

# Update on Systemic JAK inhibitors for Atopic Dermatitis

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# Disclosures

- Investigator: Regeneron (Dupilumab), Pfizer (Abrocitinib); Galderma (Nemolizumab); UCB (Certrolizumab); Castle
- Consultant: Lilly (Tralokinumab); Leo (Lebrikizumab); Arcutis (Roflumilast); Dermavent (Tapinarof); Alphyn
- Speaker's Bureau: Beiersdorf

# Outline

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Placement in AD Armamentarium

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Upadacitinib, Abrocitinib

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Safety concerns

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Comparative data

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# AD Pipeline

- 39 injectable under study
- 21 oral agents
- 49 topicals

# Systemic Therapies for AD: Mechanisms of Action

## Th2 cytokines and receptors

Dupilumab  
Tralokinumab  
Lebrikizumab

## Janus Kinase inhibitors

Upadacitinib  
Abrocitinib  
Baricitinib (Europe)  
Tofacitinib

## IgE

Omalizumab (IV)

## Microbiome

OM-85-BV

## Antigen presentation

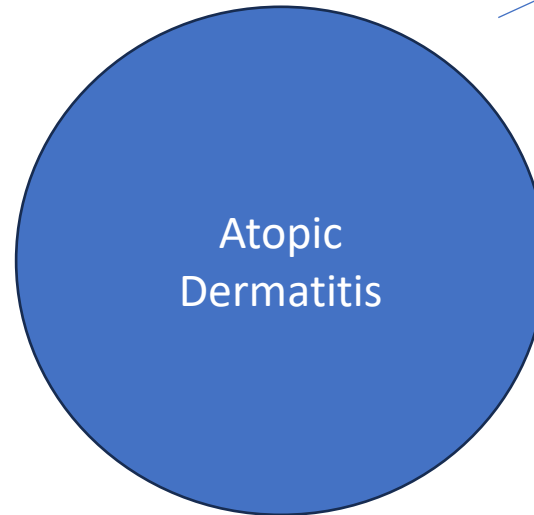
OX40 (III)

## Pruritus

Nemolizumab (III)  
Tradipitant (III)  
Difelikefalin (III)  
Serlopitant (III)

## Mesenchymal stem cells (human umbilical cord blood derived)

FURESTEM (III)



# Systematic Review and Meta-Analysis of AD Systemic Therapies

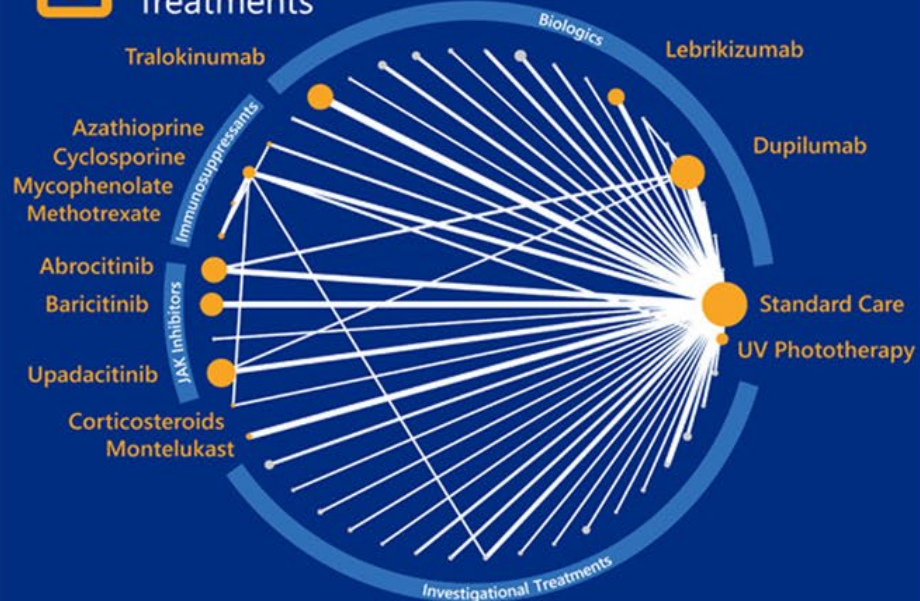
**149**  
RCTs

**28 686**  
Participants

**Age Groups**  
Pediatric + Adult

**Eczema Severity**  
Moderate-to-Severe

**75**  
Treatments



**!** Disease Activity

**✋** Itch Severity

**🌙** Sleep Disturbance

**😊** Quality of Life

**🔥** Eczema Flares

**😡** Adverse Events

## GRADE Summary Table

Decision-Making Aid

	Outcomes			
Treatments	Green	Green	Green	Red
	Green	Green	Green	Red
	Green	Green	Green	Red
	Green	Green	Green	Red
	Green	Green	Green	Red

## Conclusions

High-dose upadacitinib was among the most effective for multiple outcomes, but also among the most harmful

Dupilumab, lebrikizumab, and tralokinumab are generally of intermediate effectiveness and favourable safety

# 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)‡



# Upadacitinib versus Placebo in Adolescents and Adults

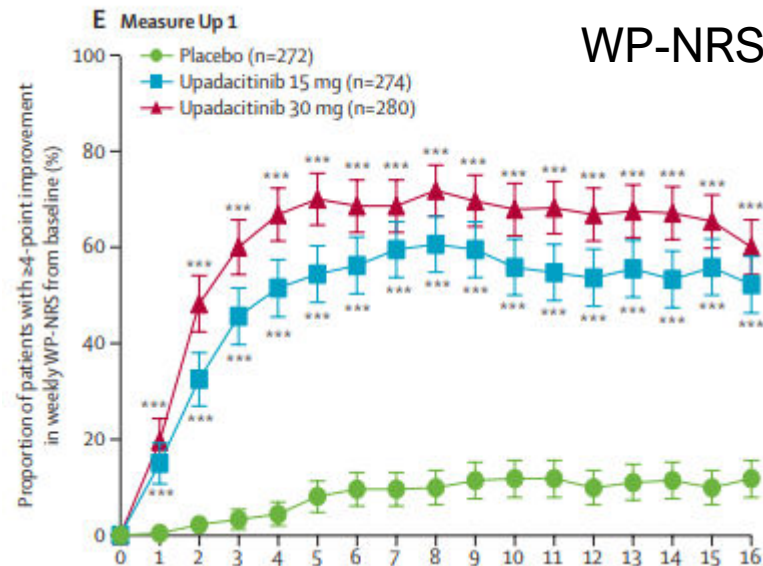
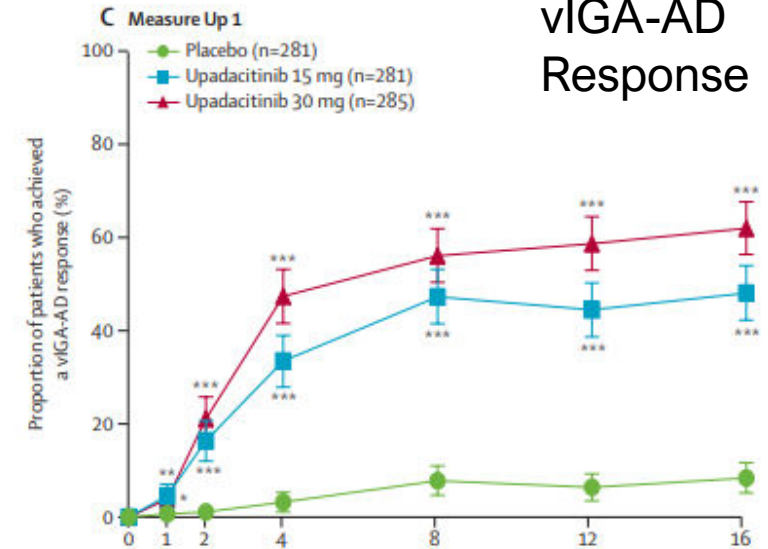
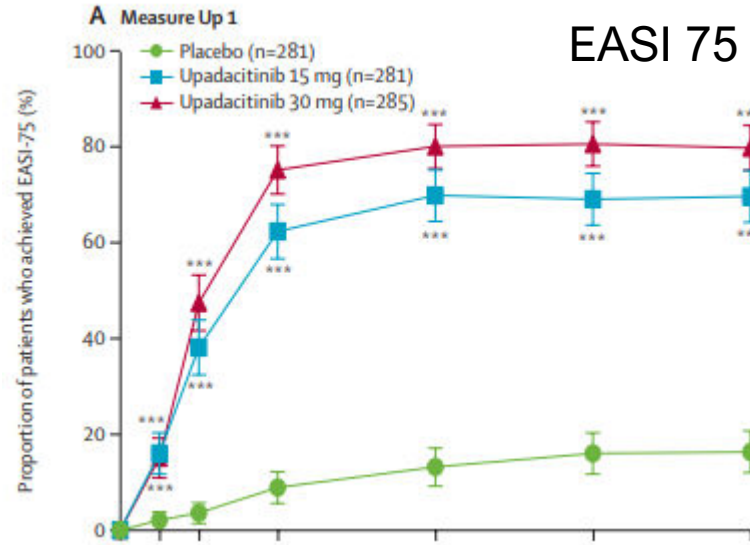
## Primary Outcomes

EASI 75

IGA

WP-NRS (itch)

✓ Once a day pill



## Findings

- Remarkable efficacy
- Rapid onset of action

WP-NRS = Worst Pruritus Numerical Rating Scale.  
Guttman-Yassky E, et al. *Lancet*. 2021;397:2151-2168.



# Upadacitinib in dupilumab non responders

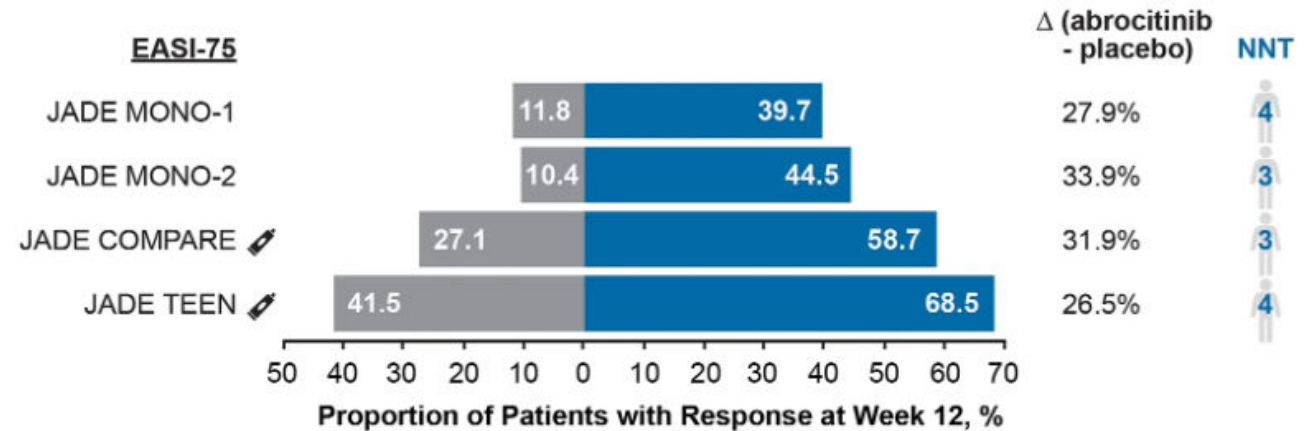
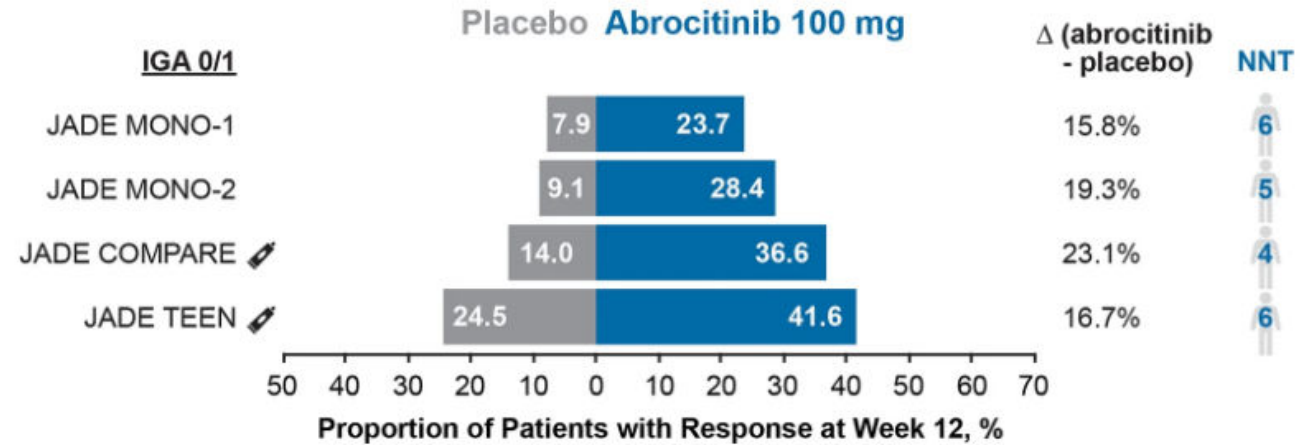
- Multicenter, retrospective adult (n = 39, x = 46 yr) x 16 weeks
  - Dupilumab non-response (86%) or adverse event
  - 50% had failed > 2+ systemics
  - EASI 100 (IGA = 0) achieved by 56%
  - Mean EASI improvement = 92%
  
- Dupilumab non responders should improve on Upadacitinib
  
  
- Georgakopoulos 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)



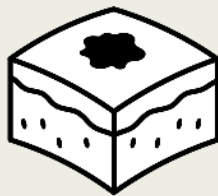
# Newer Systemics: JAKS vs Biologics

- JAK Inhibitors
  - Abrocitinib (JAK 1)--- FDA approved--44% clear or almost clear MONOTHERAPY
  - Upadacitinib (JAK 1)---FDA approved--62% clear or almost clear MONOTHERAPY
  - Baricitinib (EMA but not FDA approved for AD)
- 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)
  - Lebrikizumab (IL-13)--- FDA approved 43% clear or almost clear MONOTHERAPY
  - Nemolizumab (IL-31)---FDA approved 36% clear or almost clear (plus TCS)
    - > approved 12/14/24 12+ mod to severe AD
- 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

## 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  $\geq 3$  y and an Eczema Area and Severity Index (EASI)  $\geq 16$   
**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

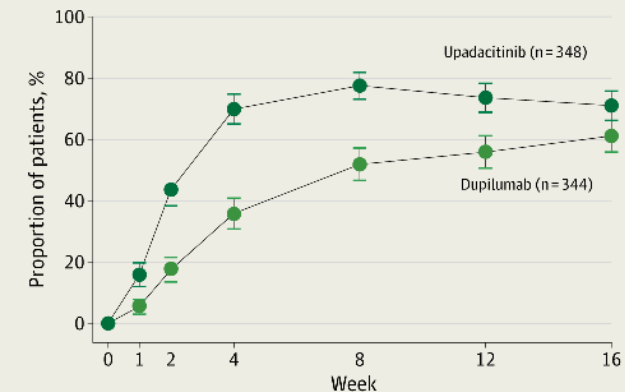
**348 Upadacitinib**  
Oral tablet of  
upadacitinib,  
30 mg, once daily

### 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)

Safety

# 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	<ul style="list-style-type: none"><li>• Oral therapy: active TB, invasive fungal infections and bacterial, viral, and other infections due to opportunistic pathogens; may lead to hospitalization or death</li><li>• Topical therapy: avoid in patients with active, serious infections</li></ul>
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



# Do JAKS increase MACE in AD patients? No

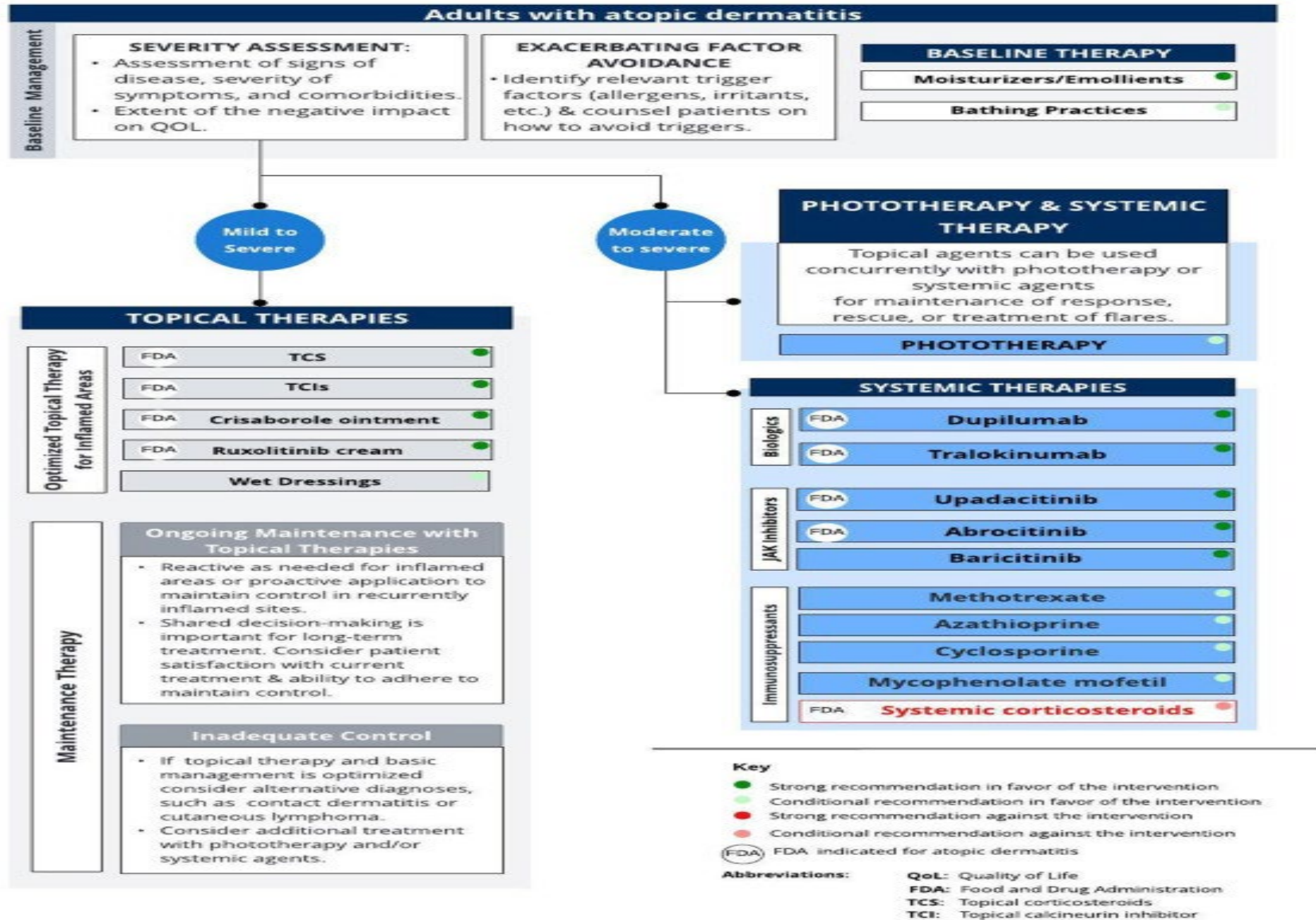
- El Ayadi et al examined AD patients taking upadactinib or abrocitinib vs AD patients with no JAK exposure
- TriNetX database
  - All AD patients
  - AD patients older than 50 years
- RR for MACE < 1 even for patients older than 50 years

El Ayadi et al. Presented at EADV, 2024

# EMA Pharmacologic Risk Assessment

- JAK inhibitor use in special populations ONLY IF NO SUITABLE ALTERNATIVE
  - > 65 years of age
  - Current or past smoker
  - Other patients at risk including history of MACE, VTE, malignancy
- Use in others guided by shared decision making

# AAD Summary



# ATOPIC DERMATITIS



INTERVENTION	SEVERITY	RECOMMENDATION	STRENGTH	CERTAINTY
<b>ELIMINATION DIETS</b> <p>Oykhman et al Systematic review</p>	MILD MODERATE SEVERE	We <b>suggest against</b> the use of elimination diets	Conditional against	Low certainty evidence
<b>ALLERGEN IMMUNOTHERAPY</b> <p>Sublingual Subcutaneous Best evidence for dust mite allergy Yepes-Nuñez &amp; Chu et al Systematic review</p>	MILD MODERATE SEVERE	We <b>suggest adding</b> allergen immunotherapy If refractory, intolerant, or unable to use mid potency topical treatments	Conditional in favor	Moderate certainty evidence
	MILD MODERATE SEVERE	We <b>suggest against</b> adding allergen immunotherapy See conditions to consider, e.g. comorbidities, values and preferences	Conditional against	Moderate certainty evidence
<b>SYSTEMIC TREATMENTS</b> <p>Consider if refractory, intolerant, or unable to use mid to high potency topical treatment</p> <p>Consider if refractory, intolerant, or unable to use mid to high potency topical treatment and systemic treatment inclusive of a biologic recommended above</p> <p>See conditions to consider, e.g. comorbidities, risk factors, values and preferences, and exceptional circumstances</p> <p>Chu et al Network meta-analysis</p>	MILD MODERATE SEVERE	<b>BIOLOGICS/ MONOCLONAL ANTIBODIES</b> <b>DUPILUMAB</b> We <b>recommend adding</b> dupilumab Age 6mo+	Strong in favor	High certainty evidence
	MILD MODERATE SEVERE	<b>TRALOKINUMAB</b> We <b>recommend adding</b> tralokinumab Age 12yo+	Strong in favor	High certainty evidence
	MILD MODERATE SEVERE	<b>UVB TREATMENT</b> We <b>suggest adding</b> clinic-based narrow band UVB treatment	Conditional in favor	Low certainty evidence
	MILD MODERATE SEVERE	<b>ABROCITINIB, BARICITINIB, OR UPADACITINIB</b> We <b>suggest adding</b> one of these three JAK inhibitors Age varies: 12 or 18 yo+ Suggested daily doses: Abrocitinib 100-200 mg, Baricitinib 2-4 mg, Upadacitinib 15-30 mg	Conditional in favor	Low certainty evidence
	MILD MODERATE SEVERE	<b>SMALL MOLECULE IMMUNOSUPPRESSANTS</b> <b>BARICITINIB 1 mg DAILY</b> We <b>recommend against</b> adding baricitinib 1 mg daily	Strong against	Low certainty evidence
	MILD MODERATE SEVERE	<b>AZATHIOPRINE</b> We <b>suggest against</b> adding azathioprine	Conditional against	Low certainty evidence
	MILD MODERATE SEVERE	<b>CYCLOSPORINE</b> We <b>suggest adding</b> cyclosporine Shared-decision making should determine whether to start therapy at high dose (5mg/kg) or low dose (3 mg/kg)	Conditional in favor	Low certainty evidence
	MILD MODERATE SEVERE	<b>METHOTREXATE</b> We <b>suggest against</b> adding methotrexate	Conditional against	Low certainty evidence
	MILD MODERATE SEVERE	<b>MYCOPHENOLATE</b> We <b>suggest against</b> adding mycophenolate	Conditional against	Low certainty evidence
	MILD MODERATE SEVERE	<b>SYSTEMIC CORTICOSTEROIDS</b> We <b>suggest against</b> systemic corticosteroids for all patients with atopic dermatitis	Conditional against	Low certainty evidence



# Guideline discordance : Systemic JAK inhibitors

## **AAD**

- Strong, in favor

## **AAAI**

- Conditionally in favor, moderate evidence
- Short duration of studies (16 weeks)
- “Most well-informed patients would place a greater value on the certain benefits than the burdens and lower certainty of for serious harms but that such values could vary from patient to patient. Such variability and the low certainty for serious harms drove the conditional recommendation.”

# Summary

- Oral JAK inhibitors work quickly and durably
- Safety warnings are daunting but not clearly generalizable to AD patients
- Listen to our patients and tailor treatment through shared decision making



A nighttime photograph of the Seattle skyline. The Space Needle is illuminated and stands prominently on the left. In the background, snow-capped mountains are visible under a dark blue sky with wispy clouds. The city lights are visible in the foreground, including the KeyArena and the Olympic stadium. The text "Thank you" is centered in the image.

Thank you