Atopic Dermatitis: JAK inhibitors

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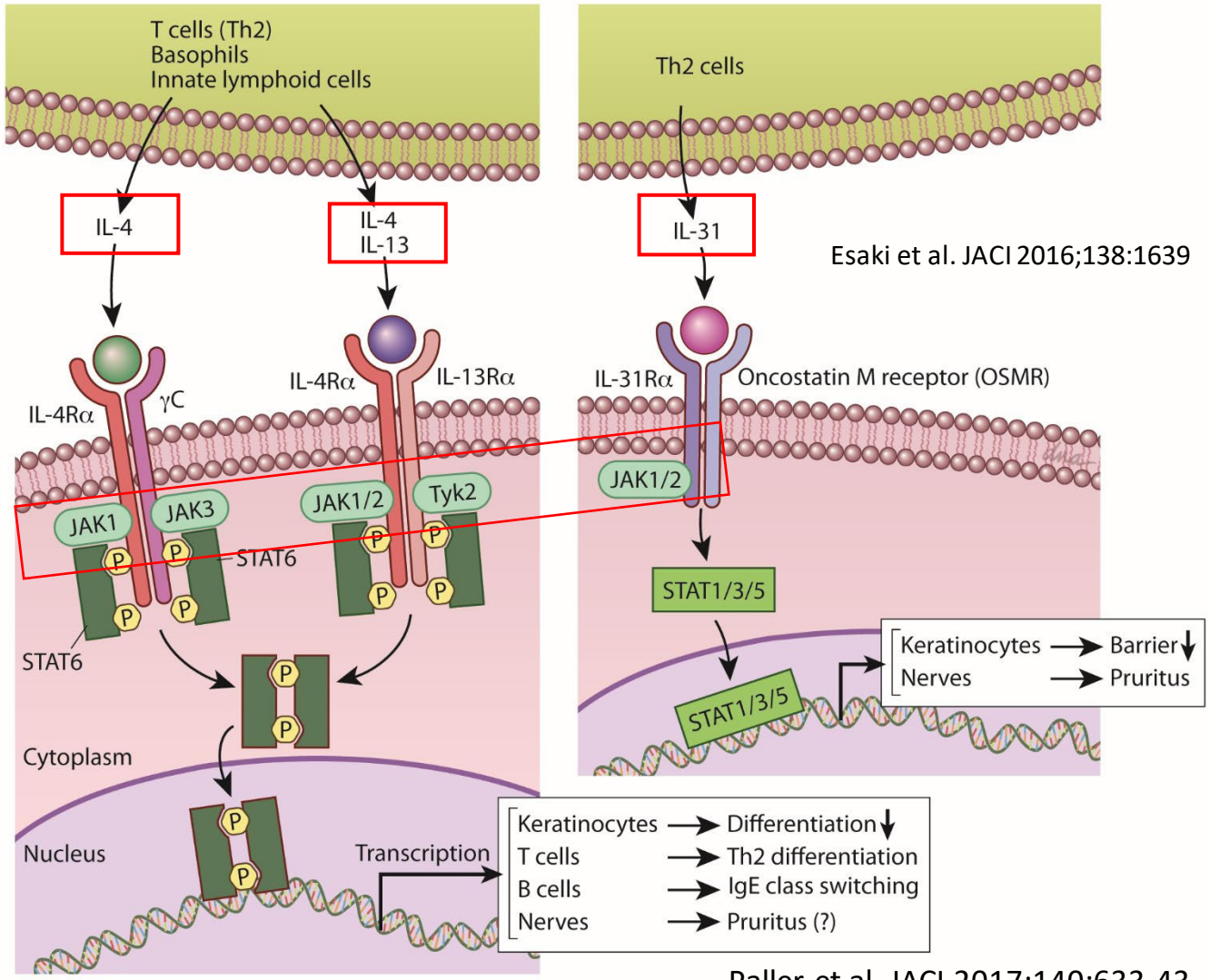
Disclosures

- Investigator: Regeneron (Dupilumab), Pfizer (Abrocitinib); Galderma (Nemolizumab); UCB (Certrolizumab); Castle
- Consultant: Lilly (Tralokinumab); Leo (Lebrikizumab); Arcutis (Roflumilast); Dermavent (Tapinarof)
- Speaker's Bureau: Beiersdorf
- Comments do not represent AAD unless so stated

Outline

- Why AD?
- Agents used for AD
  - FDA approved
  - Topical : ruxolitinib
  - Systemic: Upadacitinib, abrocitinib
- Used but not FDA approved: baricitinib (EMA approved), tofacitinib
- Safety and Efficacy
- Comparative data
- Transitions

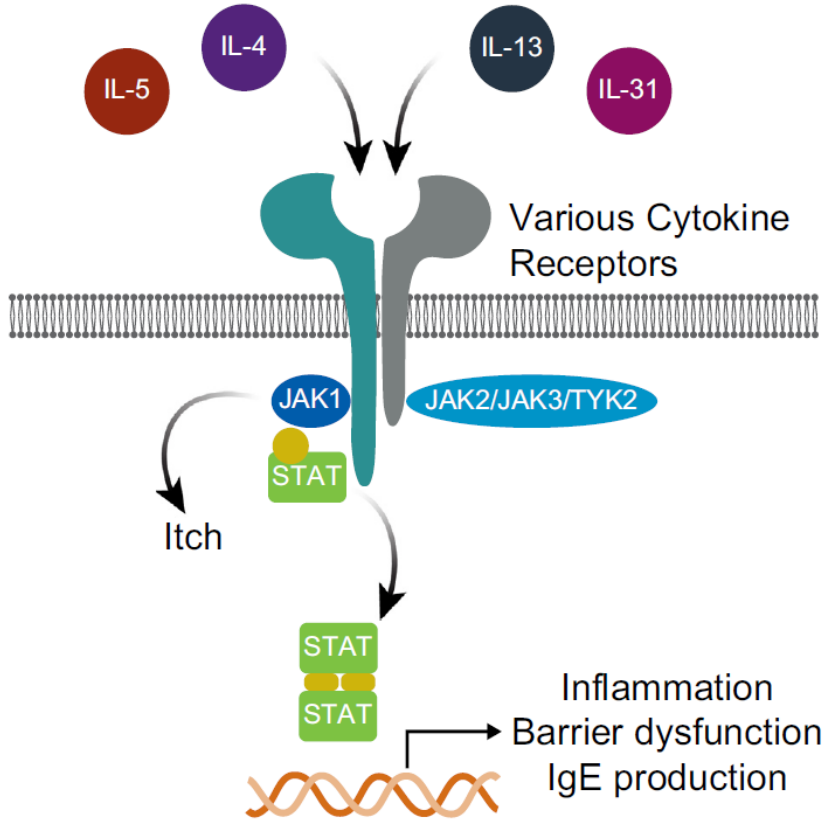
JAK inhibitors for Atopic Dermatitis



Esaki et al. JACI 2016;138:1639

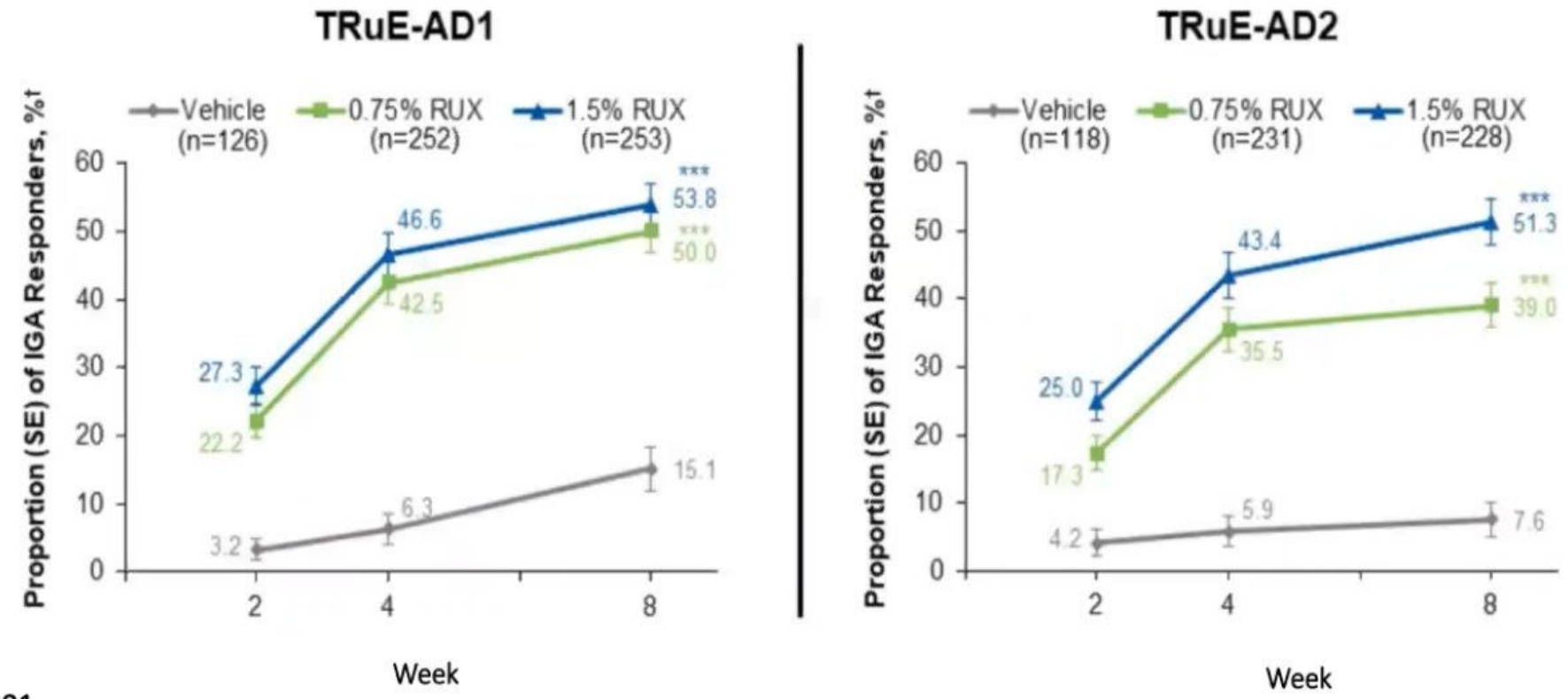
Paller et al. JACI 2017;140:633-43

- **JAK activation is downstream of IL4RA and IL31RA**



Topical Ruxolitinib: TRuE-AD1 and TRuE-AD2

- Aged ≥12 years, IGA score of 2 or 3, 3%-20% affected BSA



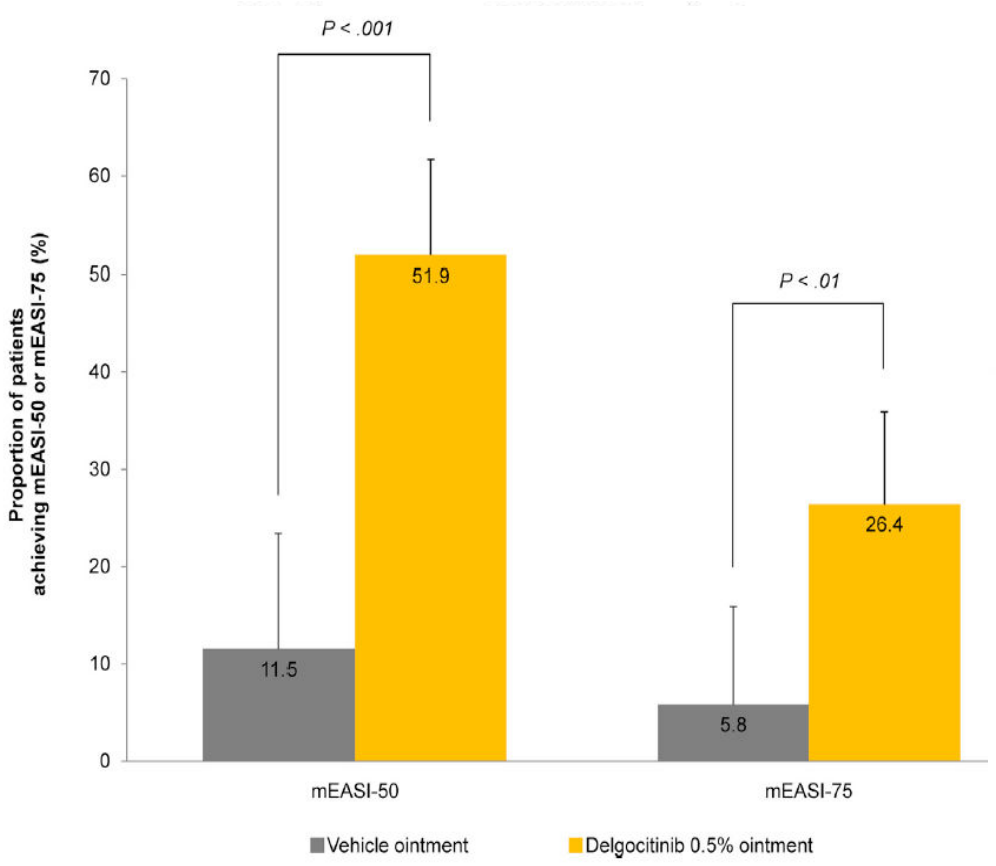
- **No significant application site reactions (burn/sting)**
- **Low systemic exposure**
- **No clinically significant lab abnormalities**

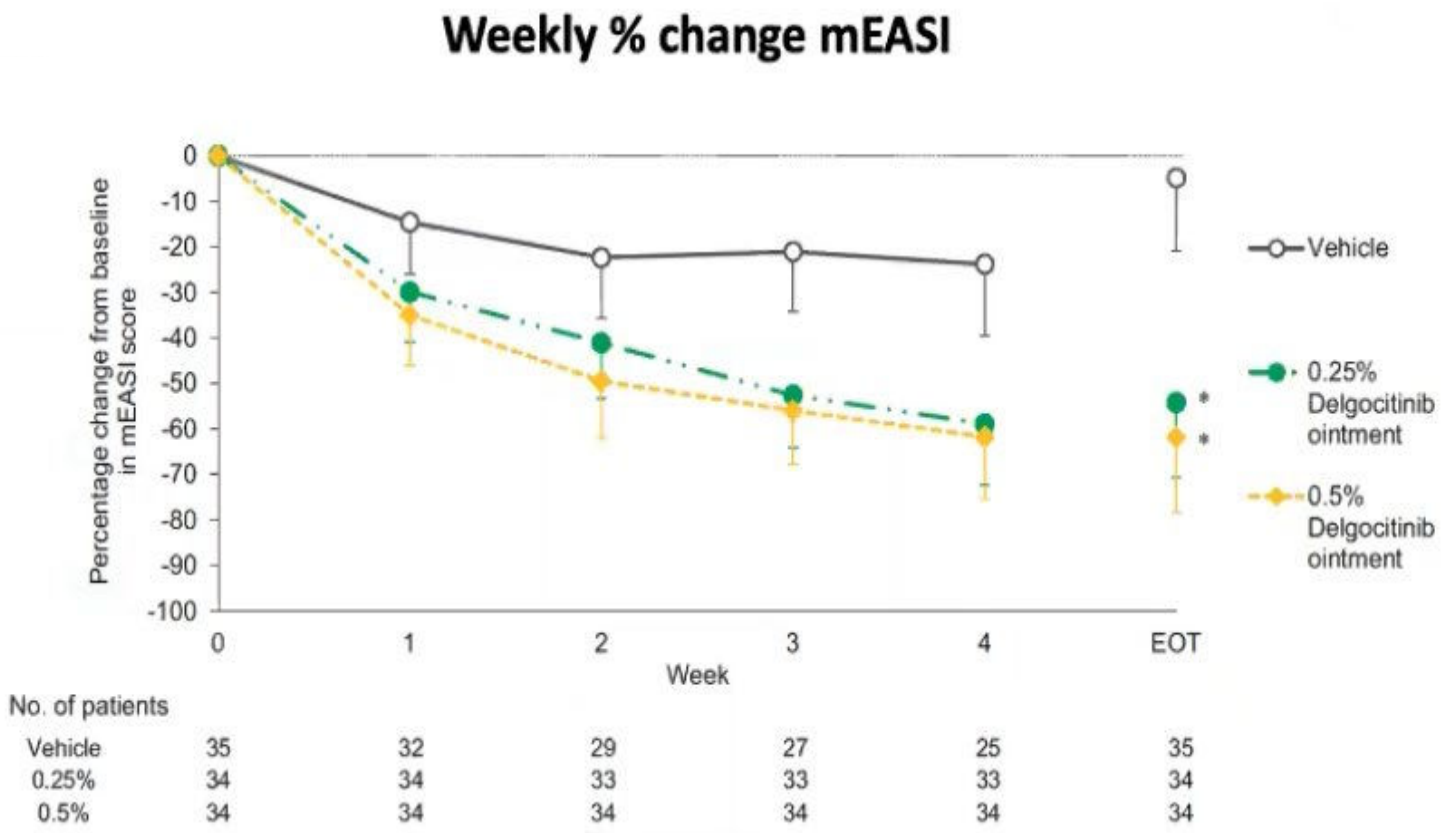
*** P<0.0001.

†Defined as patients achieving an IGA score 0 or 1 with an improvement of ≥2 points from baseline

Papp et al. Presented at VMX July 2020; Kim et al. J Allergy Clin Immunol 2020;145:572

Topical delgocitinib 0.5% approved ≥16 y.o. in Jan 2020 in Japan
28 day Phase 2b trial in 2-15 y.o with moderate to severe AD



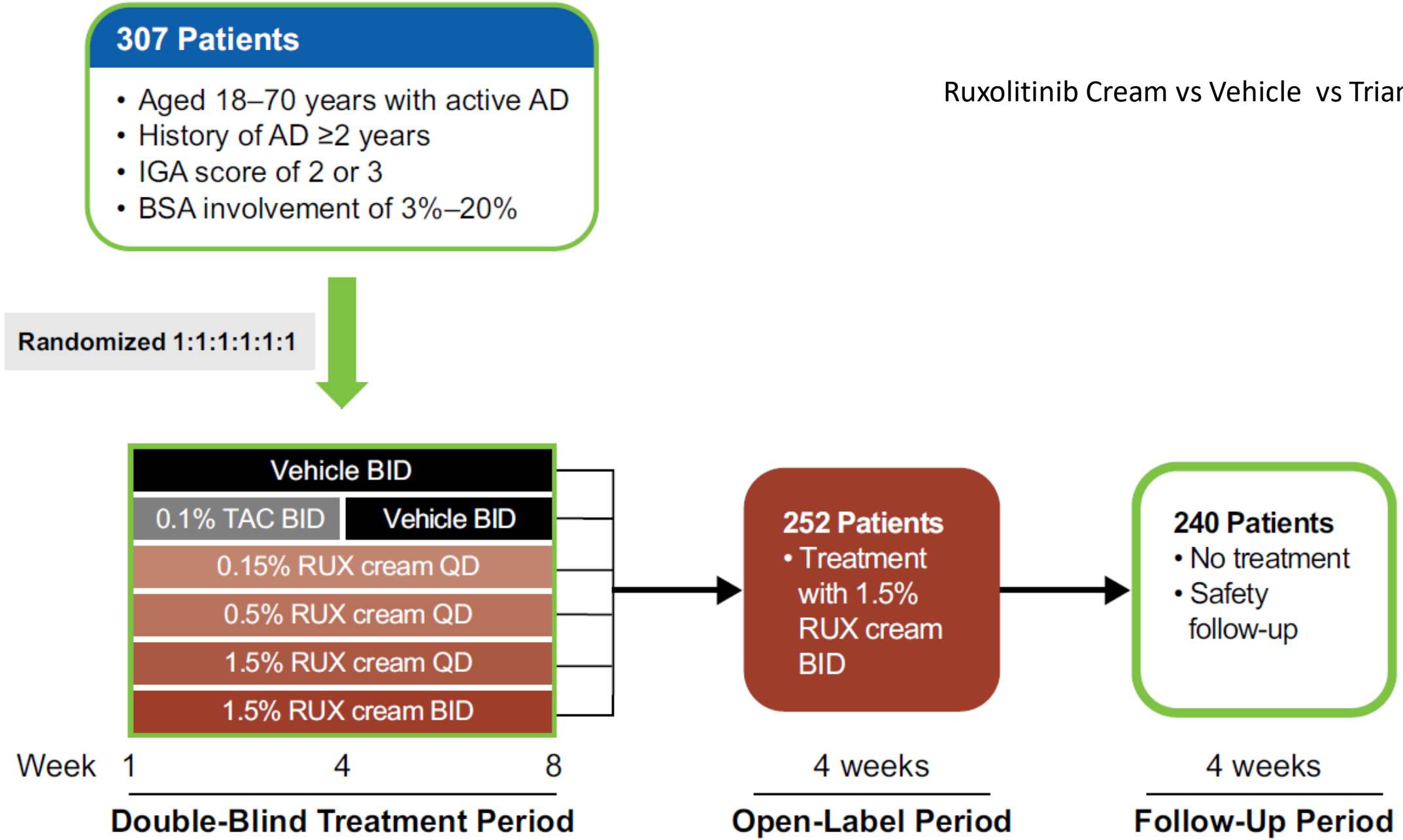


6 cases of eczema herpeticum (3.9%) and 5 acne (3.2%) among 154 subjects

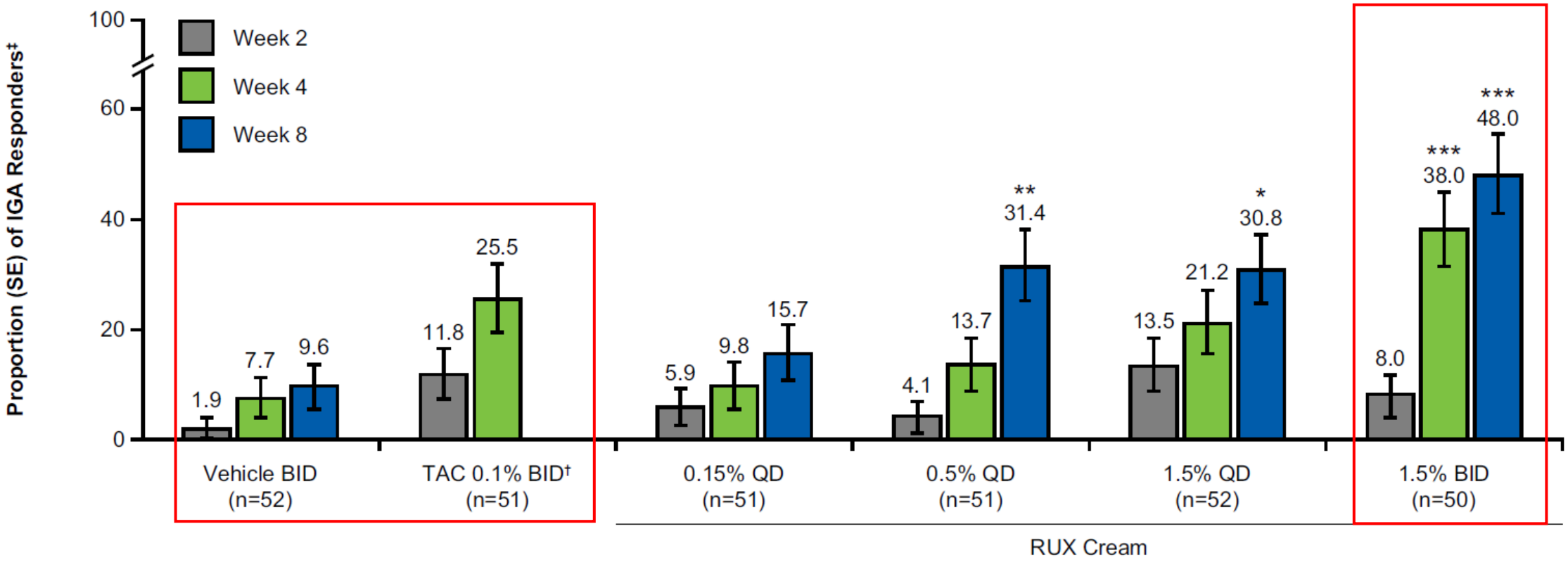
No stinging/burning/irritation

Nakagawa et al. J Am Acad Dermatol 2020;82:823-31

Ruxolitinib Cream vs Vehicle vs Triamcinolone



Topical Ruxolitinib vs Vehicle vs Triamcinolone 0.1% cream (% IGA responders)

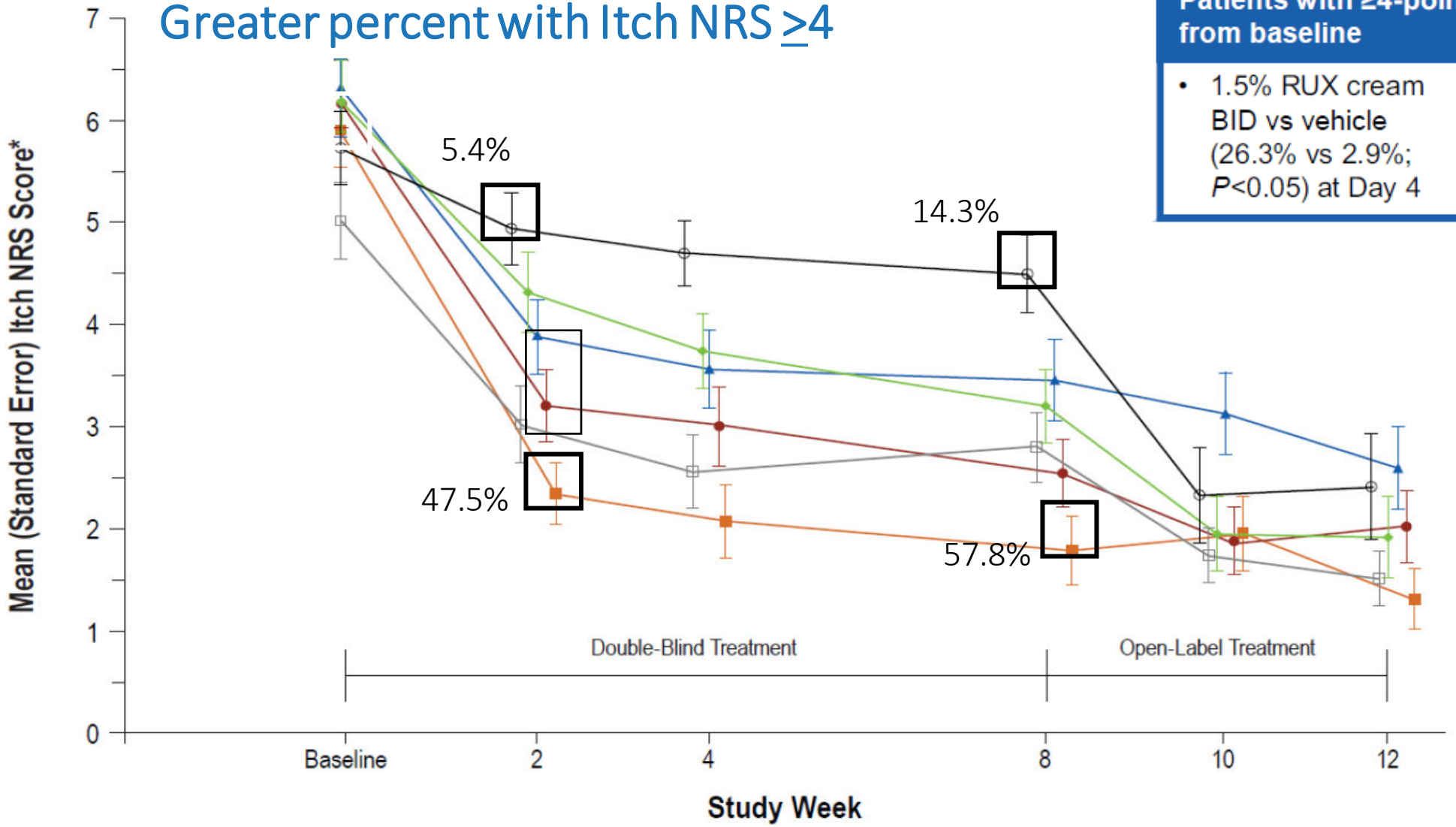


Kim et al. J Allergy Clin Immunol 2020;145:572

Greater percent with Itch NRS ≥4

Patients with ≥4-point reduction in itch NRS from baseline

- 1.5% RUX cream BID vs vehicle (26.3% vs 2.9%; *P*<0.05) at Day 4
- 1.5% RUX cream BID vs triamcinolone (47.5% vs 19.4%; *P*<0.05) at Week 2



Number of Patients

Vehicle BID	37	39	38	35	31	30
0.1% TAC BID†	35	38	37	35	36	31
0.15% RUX QD	41	43	42	40	40	38
0.5% RUX QD	39	38	37	37	35	32
1.5% RUX QD	40	38	38	37	35	33
1.5% RUX BID	40	41	42	39	36	34

No clinically significant application site reactions

Kim et al. J Am Acad Dermatol 2020;82:1305-13.

Topical JAK for AD summary

- Effective –comparable to a mid potency TCS
- Safe--- no serious Aes
- Limits: < 20% BSA, 60 g/week
- Barriers: Cost, mild to moderate indication, boxed warning

Systemic JAKs

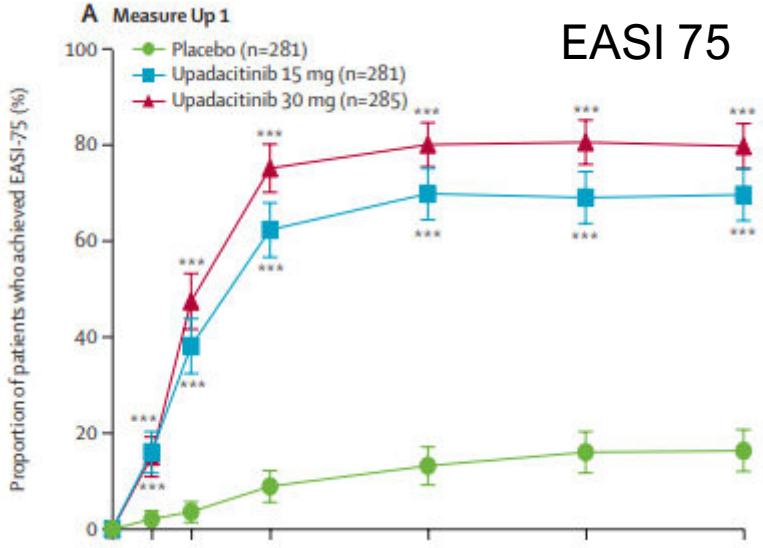
Upadacitinib versus Placebo in Adolescents and Adults

Primary Outcomes

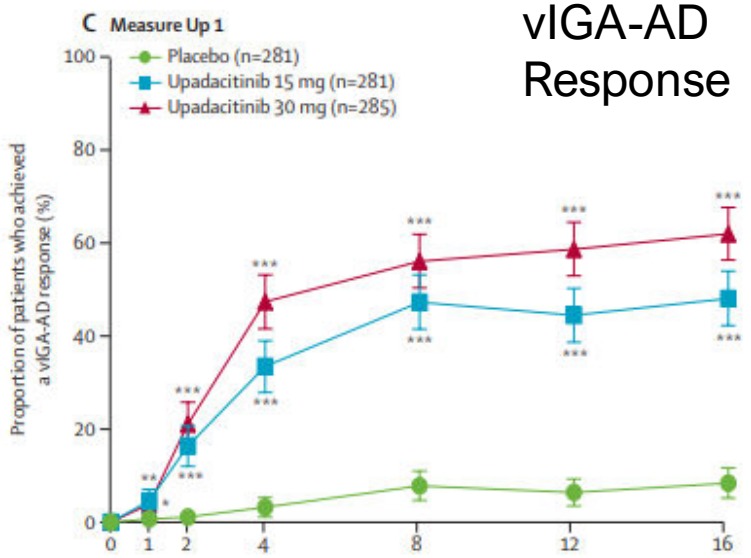
EASI 75
IGA
WP-NRS (itch)

√ Once a day pill

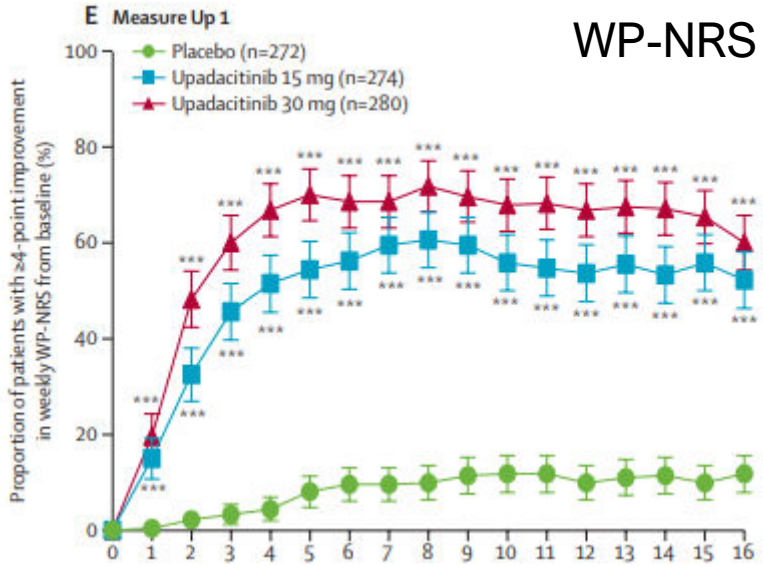
EASI 75



vIGA-AD Response



WP-NRS



WP-NRS = Worst Pruritus Numerical Rating Scale.

Guttman-Yassky E, et al. *Lancet.* 2021;397:2151-2168.

Findings

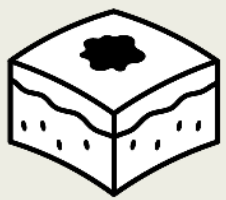
- Remarkable efficacy
- Rapid onset of action

JAMA Dermatology

RCT: Upadacitinib vs Dupilumab in Adults With Moderate-to-Severe Atopic Dermatitis

POPULATION

377 Men, 315 Women



Adults aged 18-75 y with atopic dermatitis symptoms for ≥3 y and an Eczema Area and Severity Index (EASI) ≥16

Mean (SD) age, 36.7 (14.3) y (range, 18-76 y)

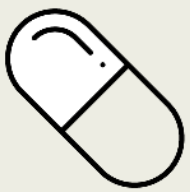
SETTINGS / LOCATIONS

126 Centers in 22 countries

INTERVENTION

692 Patients randomized and analyzed

344 Dupilumab
Subcutaneous dupilumab, 300 mg, every other week



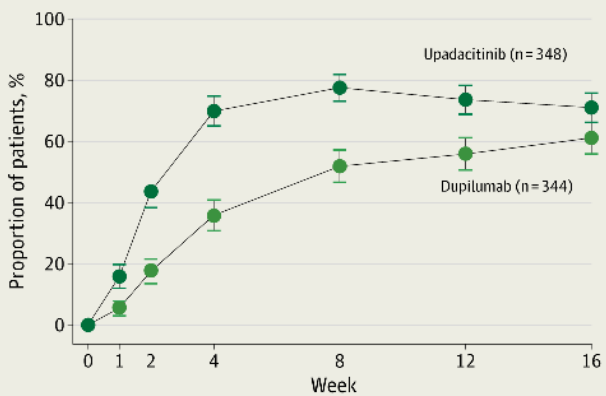
348 Upadacitinib
Oral tablet of upadacitinib, 30 mg, once daily

PRIMARY OUTCOME

Achievement of 75% improvement in EASI (EASI75) at week 16

FINDINGS

Proportion of patients achieving EASI75 at week 16 was significantly greater in upadacitinib group than in dupilumab group, with adjusted difference of 10.0% (95% CI, 2.9%-17.0%) (*P* =.006)



Proportion of patients achieving EASI75 at week 16 with dupilumab, 61.1% (210 of 344)
Proportion of patients achieving EASI75 at week 16 with upadacitinib, 71.0% (247 of 348)

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 4, 2021. doi:10.1001/jamadermatol.2021.3023

Upadacitinib in dupilumab non responders

- Multicenter, retrospective adult (n = 39, x = 46 yr) x 16 weeks
  - Dupilumab non-response (86%) or adverse event
  - 50% had failed > 2+ systemics
  - EASI 100 (IGA =) achieved by 56%
  - Mean EASI improvement = 92%

- Dupilumab non responders should improve on Upadacitinib

- 31% experience an adverse event
  - 44% in dupilumab-naïve Phase 3 trials
  - 1 patient had severe dupi-conjunctivitis that resolved

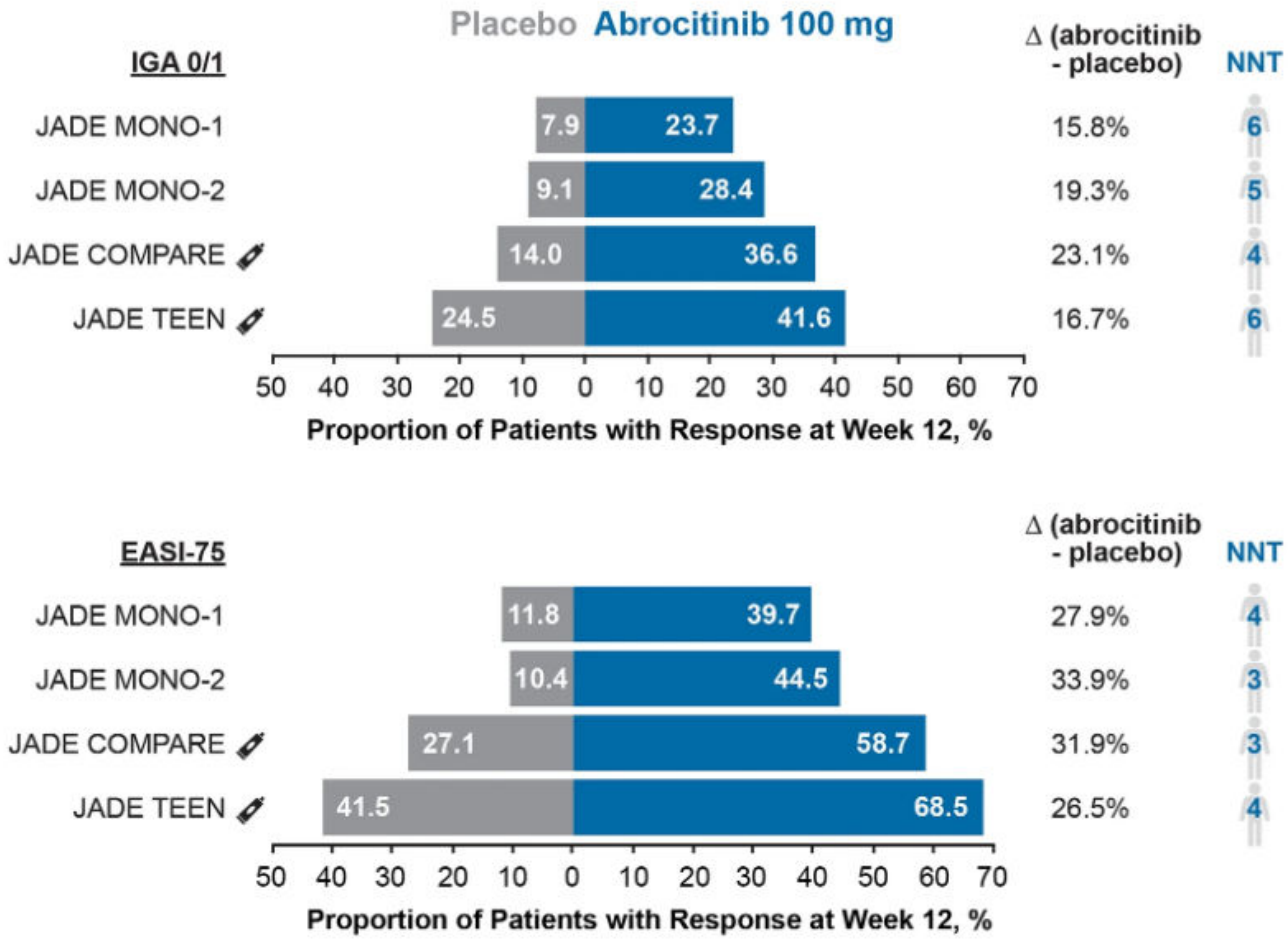
- Georgakopoulos JR et al. Real-world effectiveness and safety of Upadacitinib for the treatment of atopic dermatitis in adult patients switched from dupilumab: A multicenter retrospective study. J Am Acad Dermatol 2023;89(6):1308-10

Abrocitinib Versus Placebo in Adolescents and Adults

JADE MONO-1 and MONO-2: Abrocitinib monotherapy in adolescents and adults (N = 387 and 391 adolescents and adults)

JADE COMPARE: Abrocitinib in combination with topical medications (838 adults)

JADE TEEN: Abrocitinib in combination with topical medications (285 adolescents)



Flohr C, et al. *J Dermatolog Treat*. 2023;34(1):2200866; Gooderham MJ, et al. *Dermatol Ther (Heidelb)*. 2023;13(9):1893-1907

Abrocitinib label update

- Updated label as of 12-21-23: if adequate response is not achieved at 100 mg PO once daily, consider increasing to 200 mg PO once daily. Discontinue if adequate response not achieved at 200 mg. Use lowest efficacious dose

Systemic JAK Inhibitor Efficacy

- **JADE EXTEND Trial**
  - Extension of JAKE COMPARE
  - Abrocitinib after:
    - 16 wk of dupilumab
    - 4 wk of placebo washout

	DUP Responders		DUP Nonresponders	
Outcome, %	ABR 100	ABR 200	ABR 100	ABR 200
IGA 0/1	76.9	83.3	35.2	47.2
EASI-75	90.2	93.5	67.7	80.0
EASI-90	78.2	82.8	39.7	59.5
PP-NRS 0/1	53.1	73.7	25.8	42.9

- **Heads Up Trial**
  - Comparison of upadacitinib and dupilumab
  - Results after 16 wk of therapy

Outcome, %	DUP (N = 344)	UPA (N = 348)
EASI-75	61.1	71.0
EASI-90	38.7	60.6
Decrease in Worst Pruritis NRS	49.0	66.9

Shi. J Am Acad Dermatol. 2022;87:351. Blauvelt. JAMA Dermatol. 2021;157:1047.

JAK Inhibitor Safety Considerations

- **Common AEs**: acne vulgaris (OR 3.83), nasopharyngitis, nausea, urinary tract infections, upper respiratory tract infections
- Awareness: herpes zoster
- MONITOR: Baseline Tb test, CBC, lipids, Cr, ALT

Boxed Warnings	
Serious infections	• Oral therapy: active TB, invasive fungal infections and bacterial, viral, and other infections due to opportunistic pathogens; may lead to hospitalization or death • Topical therapy: avoid in patients with active, serious infections
Mortality	Higher all-cause mortality, including sudden cardiovascular death
Malignancies	Lymphoma and other malignancies have been observed
MACE	Cardiovascular death, MI, and stroke
Thrombosis	DVT, PE, and arterial thrombosis

Martinez J et al. JAK inhibitors and adverse events of acne: a systematic review and meta-analysis. JAMA Derm 2023
Ytterberg SR et al. Cardiovascular and cancer risk with tofacitinib in RA patients. N Eng J Med 2022

JAK inhibitors and malignancy

- Systematic searches to December 2022
- Tofacitinib, Upadacitinib, baricitinib, filgotinib, peficitinib
- 62 RCTS, 16 LTEs for 82k person-years exposure
- JAK inhibitors were associated with higher incidence of malignancy vs TNFi but NOT PLACEBO or methotrexate

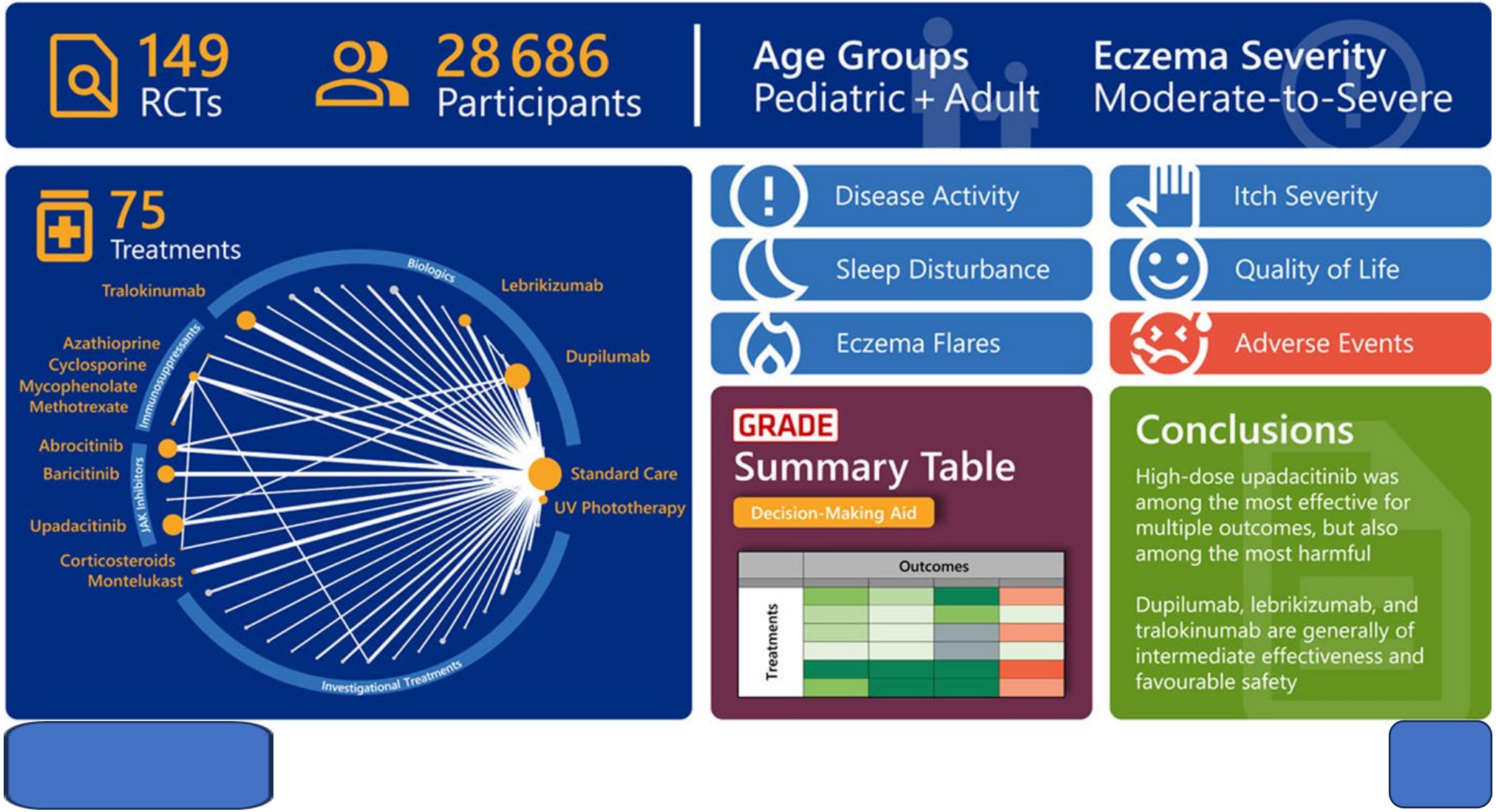
- Russell MD et al. JAK inhibitors and the risk of malignancy: a meta-analysis across disease indications. Ann Rheum Dis 2023

JAK inhibitors and Cardiovascular/VTE risk

- Systematic review of Phase 3 RCTs of JAKs for dermatologic indications
- 35 RCTS with 20,651 patients (21 AD trials)
  - AA, psoriasis, vitiligo
- Mean age = 38.5 years
- No significant difference between JAK and placebo/active comparator in MACE (OR = 0.83 95CI 0.44-1.57) or VTE (OR =0.52 95CI = 0.26-1.04)
- NOTE short term follow up
- Short term use of JAKS for dermatologic indications showed NO INCREASE in MACE, VTE, all cause mortality

- Ingrasssia JP et al. Cardiovascular and VTE risk with JAK inbibitors in Immune mediated skin diseases: a systematic review and meta analysis. JAMA Dermatol 2023, Nov 1:e234090

Systematic Review and Meta-Analysis of AD Systemic Therapies



Chu AWL, et al. *JACI* 2023 Sep 5:S0091-6749(23)01112-0

Systematic Review and Meta-Analysis of AD Systemic Therapies

High to moderate certainty evidence	Low to very low certainty evidence
Among the most effective	Possibly among the most effective
Among the intermediate (superior) effective	Possibly among the intermediate (superior) effective
Among the intermediate (inferior) effective	Possibly among the intermediate (inferior) effective
Not clearly different from placebo	Possibly not clearly different from placebo
Among the intermediate harmful	Possibly among the intermediate harmful
Among the most harmful	Possibly among the most harmful

Agent and Dose	Clinician-Rep AD Severity	Pt-Rep AD Severity	Itch NRS	Sleep Disturbance NRS	AD-related QoL	AD Flares	Any AE	Serious AEs
Dupilumab 300mg Q2W (Standard Dose)	-10.72 (-12.30 to -9.19)	-7.05 (-7.64 to -6.50)	-2.14 (-2.38 to -1.90)	-1.84 (-2.26 to -1.42)	-4.56 (-5.18 to -3.98)	-74 (-83 to -64)	-20 (-50 to 10)*	-11 (-14 to -7)
Tralokinumab 300mg Q2W (Standard Dose)	-6.45 (-8.67 to -4.27)	-4.47 (-5.37 to -3.58)	-1.08 (-1.51 to -0.65)	-0.93 (-1.36 to -0.49)	-2.36 (-3.21 to -1.51)	-57 (-72 to -40)	-1 (-43 to 40)*	-8 (-13 to 1)
Oral JAK Inhibitors								
Abrocitinib 200mg (High Dose)	-9.44 (-11.90 to -6.98)	-7.38 (-8.23 to -6.51)	-2.22 (-2.62 to -1.83)	-1.74 (-2.17 to -1.29)	-4.56 (-5.39 to -3.71)	-121 (-127 to -114)	85 (45 to 122)†	0 (-10 to 18)‡
Abrocitinib 100mg (Low Dose)	-6.89 (-9.49 to -4.28)	-4.69 (-5.62 to -3.74)	-1.40 (-1.82 to -0.99)	-0.96 (-1.40 to -0.51)	-2.81 (-3.73 to -1.92)	-93 (-105 to -78)	5 (-42 to 51)†	-1 (-11 to 16)‡
Upadacitinib 30mg (High Dose)	-13.99 (-16.62 to -11.37)	-8.26 (-9.41 to -7.20)	-2.91 (-3.35 to -2.49)		-9.76 (-11.23 to -8.28)	-125 (-132 to -111)	108 (72 to 141)†	-4 (-11 to 7)‡
Upadacitinib 15mg (Low Dose)	-11.43 (-14.25 to -8.64)	-6.54 (-7.64 to -5.45)	-1.90 (-2.35 to -1.45)		-8.36 (-9.83 to -6.89)	-115 (-124 to -101)	55 (14 to 95)†	-5 (-12 to 7)‡

Excerpted from Chu AWL, et al. *J Allergy Clin Immunol*. 2023 Sep 5:S0091-6749(23)01112-0.

Newer Systemics: JAKS vs Biologics

- JAK Inhibitors
  - Abrocitinib (JAK 1)--- FDA approved--44% clear or almost clear MONOTHERAPY
  - Upadacitinib (JAK 1)---FDA approved--62% clear or almost clear MONOTHERAPY

- Biologics
  - Dupilumab (IL 4/13)--- FDA approved---38% clear or almost clear MONOTHERAPY
  - Tralokinumab (IL13)--- FDA approved22% clear or almost clear MONOTHERAPY (39% plus TCS)
  - Nemolizumab (IL-31)---TBD
  - Lebrikizumab (IL-13)--- TBD

- Comorbidities (eg dupilumab is FDA approved asthma therapy)
- PO vs injectable
- Blood monitoring vs none
- Boxed warning vs none
- Onset of action of JAKS is quicker

- Thyssen JP, Thomsen SF Treatment of atopic dermatitis with biologics and Janus Kinase Inhibitors. Lancet 2021;397:2126

Current AAD Guidelines: JAK inhibitors

- For adults with moderate to severe AD, we recommend Upadacitinib, abrocitinib, and baricitinib
- Strength of recommendation: Strong
- Certainty of evidence: Moderate
- Remarks: Baricitinib not US FDA approved

Davis DMR et al. Guidelines of care for the management of atopic dermatitis in adults with phototherapy and systemic therapies. J Am Acad Dermatol 2023

Summary

- Safe and effective option for many dermatologic diseases
- Labs must be monitored with attention to lipids
- Box warning must be considered


Thank you