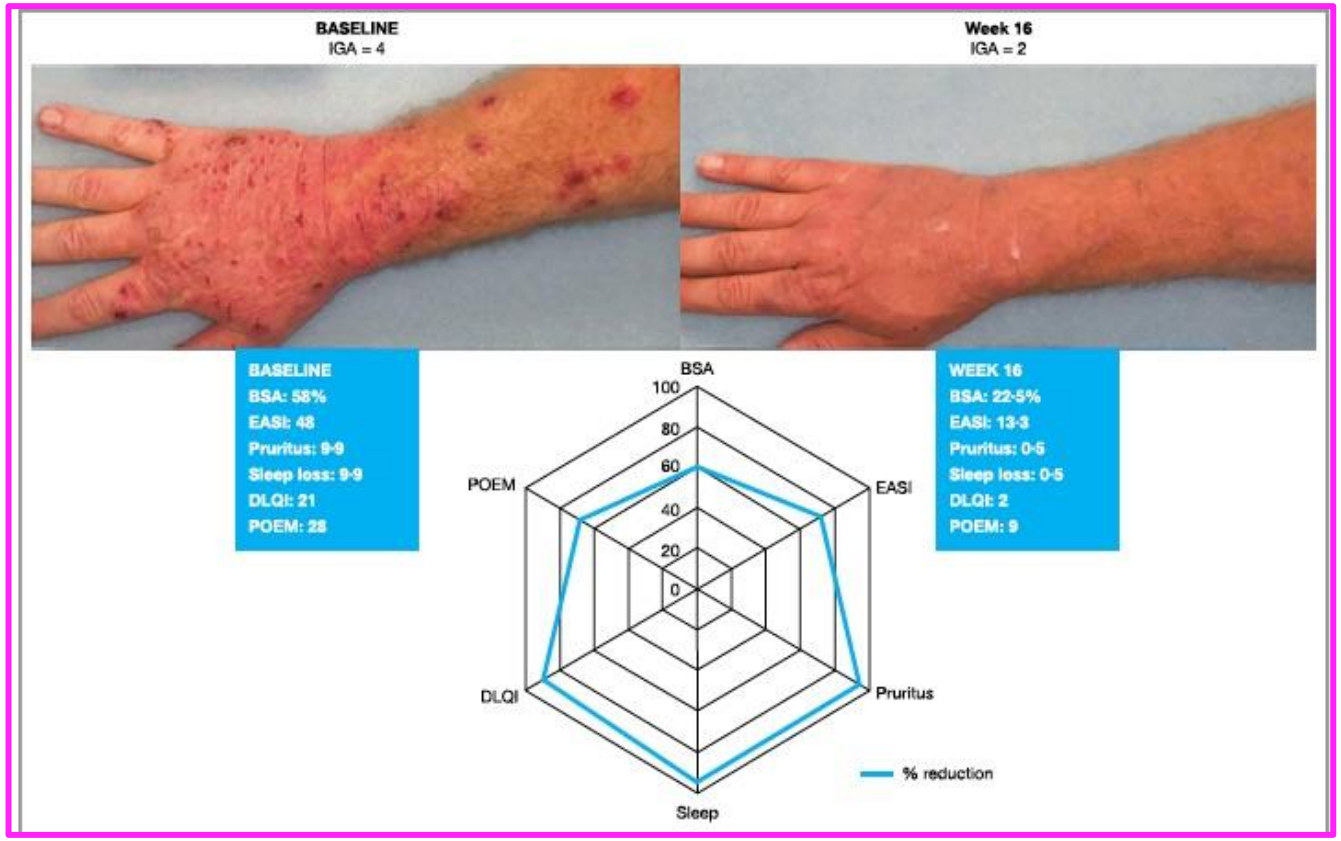
Current dupilumab approval in the United States

- Dupilumab approved in
  - Patients aged ≥ 12 years with moderate-to-severe AD uncontrolled by topical prescription medicines or when those medications are not advised
  - As add-on maintenance treatment in patients with moderate-to-severe asthma aged ≥ 12 years with an eosinophilic phenotype or with oral steroid dependent asthma
  - As add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis
  - Patients aged ≥ 6 years with moderate-to-severe AD uncontrolled by topical prescription medicines or when those medications are not advised [May 26, 2020]
- Dupilumab pediatric dosing in AD (subcutaneous injection)
  - ≥ 60 kg 600 mg x 1, 300 mg Q2W
  - 30 kg - < 60 kg 400 mg x 1, 200 mg Q2W
  - 15 kg - < 30 kg 600 mg x1, 300 mg Q4W

No laboratory monitoring required

- Safety, pharmacokinetics and efficacy of dupilumab in patients ≥6 mo to <6 yrs with severe AD (Liberty AD PRESCHOOL) (NCT03346434) – FDA submission anticipated 2022

Dupilumab provides important clinical benefits to patients with AD who do not achieve clear or almost clear skin according to the IGA: a pooled analysis of data from two phase III trials

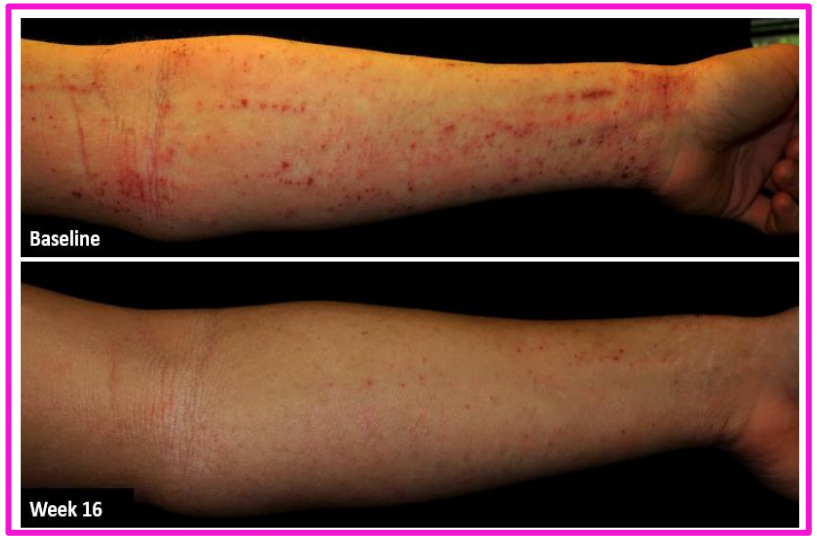


Among patients with IGA > 1 at wk 16, dupilumab significantly improved several outcome measures compared with placebo:

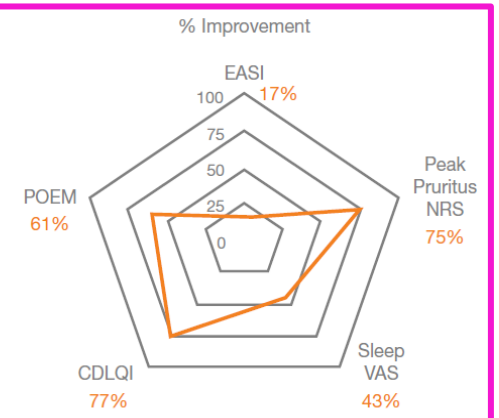
- EASI (-48·9% vs. -11·3%, P < 0·001)
- pruritus NRS (-35·2% vs. -9·1%, P < 0·001)
- affected BSA (-23·1% vs. -4·5%, P < 0·001)
- POEM score ≥ 4-point improvement (57·4% vs. 21·0%, P < 0·001)
- DLQI score ≥ 4-point improvement (59·3% vs. 24·4%, P < 0·001)

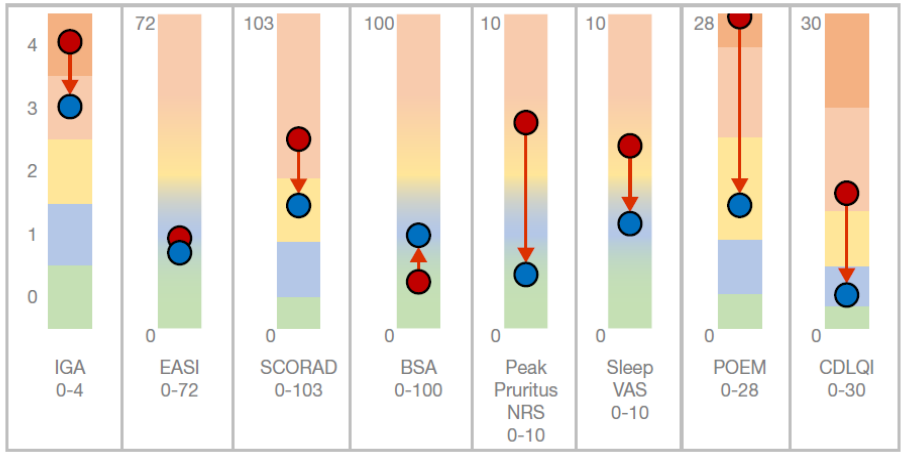
Silverberg JI, et al. Br J Dermatol 2019;181:80-87

Baseline and week 16 responses of two patients in the IGA > 1 subgroup: Patient 1



Outcome Threshold	Patient Response
IGA 0 or 1	No
EASI-50	No
Peak Pruritus NRS ≥3-point improvement from baseline	Yes
CDLQI ≥6-point improvement from baseline	Yes





Am J Clin Dermatol 2020;21:119-31

Conjunctivitis in dupilumab clinical trials

- Evaluation of randomized placebo-controlled trials of dupilumab in AD (n = 2629), asthma (n = 2876), CRSwNP (n = 60) and EoE (n = 47)
- Conjunctivitis more frequent with dupilumab treatment in most AD trials
- In dupilumab trials in other type 2 diseases, incidence of conjunctivitis overall very low and similar for dupilumab and placebo
- In AD, incidence of conjunctivitis associated with AD severity and prior history of conjunctivitis
- Etiology and treatment of conjunctivitis in dupilumab-treated patients require further study

Akinlade B, et al. Br J Dermatol 2019;181:459-473

Adolescent study pt on dupilumab, eczema well controlled but significant ocular irritation, tearing, photophobia x 1 month despite nedocromil gtt & artificial tears

- Evaluated and treated by Ophthalmology with topical steroid gtt (FML QID x1 wk, taper over next 4 wks)
- Continued on dupilumab, nedocromil gtt & artificial tears
- Considering changing dupilumab dosing to Q3-4 wks

Patient photo

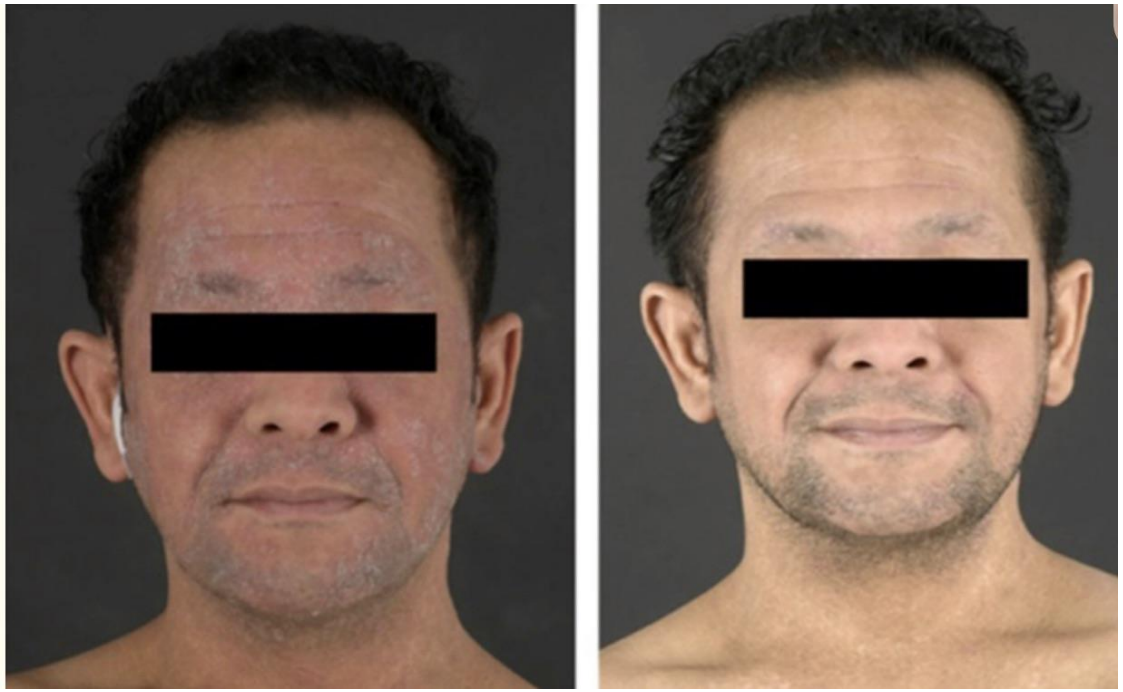
Periocular dermatitis

Patient photo

Bilateral conjunctivitis

Dupilumab facial redness: Positive effect of itraconazole

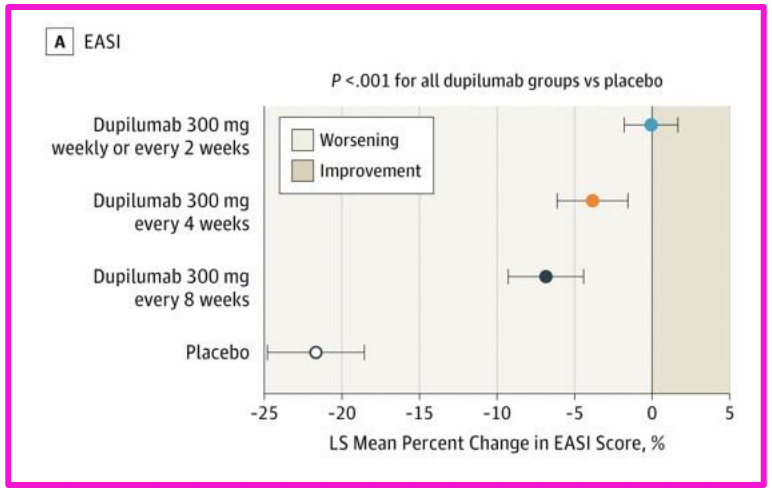
› Case reports describe ACD, *Malassezia* hypersensitivity, rosacea, drug reaction and psoriasis

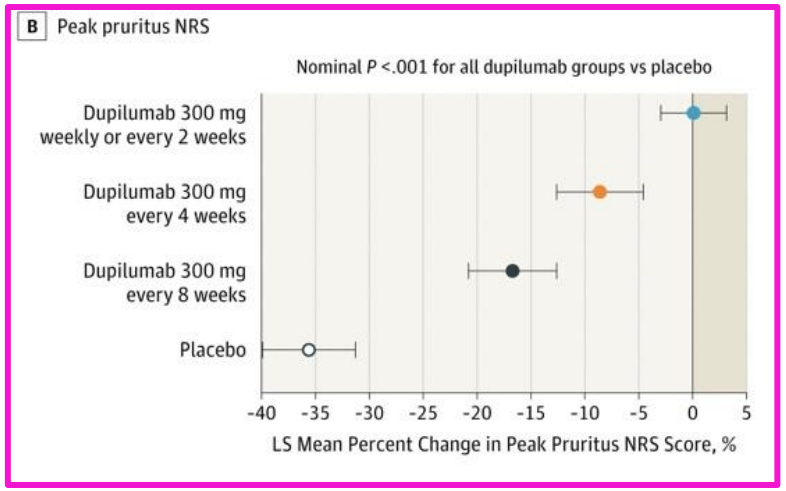


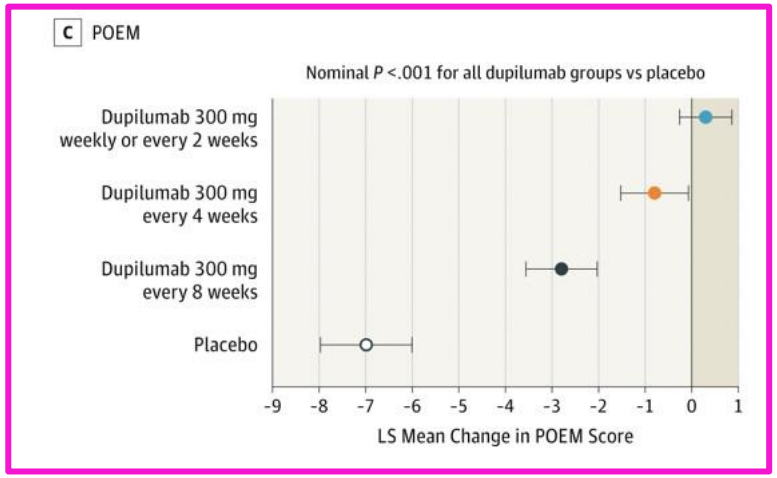
Adult with DFR & elevated serum *Malassezia*-specific IgE, responsive to itraconazole while continuing on dupilumab

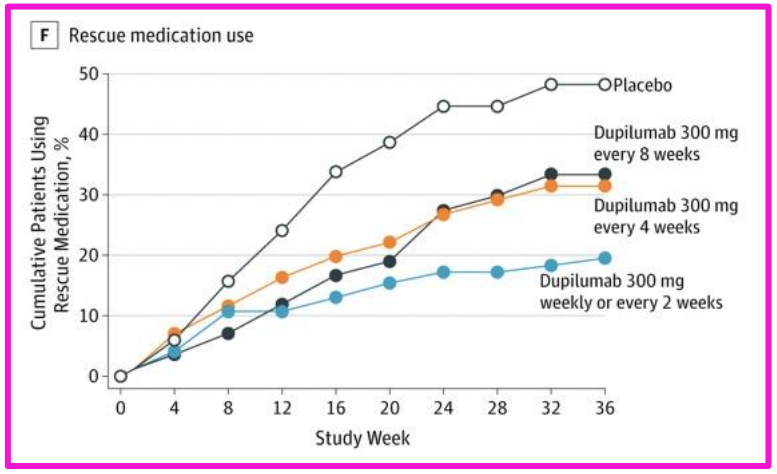
JAAD Case Rep 2019;5: 888; Br J Dermatol 2020;183:745-9

Efficacy and safety of multiple dupilumab dose regimens after initial successful treatment in patients with atopic dermatitis: A randomized clinical trial



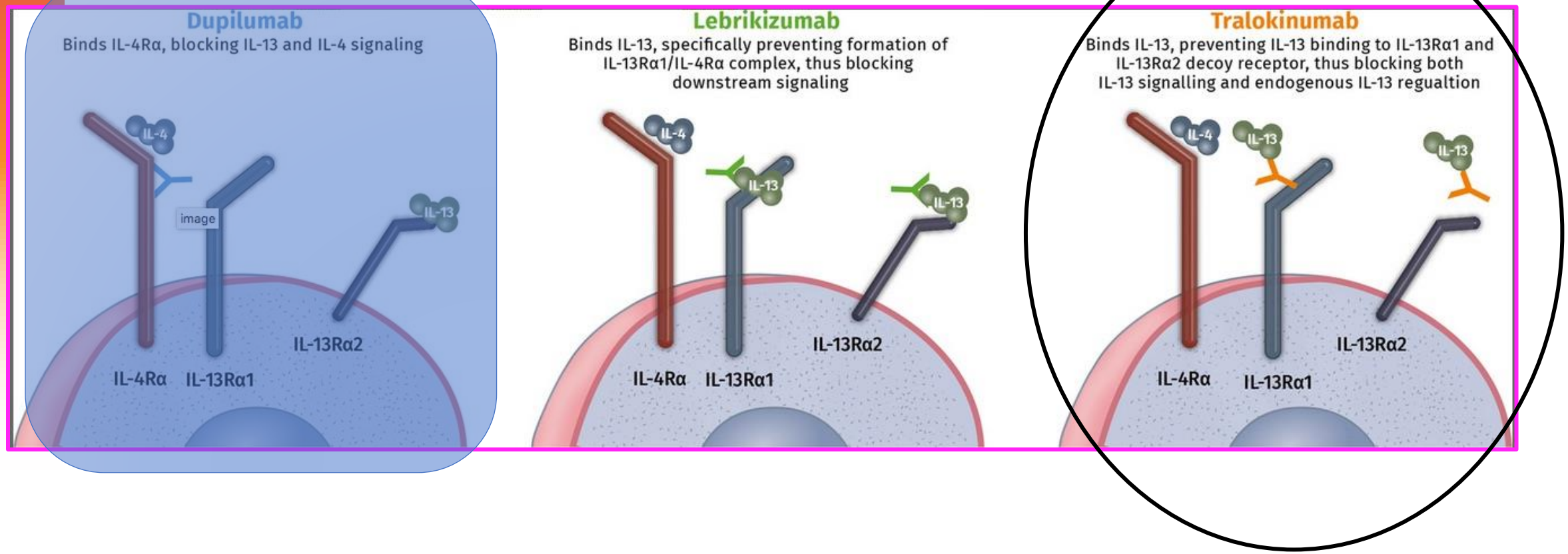






JAMA Dermatol 2020;156:131-143

Mechanism of action for biologics targeting the IL-4 and/or IL-13 pathways



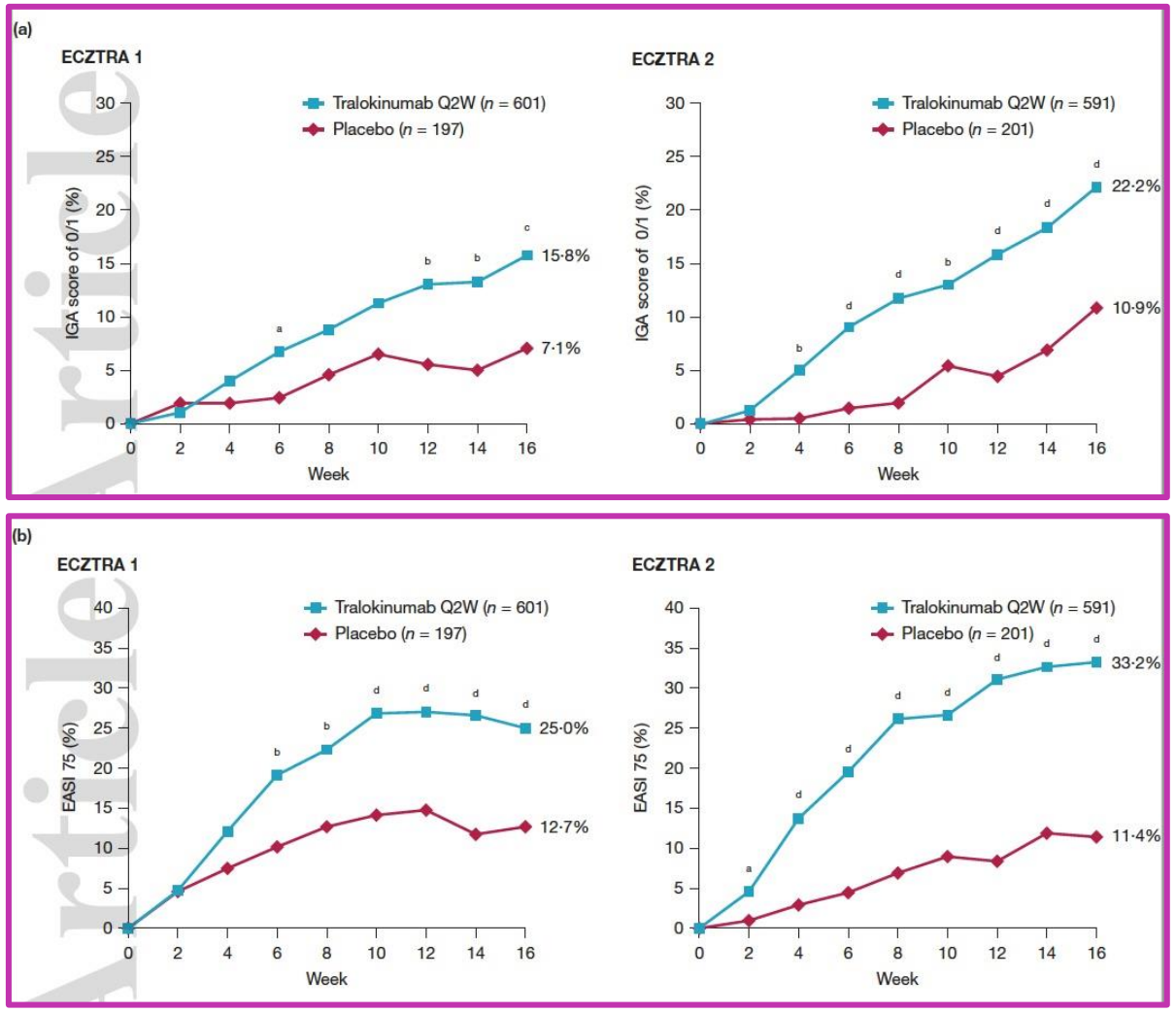
Exp Dermatol 2019;28:756

Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2)

- Adults with moderate-to-severe AD randomized (3 : 1) to subQ tralokinumab 300 mg Q2W or placebo
- Primary endpoints were IGA 0 /1 at wk 16 and EASI 75 at wk 16; Pts with IGA 0/1 and/or EASI 75 with tralokinumab at wk 16 re-randomized to tralokinumab Q2W or Q4W or placebo for 36 wks
- At wk 16, more pts on tralokinumab vs placebo achieved IGA 0/1: 15.8% vs 7.1% in ECZTRA 1 [$P = 0{\cdot}002$] and 22.2% vs 10.9% in ECZTRA 2 [$P < 0{\cdot}001$] and EASI 75: 25% vs 12.7% [$P < 0{\cdot}001$] and 33.2% vs 11·4% [$P < 0{\cdot}001$]
- AEs reported in 76.4% and 61.5% of pts on tralokinumab and in 77.0% and 66% of pts on placebo in 16-wk initial period (conjunctivitis 7%/3%)
- Tralokinumab monotherapy was superior to placebo at 16 wks of treatment and was well tolerated up to 52 wks of treatment

Br J Dermatol 2021;184:437-49

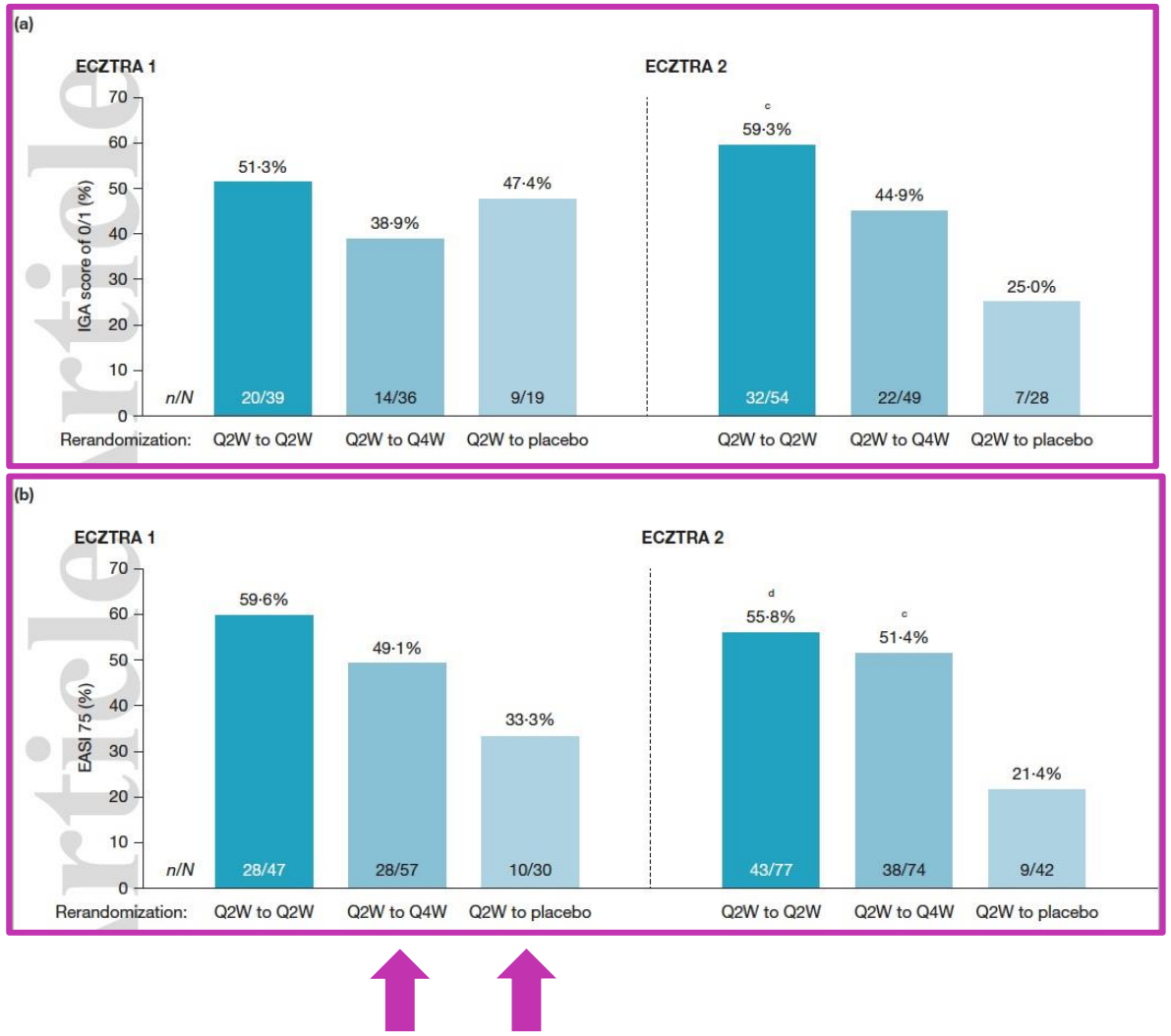
Achievement of (a) IGA score of 0/1 and (b) EASI 75 in the 16-week initial treatment period in ECZTRA 1 and ECZTRA 2



[a]P < 0·05 vs. placebo, [b]P < 0·01 vs. placebo, [c]P = 0·002 vs. placebo, [d]P < 0·001 vs. placebo

Br J Dermatol 2021;184:437-49

Maintenance of (a) IGA score of 0/1* and (b) EASI 75* clinical response at week 52 in ECZTRA 1 and ECZTRA 2



*Assessed in pts achieving W16 primary outcome of IGA or EASI75 score without use of rescue medication after initial randomization to tralokinumab

Br J Dermatol 2021;184:437-49

Tralokinumab plus topical corticosteroids for the treatment of moderate-to-severe atopic dermatitis: results from the double-blind, randomized, multicentre, placebo-controlled phase III ECZTRA 3 trial

- Pts randomized 2 : 1 to subQ tralokinumab 300 mg or placebo Q2W & PRN TCS for 16 wks. Pts achieving IGA of 0/1 and/or EASI 75 at wk 16 with tralokinumab re-randomized 1 : 1 to tralokinumab Q2W or Q4W, with TCS as needed, for another 16 wks
- At wk 16, more tralokinumab-treated patients than placebo achieved IGA 0/1: 38.9% vs. 26.2% [$P = 0{\cdot}015$] and EASI 75: 56% vs. 35.7% [$P < 0{\cdot}001$]
  - Of tralokinumab responders at wk 16, 89.6% and 92.5% treated with tralokinumab Q2W and 77.6% and 90.8% treated with tralokinumab Q4W maintained an IGA 0/1 and EASI 75 response at wk 32, respectively
  - Among patients who did not achieve an IGA 0/1 and EASI 75 with tralokinumab Q2W at 16 weeks, 30.5% and 55.8% achieved these endpoints, respectively, at week 32
- Overall incidence of AEs was similar across treatment groups
  - Conjunctivitis reported in 11% in tralokinumab pts
- Tralokinumab 300 mg in combination with TCS as needed was effective and well tolerated in pts with moderate-to-severe AD

Br J Dermatol 2021;184:450-63

Other tralokinumab trials

- Tralokinumab Monotherapy for Adolescent Subjects With Moderate to Severe Atopic Dermatitis - ECZTRA 6 (NCT03526861)
- Long-term Extension Trial in Subjects With Atopic Dermatitis Who Participated in Previous Tralokinumab Trials – ECZTEND (NCT03587805) **-** Up to week 142
- Vaccine Responses in Tralokinumab-Treated Atopic Dermatitis - ECZTRA 5 (NCT03562377) - Tdap, meningococcal [JAAD 2021; in press]
- Tralokinumab in Combination With Topical Corticosteroids in Subjects With Severe Atopic Dermatitis Who Are Not Adequately Controlled With or Have Contraindications to Oral Cyclosporine A (ECZTRA 7) (NCT03761537)
- Drug-drug Interaction Trial With Tralokinumab in Moderate to Severe Atopic Dermatitis - ECZTRA 4 (NCT03556592)
  - Investigate Effects of Tralokinumab on Pharmacokinetics of Selected Cytochrome P450 Substrates in Adult Subjects With Moderate-to-severe AD (caffeine, warfarin, omeprazole, metoprolol, midazolam)

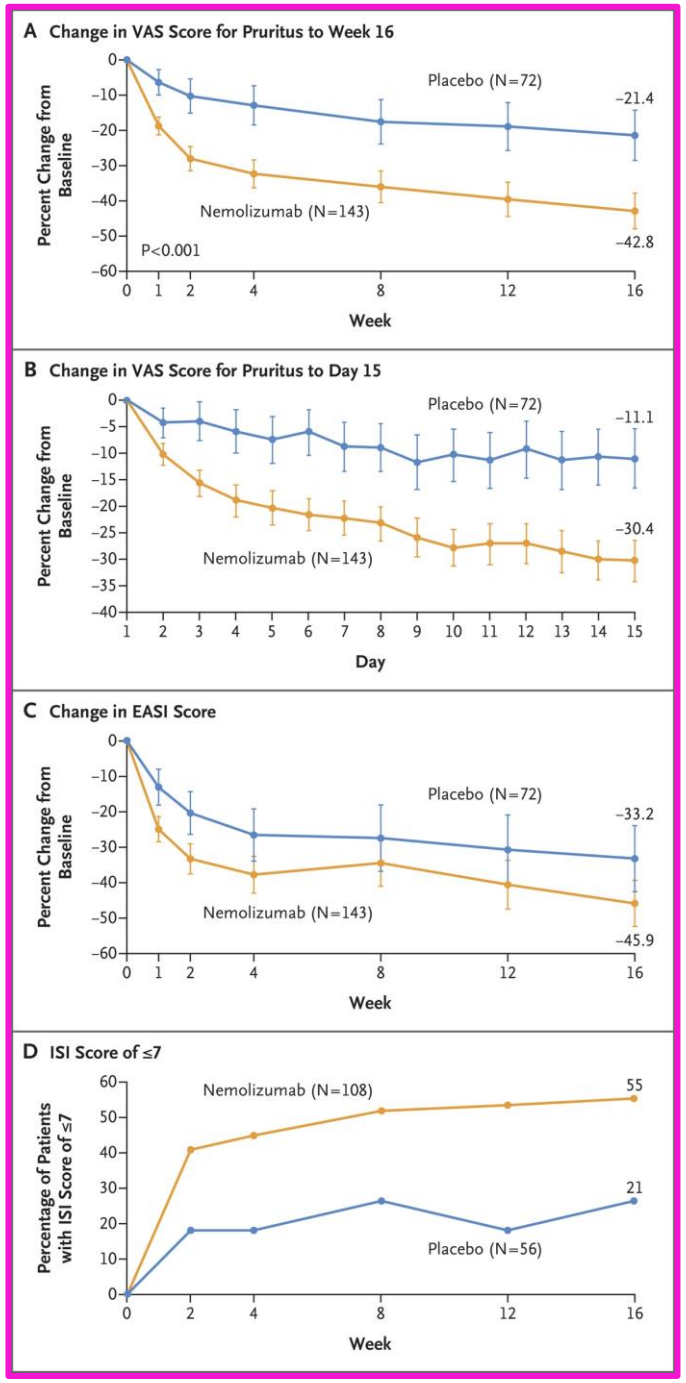
Trial of nemolizumab and topical agents for AD with pruritus

- Nemolizumab is a subcutaneously administered humanized monoclonal antibody against interleukin-31 receptor A
- 16 wk, double-blind, phase 3 trial in Japanese patients with AD and moderate-to-severe pruritus and inadequate response to topical agents 2:1 to subcut nemolizumab (60 mg) or placebo Q 4 wks with concomitant topical agents
  - 143 patients randomly assigned to nemolizumab and 72 to placebo
- Primary end point was mean % change in VAS score for pruritus (0 to 100) from baseline to wk 16
  - Median VAS score for pruritus at baseline was 75
- At wk 16 mean % change in VAS score was -42.8% in nemolizumab group and -21.4% in placebo group ($P<0.001$)
- Mean % change in EASI score was -45.9% with nemolizumab and -33.2% with placebo

Kabashima K, et al. N Engl J Med 2020 383:141

Trial of nemolizumab and topical agents for AD with pruritus

- Subcutaneous nemolizumab in addition to topical agents for AD resulted in a greater reduction in pruritus than placebo plus topical agents
- Incidence of injection-site reactions was greater with nemolizumab than with placebo



Kabashima K, et al. N Engl J Med 2020 383:141

Use of biologics during COVID-19 pandemic

Considerations on Biologicals for Patients with allergic disease in times of the COVID-19 pandemic: an EAACI Statement

- Non-infected patients on biologicals for the treatment of asthma, atopic dermatitis, chronic rhinosinusitis with nasal polyps or chronic spontaneous urticaria should continue their biologicals targeting type 2 inflammation
- In case of an active SARS-CoV-2 infection, biological treatment needs to be stopped until clinical recovery and SARS-CoV-2 negativity is established and treatment with biologicals should be re-initiated

Allergy 2020;75:2764

Biologics for Atopic Dermatitis

Mark Boguniewicz, MD

KEYWORDS

• Atopic dermatitis • Biologics • Dupilumab • Immune dysregulation • Lebrikizumab • Nemolizumab • Omalizumab • Tralokinumab

KEY POINTS

- The pathophysiology of atopic dermatitis includes both skin barrier and immune abnormalities, with type 2 immune deviation central to several clinical phenotypes and underlying endotypes.
- Recognition of the persistent nature and systemic aspects of atopic dermatitis provides a rationale for treatment with a biologic.
- Dupilumab, a biologic that targets type 2 immunity by blocking interleukin (IL)-4 and IL-13 binding to IL-4 receptor alpha, has been approved for patients 6 years of age and older with moderate to severe atopic dermatitis.
- Monoclonal antibodies targeting IL-13 and IL-31 receptor A are in phase 3 trials, whereas other targets include IL-33, thymic stromal lymphopoietin, OX40, and IL-22 and may become part of a precision medicine approach to atopic dermatitis.

INTRODUCTION

Atopic dermatitis (AD) is a common chronic inflammatory skin disease that has become a global health problem.[1,2] The Global Burden of Disease Study showed that dermatitis, including AD, was the leading skin disease in terms of global burden of disease measured by disability-adjusted life years.[3] Epidemiologic studies in the United States have shown prevalence of up to 18% in school-aged children[4] and 7% in adults responding in the Atopic Dermatitis in America survey.[5] In this survey, 29% were classified as having moderate disease and 11% as having severe disease. As a chronic, relapsing pruritic disease, AD has a profound impact on the quality of life of patients and families.[6] In a study of adults with moderate to severe AD, 85% reported problems with itch frequency, 41.5% reported itching greater than or equal to 18 h/d, 55% reported AD-related sleep disturbance greater than or equal to 5 d/wk, and 21.8% reported clinically relevant anxiety or depression.[7] Atopic comorbidities of AD, including asthma and allergies, are well recognized, although identifying patients at increased risk for an atopic march remains problematic.[8] Nonatopic comorbidities, including neuropsychiatric and cardiovascular disorders, are also being reported.[9–11]

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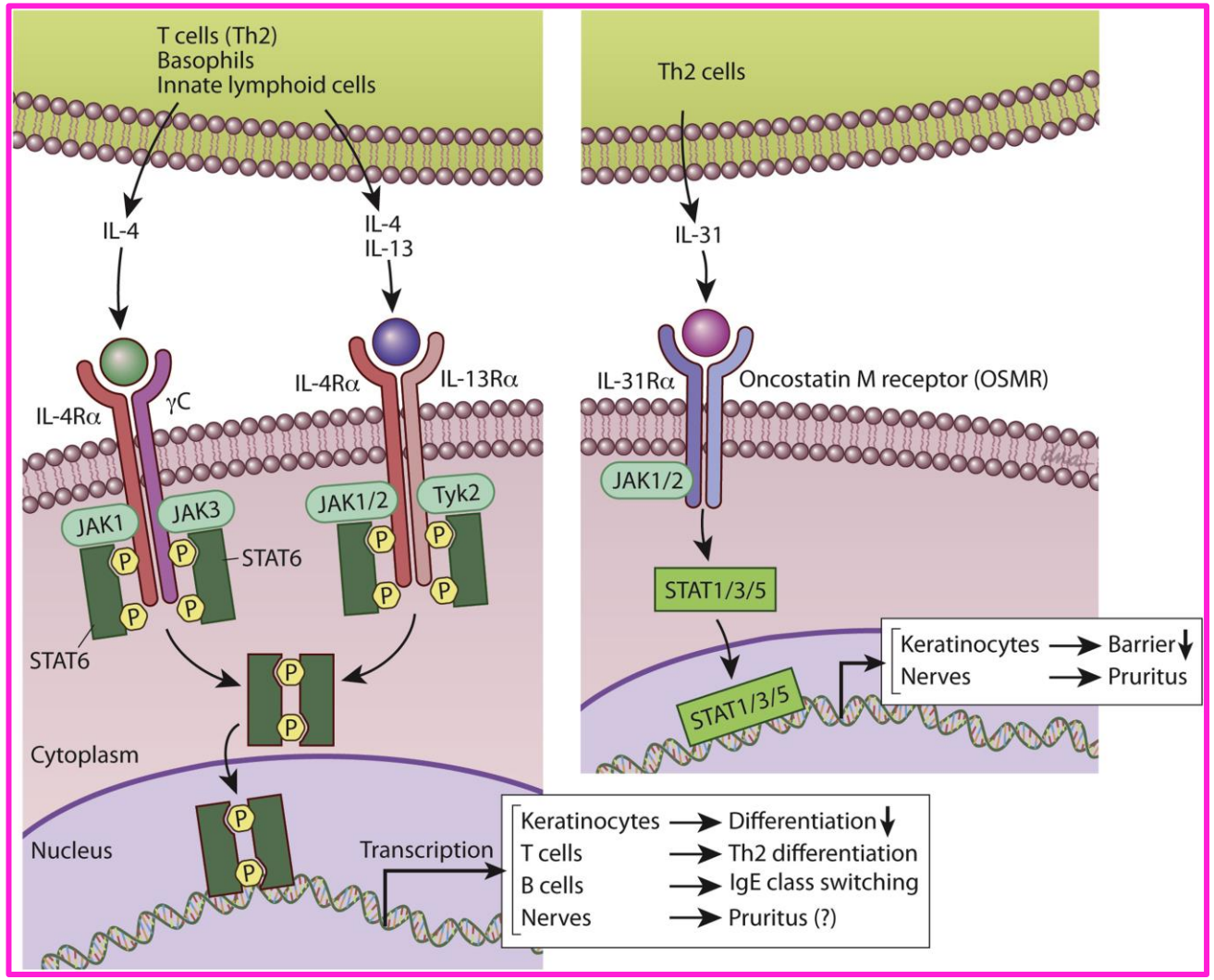
Denver COVID-19 street art

JAK-STAT signaling as a therapeutic target

Biologic

Biologic

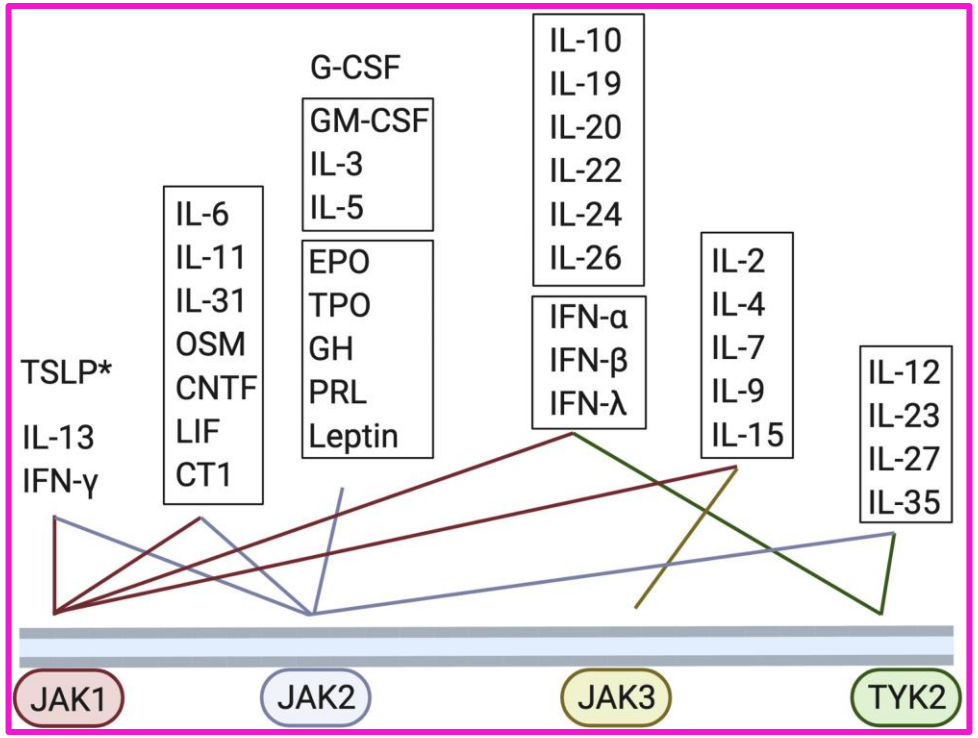
JAKi



The JAK-STAT pathway is a master regulator
of immune function, implicated in the downstream signaling of inflammatory cytokines, including ILs, IFNs, and multiple growth factors

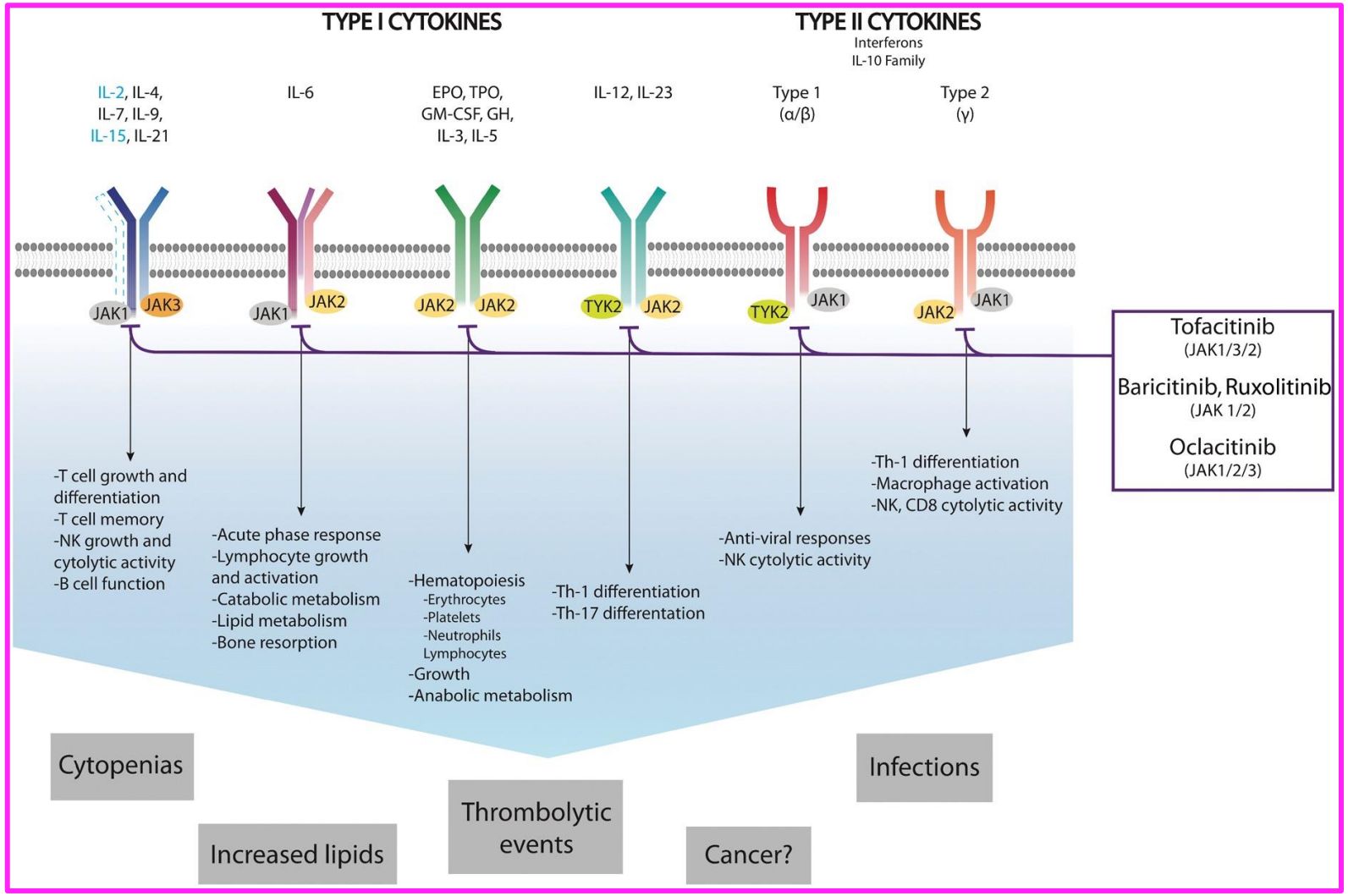
Paller AS, et al. J Allergy Clin Immunol 2017;140:633

Cytokine, growth factor and IFN signaling via distinct JAK proteins



Damsky W, et al. J Allergy Clin Immunol 2021;147:814-26

JAK usage and putative relationship to adverse events



Gadina M, et al. Rheumatology 2019;58:i4

JAK inhibitors in AD

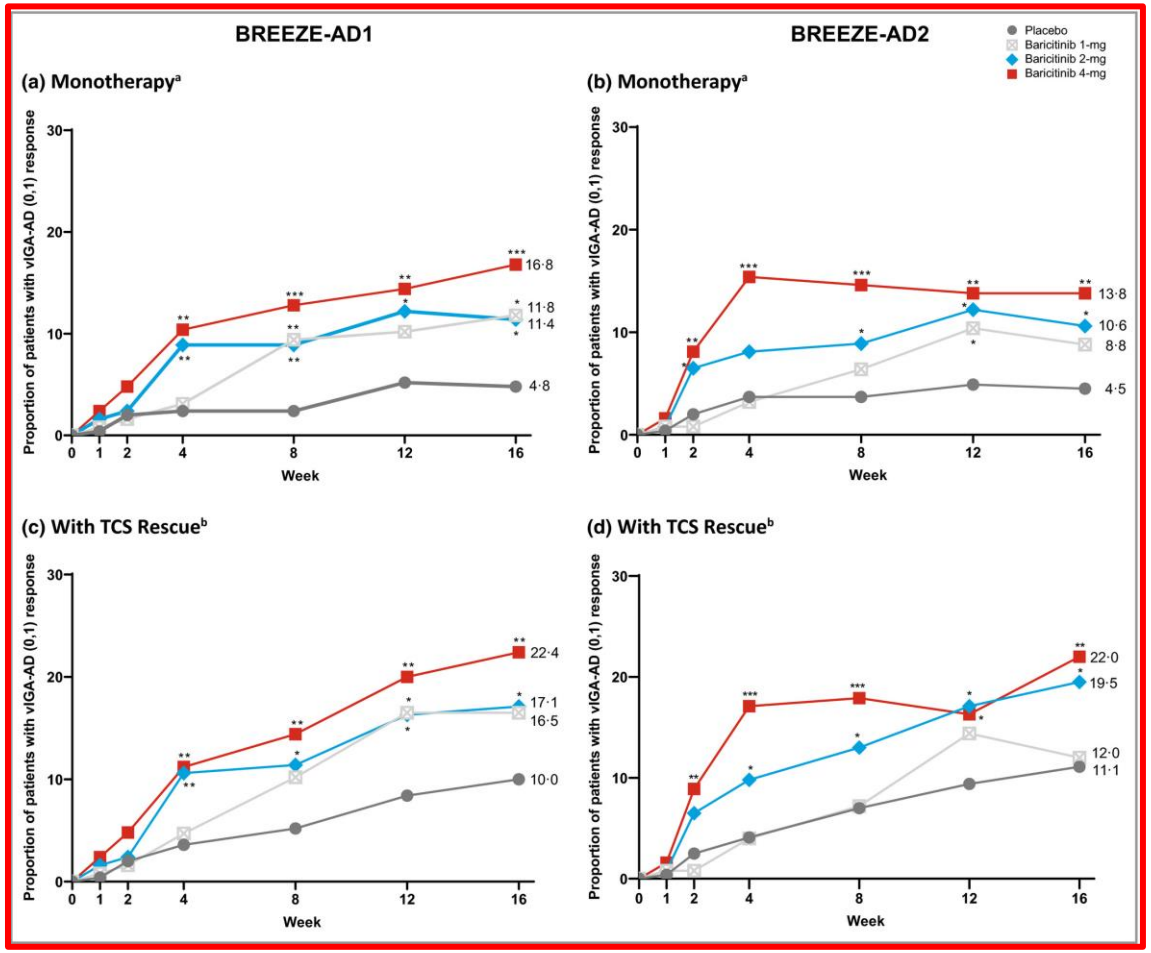
- Oral
  - Baricitinib (JAK1/2)
  - Abrocitinib (JAK 1)
  - Upadacitinib (JAK 1)
- Topical
  - Ruxolitinib (JAK 1/2)
  - Delgocitinib (pan-JAK)

Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials

- 2 multicentre, DB, P3 monotherapy trials (BREEZE-AD1 and-AD2), adults with moderate-to-severe AD randomized 2 : 1 : 1 : 1 to once-daily placebo, baricitinib 1 mg, 2 mg, or 4 mg for 16 wks
- At wk 16, more pts achieved primary end point of Validated IGA-AD (0, 1) on baricitinib 4 mg and 2 mg vs placebo in BREEZE-AD1 [*N* = 624; baricitinib 4 mg 16·8% (*P* < 0·001), 2 mg 11·4% (*P* < 0·05), 1 mg 11·8% (*P* < 0·05), placebo 4·8%] and BREEZE-AD2 [*N* = 615; baricitinib 4 mg 13·8% (*P* = 0·001), 2 mg 10·6% (*P* < 0·05), 1 mg 8·8% (*P* = 0·085), placebo 4·5%]
- Improvement in itch achieved as early as wk 1 for 4 mg and wk 2 for 2 mg
- Improvements in night-time awakenings, skin pain and QoL measures observed by wk 1 for both 4 mg and 2 mg (*P* ≤ 0·05, all comparisons)
- Most common AEs in pts treated with baricitinib were nasopharyngitis and H/A

Br J Dermatol 2020;183:242-55

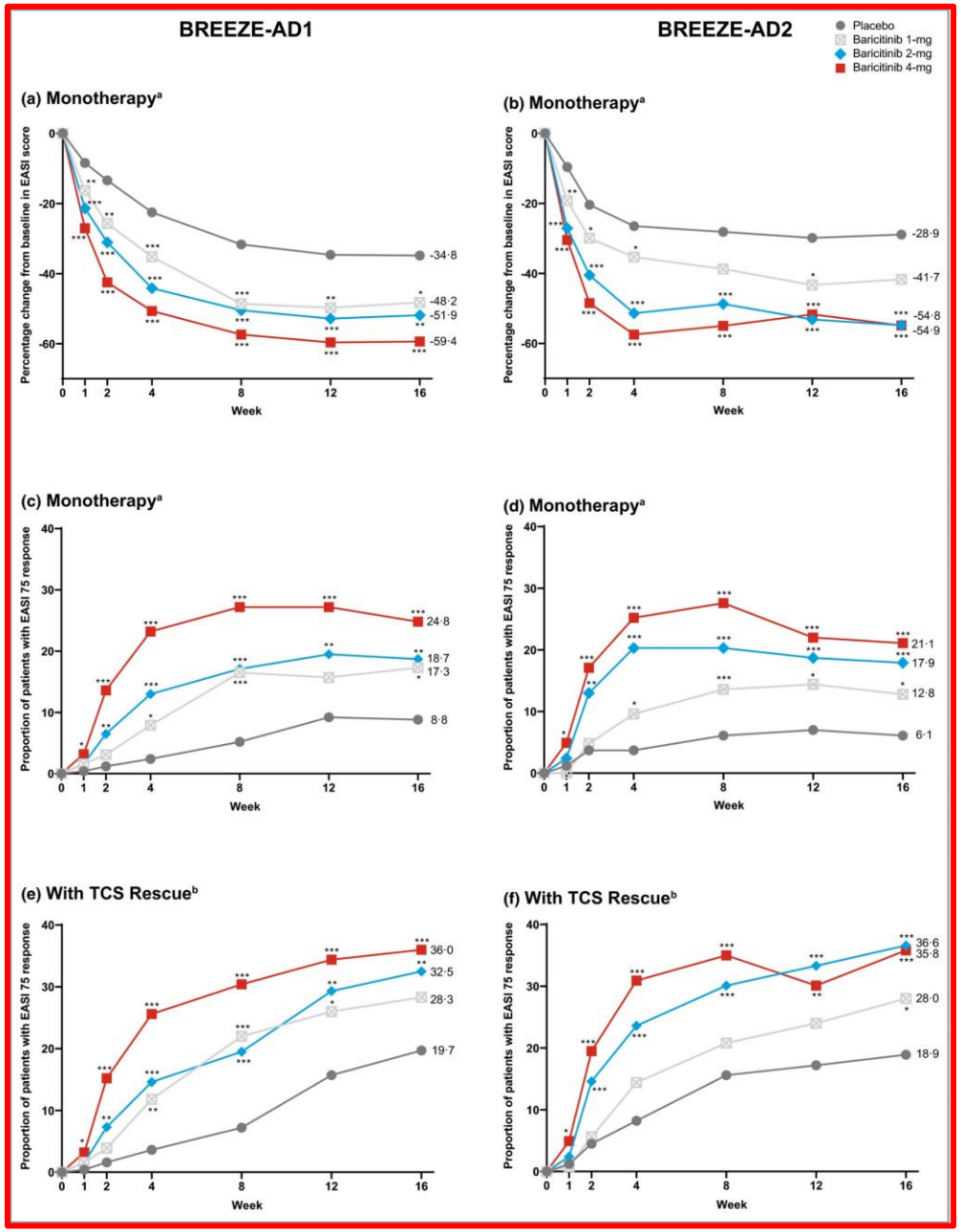
Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials



*$P \leq 0{\cdot}05$, **$P \leq 0{\cdot}01$ and ***$P \leq 0{\cdot}001$ comparing baricitinib with placebo

Br J Dermatol 2020;183:242-55

Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials



*$P \leq 0{\cdot}05$, **$P \leq 0{\cdot}01$ and ***$P \leq 0{\cdot}001$ baricitinib vs placebo

Br J Dermatol 2020;183:242-55

Extended Safety Analysis of Baricitinib 2 mg in Adult Patients with Atopic Dermatitis: An Integrated Analysis from Eight Randomized Clinical Trials

- In 6 DBPC randomized studies and 2 long-term extension studies, 1598 pts received QD baricitinib 2 mg for 1434.2 pt-yrs of exposure (median 330 days/max 2.4 yrs)
- TEAEs higher for baricitinib 2 mg (57.9%) vs placebo (51.6%)
- Serious AEs, serious infections, and opportunistic infections were low in frequency and similar between baricitinib 2 mg and placebo
- No malignancies, GI perforations, or MACE with baricitinib 2 mg in placebo-controlled period
- HSV (cluster) higher for baricitinib 2 mg (3.8%) vs placebo (2.8%); rates decreased with extended 2 mg exposure
- In All-bari-2-mg-AD, 5 malignancies other than NMSC, 2 MACE, 1 peripheral venous thrombosis, one arterial thrombosis and no PE, deep vein thromboses, or deaths

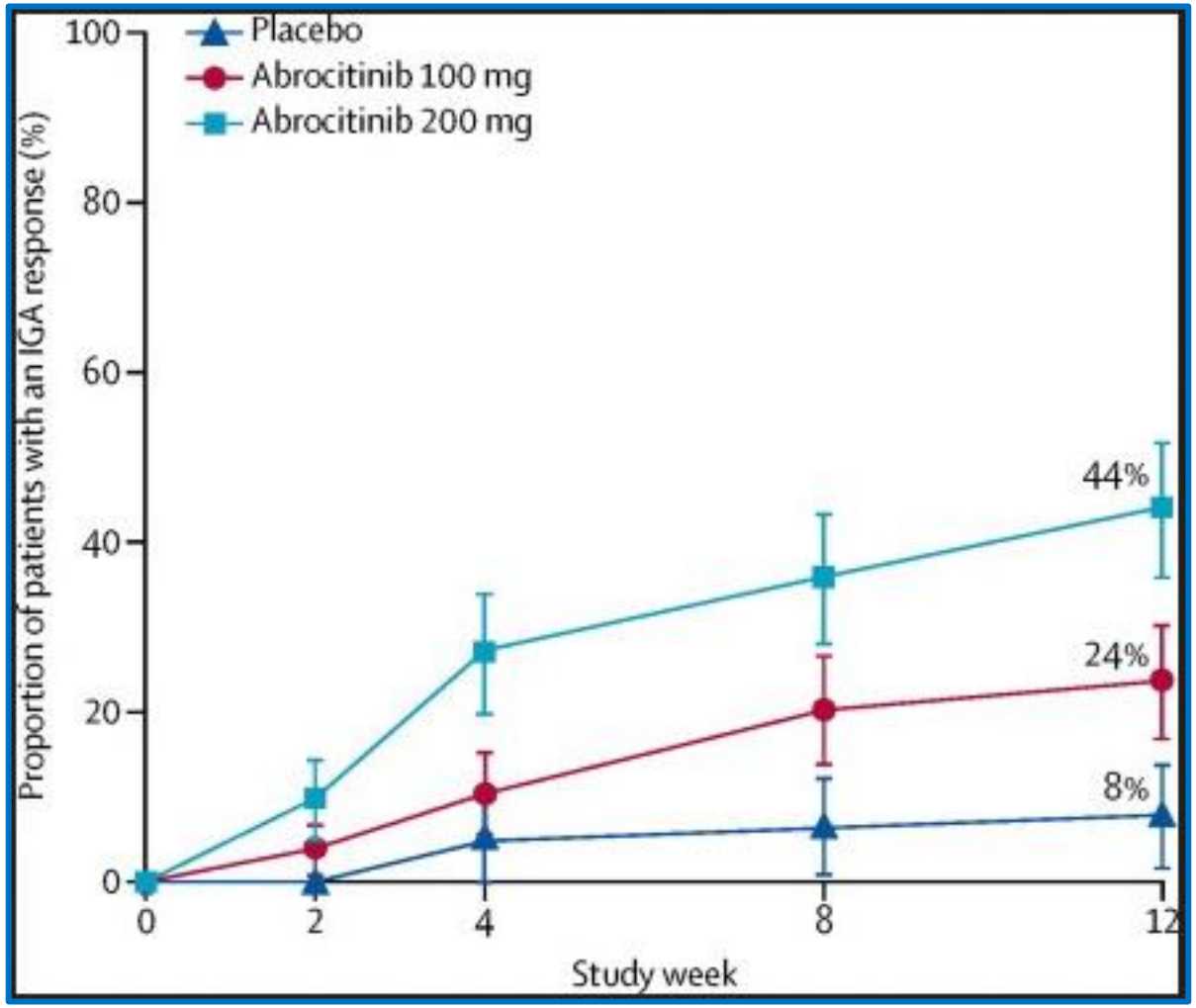
Am J Clin Dermatol 2021 May;22:395-405

Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial

- Multicentre, double-blind, randomised P3 trial (JADE MONO-1), pts ≥12 years (≥ 40 kg) with moderate-to-severe AD (IGA ≥3, EASI ≥16, BSA ≥10%, and PP-NRS score ≥4 enrolled at 69 sites in Australia, Canada, Europe, and USA
- Pts randomly assigned (2:2:1) to oral abrocitinib 100 mg, abrocitinib 200 mg or placebo once daily for 12 wks

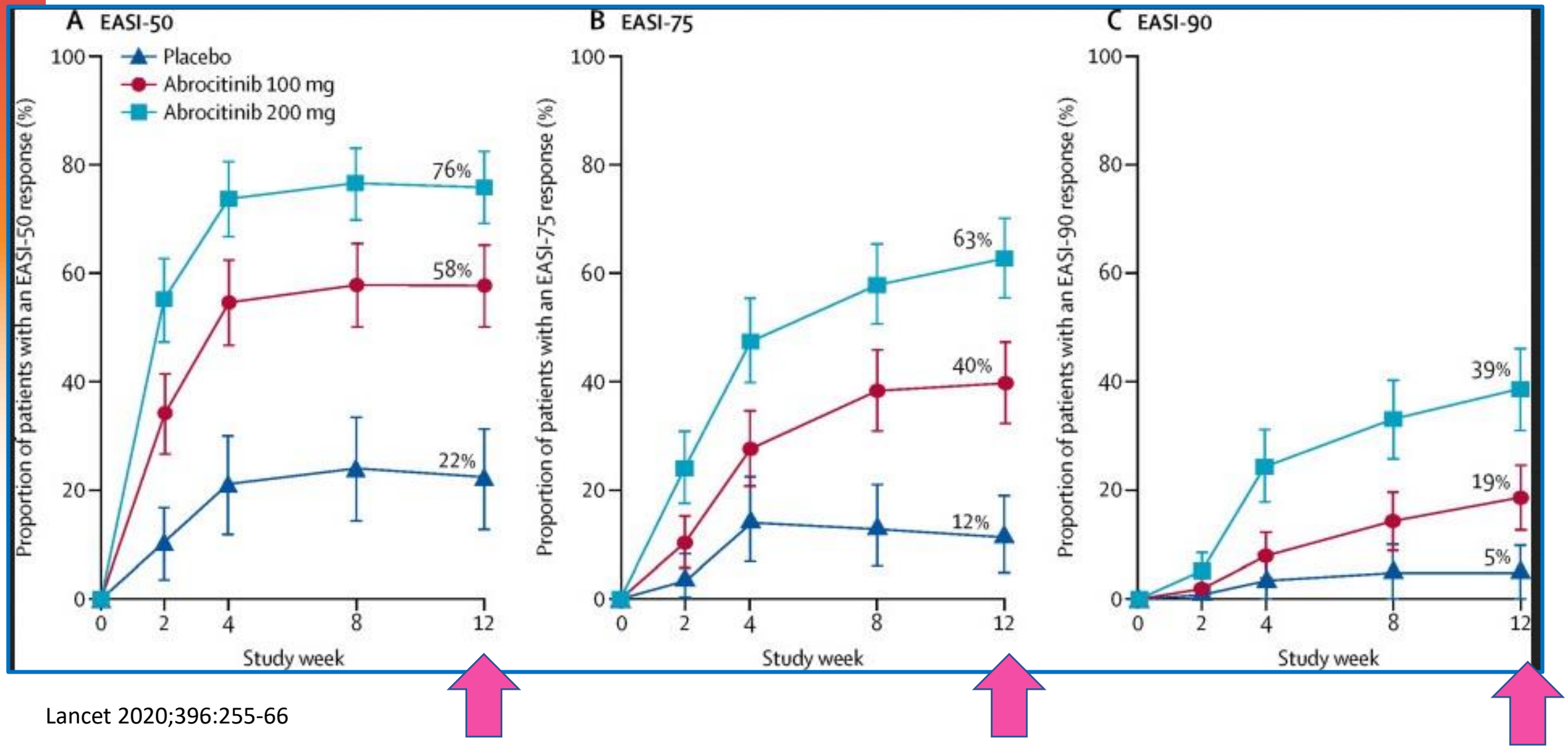
Lancet 2020;396:255-66

Proportion of patients who achieved an IGA response over the 12-week treatment period



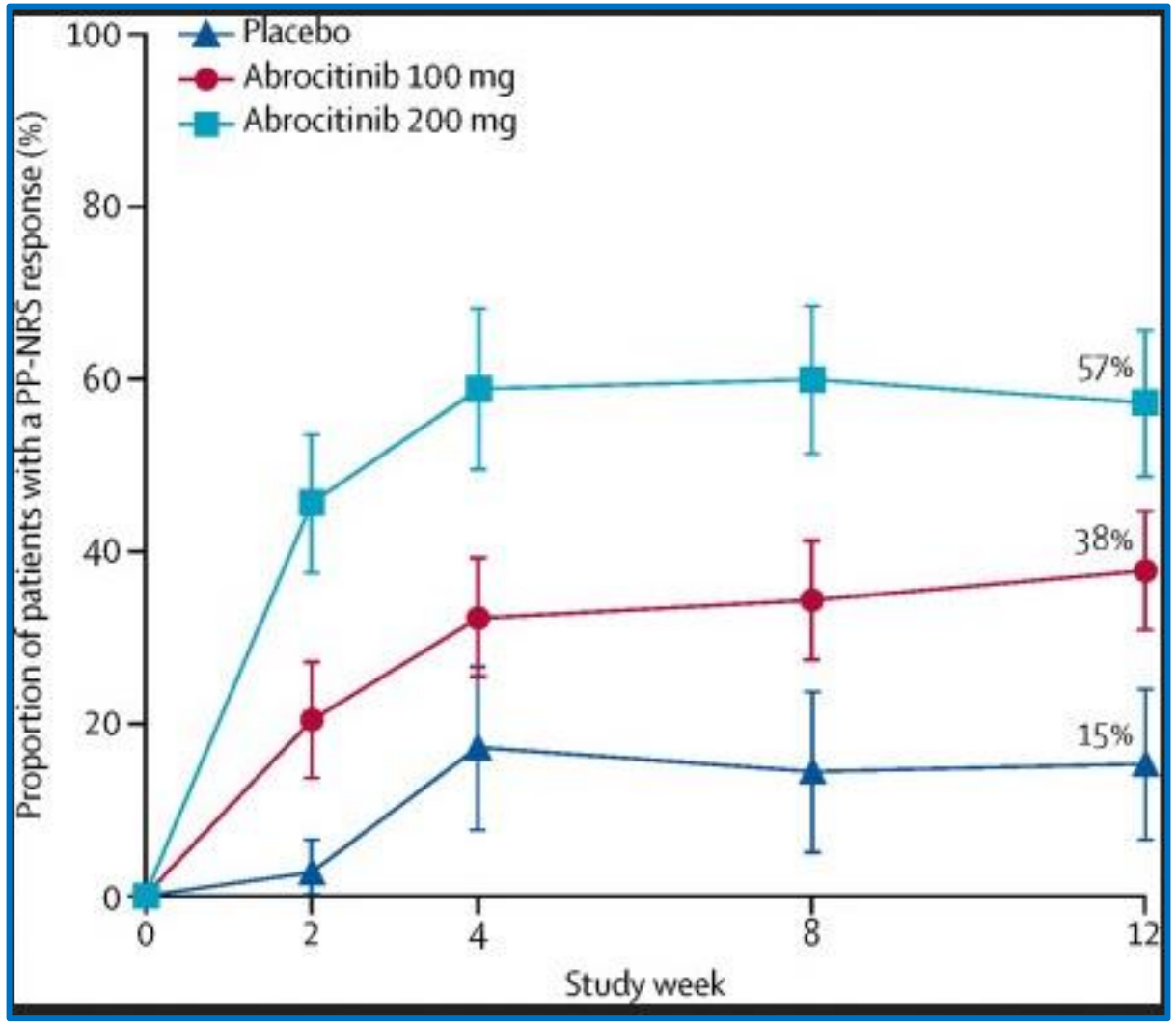
Lancet 2020;396:255-66

Proportion of patients who achieved an EASI-50 (A), EASI-75 (B), and EASI-90 (C) response over the 12-week treatment period



Lancet 2020;396:255-66

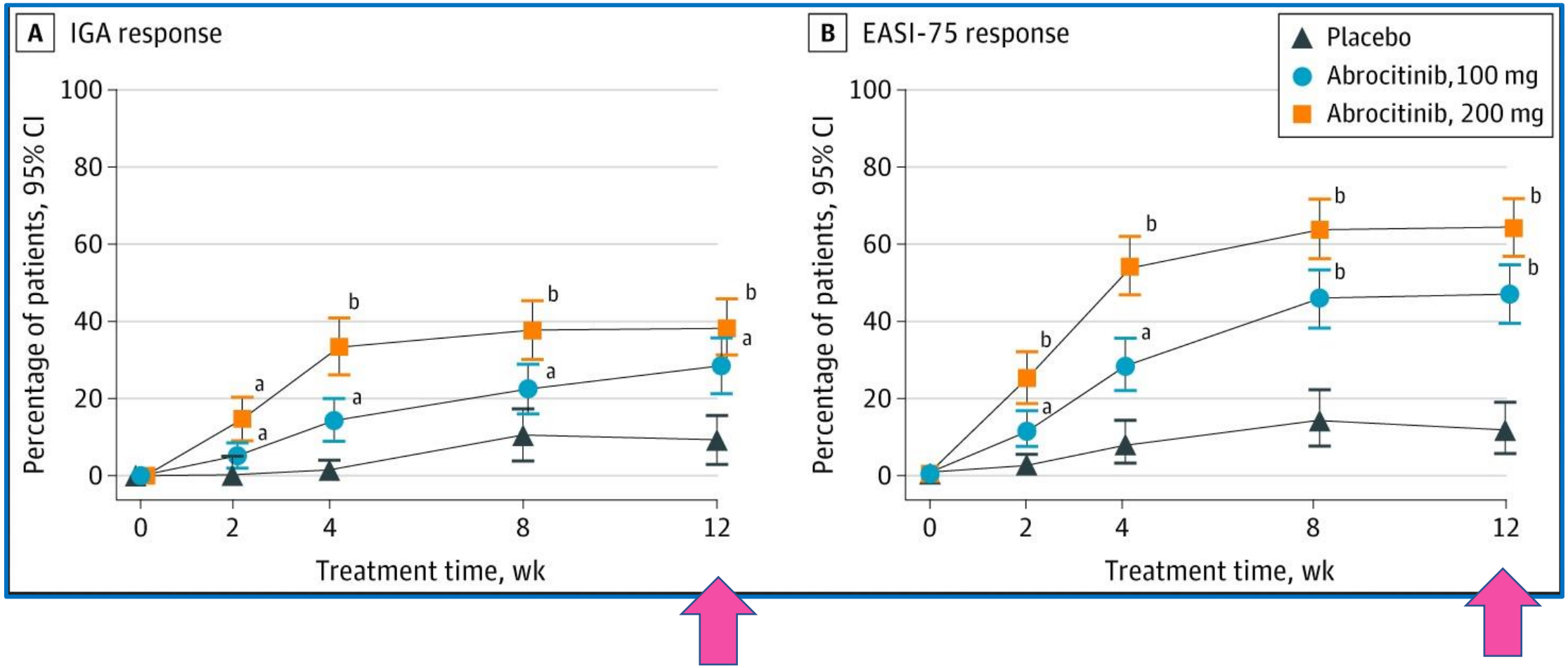
Proportion of patients who achieved a PP-NRS response* over the 12-week treatment period



Lancet 2020;396:255-66

*Defined as a ≥4-point improvement from baseline in PP-NRS score

Efficacy and Safety of Abrocitinib in Patients With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial



JAMA Dermatol 2020;156:863-73

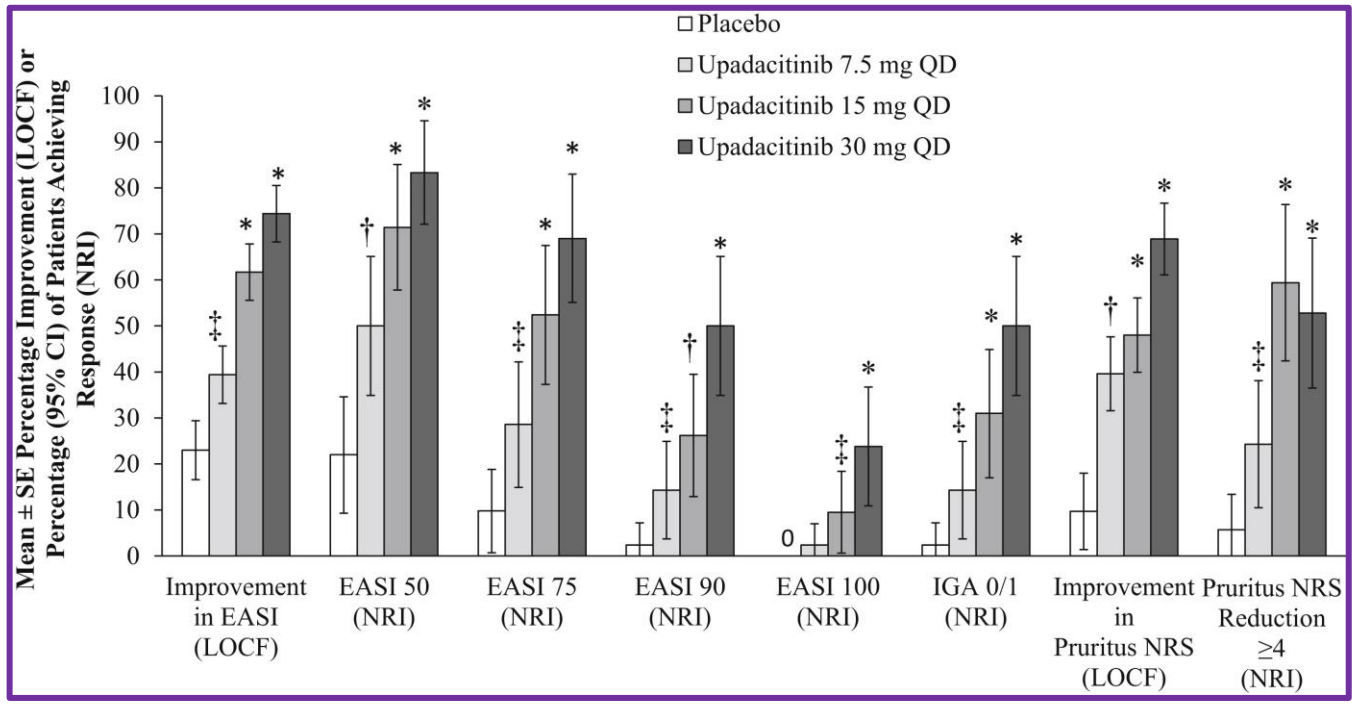
Efficacy and safety of abrocitinib in patients with moderate-to-severe atopic dermatitis: A randomized clinical trial

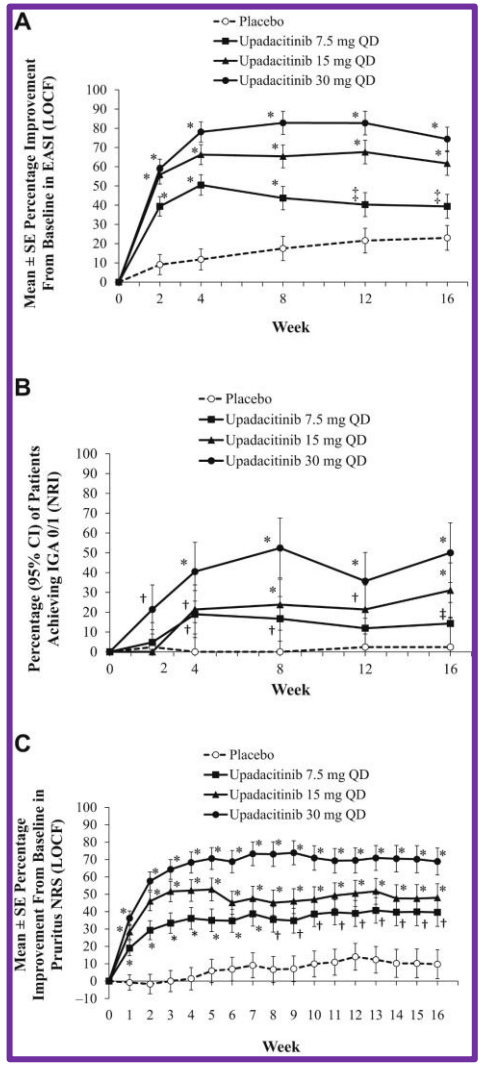
Table 2. Summary of Adverse Events

	Treatment group, No. (%)		
		Abrocitinib	
Event	Placebo (n = 78)	100 mg (n = 158)	200 mg (n = 155)
Deaths	0	1 (0.6)	0
Serious adverse events of any cause	1 (1.3)	5 (3.2)	2 (1.3)
Most frequently reported TEAEs of any cause (≥3% in any treatment group)			
Nausea	2 (2.6)	12 (7.6)	22 (14.2)
Nasopharyngitis	5 (6.4)	20 (12.7)	12 (7.7)
Headache	2 (2.6)	9 (5.7)	12 (7.7)
Upper respiratory tract infection	3 (3.8)	14 (8.9)	5 (3.2)
Dermatitis atopic	12 (15.4)	9 (5.7)	6 (3.9)
Acne	0	2 (1.3)	9 (5.8)
Vomiting	1 (1.3)	2 (1.3)	8 (5.2)
Upper abdominal pain	0	2 (1.3)	6 (3.9)
Blood creatine phosphokinase increased	2 (2.6)	3 (1.9)	5 (3.2)
Folliculitis	2 (2.6)	0	5 (3.2)
Thrombocytopenia	0	0	5 (3.2)

JAMA Dermatol 2020;156:863-73

Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial

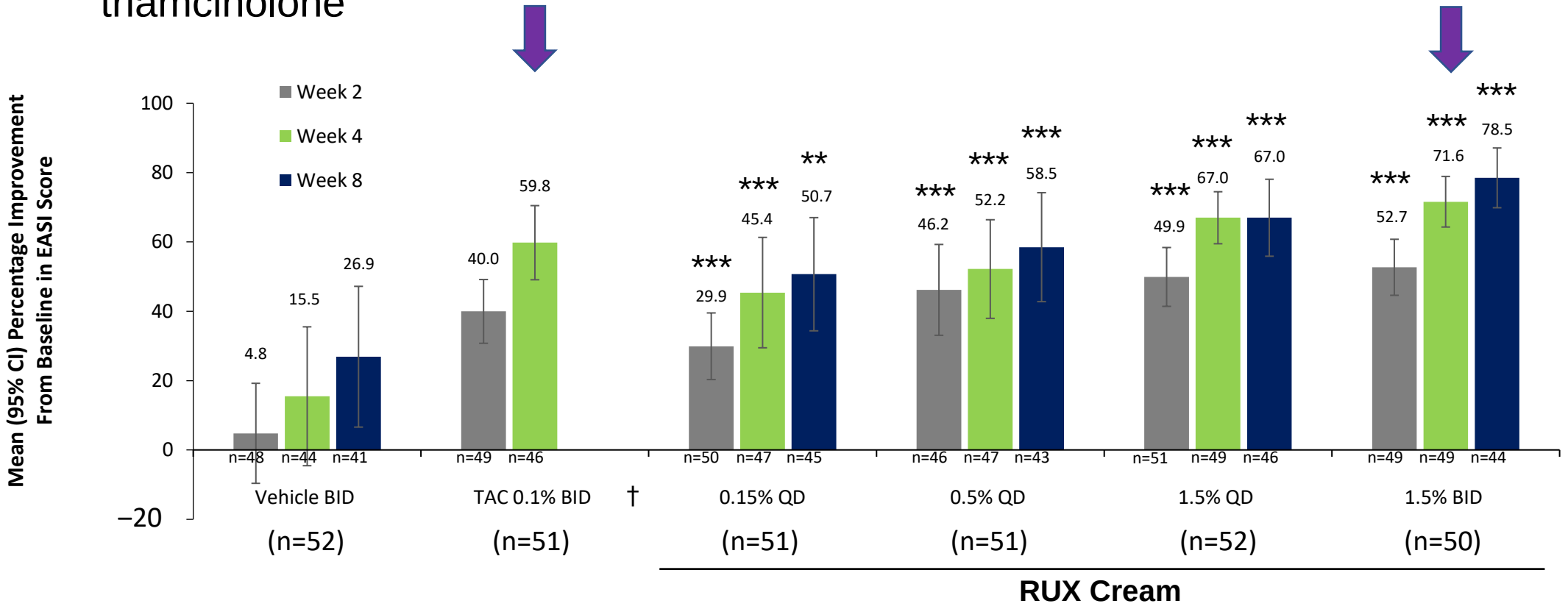




J Allergy Clin Immunol 2020;145:877-84

Treatment of atopic dermatitis with ruxolitinib cream (JAK1/JAK2 inhibitor) or triamcinolone cream

- RUX 1.5% BID resulted in greater improvement in EASI scores versus triamcinolone



Kim BS, et al. J Allergy Clin Immunol 2020;145:572

*** *P*<0.001 vs vehicle; ** *P*<0.01 vs vehicle

Abrocitinib vs. Placebo or Dupilumab for Atopic Dermatitis

MULTIGROUP, DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIAL

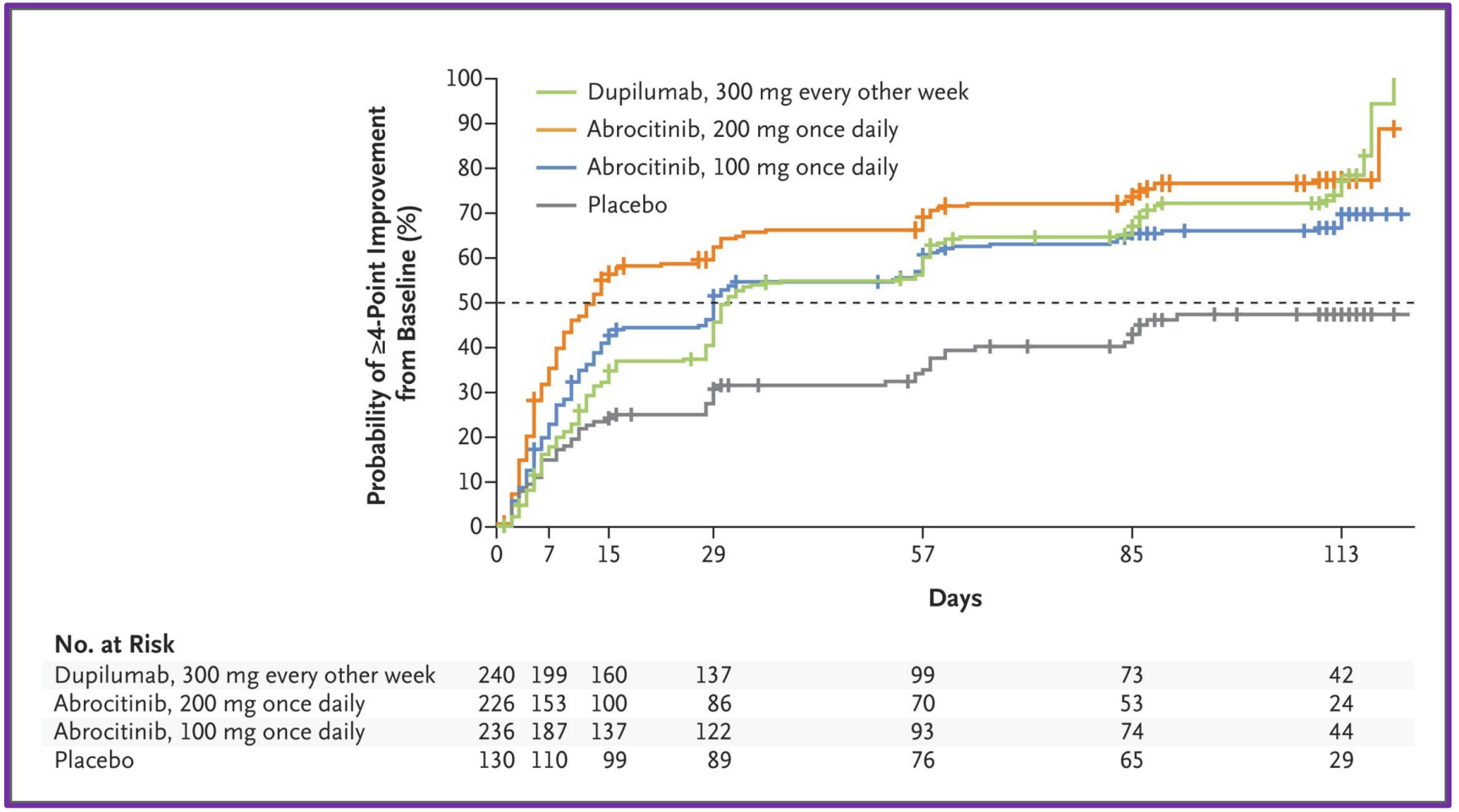
838 Adults with atopic dermatitis unresponsive to topical agents	IGA Response (improvement of ≥2 points at 12 wk)	EASI-75 Response (≥75% improvement at 12 wk)
Abrocitinib, 200 mg/day (orally; N=226)	48.4% P<0.001 vs. placebo	70.3% P<0.001 vs. placebo
Abrocitinib, 100 mg/day (orally; N=238)	36.6% P<0.001 vs. placebo	58.7% P<0.001 vs. placebo
Dupilumab, 300 mg every 2 wk (subcutaneously; N=243)	36.5%	58.1%
Placebo (N=131)	14.0%	27.1%

The 200-mg dose of abrocitinib reduced itch at 2 wk as compared with dupilumab but did not differ in most other secondary end points.

N Engl J Med 2021; 384:1101-12

Abrocitinib versus placebo or dupilumab for atopic dermatitis

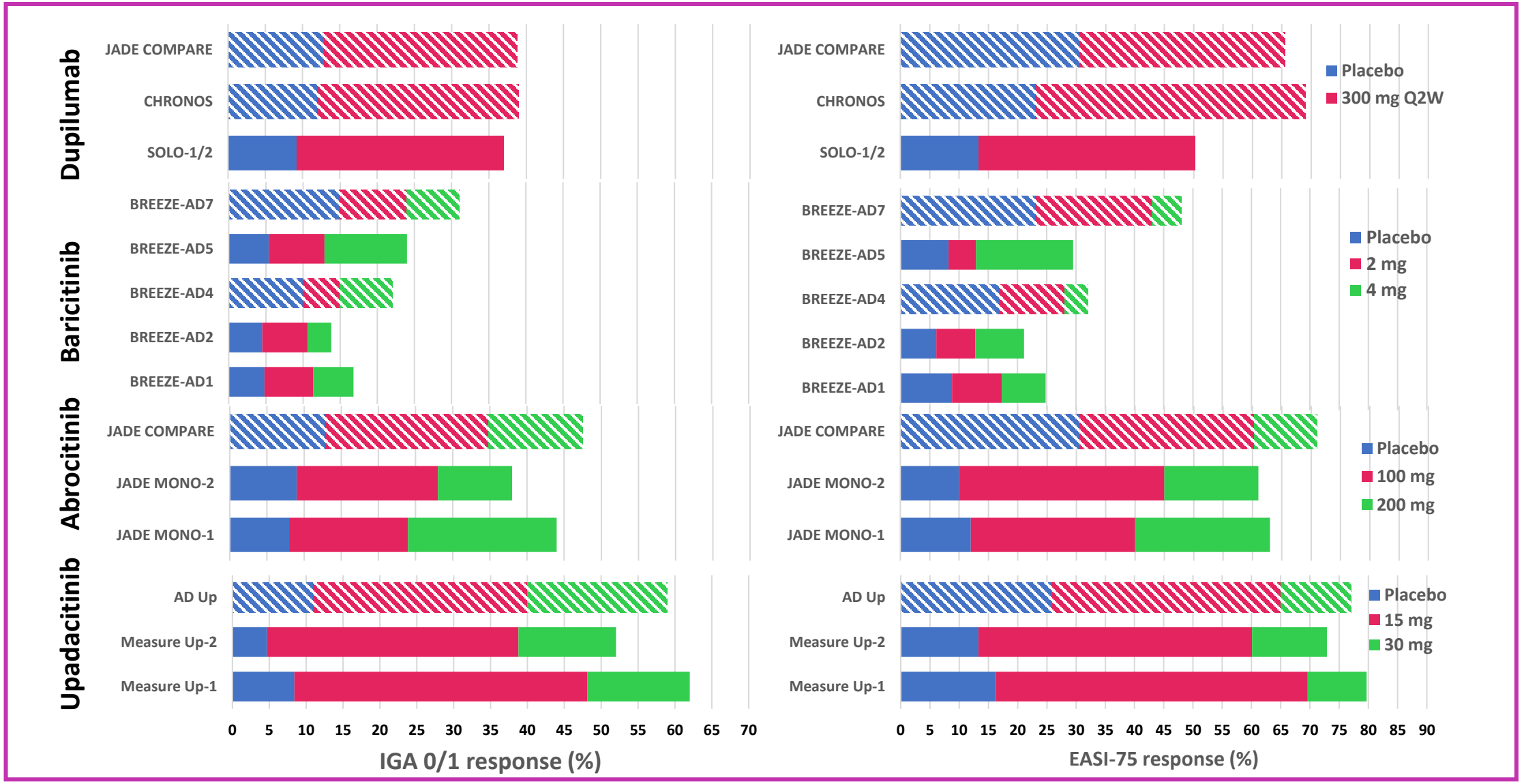
Median Time to Itch Response



No. at Risk							
Dupilumab, 300 mg every other week	240	199	160	137	99	73	42
Abrocitinib, 200 mg once daily	226	153	100	86	70	53	24
Abrocitinib, 100 mg once daily	236	187	137	122	93	74	44
Placebo	130	110	99	89	76	65	29

N Engl J Med 2021; 384:1101-12

Comparison of biologic & oral JAK inhibitors in AD at wks 12-16



Adapted from Silverberg JI. RAD 2020

Solid bars = monotherapy trials, stripes +/-TCS

Safety of JAK inhibitors

- Most safety data comes from clinic trials of tofacitinib or baricitinib in patients with rheumatoid arthritis
- Patients treated with concomitant methotrexate with or without nonsteroidal anti-inflammatory drugs and glucocorticoids
- Box warning for serious infections, malignancy and thrombosis
- FDA warns of risk for PE, death with higher dose tofacitinib (10 mg bid) in patients with RA (Feb 25, 2019); new warning Jul 26, 2019 re increased risk blood clots & death with 10 mg bid tofacitinib
- Will new Jakinibs inherit same boxed warning?
- Will Jakinibs be used as short term oral/topical intervention (AD tends to relapse quickly when D/C'd) and titrated to lowest effective dose ?

JAK inhibitors vs biologics

- JAK inhibitors have several advantages compared with biologics
  - orally bioavailable
  - rapid efficacy*
  - predictable pharmacokinetics
  - elicit no immunogenicity [can be stopped and re-started]
  - may allow flexible dosing regimens according to disease activity
  - could be used as induction regimen in acute phases

*e.g. significant difference in clinically meaningful improvement in peak pruritus was observed in patients given abrocitinib 200 mg compared with placebo as early as day 2

Lancet 2020;396:215

Take Home Messages

- Pathophysiology of AD is complex and involves immune dysregulation and skin barrier abnormalities
- Type 2 inflammation is seen across the spectrum of clinical phenotypes
- Dupilumab blocks the receptor for 2 key type 2 cytokines: IL-4 & -13
- Multiple studies including long term trials point to dupilumab's efficacy and safety in patients with moderate-to-severe AD (as well as other atopic diseases) with FDA approval down to age 6 years
- Biologics selectively targeting IL-13, IL-31Ra, TSLP and others (e.g. IL-33, OX40) are being studied and will add to the therapeutic landscape
- Oral & topical JAK inhibitors target multiple cytokines and have been shown to be rapidly effective and relatively safe in short term trials with long term data emerging; several expecting FDA approval in 2021