Raising the bar for AD treatments: You don’t know JAK

Jennifer Soung, MD
Director of Clinical Research
Southern California Dermatology, Santa Ana, CA
Clinical Professor
Harbor University of California Los Angeles

Conflicts of Interest

Amgen, Eli Lilly, Abbvie, Pfizer, National Psoriasis Foundation, LEO, Regeneron, Sanofi, Arcutis, Dermavant, Novartis

Objectives:

1. Understand the JAK signalling process and inflammatory pathways
2. Review of currently approved JAKs for AD– abrocitinib & upadacitinib
3. Recognize the ideal candidate for JAKi
4. Utilize laboratory tests to monitor your patient

Available and emerging therapies for AD

Conventional systemic drugs
More side effects
Risk of organ damage

- Cyclosporine
- Methotrexate
- Azathioprine
- Mycophenolate
- Prednisone

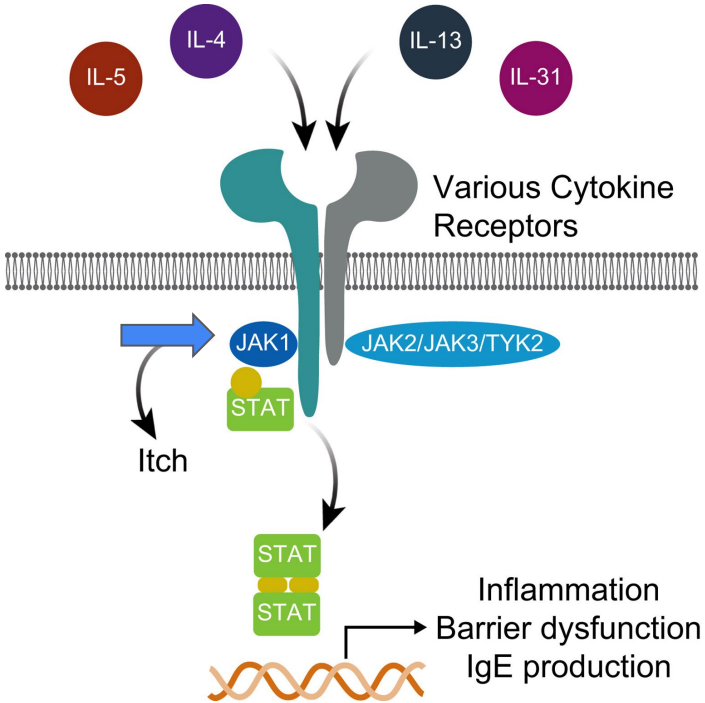
Biologics:
Target cytokines & receptors
Safer, more effective

- IL-4,13 inhibitor (IL-4Rα) *(dupilumab)*
- IL-13 inhibitors *(tralokinumab, lebrikizumab)*
- IL-31 inhibitor (IL-31RA) *(nemolizumab)*

Small molecule targeted therapies:
Target signaling of various cytokines
Safer, more effective

- JAK 1 inhibitors *(abrocitinib, upadacitinib)*
- JAK 1,2 inhibitor *(baricitinib)*

JAK = Janus Kinase enzymes JAK1/2/3/TYK2



Signaling proteins that transmit the cytokine signal (from outside the cell) to inside the cell → gene transcription of inflammatory cytokines

JAK1/JAK3 appear to impact TH2/atopic dermatitis pathways

JAK2/TYK2 more psoriasis

Kim BS, Howell MD, Sun K, Papp K, Nasir A, Kuligowski ME; INCB 18424-206 Study Investigators. Treatment of atopic dermatitis with ruxolitinib cream (JAK1/JAK2 inhibitor) or triamcinolone cream. J Allergy Clin Immunol. 2020 Feb;145(2):572-582. doi: 10.1016/j.jaci.2019.08.042. Epub 2019 Oct 17. PMID: 31629805.

JAK Cytokine signaling involves many immune pathways:

Th1 and Th17 differentiation

IL-17, TNFα, and IFNγ secretion

T cell survival/Treg maintenance

Lymphoid cell maturation and function

Hematopoiesis/Granulopoiesis/Myelopoiesis

Metabolic activity regulation

Osteoclast formation

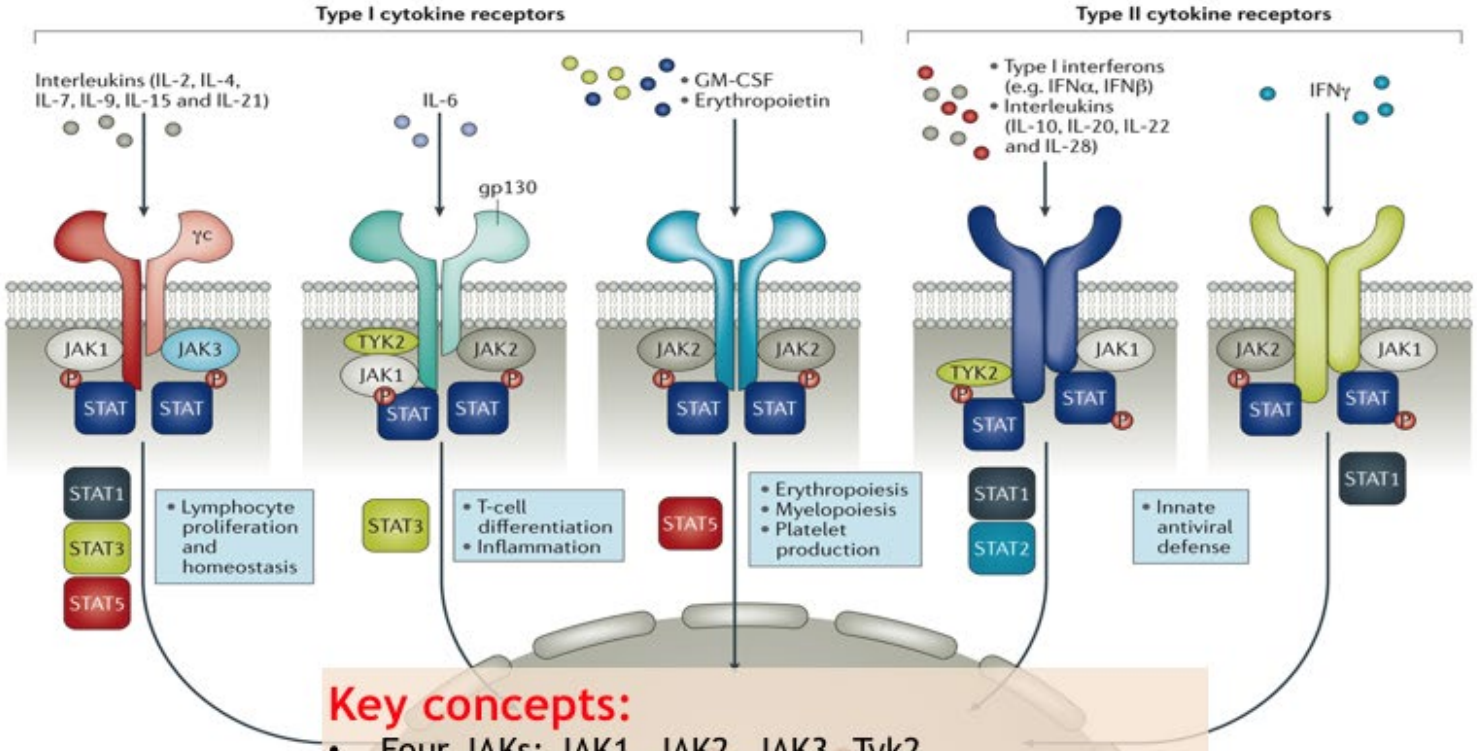
Neuronal survival

Lipid metabolism

Glucose metabolism

Growth factor response

Kim BS, Howell MD, Sun K, Papp K, Nasir A, Kuligowski ME; INCB 18424-206 Study Investigators. Treatment of atopic dermatitis with ruxolitinib cream (JAK1/JAK2 inhibitor) or triamcinolone cream. J Allergy Clin Immunol. 2020 Feb;145(2):572-582. doi: 10.1016/j.jaci.2019.08.042. Epub 2019 Oct 17. PMID: 31629805.



Key concepts:

- Four JAKs: JAK1, JAK2, JAK3, Tyk2
- JAKs work in pairs
- Different receptors bind different JAKs
- Different immunomodulatory signals are generated

Winthrop, K. L., *Nat. Rev. Rheumatol.* 2017

Nature Reviews | Rheumatology

FDA approved in Atopic Dermatitis

refractory, moderate-to-severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable.

Rinvoq

12 years and up

Cibinqo

18 years and up

Kim BS, Howell MD, Sun K, Papp K, Nasir A, Kuligowski ME; INCB 18424-206 Study Investigators. Treatment of atopic dermatitis with ruxolitinib cream (JAK1/JAK2 inhibitor) or triamcinolone cream. J Allergy Clin Immunol. 2020 Feb;145(2):572-582. doi: 10.1016/j.jaci.2019.08.042. Epub 2019 Oct 17. PMID: 31629805.

JAK FAMILY SELECTIVITY PROFILES

- Selectivity depends on dose used and assay used to measure activity.

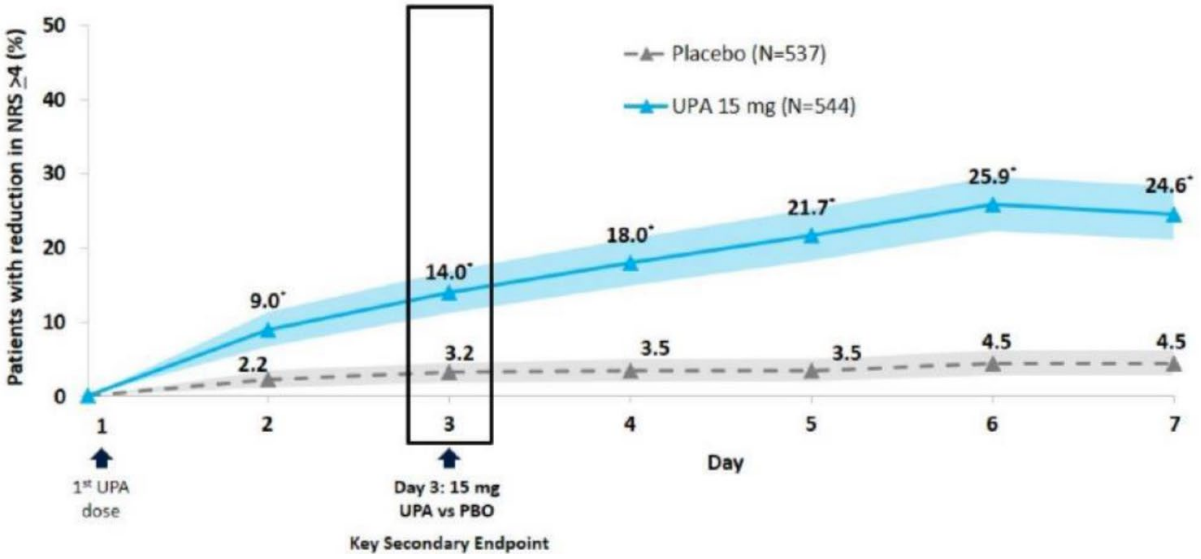
JAKi	Selectivity	Actual
BARI	JAK1/2	**JAK1/2 > JAK3/Tyk2**
UPA	JAK1	**JAK1 > JAK2 > JAK3 > Tyk2**
ABRO	JAK1	**JAK1 > JAK2 > Tyk2 > JAK3**
TOFA	JAK1/3	**JAK1/3 > Tyk2/JAK2**

Lin et al. Mediterr J Rheumatol 2020;31(Supp 1):100-4

Do you know JAK? *The Good*

Upadacitinib (*Abbvie*): relieves itch as early as day 3

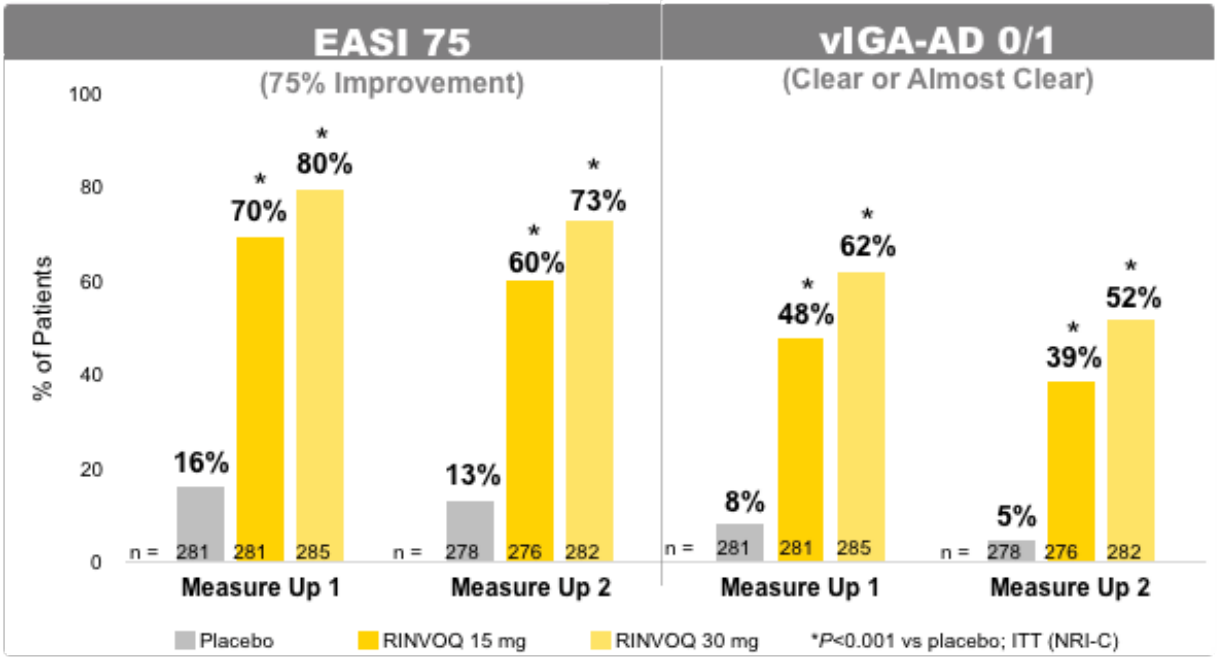
Integrated Measure Up 1 & 2: Daily NRS itch reduction ≥ 4 points from baseline



Kim BS, Howell MD, Sun K, Papp K, Nasir A, Kuligowski ME; INCB 18424-206 Study Investigators. Treatment of atopic dermatitis with ruxolitinib cream (JAK1/JAK2 inhibitor) or triamcinolone cream. J Allergy Clin Immunol. 2020 Feb;145(2):572-582. doi: 10.1016/j.jaci.2019.08.042. Epub 2019 Oct 17. PMID: 31629805.

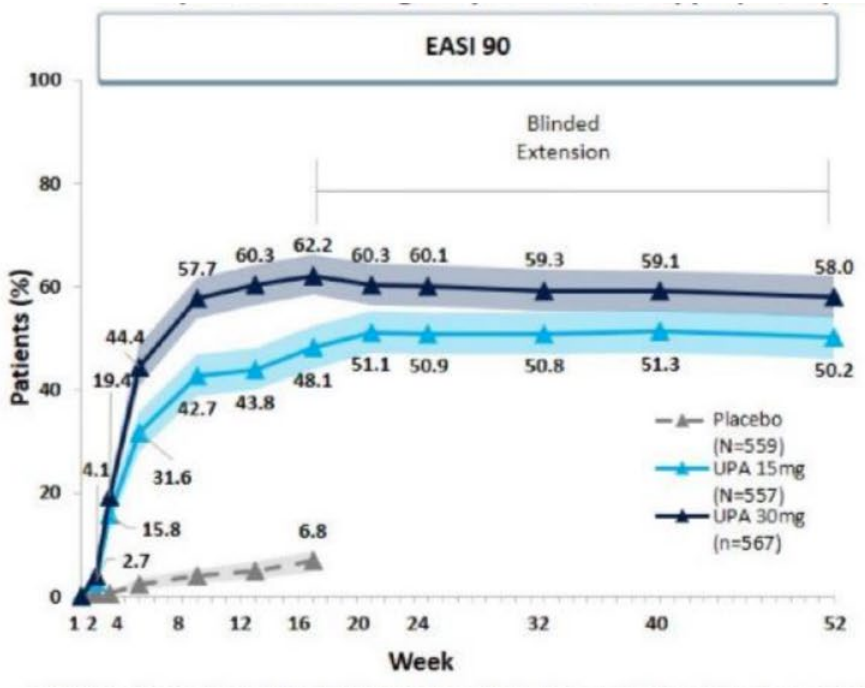
Upadacitinib (*Abbvie*): powerful skin clearance at week 16

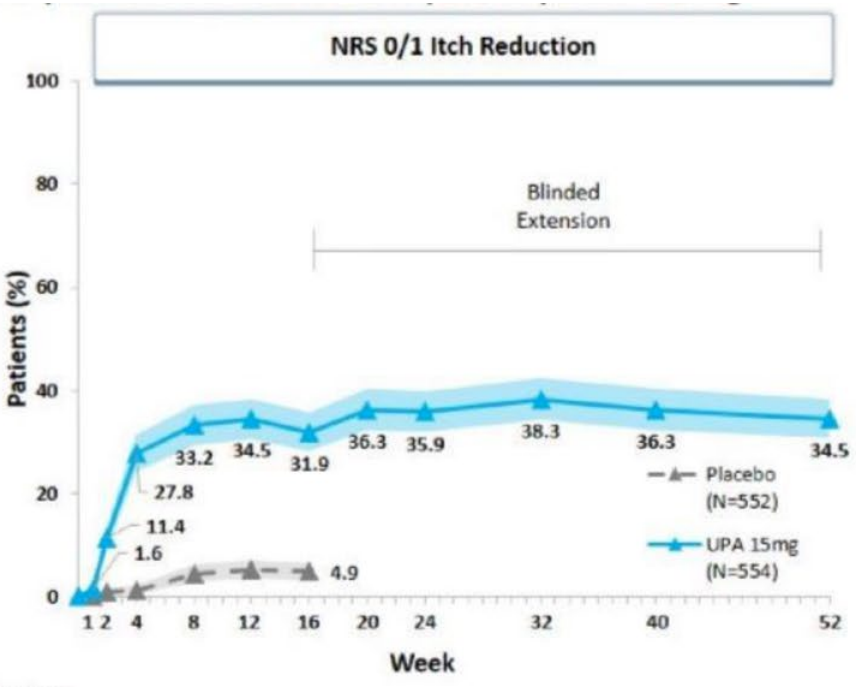
Adult and adolescent patients ≥ 12 yo



Kim BS, Howell MD, Sun K, Papp K, Nasir A, Kuligowski ME; INCB 18424-206 Study Investigators. Treatment of atopic dermatitis with ruxolitinib cream (JAK1/JAK2 inhibitor) or triamcinolone cream. J Allergy Clin Immunol. 2020 Feb;145(2):572-582. doi: 10.1016/j.jaci.2019.08.042. Epub 2019 Oct 17. PMID: 31629805.

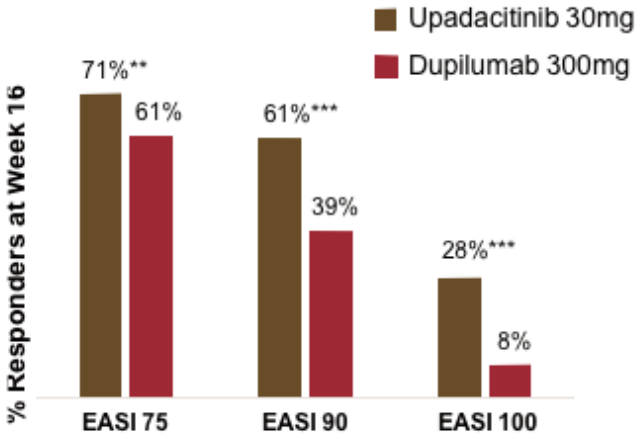
Steroid sparing oral agent: durable EASI90 skin clearance rates at week 52





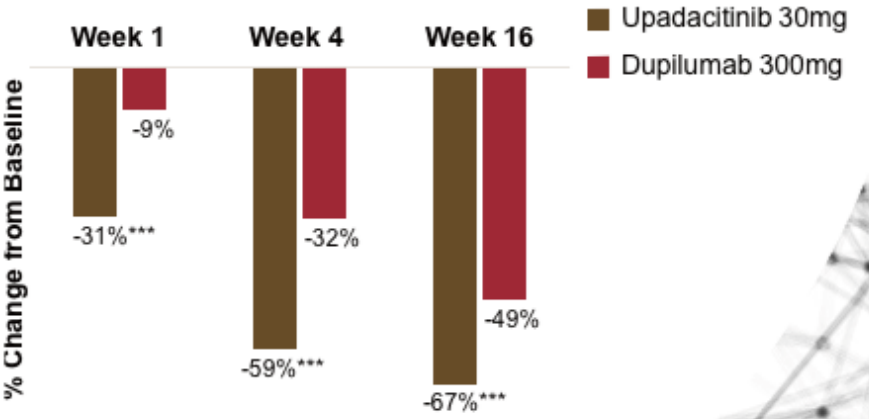
Upadacitinib Head to Head trial with Dupilumab Heads Up

Upadacitinib vs. Dupilumab on EASI Thresholds at Week 16



Upadacitinib vs. Dupilumab Improvements in Itch

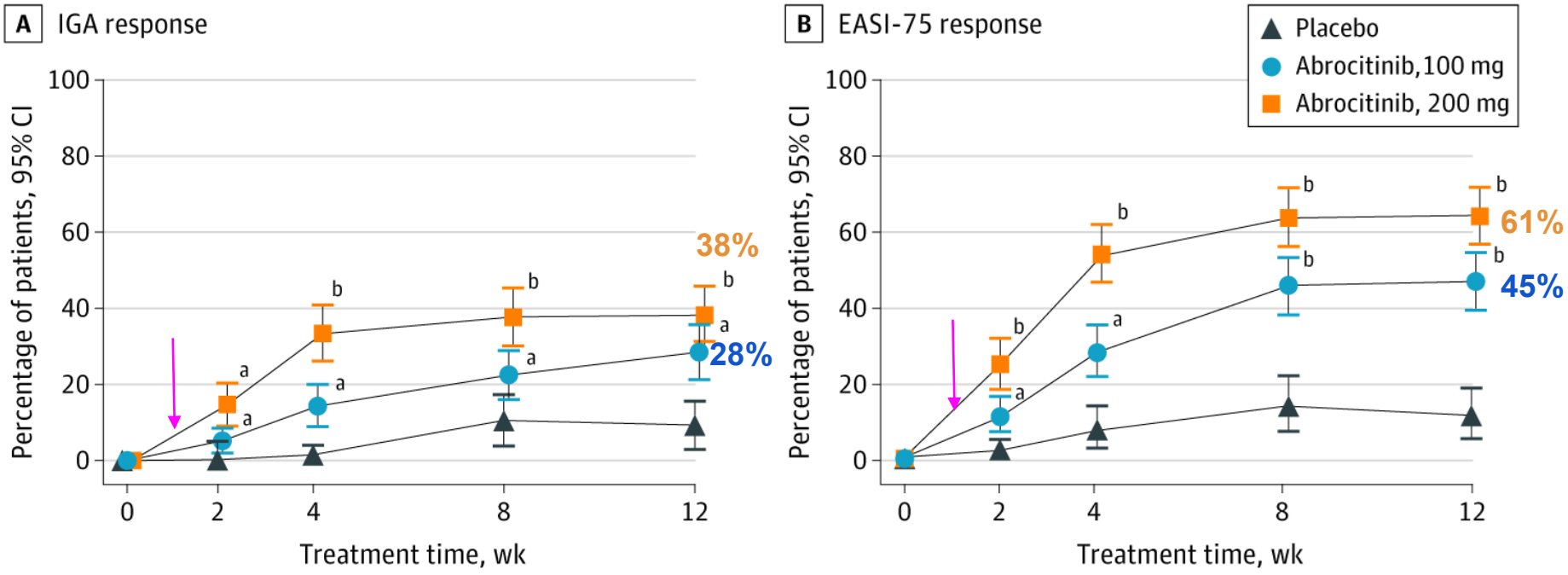
(% Change from Baseline in Worst Pruritus Numerical Rating)



*p-value < 0.05; **0.001< p-value ≤ 0.01; ***p-value ≤ 0.001. Upadacitinib has not been approved in AD and its safety and efficacy in this indication has not been evaluated by regulatory agencies.

Ref: AbbVie Immunology Strategy Update and Long-Term Outlook | December 2020; https://investors.abbvie.com/static-files/af90f072-f816-4dd3-9031-dd3389145545

Abrocitinib (*Pfizer*): powerful and rapid skin clearance. No TCS use.

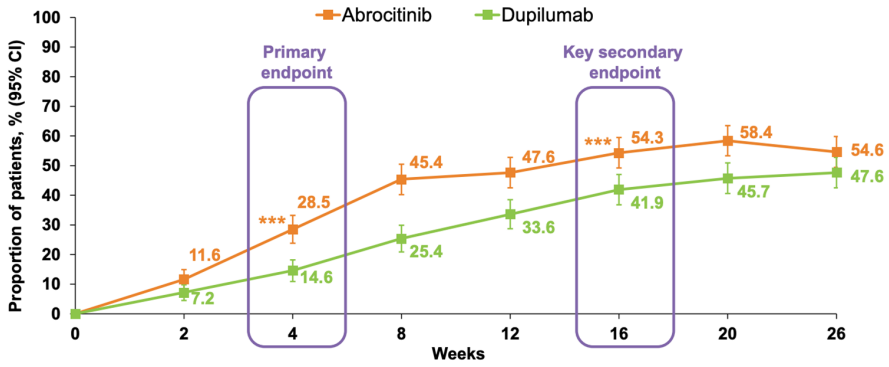


Silverberg JI, Simpson EL, Thyssen JP, et al. Efficacy and Safety of Abrocitinib in Patients With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial. *JAMA Dermatol.* 2020;156(8):863–873.

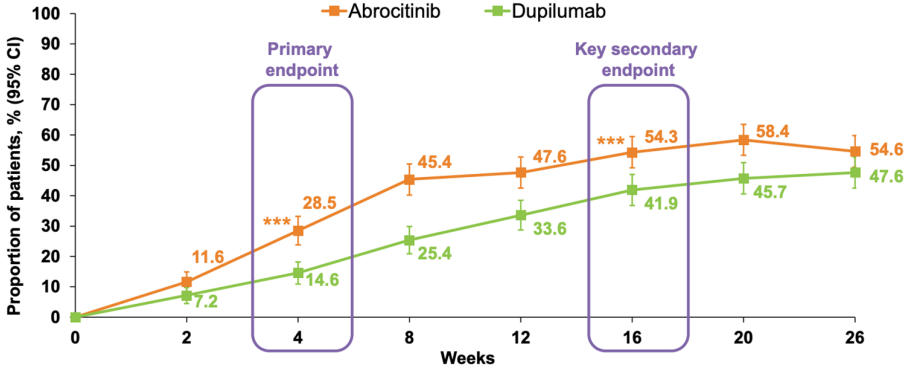
Abrocitinib superior to dupilumab in early itch & AD

Abrocitinib 200 mg per day was more efficacious than dupilumab in adults with moderate-to-severe atopic dermatitis on background topical therapy in inducing early reductions of itch and atopic dermatitis disease signs. Both treatments were well tolerated over 26 weeks.

⩾ 4 pt reduction in PNRS from baseline



⩾ 90% EASI improvement



Reich K, Thyssen JP, Blauvelt A, Eyerich K, Soong W, Rice ZP, Hong HC, Katoh N, Valenzuela F, DiBonaventura M, Bratt TA, Zhang F, Clibborn C, Rojo R, Valdez H, Kerkmann U. Efficacy and safety of abrocitinib versus dupilumab in adults with moderate-to-severe atopic dermatitis: a randomised, double-blind, multicentre phase 3 trial. Lancet. 2022 Jul 23;400(10348):273-282.

SAFETY SUMMARY OF PHASE 2/3 TRIALS IN AD

Short term (12-16 week)

	Abrocitinib			Upadacitinib		
	PBO	100mg	200mg	PBO	15mg	30mg
	%	%	%	%	%	%
All AEs	54 - 57	63 - 69	66 - 78	53 - 63	60 - 76	61 - 79
SAEs	1.3 - 4	3 - 5.4	1.3 - 3.6	2.5 - 3	1.8 - 2.4	0 - 2.8
Serious infection	1.3	1.9	0	0-1	0.4 - 2.4	0.7
VTE	0	0	0-1.8	0-0.4	0	0
Malignancy	0	0	0	0	0	0-0.7
Herpes simplex	1.8	0 - 1.8	0 - 2	1.7	3.3	7.7
Herpes zoster	0	0-1	0-1.3	0-1	0-2.2	0-2.1
Death	0	0-0.6	0	0	0	0
URTI	4 - 9	5 - 9	3 - 9	5 - 10	5 - 12	5 - 12
Nasopharyngitis	6 - 10	13 - 18	8 - 13	2.5 - 11	5 - 12	5 - 13
Nausea	2 - 3	2 - 9	14 - 20	2.5	2.4	7.1
Vomiting	0-1.3	0-1.3	0 - 5.2	*	*	*
Headache	2.6 - 3.6	5.7 - 8.9	7.3 - 10	2.5 - 5.5	5 - 7	5 – 9.5
CK elevation	0 - 2.6	0 - 1.9	0 - 3.2	2.3 - 5	4 - 7	5 – 9.5
Acne	0	2	5	2	7 - 13	14 - 17

Guttman et al. JAAD 2019; Simpson et al BJD 183 (2) 2020; Reich et al JAMA Dermatol 2020; 156(12): 1–11; Gooderham et al. JAMA Dermatol 2019; 155(12); Silverberg et al. JAMA Dermatol 156(80; Simpson et al. The Lancet 2020; Guttman et al. JACI 2019; 145(3); Guttman et al. RAD 2020; Reich et al. RAD 2020; Simpson EL, Silverberg JI, Nosbaum A, et al. Am J Clin Dermatol. 2021;22(5):693-707.

Abrocitinib: Integrated safety analysis across 6 studies

Incidence Rates (All-Abrocitinib Cohort)

	Abrocitinib 100 mg N=885 n/100 PY (95% CI)	Abrocitinib 200 mg N=1971 n/100 PY (95% CI)
Serious infections	2.65 (1.55–4.25)	2.33 (1.49–3.47)
Herpes zoster	2.04 (1.09–3.49)	4.34 (3.15–5.82)
Herpes simplex	8.73 (6.56–11.39)	11.83 (9.77–14.19)
Eczema herpeticum	2.34 (1.31–3.86)	0.78 (0.34–1.53)

- Incidence rates across all abrocitinib-treated patients, including both doses (n/100 PY [95% CI]), were:

OI: 0.60 (0.29–1.10)
MACE: 0.18 (0.04–0.52)
VTE: 0.30 (0.10–0.70)

Malignancies[a]: 0.24 (0.07–0.61)
NMSC: 0.42 (0.17–0.86)
GI perforation: 0.18 (0.04–0.52)

Simpson, E.L., Silverberg, J.I., Nosbaum, A. *et al.* Integrated Safety Analysis of Abrocitinib for the Treatment of Moderate-to-Severe Atopic Dermatitis From the Phase II and Phase III Clinical Trial Program. *Am J Clin Dermatol* 22, 693–707 (2021).

Abrocitinib: Integrated safety analysis across 6 studies

The most common adverse events were nausea, headache, and acne, which were all non-serious; most patients had events that were mild or moderate in severity.

With proper patient and dose selection, abrocitinib has a manageable tolerability and long-term safety profile appropriate for long-term use in patients with moderate-to-severe atopic dermatitis.

Simpson, E.L., Silverberg, J.I., Nosbaum, A. *et al.* Integrated Safety Analysis of Abrocitinib for the Treatment of Moderate-to-Severe Atopic Dermatitis From the Phase II and Phase III Clinical Trial Program. *Am J Clin Dermatol* 22, 693–707 (2021).

Do you know JAK? *The Bad*

Understanding & explaining the Black Box warning

Serious Infections

Malignancies

Thrombosis

Mortality

MACE major adverse cardiac events

ORAL Surveillance

Study A3921133 (ClinicalTrials.gov NCT02092467)

- TOFA 5mg BID, 10 mg BID, ETN, ADA in RA
- Patients >50y, ≥1 cardiac risk factor
- Blinded end-point of malignancy and MACE

Infections

- **Serious Infections**
  - Rates of serious infection with JAKi are low, but have been reported, some fatal, most with concomitant MTX or steroids
  - TB is a concern, and should be screened and treated with prophylaxis, similar to TNFi
- **Herpes infections**
  - JAKi, across studies in RA, psoriasis, AD and UC, are associated with a dose dependent increased incidence of herpes zoster infection

- Rinvoq product monograph, Olumiant product monograph, Xeljanz product monograph

Malignancy

- **Cases of lymphoma in the RA trials**
  - Lymphoma and other malignancies noted in boxed warning
  - Recent malignancy warning from FDA according to topline results from the ORAL Surveillance study

- **Cases of EBV-associated post-transplant lymphoproliferative disorder was observed at an increased rate in renal transplant patients treated with tofacitinib**
  - Cases were also on other immunosuppressants

- Rinvoq product monograph, Olumiant product monograph, Xeljanz product monograph; Mease P, Charles- Schoeman C, Cohen S, *et al*. *Ann Rheum Dis* 2020;**79**:1400–1413.

Venous Thrombosis

- **Venous Thromboembolic events (VTE)**
  - DVT and PE were noted in RA patients in baricitinib and tofacitinib trials
  - Recent meta-analyses of multiple studies do not support the warning, with rates similar to placebo and population rates
  - Real world reporting also did not support
  - ORAL surveillance study - increased rates with the 10 mg dose
    - Added boxed warning 2019

- Rinvoq product monograph, Olumiant product monograph, Xeljanz product monograph

Adverse events during UPA through week 52

Table 3. Treatment-Emergent Adverse Events (TEAEs) During Administration of UPA Through Week 52

	UPA 15 mg			UPA 30 mg		
	Measure Up 1 (n = 401)[a]	Measure Up 2 (n = 396)[a]	Combined (n = 797)[b]	Measure Up 1 (n = 408)[a]	Measure Up 2 (n = 403)[a]	Combined (n = 811)[b]
	Events (events/100 PY)					
AEs	PY = 490.9	PY = 462.4	PY = 953.3	PY = 501.0	PY = 477.2	PY = 978.2
Any TEAE	1288 (262.4)	1114 (240.9)	2402 (252.0)	1658 (330.9)	1293 (270.9)	2951 (301.7)
Serious AEs	32 (6.5)	33 (7.1)	65 (6.8)	50 (10.0)	33 (6.9)	83 (8.5)
AEs leading to discontinuation of study drug	22 (4.5)	21 (4.5)	43 (4.5)	39 (7.8)	31 (6.5)	70 (7.2)
Deaths	0	0	0	1 (0.2)[c]	0	1 (0.1)
AESIs[d]						
Serious infections	10 (2.0)	11 (2.4)	21 (2.2)	23 (4.6)	12 (2.5)	35 (3.6)
Opportunistic infection excluding tuberculosis and herpes zoster	5 (1.0)	13 (2.8)	18 (1.9)	15 (3.0)	5 (1.0)	20 (2.0)
Herpes zoster[e]	17 (3.5)	17 (3.7)	34 (3.6)	28 (5.6)	25 (5.2)	53 (5.4)
Active tuberculosis	1 (0.2)	0	1 (0.1)	0	1 (0.2)	1 (0.1)
NMSC[f]	1 (0.2)	3 (0.6)	4 (0.4)	3 (0.6)	1 (0.2)	4 (0.4)
Cancer other than NMSC[g]	2 (0.4)	0	2 (0.2)	2 (0.4)	3 (0.6)	5 (0.5)
Lymphoma	0	0	0	0	1 (0.2)[h]	1 (0.1)
Hepatic disorder	29 (5.9)	27 (5.8)	56 (5.9)	52 (10.4)	42 (8.8)	94 (9.6)
Adjudicated gastrointestinal perforation	0	0	0	0	0	0
Anemia	3 (0.6)	12 (2.6)	15 (1.6)	19 (3.8)	18 (3.8)	37 (3.8)
Neutropenia	11 (2.2)	5 (1.1)	16 (1.7)	23 (4.6)	11 (2.3)	34 (3.5)
Lymphopenia	4 (0.8)	3 (0.6)	7 (0.7)	7 (1.4)	2 (0.4)	9 (0.9)
CPK elevation	36 (7.3)	31 (6.7)	67 (7.0)	58 (11.6)	51 (10.7)	109 (11.1)
Kidney dysfunction	0	0	0	2 (0.4)	1 (0.2)	3 (0.3)
Adjudicated MACE	1 (0.2)	0	1 (0.1)	0	0	0
Adjudicated VTE	1 (0.2)	0	1 (0.1)	0	1 (0.2)	1 (0.1)

Do you know JAK? *The reality*

Laboratory Monitoring

Baseline: CBC, LFTs, GFR/Cr, TB screening, fasting lipid panel, hepatitis B/C, pregnancy test?

4-6 weeks: recheck CBC, LFTs, GFR/Cr

12 weeks later: lipid panel, CBC, LFTs, GFR/Cr
12 weeks later: lipid panel

Then every 6 months

Cautions/Contraindications

AVOID:
- Use in women planning pregnancy or lactation
- Live vaccines

CAUTION:
- Patients with comorbidities or risk factors for VTE and MACE
  - history of VTE, hypercoagulable state, smoking, immobilisation, recent trauma or surgery, cardiovascular disease, cancer, obesity, frequent long flights, and hormonal therapy
- Patients >50 years old
- Patients with history of serious infections

Don't forget:
- HZ vaccination
  - Shingrix
- Advise on contraception
- Use lowest dose of JAKi necessary

Antiplatelet therapy is contraindicated except for aspirin 81mg

In Summary:

1. Atopic dermatitis is a heterogeneous disease with multiple inflammatory cytokines.
2. JAKi treat AD by targeting multiple cytokines, not just one or two cytokines.
3. High levels of skin clearance
4. Long term safety showing no new signals