Leon H. Kircik, MD, FAAD

Clinical Professor of Dermatology
Icahn School of Medicine at Mount Sinai, New York, NY
Indiana University Medical Center, Indianapolis, IN
Medical Director
Physicians Skin Care, PLLC Louisville, KY
DermResearch, PLLC, Louisville, KY
Skin Sciences, PLLC, Louisville, KY

On the horizon…

EMERGING THERAPIES

I have received funding either as an investigator, consultant, or a speaker from the following pharmaceutical companies:

- Abbott
- Acambis
- Aclaris
- Allergan
- Almirall
- Amgen
- Anacor
- Anaptys
- Astellas
- Asubio
- BMS
- Berlex
- Biogen-Idec
- Biolife
- Biopelle
- Boehringer-Ingleheim
- Breckenridge Pharma
- Brickell
- Cellceutix
- Celgene
- Centocor
- Cipher
- Coherus
- Colbar
- Collagenex
- Combinatrix
- Connetics
- Coria
- Dermavant
- Dermik
- Dermira
- Dow
- Dusa Pharmaceuticals
- Eli Lilly
- Exeltis
- EOS
- Ferndale
- Galderma
- Genentech
- Glaxo-Smith Kline
- HealthPoint
- Idera
- Intendis
- Innovail
- Isdin
- Johnson & Johnson
- 3M
- Leo
- L'Oreal
- MC-2
- Maruho
- Medicis
- Merc
- Merz
- NanoBio
- Novartis
- Novan
- Nucryst
- Obagi
- Onset Therapeutics
- OrthoNeutrogena
- PediaPharma
- Pfizer
- PharmaDerm
- Promius
- Puracap
- QLT
- Quatrix
- Quinnova
- Serono
- SkinMedica
- Stiefel
- Sun Pharma
- Taro
- TolerRx
- Triax Pharmaceuticals
- UCB
- Valeant
- Warner & Chilcott
- Xenoport
- ZAGE

HOTTEST AREA

… Atopic Dematitis

JUNE 202 DermatologyTimes®

UNMET NEED

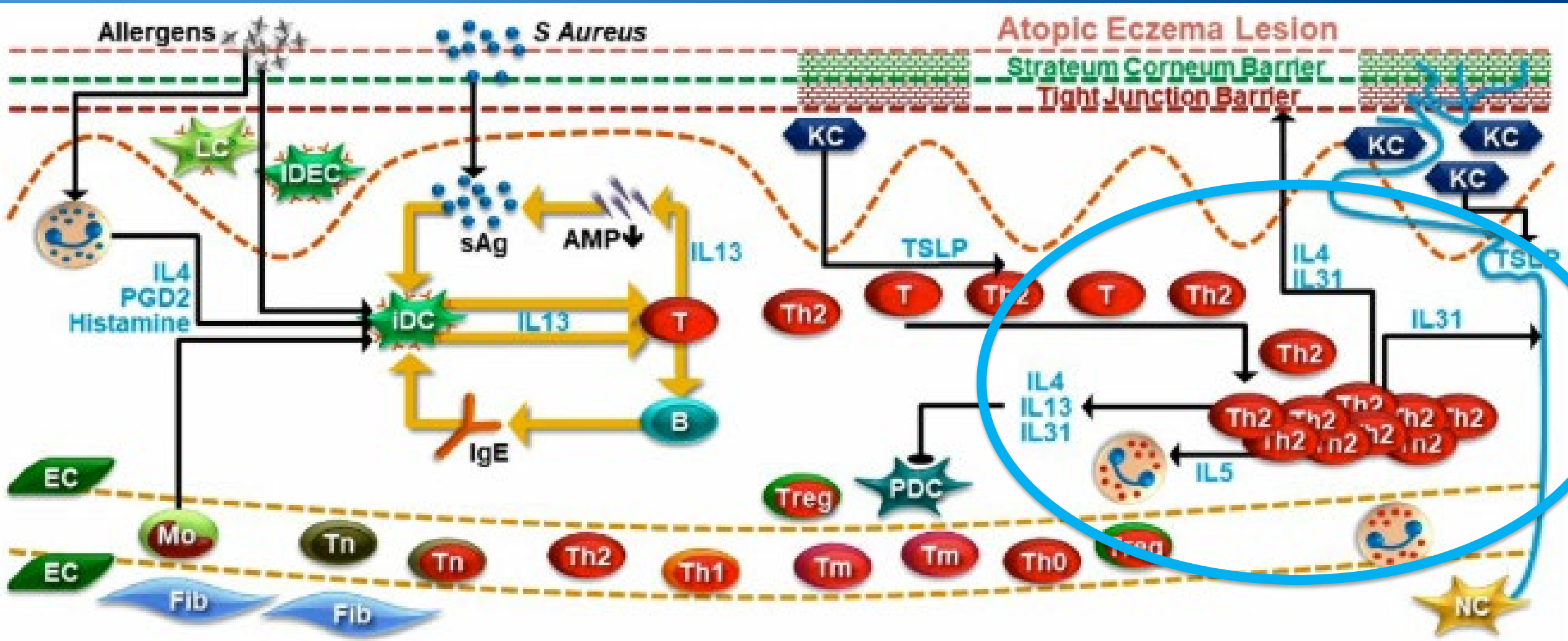
“Many patients turn to integrative management for atopic dermatitis due to a lack of efficacious prescription medication in the past.”

Vivian Shi, MD, FAAD, associate professor in the Department of Dermatology at the University of Arkansas for Medical Sciences College of Medicine in Little Rock

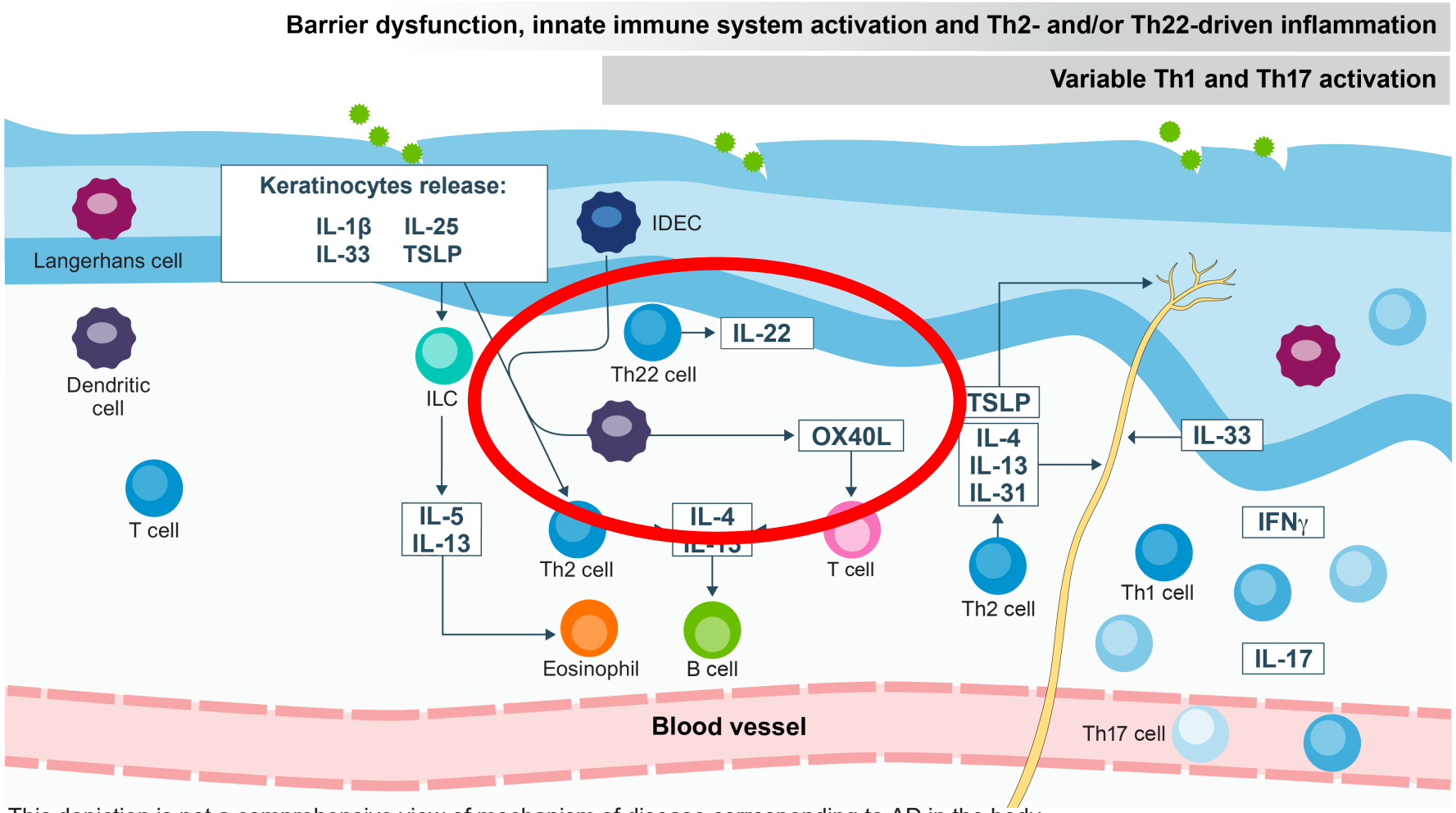
On the horizon…

EMERGING THERAPIES

ATOPIC DERMATITIS


Allergens
S Aureus
Atopic Eczema Lesion
Strateum Corneum Barrier
Tight Junction Barrier
LC
IDEC
KC
KC
KC
KC
sAg
AMP
IL13
TSLP
IL4
PGD2
Histamine
iDC
IL13
T
T
T
Th2
Th2
IL4
IL31
IL31
Th2
IL4
IL13
IL31
B
IgE
IL5
EC
EC
Mo
Tn
Tn
Th2
Th1
Treg
PDC
Tm
Tm
Th0
Fib
Fib
NC

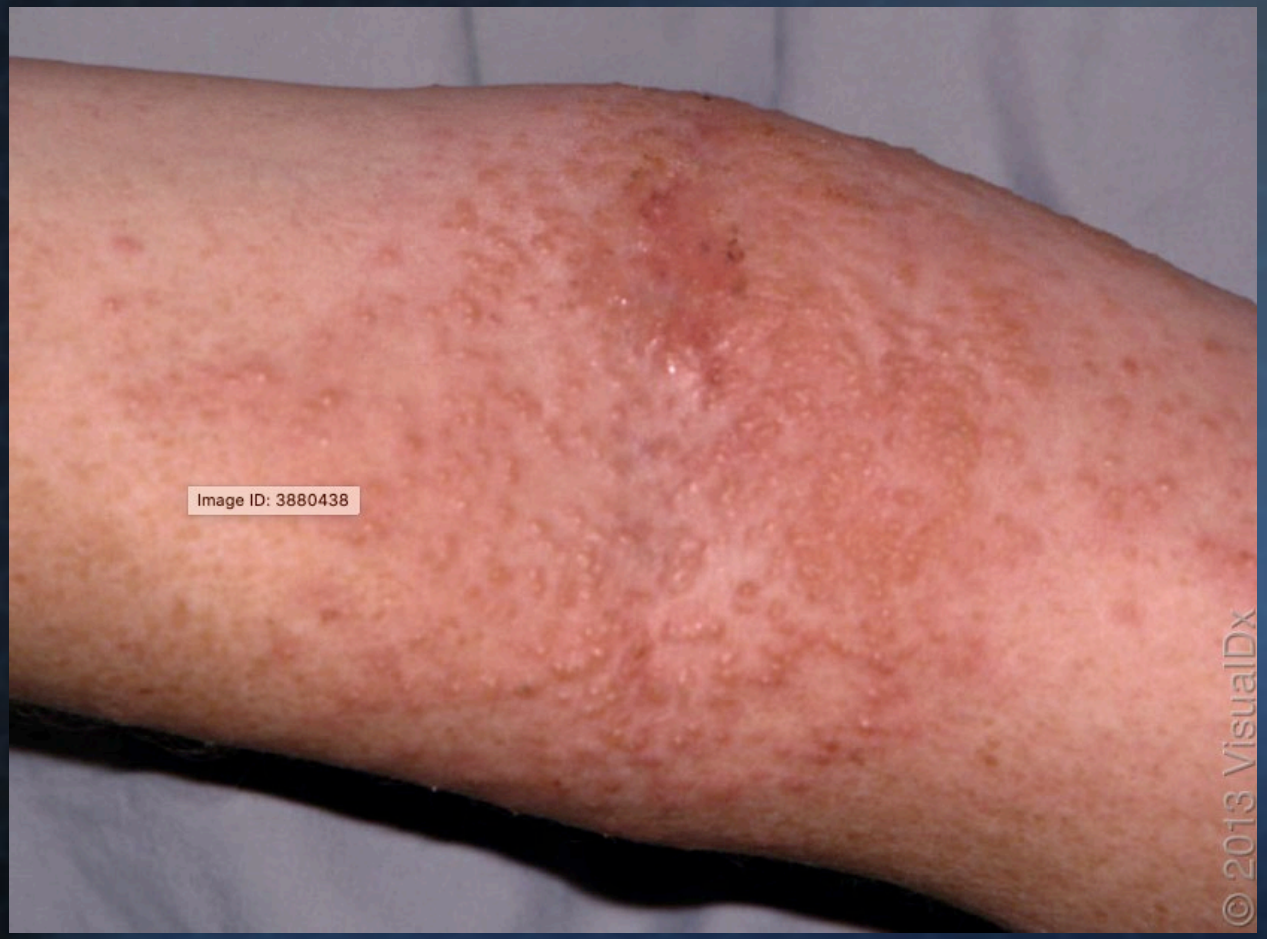
Proinflammatory Cytokines Drive AD Pathophysiology[1-3]



Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer. *Nat Rev Dis Primers.* 2018;4(1):1. Atopic dermatitis, Weidinger S, et al. © 2018.[1]

This depiction is not a comprehensive view of mechanism of disease corresponding to AD in the body.

- IDEC=inflammatory dendritic epidermal cells; IFN=interferon; IL=interleukin; ILC=innate lymphoid cells; OX40L=OX40 ligand; Th=t helper; TSLP=thymic stromal lymphopoietin.
- **1.** Weidinger S, et al. *Nat Rev Dis Primers.* 2018;4(1):1. **2.** Paller AS, et al. *J Allergy Clin Immunol* 2017;140(3):633-643. **3.** Kim J, et al. *Allergy Asthma Proc.* 2019;40(2):84-92.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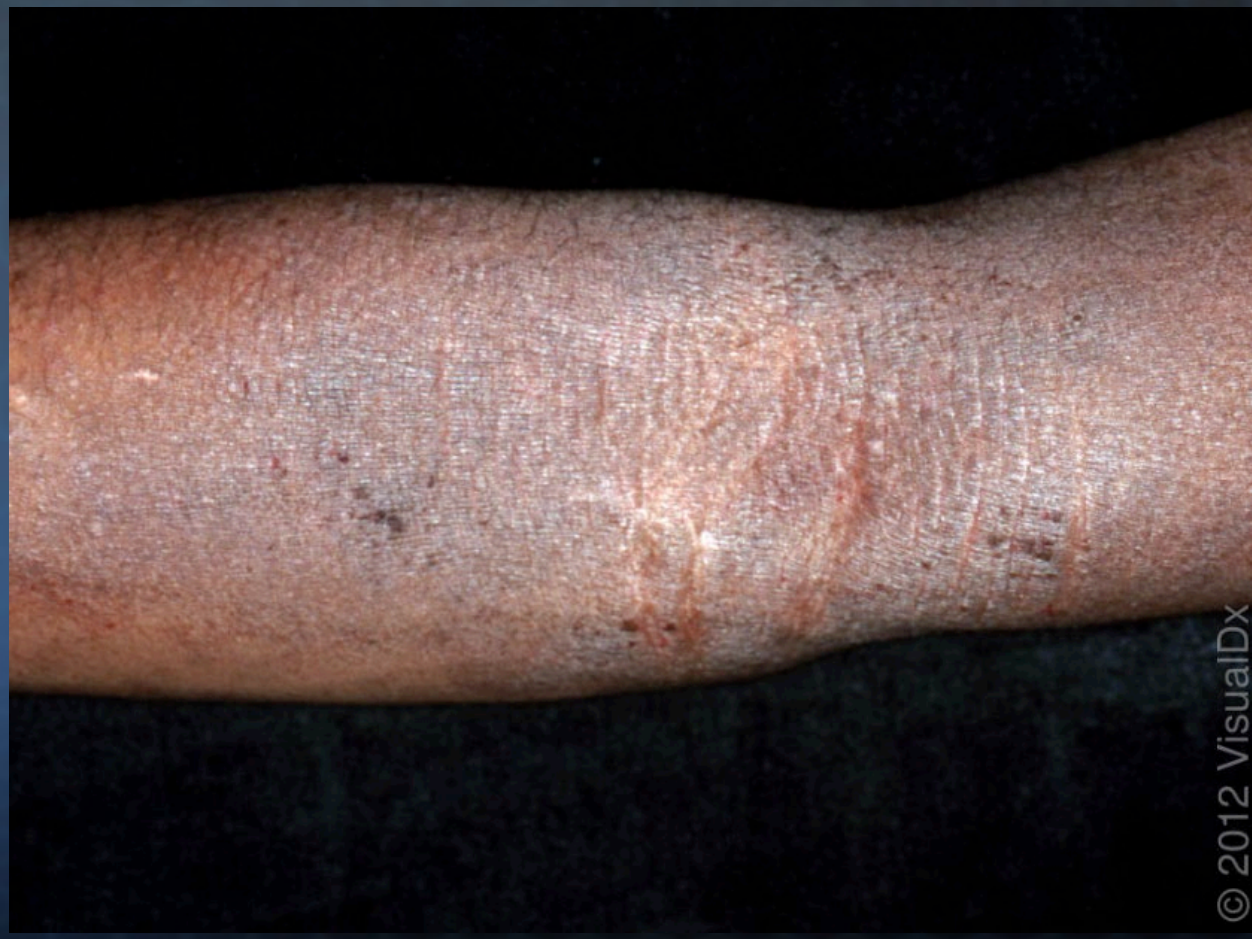
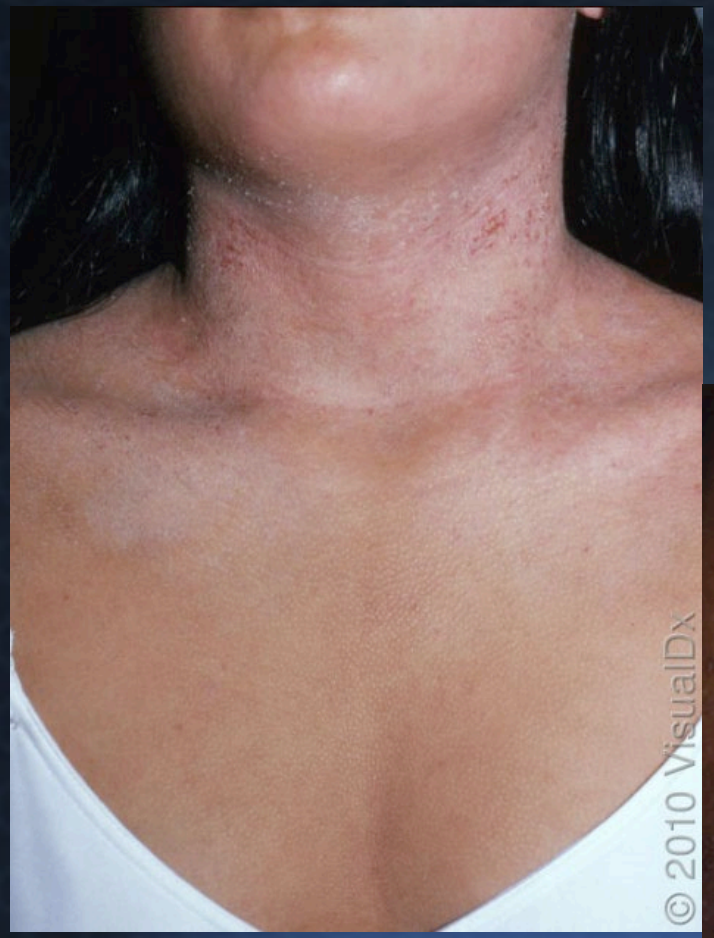
© 2013 VisualDx


© 2012 VisualDx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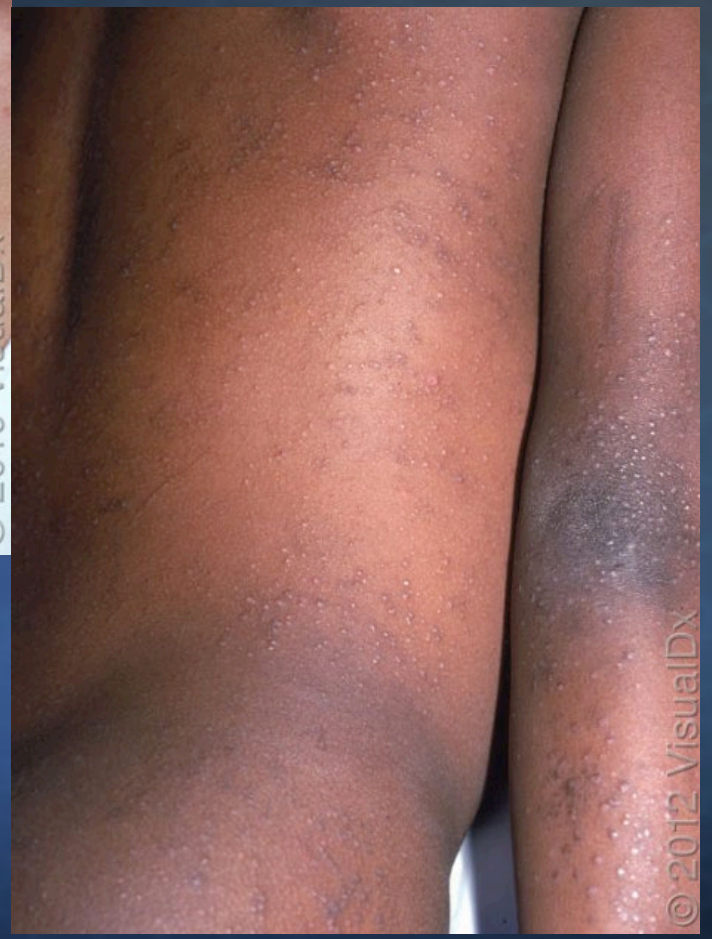
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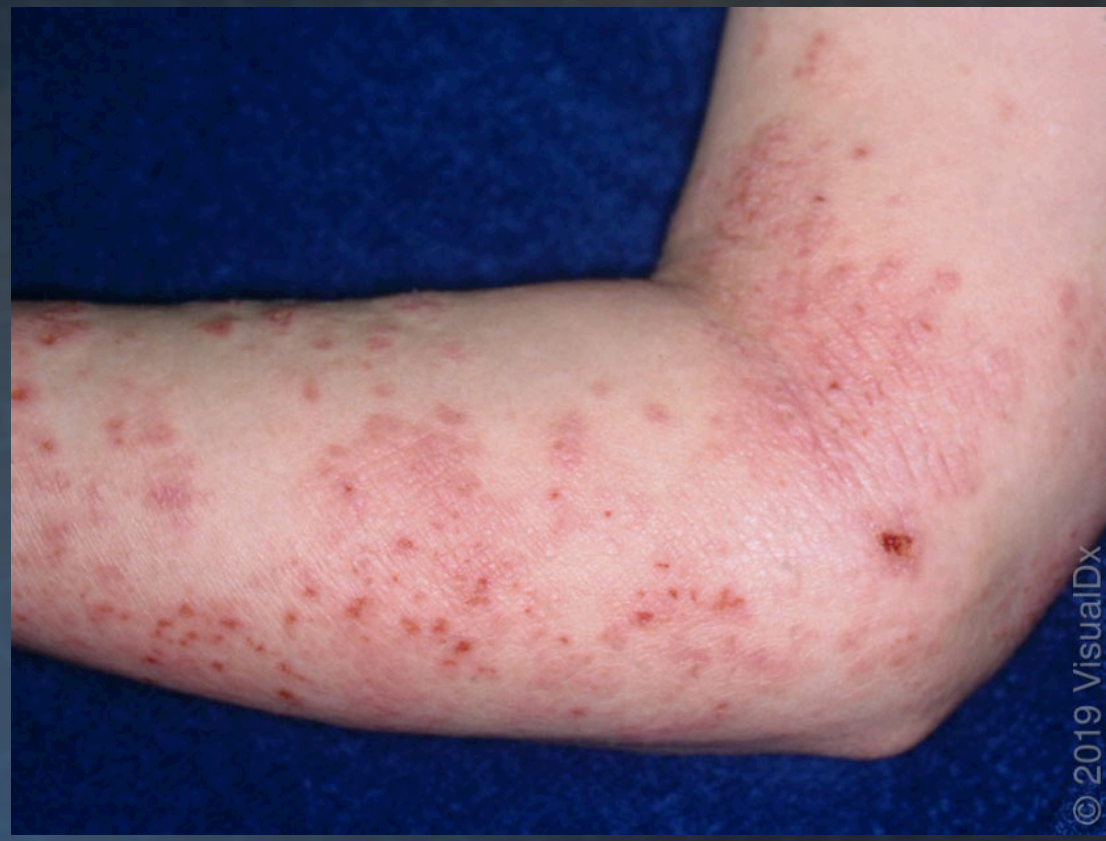
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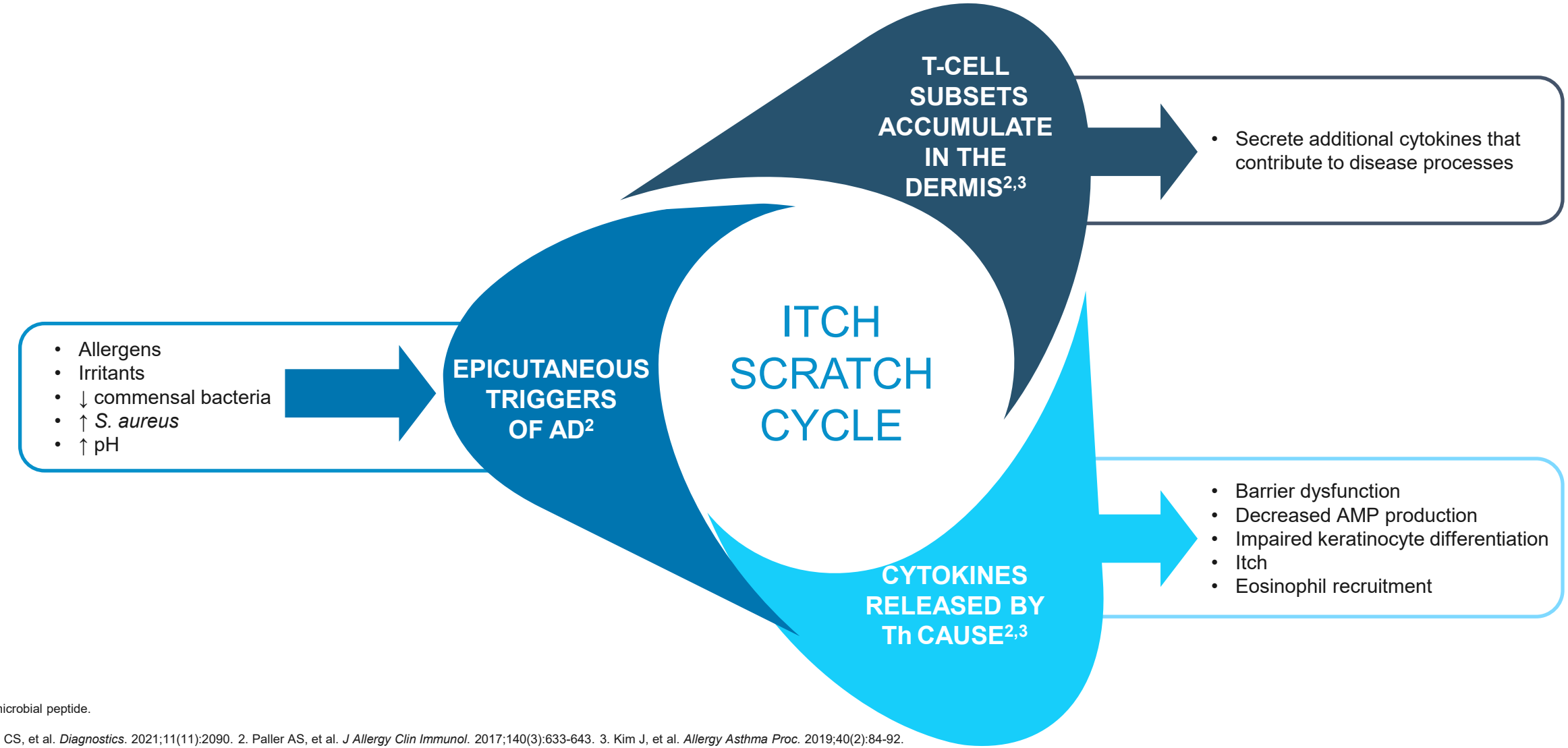
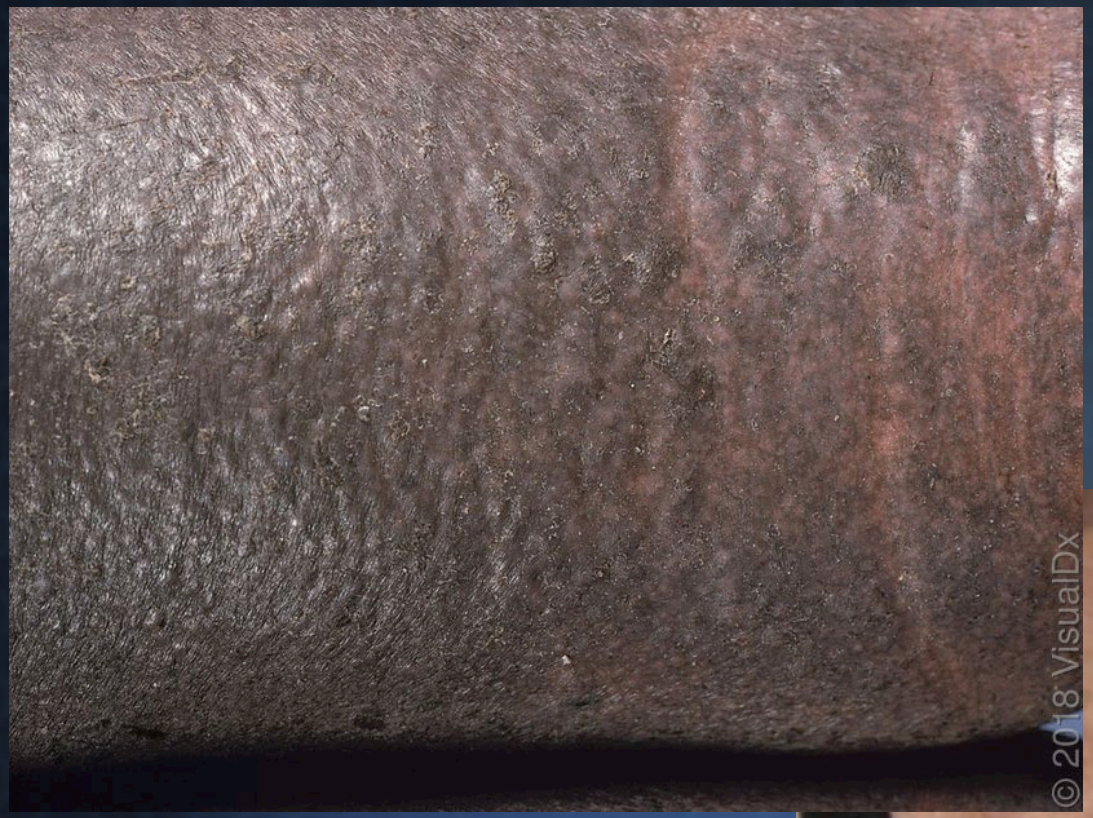
Cycle of Immune Dysfunction Mirrors AD Pathology[1]



- AMP=antimicrobial peptide.
- 1. Moniaga CS, et al. *Diagnostics*. 2021;11(11):2090. 2. Paller AS, et al. *J Allergy Clin Immunol*. 2017;140(3):633-643. 3. Kim J, et al. *Allergy Asthma Proc*. 2019;40(2):84-92.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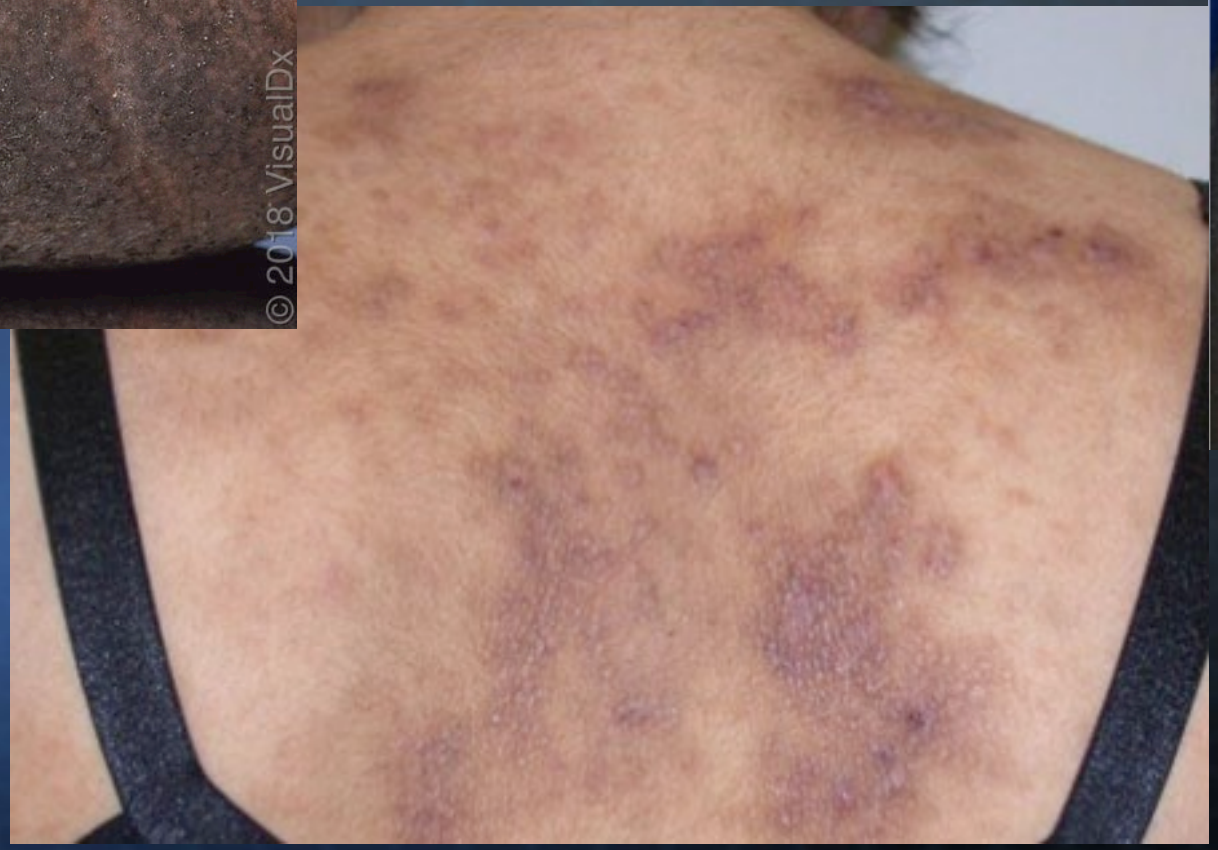
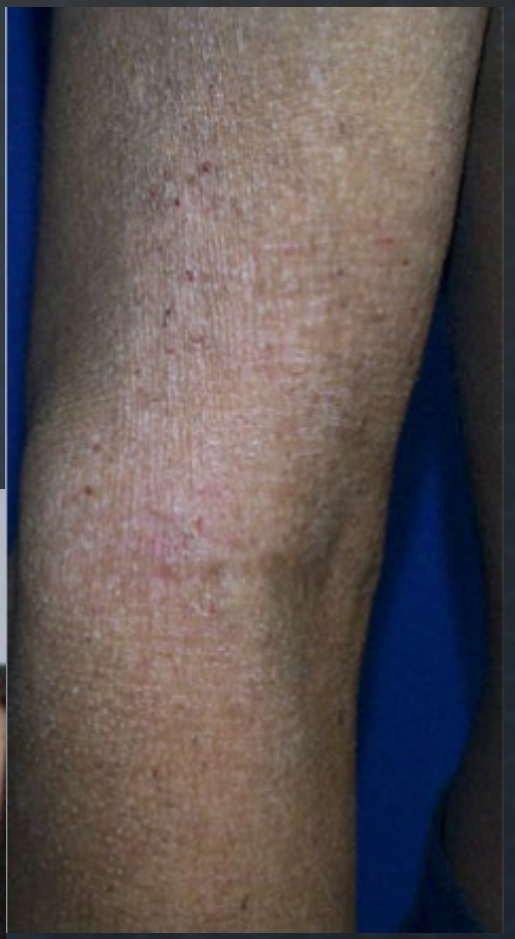
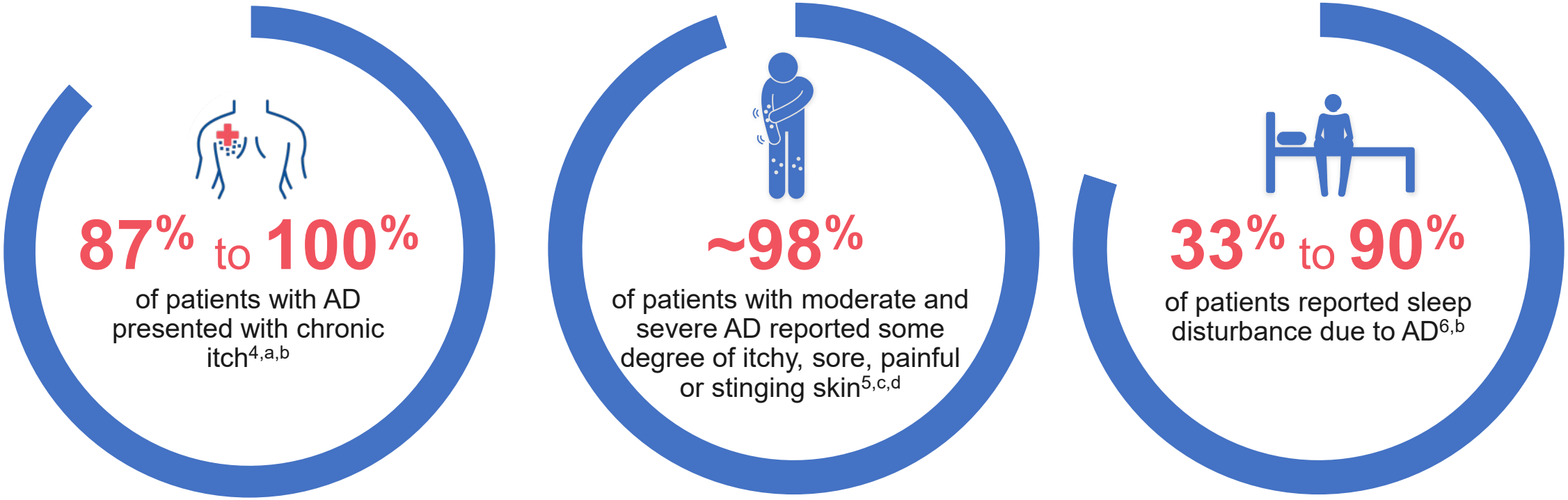




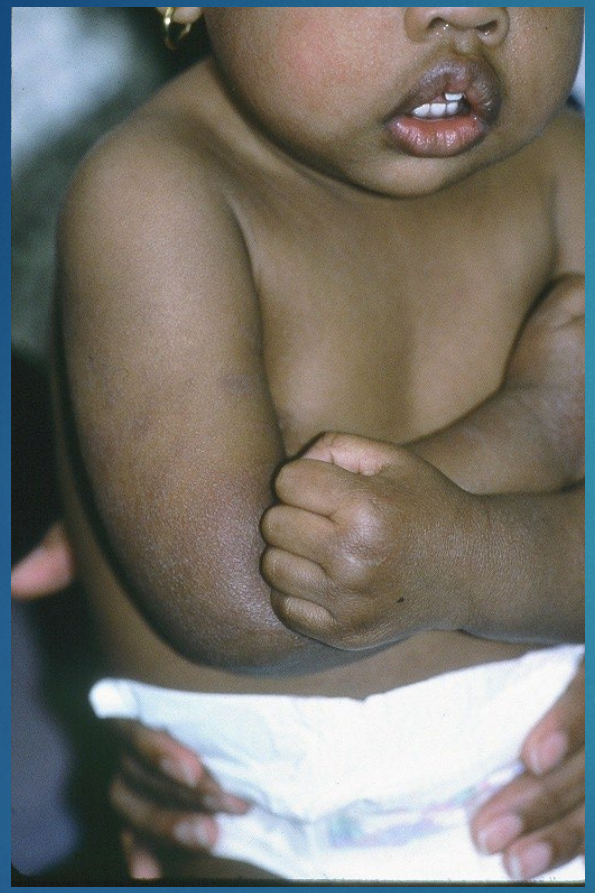
Itch: A Common Symptom for Many Patients With AD[1-3]

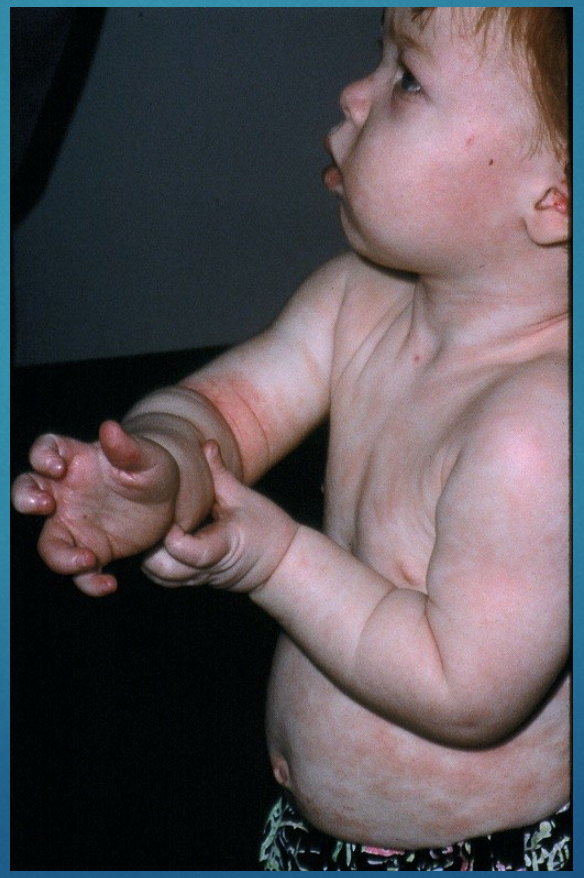


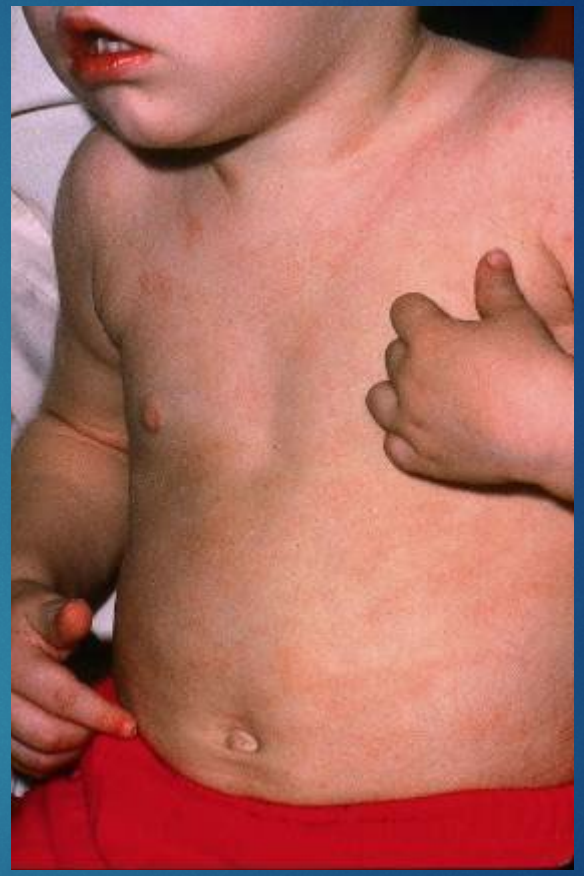
AD=atopic dermatitis; across all levels of severity.
[a]Chronic itch is defined as itch lasting more than 6 weeks.[4] [b]Review of studies in adults.[4,6] [c]Index item included itchy, sore, painful or stinging skin.[5] [d]A questionnaire-based study of 1519 adults with AD, 830 of whom had moderate-to-severe AD.[6]

1. Silverberg JI. *Ann Allergy Asthma Immunol.* 2018;121(3):340-347. **2.** Birdi G, et al. *Int J Dermatol.* 2020;59(4):e75-e91. **3.** Yew YW, et al. *J Am Acad Dermatol.* 2019;80(2):390-401. **4.** Mollanazar NK, et al. *Clinic Rev Allerg Immunol.* 2016;51(3):263-292. **5.** Simpson EL, et al. *JAMA Dermatol.* 2018;154(8):903-912. **6.** Bawany F, et al. *J Allergy Clin Immunol Pract.* 2021;9(4):1488-1500.

Atopic Dermatitis
"an itch that gets a rash"



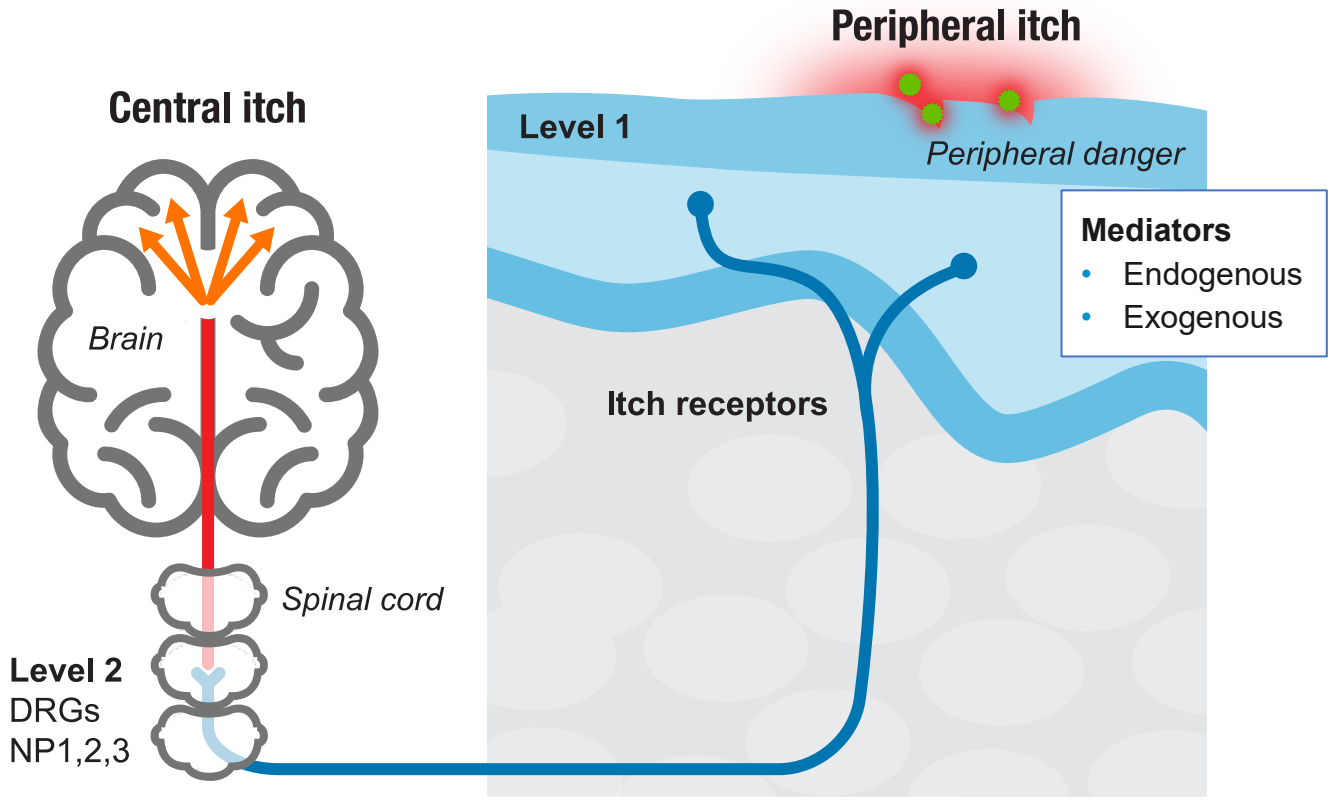




Itch Is a Cardinal Symptom of AD, but Remains Incompletely Understood

- Our understanding of the mechanisms that underlie pruritus in AD, such as the interplay of inflammation and itch, is evolving[1,2]
- While the stimulus provoking itch is in the skin lesion, the perception of itch is in the brain[3]

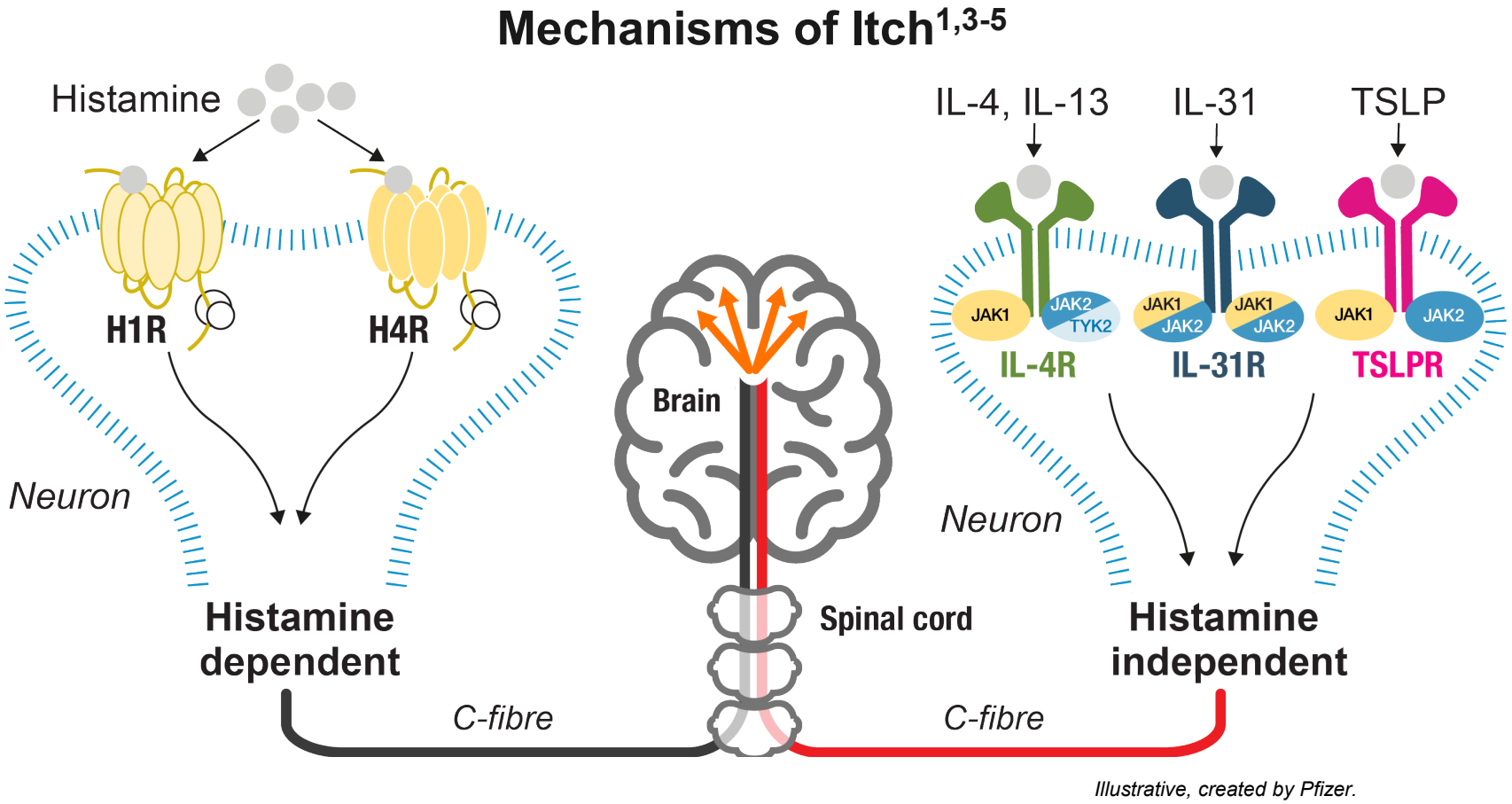
The Brain-Skin Axis[2,3]



DRG=dorsal root ganglia; NP=neuropeptide.

1. Meng J, et al. *J Allergy Clin Immunol.* 2018;141(5):1677-1689.e8. **2.** Steinhoff M, et al. *Lancet Neurol*. 2018;17(8):709-720. **3.** Paus R, et al. *J Clin Invest.* 2006;116(5):1174-1186.

In AD, Proinflammatory Cytokines Bind to and Sensitive Neuronal Networks to Propagate the Itch Signal[1-3]

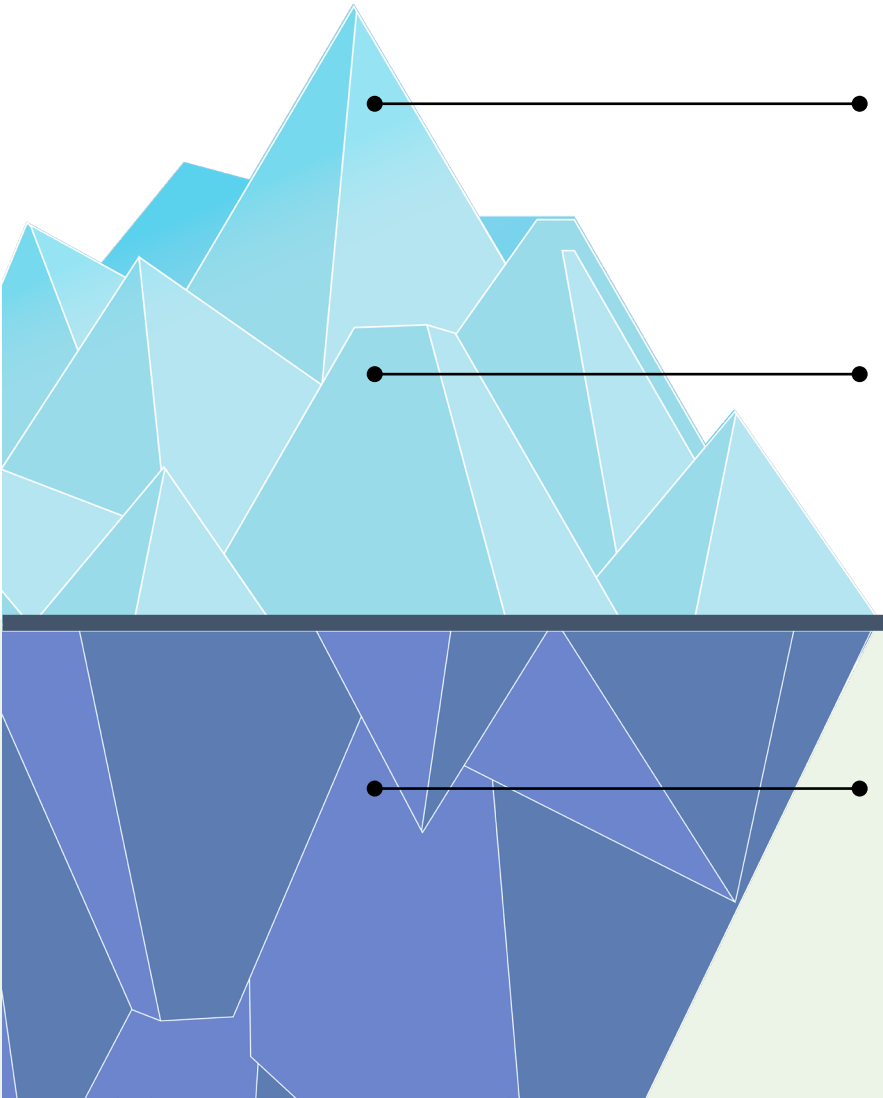


Chronic itch associated with AD is induced, at least in part, by **histamine independent** neuronal pathways[2,3]

H1R=histamine receptor type 1; TYK2=tyrosine kinase.

1. Paller AS, et al. *J Allergy Clin Immunol.* 2017;140(3):633-643. **2.** Steinhoff M, et al. *J Neurosci.* 2003;23(15):6176-6180. **3.** Steinhoff M, et al. *J Allergy Clin Immunol.* 2022;149(6):1875-1898. **4.** Wilson SR, et al. *Cell.* 2013;155(2):285-295. **5.** Yosipovitch G, et al. *J Eur Acad Dermatol Venereol.* 2020;34(2):239-250.

Sleep Disturbance in AD:
ITCH Is Only the Tip of the Iceberg



Nighttime Itch

- Insomnia
- Disturbed sleep
- Difficulty falling asleep
- Short sleep duration
- Poor sleep quality

Sleep disturbance is common in AD and directly related to poor QoL

- Increased fractures/injuries
- CVD, neurological and psychological disorders
- ↑ Healthcare utilisation/sick days
- Poor overall health

- Daytime sleepiness/fatigue
- Impaired alertness
- Falling asleep while driving

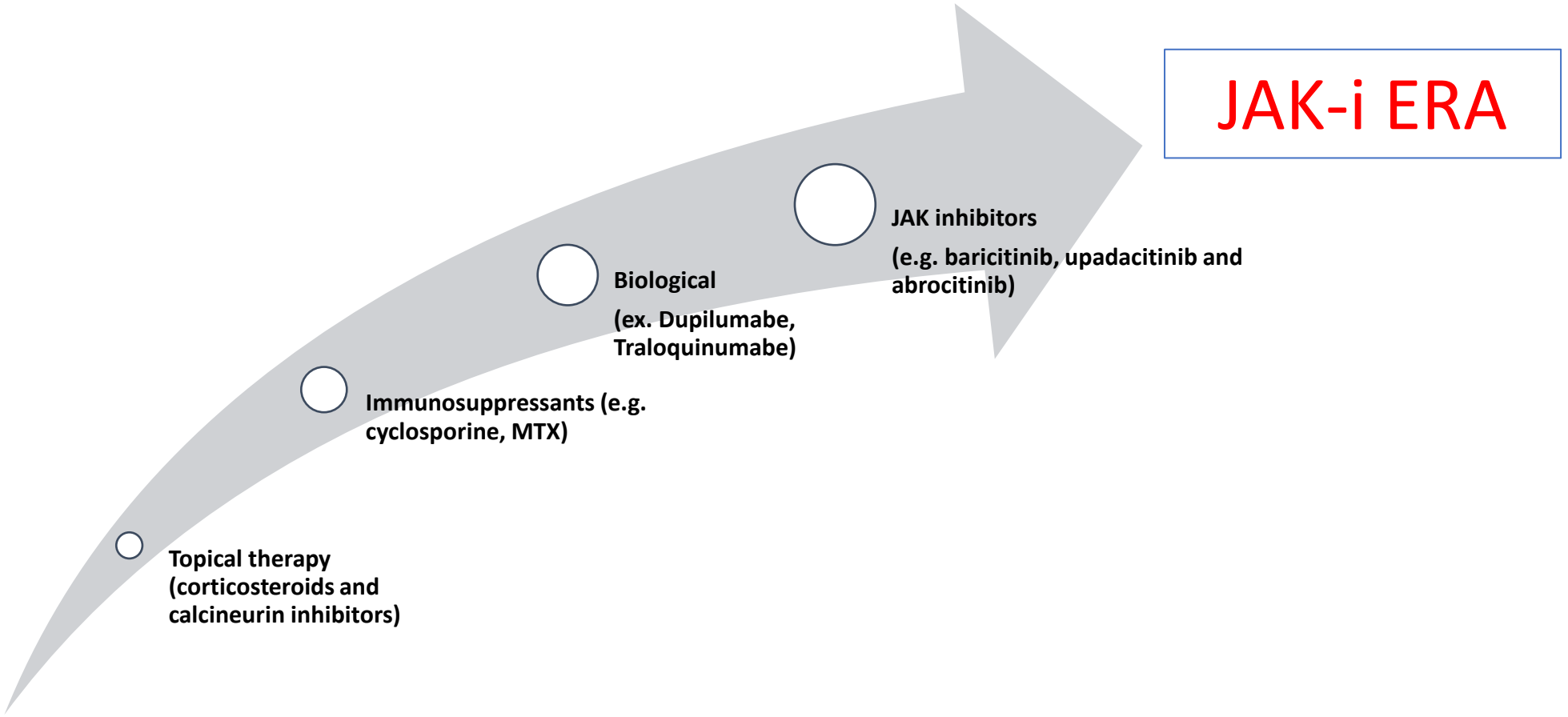
CVD=cardiovascular disease.

Li JC, et al. *Dermatitis*. 2018;29(5):270-277.


IF I DON'T SLEEP,
NOBODY SLEEPS!

Evolution of treatments in atopic dermatitis

Evolution of treatments in atopic dermatitis



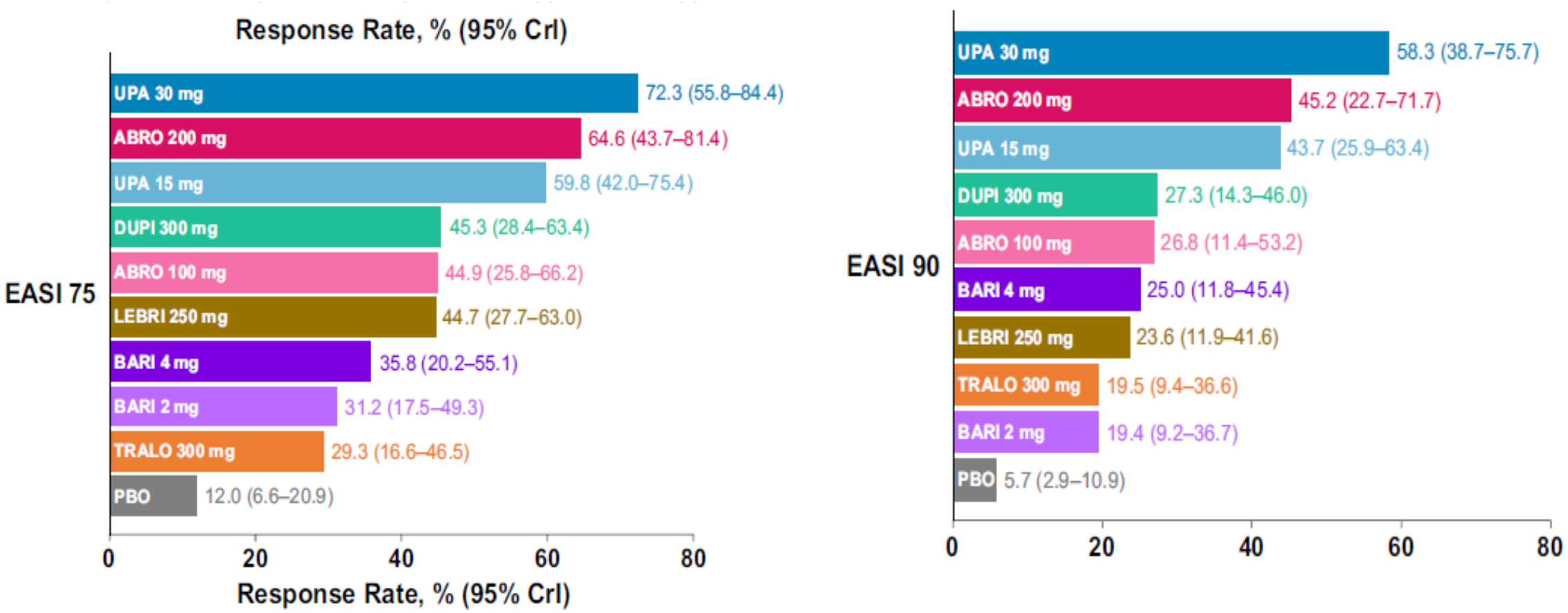
Raj Chovatiya, Amy S. Paller. JAK inhibitors in the treatment of atopic dermatites. Journal of Allergy and Clinical Immunology. Vol 148, (4). 2021. Pages 927-940. doi.org/10.1016/j.jaci.2021.08.009

“JAK inhibitors are no longer a potential treatment for AD—they are here, and the future is bright”

Raj Chovatiya, Amy S. Paller. JAK inhibitors in the treatment of atopic dermatites. Journal of Allergy and Clinical Immunology. Vol 148, (4). 2021. Pages 927-940. doi.org/10.1016/j.jaci.2021.08.009

EASI 90 and EASI 75 Absolute Response Rate Estimates for Moderate-to-Severe Atopic Dermatitis (Primary Endpoint Timepoint of Week 12/16[a])

Comparative Efficacy of Targeted Systemic Therapies for Moderate-to-Severe Atopic Dermatitis Without Topical Corticosteroids: An Updated Network Meta-analysis

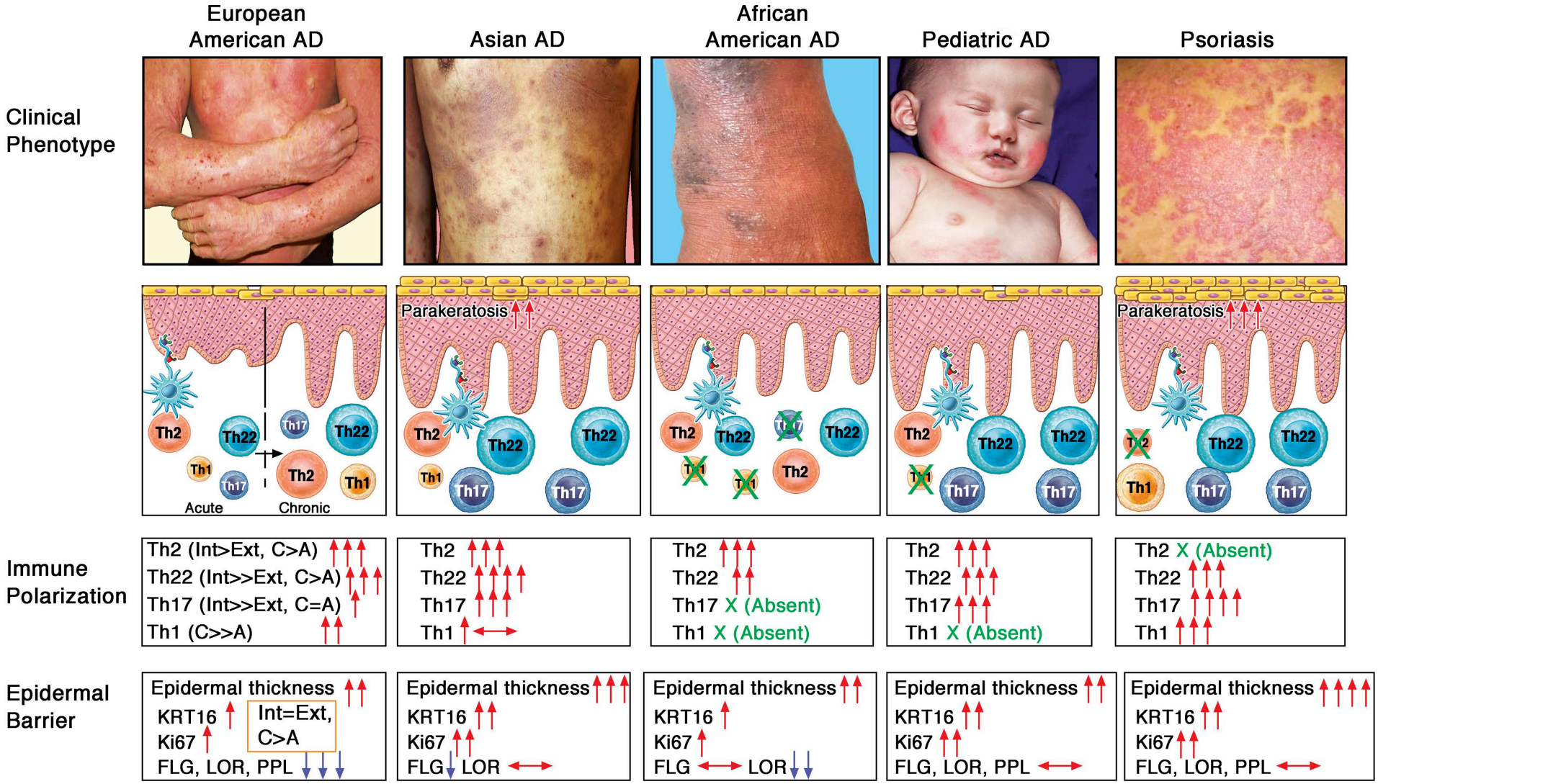


[a]Endpoints were measured at the primary endpoint timepoint for each trial (week 12 for abrocitinib and week 16 for all other targeted therapies).

Silverberg JI, Hong HC, Thyssen JP, et al. Comparative Efficacy of Targeted Systemic Therapies for Moderate to Severe Atopic Dermatitis without Topical Corticosteroids: Systematic Review and Network Meta-analysis. *Dermatol Ther (Heidelb)*. 2022;12(5):1181-1196. doi:10.1007/s13555-022-00721-1

Why Many Patients Do Not Respond to Dupilumab?

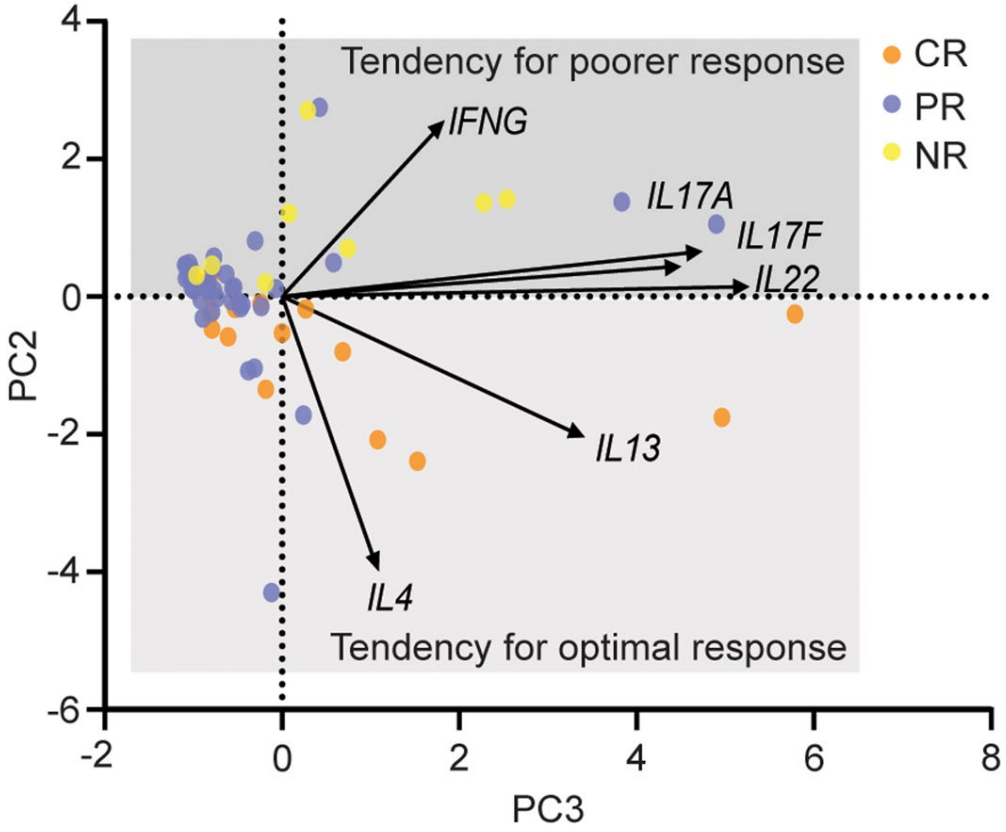
Because AD displays molecular heterogeneity, and multiple cytokines mediate the inflammation



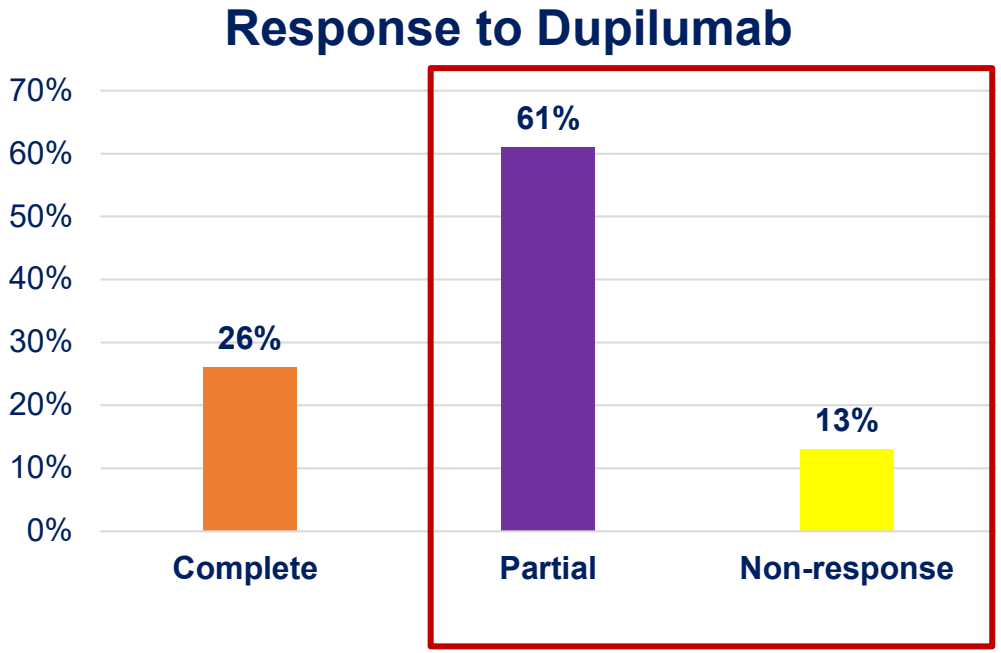
Czarnowicki T, He H, Krueger JG, Guttman-Yassky E. Atopic dermatitis endotypes and implications for targeted therapeutics. Journal of Allergy and Clinical Immunology. 2019 Jan 1;143(1):1-1.

AD is a Heterogenous Disease: Inadequate or Non-Response to Dupilumab is Correlated with Upregulation of IL-17, IL-22, and IFN-γ Cytokines

- CR: Complete response
- PR: Partial response
- NR: Non-response



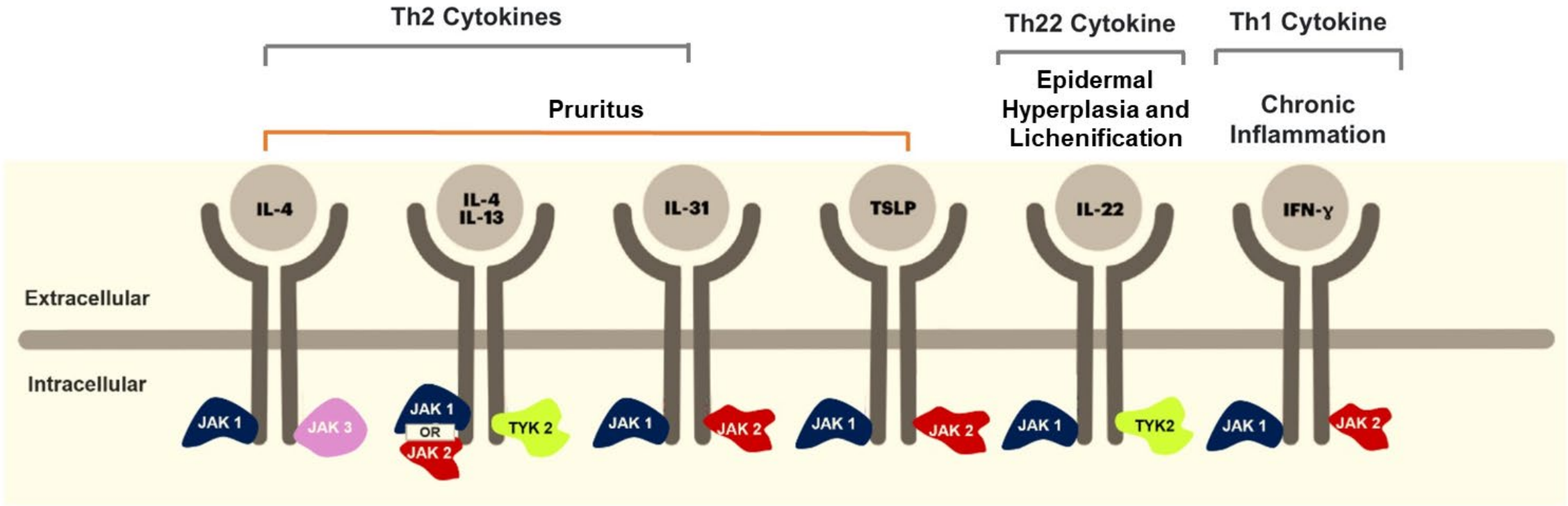
Atopic Dermatitis Endotypes: Principal components analysis of cytokine staining



74% of the AD cohort demonstrated upregulation of TH1, TH17 and TH22 cytokines

Singh K, Valido K, Swallow M, et al. Baseline skin cytokine profiles determined by RNA in situ hybridization correlate with response to dupilumab in patients with eczematous dermatitis. *J Am Acad Dermatol*. 2023;88(5):1094-1100. doi:10.1016/j.jaad.2022.12.052

Multiple Cytokines Contribute to Inflammation in Atopic Dermatitis



Class	IL-4	IL13	IL-31	TSLP	IL-22	IFN-y
Oral Selective JAKi	Upadacitinib	Upadacitinib	Upadacitinib	Upadacitinib	Upadacitinib	Upadacitinib
Oral Selective JAKi	Abrocitinib	Abrocitinib	Abrocitinib	Abrocitinib	Abrocitinib	Abrocitinib
Injectable Biologic	Dupilumab	Dupilumab	Nemolizumab*			
Injectable Biologic		Tralokinumab				
Injectable Biologic		Lebrikizumab*				

* Lebrikizumab and Nemolizumab have been studied in AD but not approved yet

Cartron AM, Nguyen TH, Roh YS, Kwatra MM, Kwatra SG. Janus kinase inhibitors for atopic dermatitis: a promising treatment modality. Clinical and experimental dermatology. 2021 Jul 1;46(5):820-4.
Huang I, Chung WH, Wu PC, Chen CB. JAK–STAT signaling pathway in the pathogenesis of atopic dermatitis: An updated review. Frontiers in immunology. 2022 Dec 8;13:1068260.

Tofacitinib Post-Marketing Study in RA Patients With CV Risk Factors[1-3]

To evaluate tofacitinib long-term safety in RA patients, the FDA required a post-marketing study

STUDY OVERVIEW

- Objective: assess long-term safety of tofacitinib 5 mg & 10 mg in RA patients vs TNF inhibitors*†
- Co-primary endpoints: Adjudicated MACE and adjudicated malignancy (excluding NMSC)
- The study was event-driven and patients were followed until primary outcome events accrued (median on-study follow-up of 4 years)

PATIENT POPULATION

- >4300 patients with active moderate to severe RA, despite methotrexate use
- Cardiovascular (CV) risk-enriched population: age ≥50 years with ≥1 cardiovascular risk factor

STUDY OUTCOME

- Co-primary endpoint: Noninferiority criteria were not met for combined tofacitinib doses vs TNFi for adjudicated MACE and adjudicated malignancy (excluding NMSC)
- Other endpoints: There was an increased risk for serious infections, death, and VTE

Some cases of serious infections, mortality, malignancy, MACE, and VTE have been reported in studies with CIBINQO.

*ORAL Surveillance (NCT02092467) was a randomized, open-label, non-inferiority, Phase 3b/4 study that assessed the relative risk of adjudicated major adverse cardiovascular (CV) events (MACE) and adjudicated malignancies with combined doses of tofacitinib at two doses 5 twice daily (n=1455) and 10 mg twice daily (n=1456) vs the TNF blocker control (N=1451) in RA patients ≥50 years of age with active, moderate to severe RA, inadequate response to MTX and ≥1 additional CV risk factor. Tofacitinib 10 mg twice daily dosage is not recommended for the treatment of RA, PsA, AS, or pcJIA. The study was conducted from March 2014 through July 2020. XELJANZ® is the registered trademark name for tofacitinib. Please visit XELJANZPI.com for full prescribing information.

†In February 2019, the tofacitinib dose of 10 mg twice daily was reduced to 5 mg twice daily.

RA=rheumatoid arthritis; FDA=US Food and Drug Administration; TNF=tumor necrosis factor; NMSC=non-melanoma skin cancer; TNFi=tumor necrosis factor inhibitor; VTE=venous thromboembolism; JAKi=Janus kinase inhibitor; MTX=methotrexate; PsA=psoriatic arthritis; AS=ankylosing spondylitis; pcJIA=polyarticular course juvenile idiopathic arthritis.

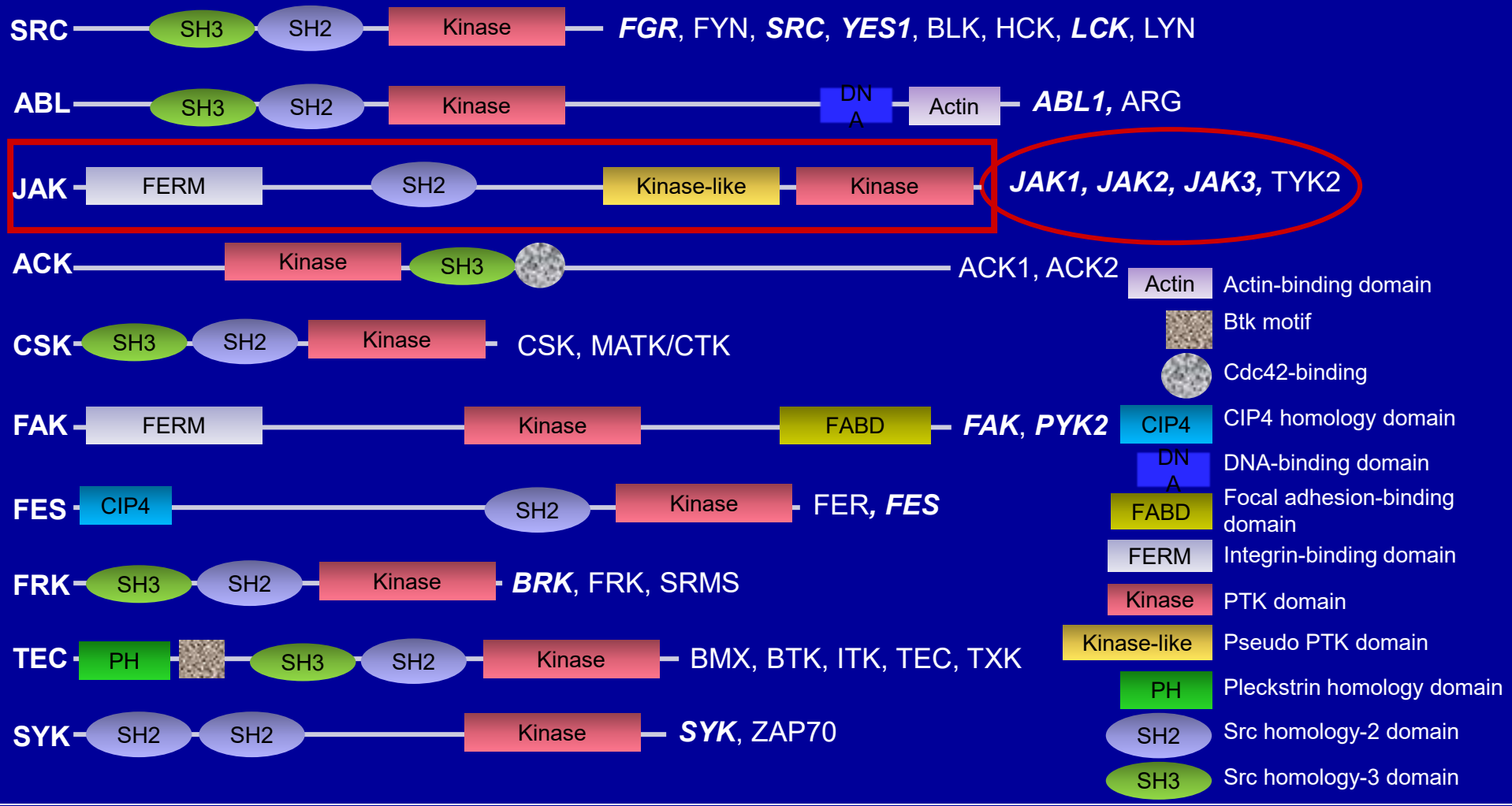
1. CIBINQO Package insert. Pfizer Inc; 2023. 2. Ytterberg SR, et al. N Eng J Med. 2022;386(4):316-326. 3. FDA.gov. December 7, 2021. Accessed November 1, 2022. https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death

For Important Safety Information see slides 24-29. Full Prescribing Information, including BOXED WARNING and Medication Guide, is available at this presentation or CIBINQOPI.com.

ONCE-DAILY CIBINQO (abrocitinib) tablets 50mg 100mg 200mg

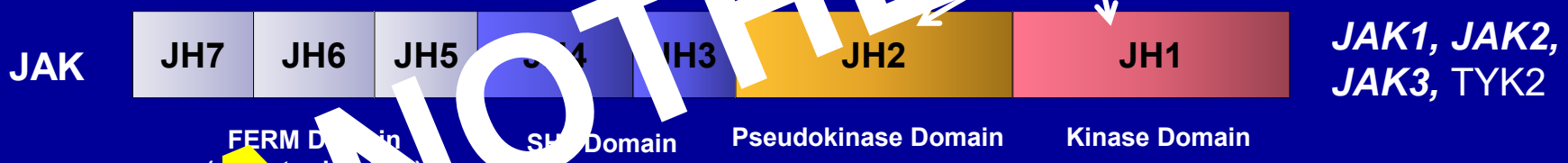
JAK/STAT Signaling Pathways

Janus Kinases (JAKs): Members of Nonreceptor Tyrosine Kinases



Blume-Jensen and Hunter. *Nature* 2001;411(6835):355-65.

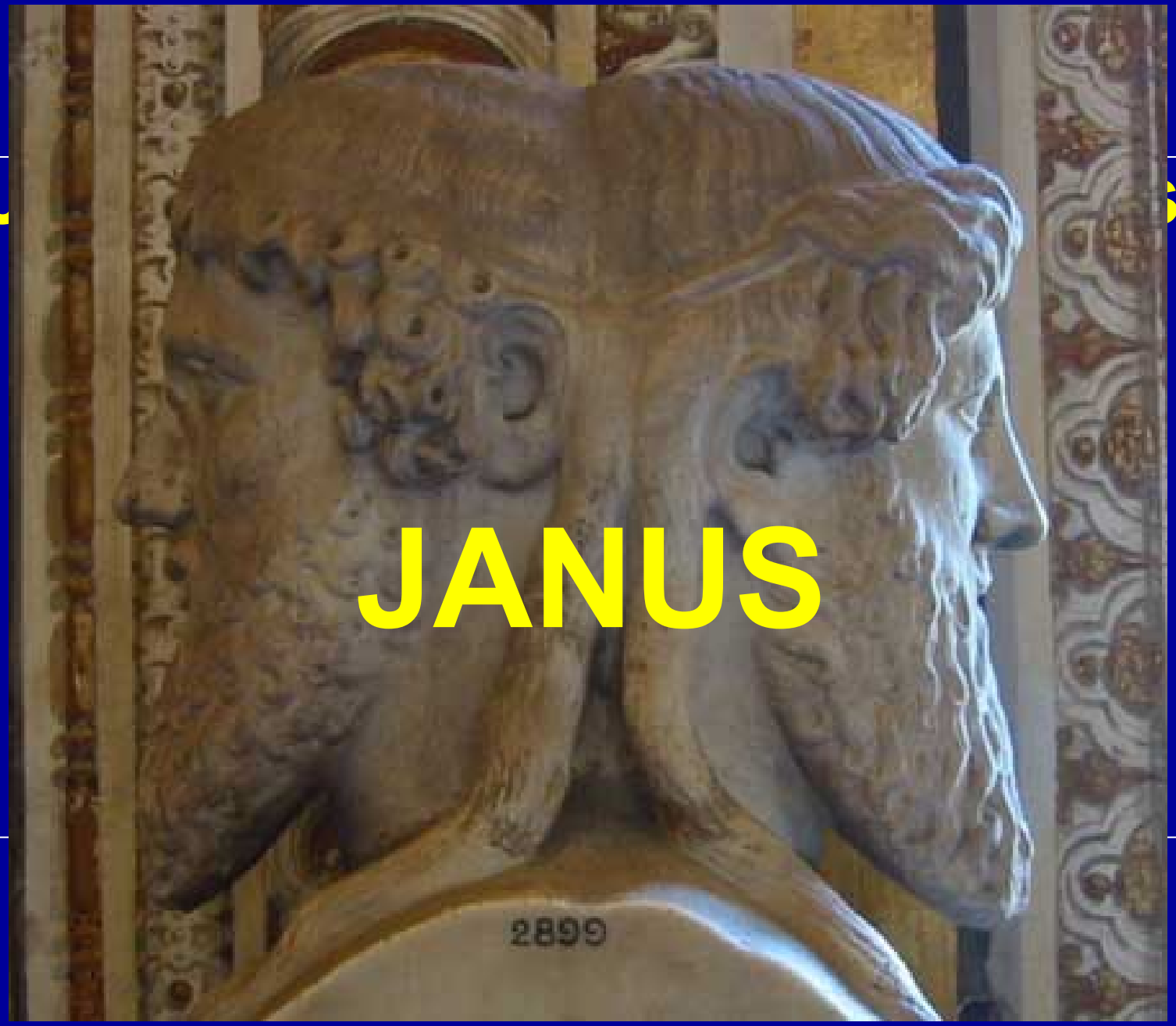
JAK Structure[1,2]



JUST ANOTHER KINASE

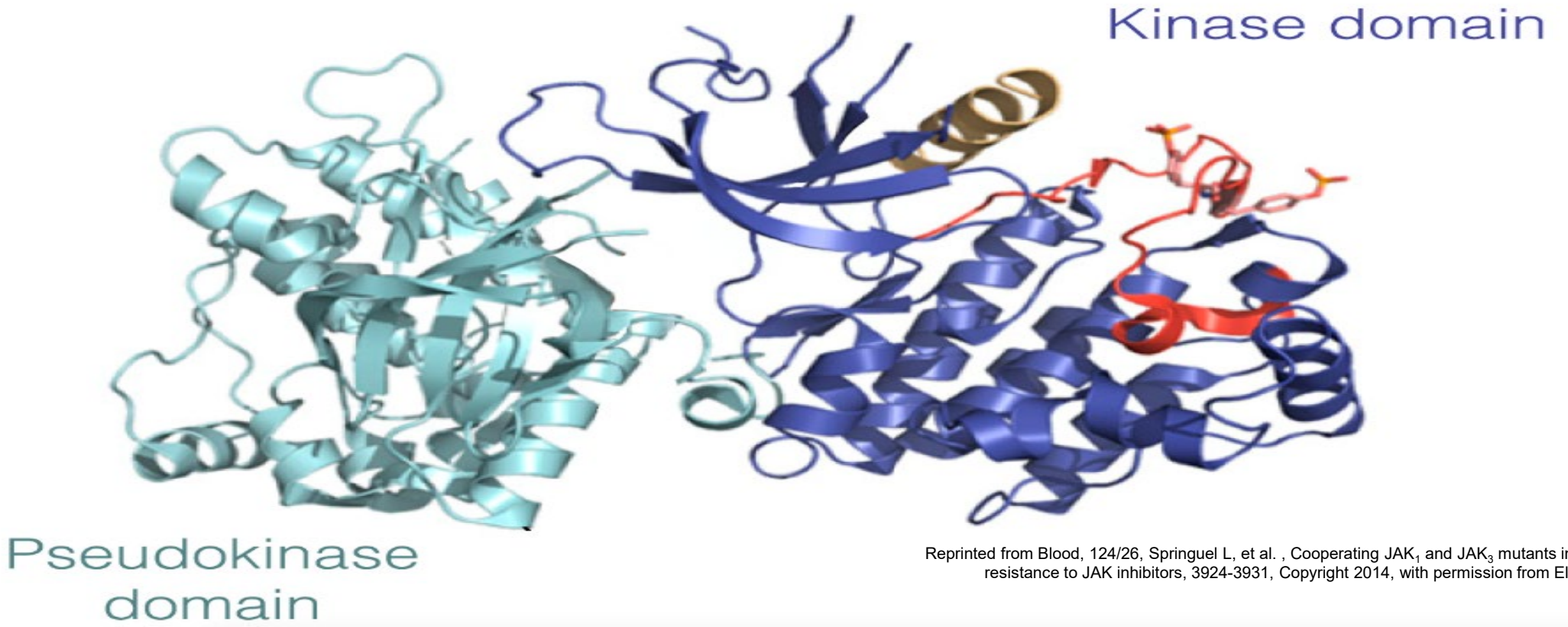
Of the 518 kinases identified in the human genome, only 5 have a pseudokinase and kinase domain present in the same protein, namely, the 4 members of the JAK family and GCN2, a serine threonine kinase

1. Pesu et al. *Immunol Rev* 2008;223:132-42.
2. Haan et al. In: Jak-Stat Signaling: From Basics to Disease, 2012.


JANUS

Structure of JAK Proteins

JAK1 Kinase and Pseudokinase Crystal Structure[4]



Reprinted from Blood, 124/26, Springuel L, et al. , Cooperating JAK_1 and JAK_3 mutants increase resistance to JAK inhibitors, 3924-3931, Copyright 2014, with permission from Elsevier.[4]

1. Siveen KS, et al. *Mol Cancer*. 2018;17:31. **2.** Yamaoka K, et al. *Genome Biol.* 2004;5(12):253. **3.** Welsch K, et al. *Eur J Immunol*. 2017;47(7):1096-1107.
4. Springuel L, et al. *Blood*. 2014;124(26):3924-3931.

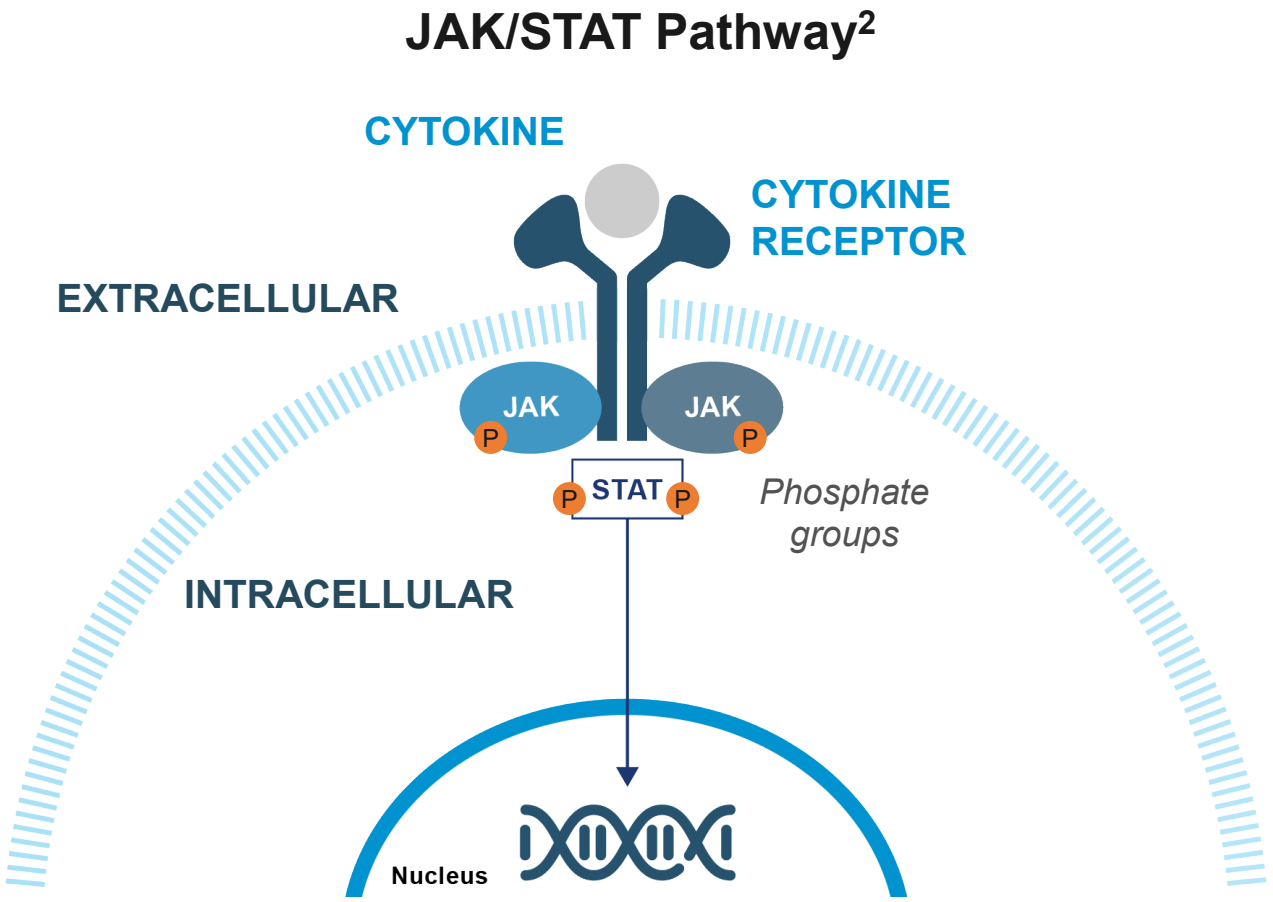
The JAK/STAT Pathway[1,2]

The JAK family has 4 members:
JAK1, JAK2, JAK3 and TYK2[2]

- Cytokine receptors dimerise upon binding of cytokines, bringing JAK pairs into close proximity[2]
- JAKs phosphorylate members of the STAT family[2]

The STAT family has 7 members: STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b and STAT6[3]

- Activated STAT dimers translocate to the nucleus where they affect gene transcription of proinflammatory cytokines[1]



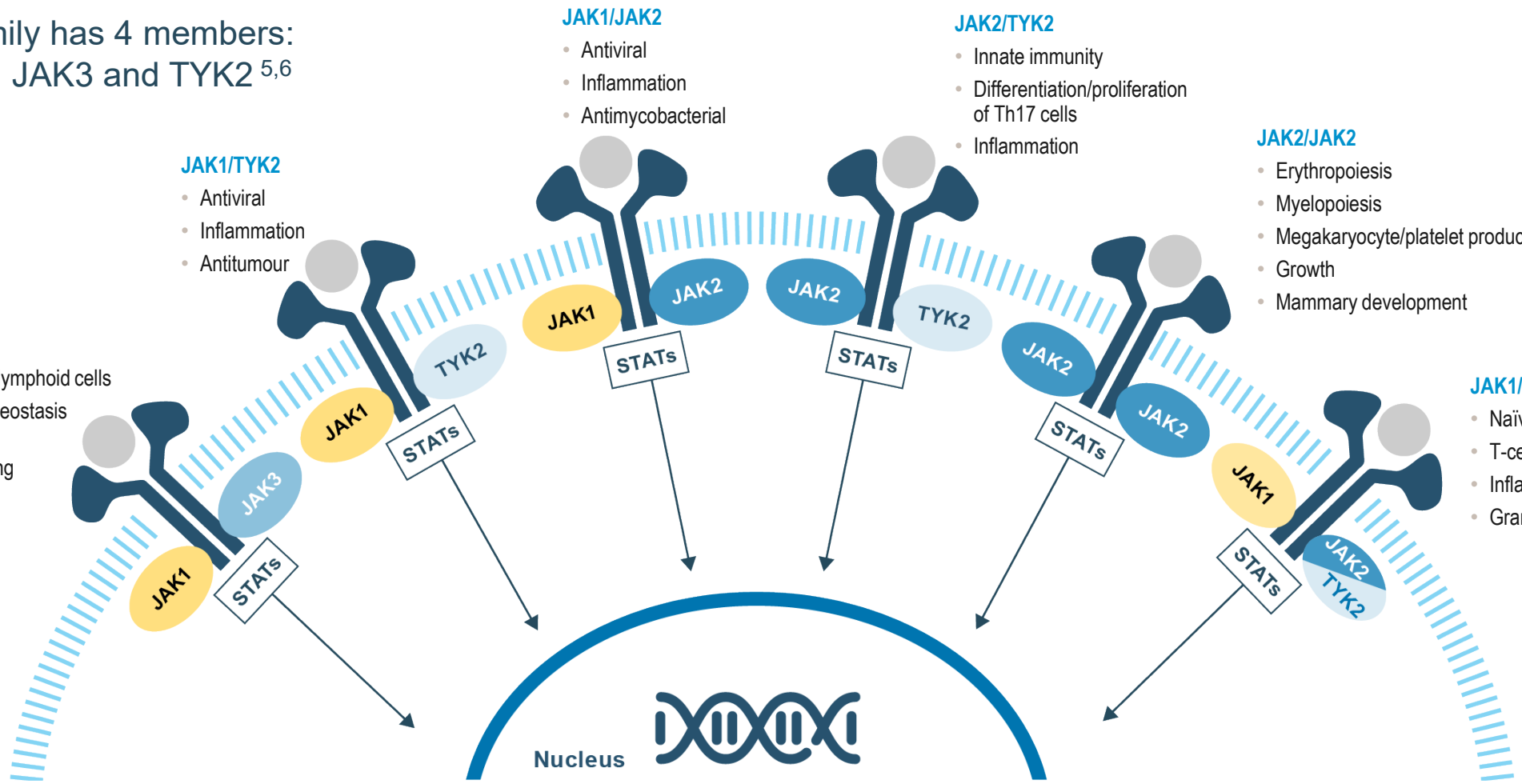
Illustrative, created by Pfizer.

STAT=signal transducer and activator of transcription; P=phosphorylation; TYK=tyrosine kinase.

1. Clark JD, et al. *J Med Chem.* 2014;57(12):5023-5038. **2.** Damsky W, King BA. *J Am Acad Dermatol.* 2017;76(4):736-744. **3.** Rawlings JS, et al. *Cell Sci.* 2004;117(Pt 8):1281-1283.

Biological Significance of Signalling Through the JAK/STAT Pathway[1-5]

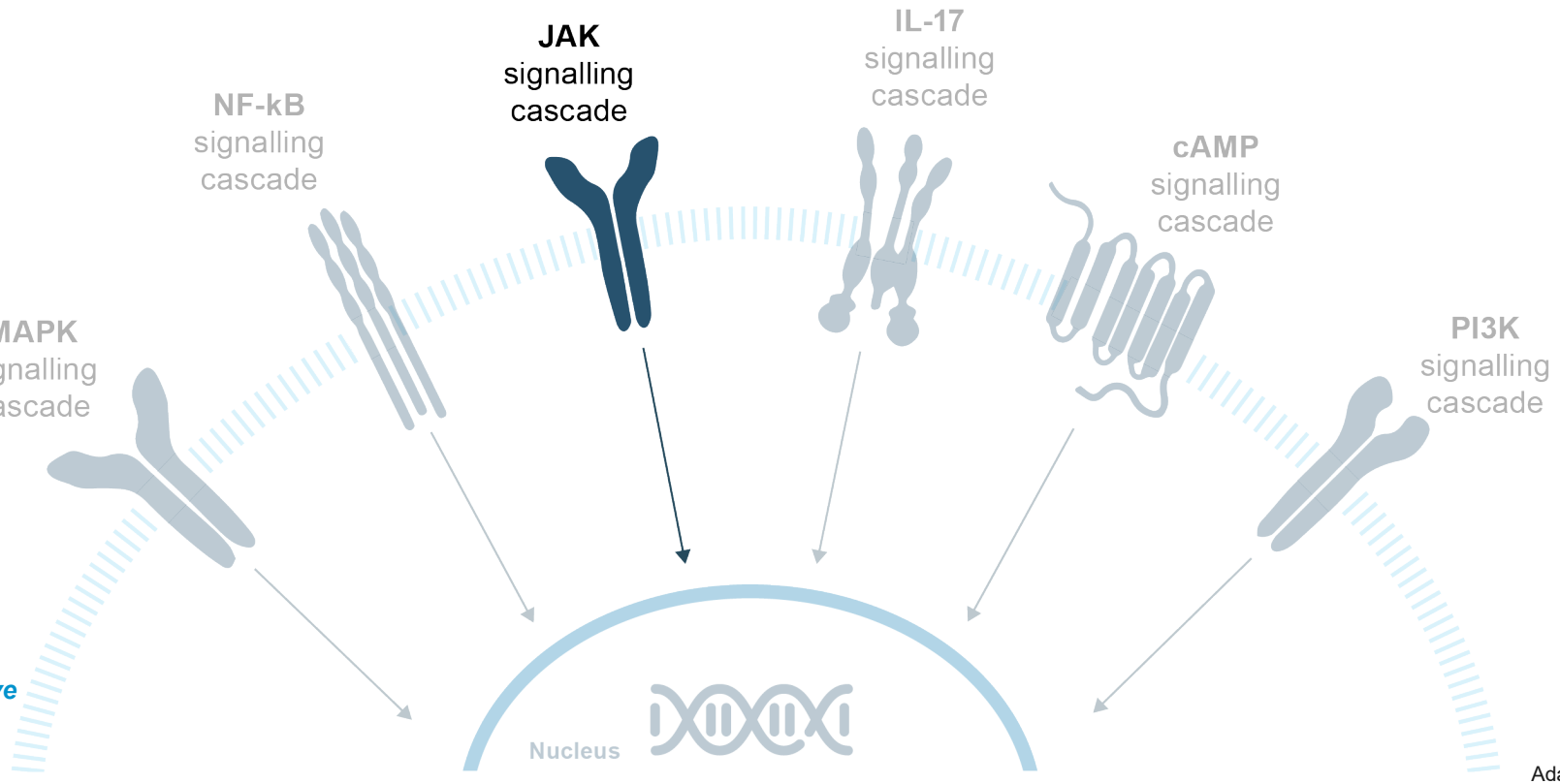
The JAK family has 4 members: JAK1, JAK2, JAK3 and TYK2 [5,6]



Illustrative, created by Pfizer.

1. Fragoulis GE, et al. *Rheumatology*. 2019;58(suppl 1):i43-i54. **2.** Paller AS, et al. *J Allergy Clin Immunol*. 2017;140(3):633-643. **3.** Hammarén HM, et al. *Cytokine*. 2019;118:48-63.
4. Morris R, et al. *Protein Sci*. 2018;27(12):1984-2009. **5.** Clark JD, *J Med Chem*. 2014;57(12):5023-5038. **6.** Damsky W, King BA. *J Am Acad Dermatol*. 2017;76(4):736-744.

The JAK/STAT Pathway Is Believed to Be One Such Mediator of the Pathophysiology in AD[1-4]

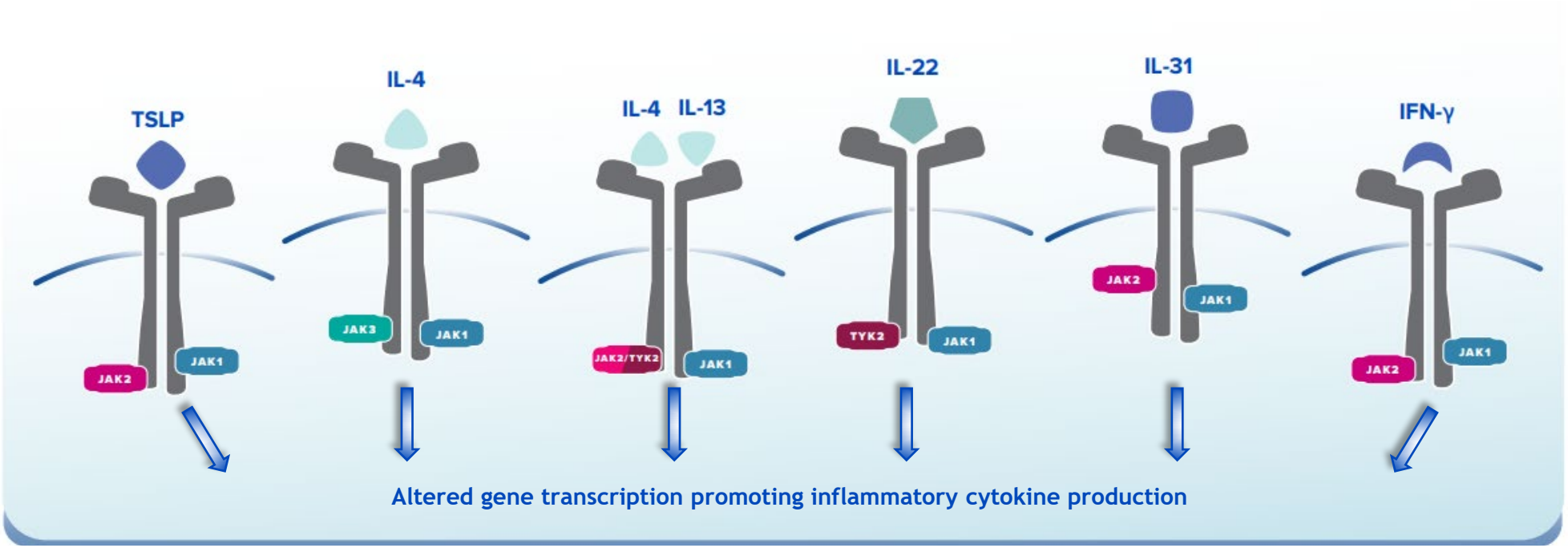


Please note that the receptors depicted are for illustrative purposes only. *Not an exhaustive representation of the cytokine receptor superfamilies.*

Adapted with permission from Clark JD, et al. *J Med Chem*. 2014;57(12):5023-5038. Copyright 2014 American Chemical Society.[4]

- 1. Paller AS, et al. *J Allergy Clin Immunol*. 2017;140(3):633-643. 2. Mollanazar NK, et al. *Clin Rev Allerg Immunol*. 2016;51(3):263-292. 3. Guttman-Yassky E, et al. *Expert Opin Biol Ther*. 2013;13(4):549-561. 4. Clark JD, et al. *J Med Chem*. 2014;57(12):5023-5038.

Several Cytokines Involved in the Development of AD Signal Through JAK/STAT Pathways That Include JAK1[1-5]



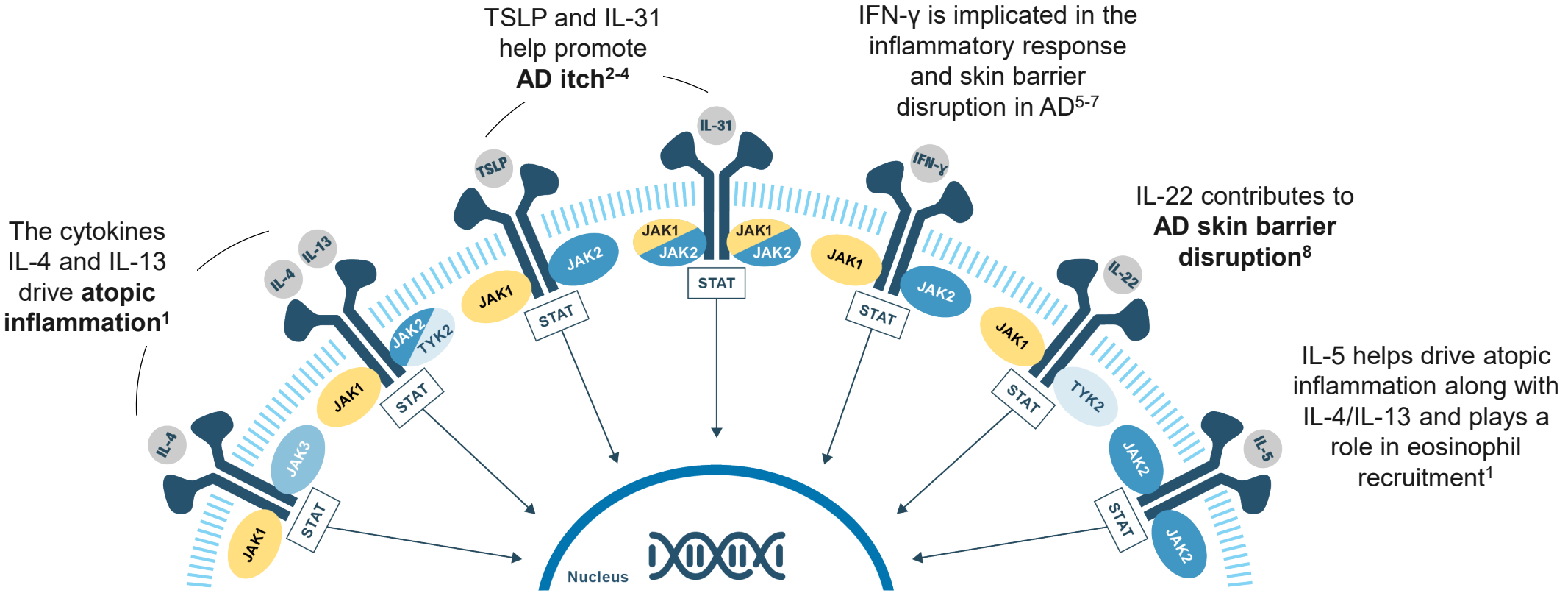
In addition to the cytokines described here, these, and other cytokines, are believed to play multiple roles in AD pathophysiology[2,4,6]

The relevance of selective enzymatic inhibition of specific JAK enzymes to therapeutic effectiveness is not currently known.[7]
These cytokines may also signal through other signalling pathways.[8]

Please note that the molecules and cell structures are for illustrative purposes only.

1. Paller AS, et al. *J Allergy Clin Immunol*. 2017;140(3):633-643. **2.** Howell MD, et al. *Front Immunol*. 2019;10:2342. **3.** Ishizaki M, et al. *Int Immunol*. 2014;26(5):257-267. **4.** Langan SM, et al. [published correction appears in *Lancet*. 2020;396(10253):758]. *Lancet*. 2020;396(10247):345-360. **5.** He H, Guttman-Yassky E. [published correction appears in Am J Clin Dermatol. 2019 Jan 10]. Am J Clin Dermatol. 2019;20(2):181-192. **6.** Weidinger S, et al. *Nat Rev Dis Primers*. 2018;4(1):1. **7.** Cibinqo (Abrocitinib) Singapore Prescribing Information Available From: http://labeling.pfizer.com/ShowLabeling.aspx?id=15308. **8.** Ferretti E, et al. *J Leukoc Biol*. 2017;102(3):711-717.

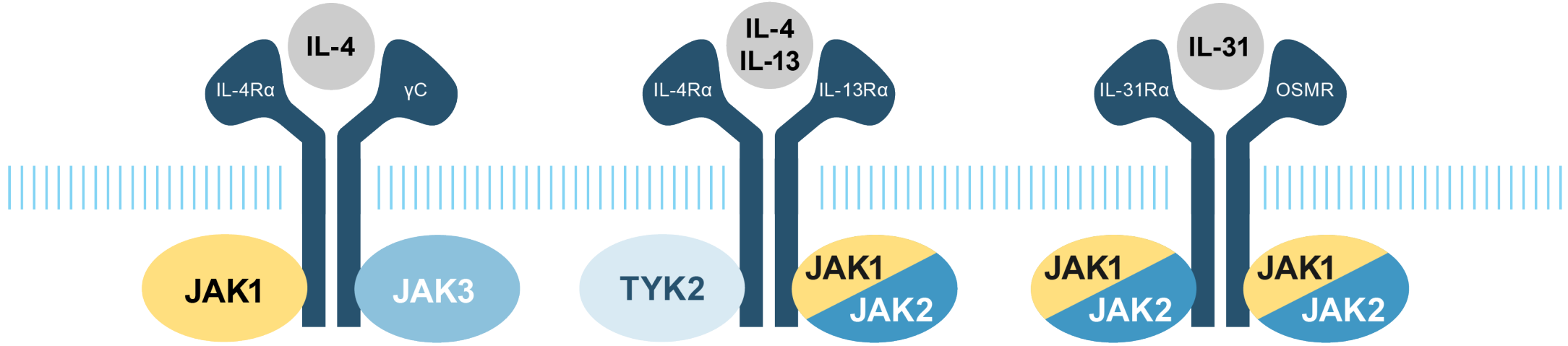
Key Cytokines Drive AD Inflammation, Itch and Skin Barrier Disruption



Illustrative, created by Pfizer.

1. Paller AS, et al. *J Allergy Clin Immunol*. 2017;140(3):633-643. **2.** Gibbs BF, et al. *Front Immunol*. 2019;10:1383. **3.** Mollanazar NK, et al. *Clinic Rev Allerg Immunol*. 2016;51(3):263-292.
4. Čepelak I, et al. *Biochem Med (Zagreb)*. 2019;29(2):020501. **5.** Hijnen D, et al. *J Invest Dermatol*. 2013;133(4):973-979. **6.** Kanoh H, et al. *J Immunol Res*. 2019;2019:3030268.
7. Liu T, et al. *Front Immunol*. 2020;11:594735. **8.** Guttman-Yassky E, et al. *Expert Opin Biol Ther*. 2013;13(4):549-561.

Multiple Cytokines Play a Role in Itch in AD[1,2]



Illustrative, created by Pfizer.

- IL-31 is predominantly expressed by Th2 cells, and its receptor, IL-31Rα, is primarily found on C-fibres[1]
- IL-4, IL-13 and IL-31 are pruritogenic cytokines that signal through JAK1, among others[1,2]
- IL-31 Is a Key Cytokine for Pruritus in AD[3-5]

OSMR=oncostatin M receptor; γC=common gamma chain.

1. Paller AS, et al. *J Allergy Clin Immunol.* 2017;140(3):633-643. **2.** Kwatra SG, et al. *Clin Transl Immunology*. 2022;11(5):e1390. 3. Datsi A, et al. *Allergy*. 2021;76(10):2982-2997. **4.** Gibbs BF, et al. *Front Immunol*. 2019;10:1383. **5.** Mollanazar NK, et al. *Clinic Rev Allerg Immunol.* 2016;51(3):263-292

Oclacitinib for itchy dogs

How effective is it?
How safe is it?
How does it compare with alternative treatments?

VETRx
VETERINARY PRESCRIBER

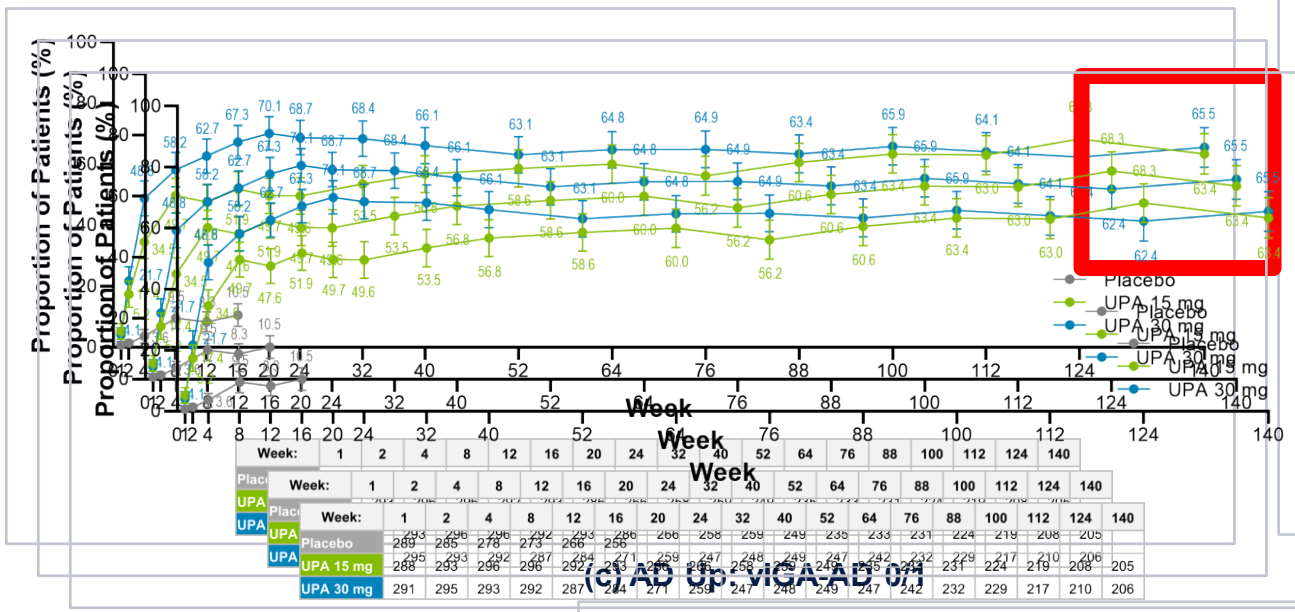
UPADACITINIB
Long-Term Efficacy (~ 140 Weeks)

Silverberg et all. 2023. RAD Conference December 2023

Results: vIGA-AD 0/1 across 140 weeks

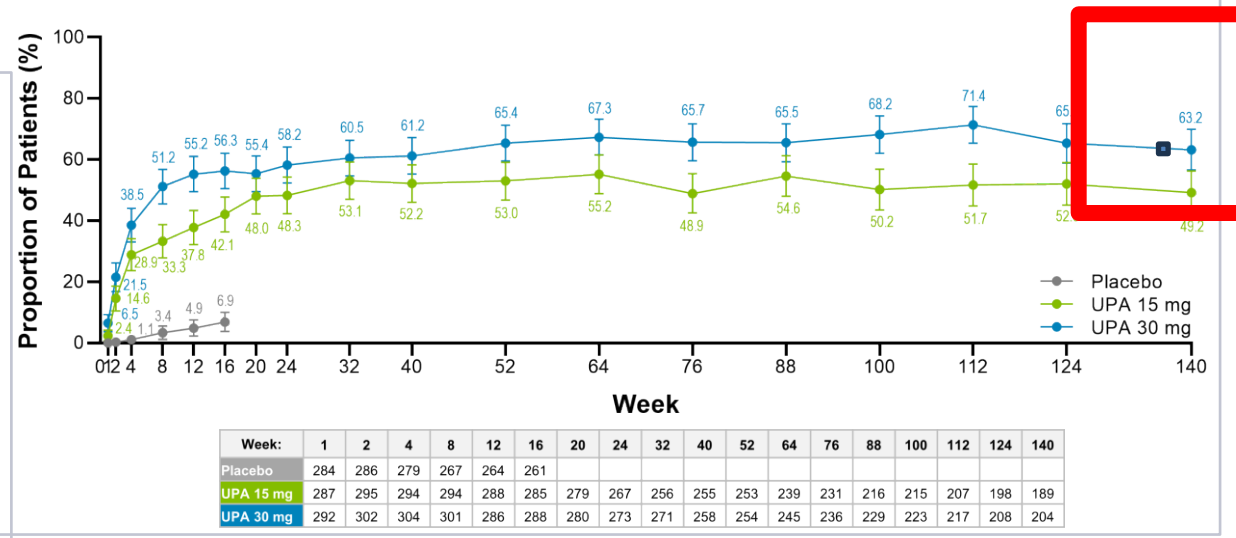
Figure 4. Proportion of patients achieving vIGA-AD 0/1 across 140 weeks in (a) Measure Up 1, (b) Measure Up 2, and (c) AD Up

(a) Measure Up 1: vIGA-AD 0/1



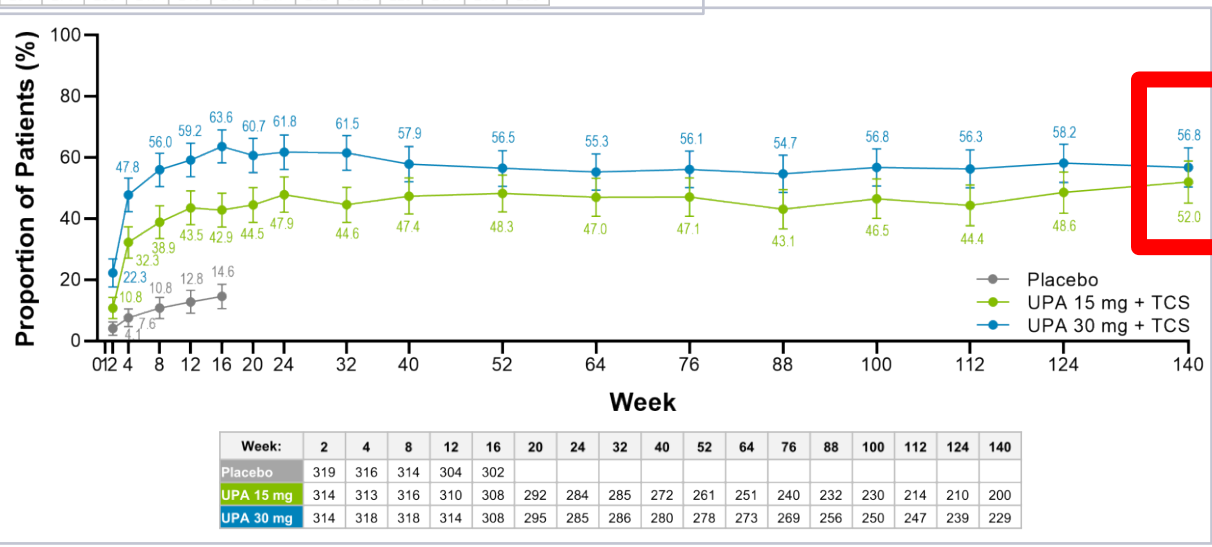
Week:	1	2	4	8	12	16	20	24	32	40	52	64	76	88	100	112	124	140
Placebo	293	296	296	292	293	286	266	258	259	249	235	233	231	224	219	208	205	
UPA 15 mg	288	293	296	296	292	283	265	259	247	248	249	247	242	232	229	217	210	206
UPA 30 mg	291	295	293	292	287	284	271	259	247	248	249	247	242	232	229	217	210	206

(b) Measure Up 2: vIGA-AD 0/1



Week:	1	2	4	8	12	16	20	24	32	40	52	64	76	88	100	112	124	140
Placebo	284	286	279	267	264	261												
UPA 15 mg	287	295	294	294	288	285	279	267	256	255	253	239	231	216	215	207	198	189
UPA 30 mg	292	302	304	301	286	288	280	273	271	258	254	245	236	229	223	217	208	204

(c) AD Up: vIGA-AD 0/1

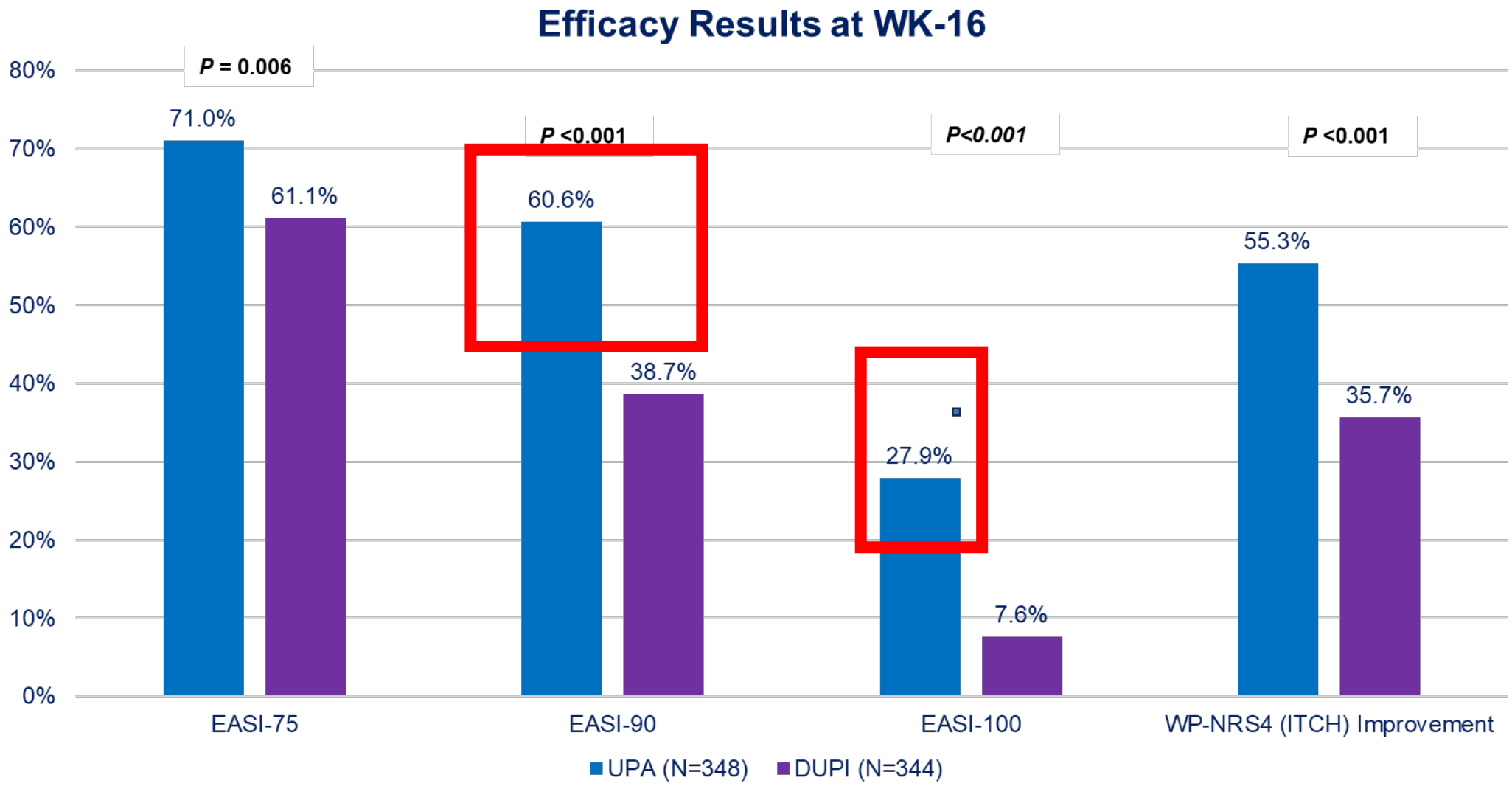


Week:	2	4	8	12	16	20	24	32	40	52	64	76	88	100	112	124	140
Placebo	319	316	314	304	302												
UPA 15 mg	314	313	316	310	308	292	284	285	272	261	251	240	232	230	214	210	200
UPA 30 mg	314	318	318	314	308	295	285	286	280	278	273	269	256	250	247	239	229

- Patients in placebo groups that were re-randomized to UPA 15 mg or 30 mg after week 16 had response rates through week 140 that were similar to patients receiving UPA continuously (*data not shown*)

UPA, upadacitinib; TCS, topical corticosteroids; vIGA-AD, Validated Investigators Global Assessment Scale for Atopic Dermatitis

HEADS UP: UPA 30 mg vs. DUPI at WK-16



Blauvelt A, Teixeira HD, Simpson EL, Costanzo A, De Bruin-Weller M, Barbarot S, Prajapati VH, Lio P, Hu X, Wu T, Liu J. Efficacy and safety of upadacitinib vs dupilumab in adults with moderate-to-severe atopic dermatitis: a randomized clinical trial. JAMA dermatology. 2021 Sep 1;157(9):1047-55.

UPA Long-Term Safety (Up to 5 Years)

An integrated analysis including over 7000 patient-years of exposure of UPA in moderate-to-severe AD

Long-term Safety Profile for Upadacitinib in AD: Up to 5 Years of Exposure

Most common AE was herpes zoster. ≤5% of pts in trial had shingles vaccine. Therefore, I recommend shingles vaccine to all my JAKi pts > 50yo (CDC age recommendation) and those immunocompromised.

Rates of Treatment-Emergent Adverse Events of Special Interest (AESIs) for all patients at ~ 1 year and up to 5 years of Treatment with Upadacitinib

	~1 Year		Up to 5 Years	
	UPA 15 mg (N=1239) PY=1373.4	UPA 30 mg (N=1246) PY=1414.2	UPA 15 mg (N=1337) PY=3823.0	UPA 30 mg (N=1346) PY=4076.9
Treatment-Emergent AE of Special Interest	Events per 100 Patient-Years (E/100 PY)			
Serious Infections	2.3	2.8	2.2	2.6
Opportunistic Infections[1]	1.6	1.9	1.7	2.2
Eczema Herpeticum	1.6	1.8	1.5	2.0
Active Tuberculosis	<0.1	<0.1	<0.1	<0.1
Herpes Zoster	3.5	5.2	3.1	5.5
Non-Melanoma Skin Cancer (NMSC)[2]	0.3	0.4	0.4	0.3
Malignancy Excluding NMSC[2]	0.1	0.5	0.3	0.4
Lymphoma[2]	0	<0.1	<0.1	<0.1
Gastrointestinal Perforations[3]	0	0	0	<0.1
Major Adverse Cardiovascular Events (MACE)[2,3]	0.1	<0.1	0.2	<0.1
Venous Thromboembolic Events (VTE)[2,3]	<0.1	<0.1	0.1	0.1

Bunick et al. 2023. RAD Conference December 2023

Incidence Rates Reflect Background Rates of these events AD population

CLINICAL TRIAL RATES:: Phase 3 Exposure-Adjusted (n/100 PY) Long-Term Incidence Rates for Malignancy Excluding NMSC, MACE, VTE in Patients With AD from Measure Up 1, Measure Up 2, and AD Up[1] (Up to 5 Years)

	UPA 15 mg N=1337 Incidence Rate Per 100 PY (95%CI)	UPA 30 mg N=1346 Incidence Rate Per 100 PY (95%CI)
Malignancy (excluding NMSC)	**0.3 (0.1, 0.5)**	**0.4 (0.2, 0.7)**
MACE (adjudicated)	**0.2 (0.1, 0.3)**	**<0.1 (0.0, 0.2)**
VTE (adjudicated)	**0.1 (0.0, 0.3)**	**0.1 (0.1, 0.3)**

BACKGROUND RATES: Observed AE Incidence Rate Estimates for Patients with AD and the General Population[3-5]

Event	Patient Population (N)	Incidence Rate per 100 PY (95% CI)
Malignancy (excluding NMSC)	UK patients of all ages with AD (mild-severe)[c,4] (N=66,258)	**0.33 (0.30, 0.36)**
	US general population[5]	**0.45 (0.45, 0.45)**
MACE	All Danish citizens 15 years or older with moderate/severe AD[a,2] (N=2527)	**0.63 (0.51-0.78)**
VTE	US adults (≥18 years old) with moderate/severe AD[b,3] (N=113,927)	**0.31 (0.29, 0.34)**

LIMITATIONS: Variability across data sources exists and observational data may potentially overestimate risk, as the results may be influenced by confounding factors including, but not limited to:

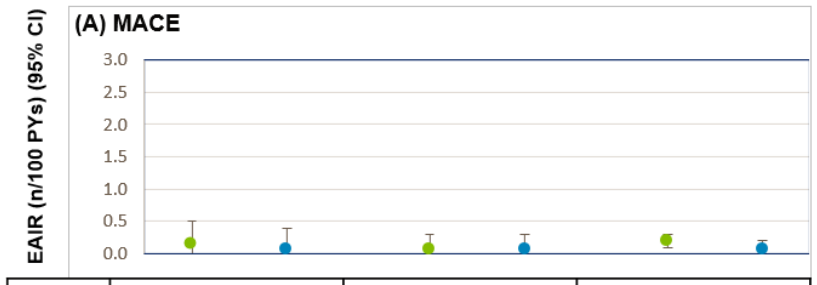
- Outcomes as defined by diagnostic codes, may be subject to measurement error (limited sensitivity or specificity) vs RCT case adjudication
- Patient heterogeneity (age/gender/geographical location)
- Variability in the distribution of risk factors (comorbidities and medication use)

[a]Moderate/severe AD was identified using systemic therapy for AD as a proxy measure including azathioprine, methotrexate, cyclosporine, and/or mycophenolate mofetil. [b]Moderate to severe AD was identified using prescription dispensing as a proxy measure, including high or ultra high potency topical corticosteroids, systemic corticosteroids, systemic immunosuppressants, phototherapies, or biologics used at any time after AD diagnosis (including index date). [c]Patients with AD were identified by the presence of at least 2 correlative codes of AD, or by the presence of AD codes entered by a specialist.

[1]Data on File AbbVie DOF ABVRRTI74922, [2]Anderson YMF, et al. *J Allergy Clin Immunol*. 2016;138(1):310-312. [3]Meyers KJ, et al. *Dermatol Ther (Heidelb)*. 2021;11:1041-1052. [4]Arana A, et al. *BJD*. 2010;163:1036-1043. [5]Surveillance, Epidemiology, and End Results (SEER). https://seer.cancer.gov. Accessed 11/8/2022. SEER=Surveillance, Epidemiology, and End Results

Safety Profile Consistent Over Time

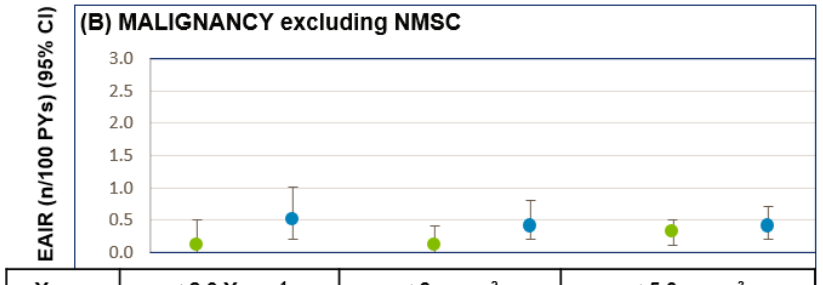
Figure 3. Event rates for AESIs including: (A) major adverse cardiovascular events (MACE), (B) malignancy excluding non-melanoma skin cancer (NMSC), and (C) venous thromboembolic events (VTE).



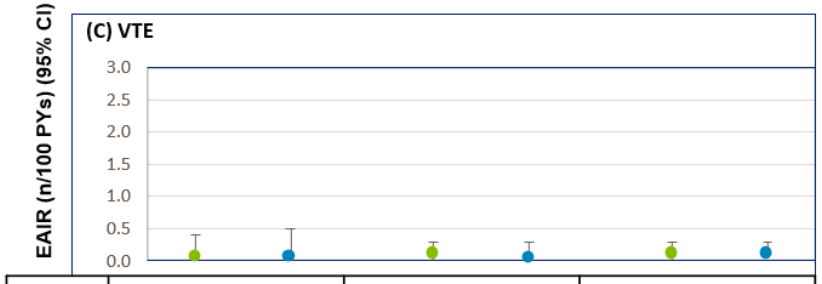
Years	≤ 2.0 Years[1]		≤ 3 years[2]		≤ 5.0 years[3]	
n/N	2/1239	1/1246	1/1340	1/1353	6/1337	2/1346
PY	1373.4	1414.2	2035.8	2118.0	3820.5	4076.9

UPA 15 mg

UPA 30 mg



Years	≤ 2.0 Years[1]		≤ 3 years[2]		≤ 5.0 years[3]	
n/N	2/1239	7/1246	3/1340	9/1353	10/1337	17/1346
PY	1373.2	1413.6	2035.6	2117.3	3821.0	4072.3



Years	≤ 2.0 Years[1]		≤ 3 years[2]		≤ 5.0 years[3]	
n/N	2/1239	1/1246	1/1340	1/1353	4/1337	6/1346
PY	1373.4	1414.2	2035.8	2118.0	3822.7	4076.1

MACE was defined as CV death, non-fatal MI, and non-fatal stroke. VTE was defined as deep vein thrombosis and pulmonary embolism. Rates shown are n/100 PY=number of subjects with at least one event per 100. EAIR, Exposure Adjusted Incidence Rate (n/100 PY); MACE, major adverse cardiovascular events; UPA, upadacitinib; VTE, venous thromboembolic events; NMSC, Non-melanoma skin cancer; TB, Tuberculosis

[1]Long term data through cut-off November 24, 2020 AbbVie Data on file ABVRRTI71865; [2]AbbVie Data on file ABVRRTI74288; [3]AbbVie Data on file ABVRRTI77022

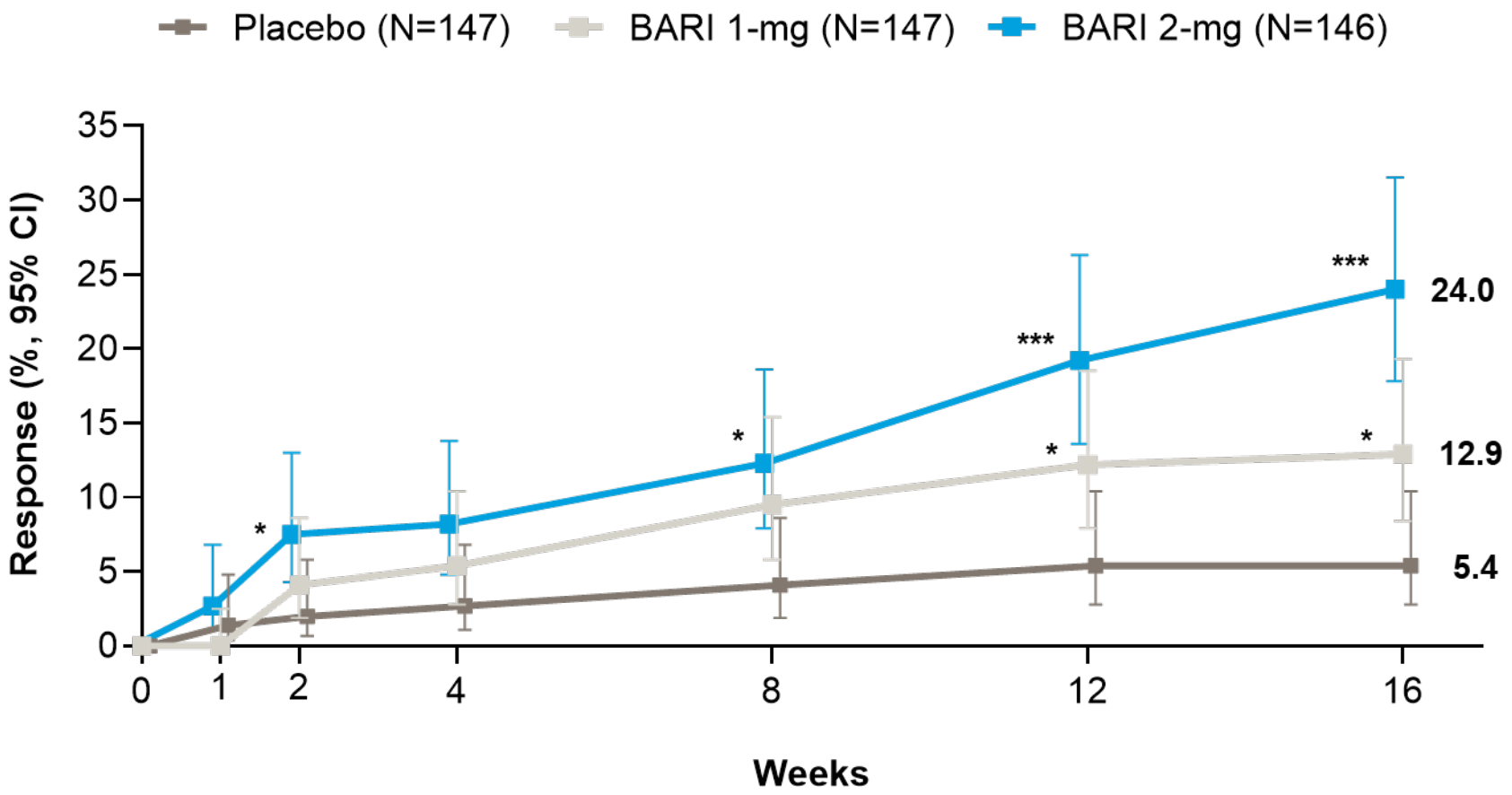
Efficacy and Safety of Baricitinib in Moderate-to-Severe Atopic Dermatitis: Results From a Randomized, Double-blinded, Placebo-controlled Phase 3 Clinical Trial (BREEZE-AD5)

Eric L. Simpson,[1] Seth Forman,[2] Jonathan I. Silverberg,[3] Matthew Zirwas,[4] Emanual Maverakis,[5] George Han,[6] Emma Guttman-Yassky,[6] Daniel Marnell,[7] Robert Bissonnette,[8] Jill Waibel,[9] Fabio Nunes,[10] Amy M. DeLozier,[10] Robinette Angle,[10] Katrin Holzwarth,[10] Orin Goldblum,[10] Jinglin Zhong,[11] Kim Papp[12]

[1]Oregon Health and Science University, Portland, USA; [2]ForCare Clinical Research, Tampa, USA; [3]George Washington University, Washington, DC, USA; [4]Bexley Dermatology Research Clinic, Bexley, USA; [5]University of California Davis, Davis, USA; [6]Icahn School of Medicine at Mount Sinai, New York, USA; Medical Center for Clinical Research- Wake Research, San Diego, USA; [8]Innovaderm Research, Montreal, Canada; [9]Miami Dermatology and Laser Institute, Miami, USA; [10]Eli Lilly and Company, Indiana, USA; [11]IQVIA, Morrisville, USA; [12]K Papp Probity Medical Research, Waterloo, Canada

Sponsored by Eli Lilly and Company, under license from Incyte Corporation

IMPROVEMENTS IN SKIN INFLAMMATION vIGA-AD 0 OR 1

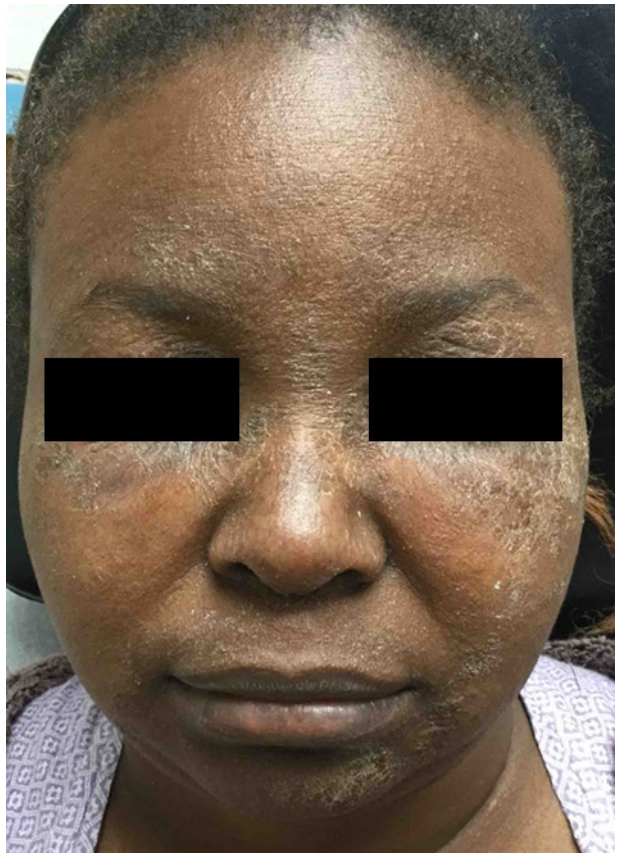


* p≤0.05; ** p≤0.01; *** p≤0.001 versus PBO (by logistic regression analysis, NRI)

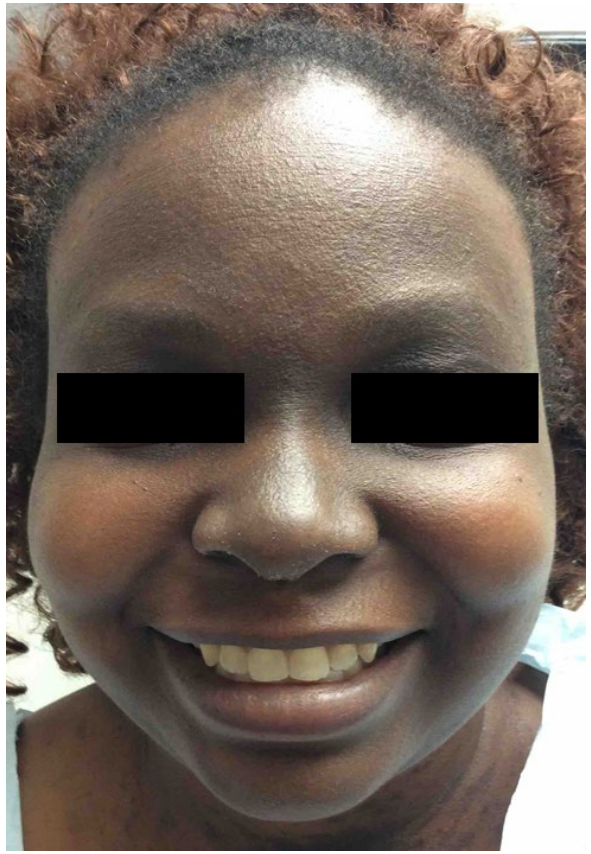
BARI=baricitinib; CI=confidence interval; NRI=non-responder imputation; PBO=placebo; vIGA-AD=validated Investigator's Global Assessment for atopic dermatitis

EXAMPLE OF RESPONSE TO BARICITINIB 2-MG

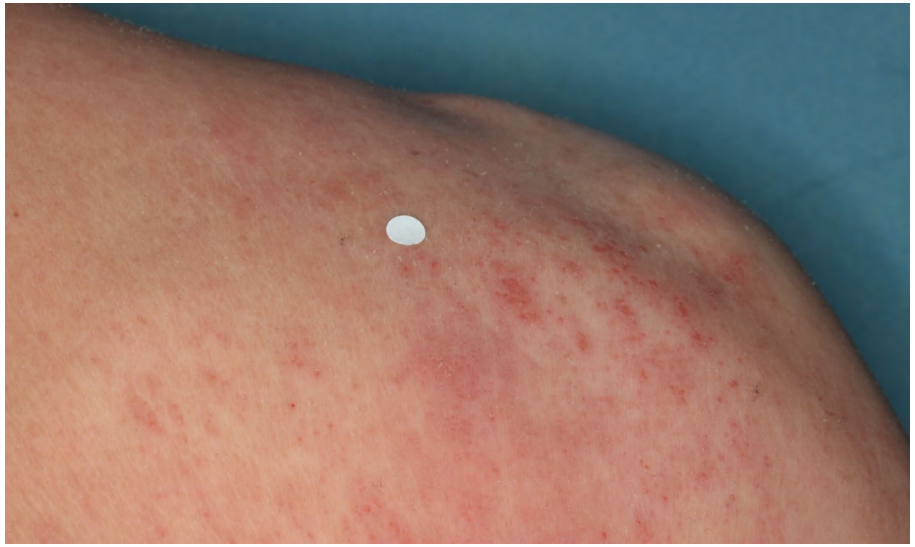
Baseline



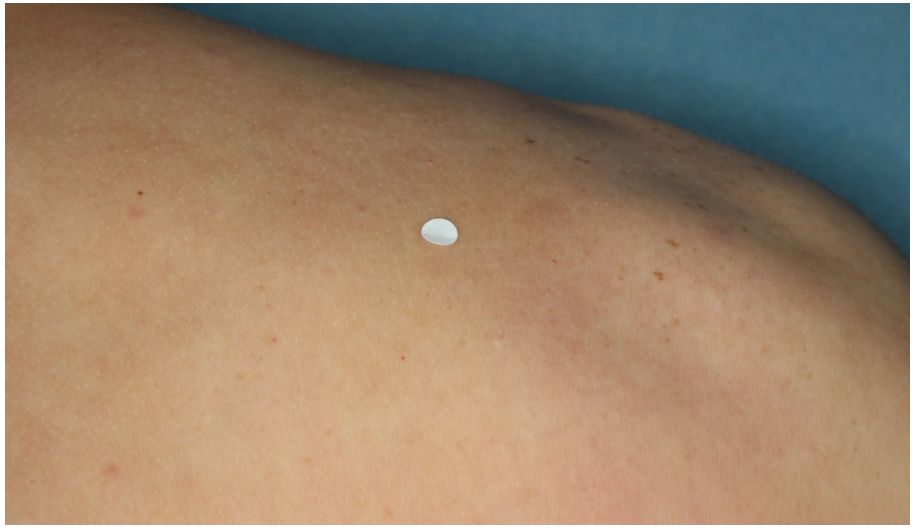
Week 2



Baseline



Week 4



OVERVIEW OF ADVERSE EVENTS OF SPECIAL INTEREST

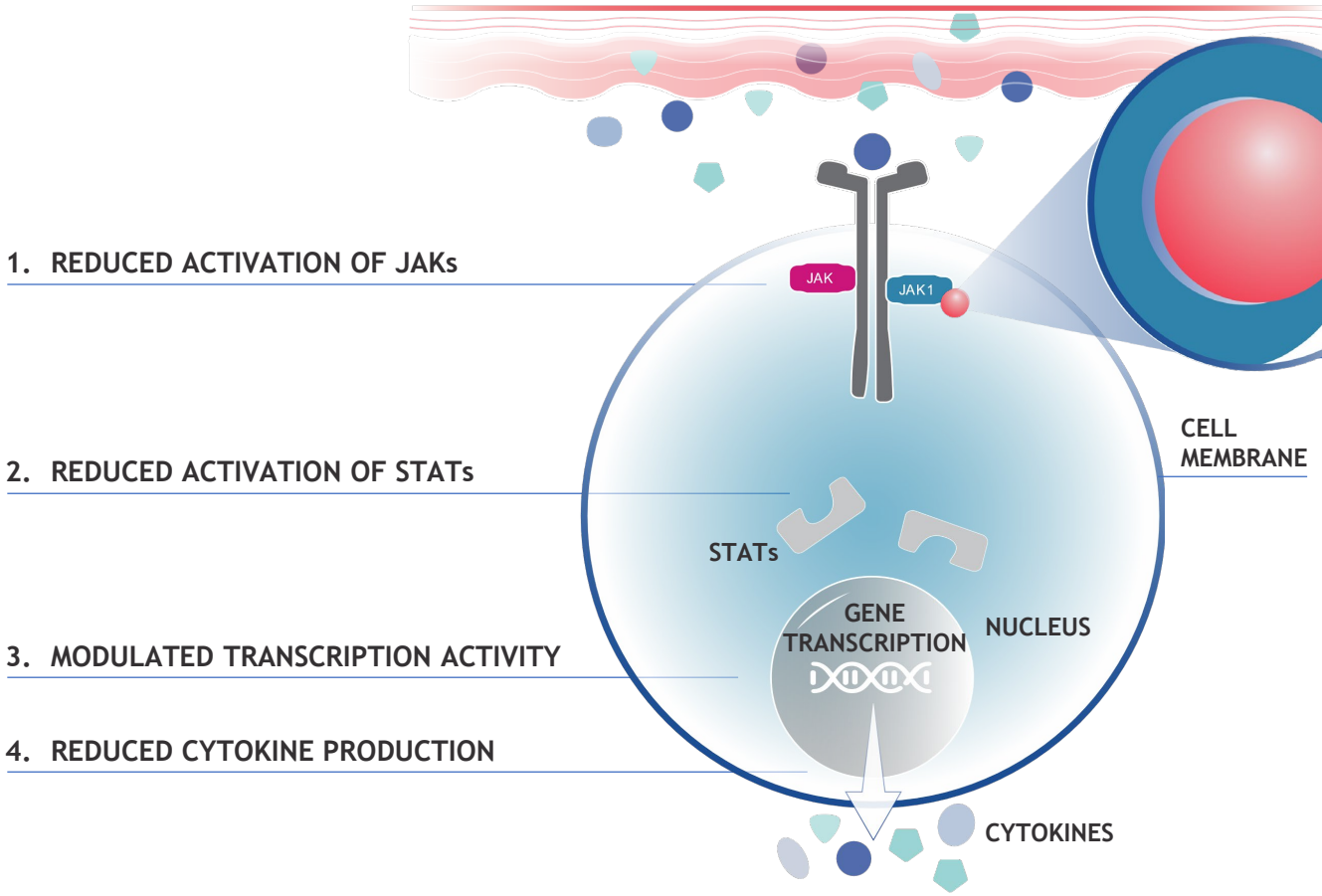
	PBO (N=146)	BARI 1-mg (N=147)	BARI 2-mg (N=145)
Serious infections	1 (0.7)	0	1 (0.7)
Opportunistic infections	0	0	0
Tuberculosis	0	0	0
Malignancies	0	0	0
Gastrointestinal perforation	0	0	0
Deep vein thrombosis	0	0	0
Pulmonary embolism	0	0	0
Major adverse coronary events	0	0	0

Data are presented as n (%)

[a] Patients with multiple occurrences of the same event are counted under the highest severity

AE=adverse event; BARI=baricitinib; PBO=placebo; TEAE=treatment-emergent adverse event

CIBINQO Is an Oral, Small Molecule JAK Inhibitor That Works Inside the Cell[1,2]



Abrocitinib

is an oral small molecule, not a biologic, that reversibly inhibits JAK1 inside the cell by blocking the adenosine triphosphate (ATP) binding site[1,2]

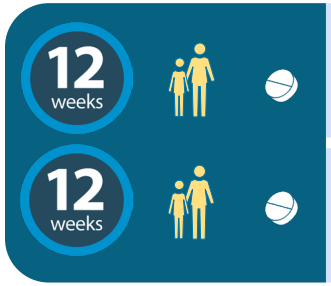
In a cell-free isolated enzyme assay, abrocitinib was selective for JAK1 over JAK2, JAK3, and TYK2.[2,4,5]

Molecules and cell structures are for illustrative purposes only. This illustrative, stepwise MOA reflects our current understanding of the way abrocitinib works intracellularly[1-5]
MOA=mechanism of action.

1. Bula de CIBINQO aprovada pela ANVISA, acesso em 27/06/2023, em www.pfizer.com.br/bulas/cibinqo. 2. Vazquez ML, et al. *J Med Chem*. 2018;61(3):1130-1152. 3. Clark JD, et al. *J Med Chem*. 2014;57(12):5023-5038. 4. Gooderham MJ, et al. *JAMA Dermatol.* 2019;155(12):1371-1379. 5. Supplement to: Gooderham MJ, et al. Published online October 2, 2019. *JAMA Dermatol.* doi:10.1001/jamadermatol.2019.2855

NO PRIOR INDICATION

JADE MONO-1 and MONO-2



JADE MONO-1 (adults: n=303; adolescents: n=84)[1]
- Efficacy and safety of Abrocitinib as monotherapy

JADE MONO-2 (adults: n=351; adolescents: n=40)[2]
- Efficacy and safety of Abrocitinib as monotherapy

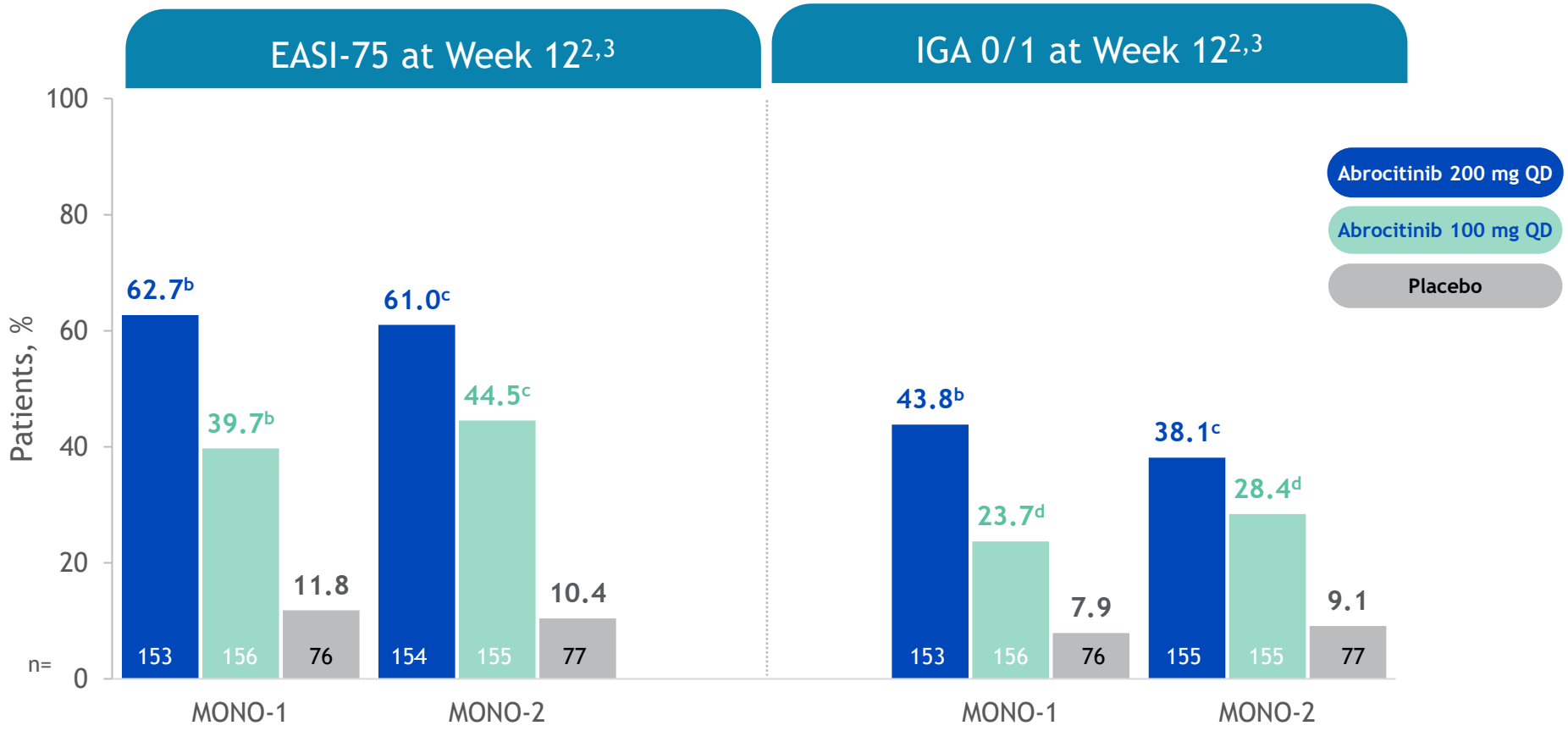
1. Simpson EL, et al. *Lancet*. 2020;396(10246):255-266. **2.** Silverberg JI, et al. *JAMA Dermatol*. 2020;156(8):863-873.

Both Doses of Abrocitinib as Monotherapy[a] Improved Skin Clearance Compared With Placebo[1,2]

JADE MONO-1 and MONO-2: Coprimary endpoints

Study Design[1,2]

- JADE MONO-1 and MONO-2 were 12 week, randomised double-blind, placebo-controlled, Phase III studies in adult and adolescent patients
- Evaluated efficacy and safety of 2 dosing regimens of Abrocitinib monotherapy[a] vs. placebo
- Patients were randomised 2:2:1 at Day 1 to receive Abrocitinib 200 mg QD, Abrocitinib 100 mg QD or placebo



[b]p<0.0001 vs. placebo. [c]p<0.001 vs. placebo. [d]p<0.05 vs. placebo.[1,2]

EASI-75=≥75% improvement from baseline in the Eczema Area and Severity Index; IGA 0/1=Investigator's Global Assessment score of clear/almost clear with ≥2-point improvement from baseline.

[a]Patients in JADE MONO-1 and MONO-2 did not receive medicated topical therapies and rescue treatment was not permitted.[1,2]

1. Simpson EL, et al. *Lancet*. 2020;396(10246):255-266. **2.** Silverberg JI, et al. *JAMA Dermatol*. 2020;156(8):863-873. 3. Data on file. Pfizer Inc, New York, NY.

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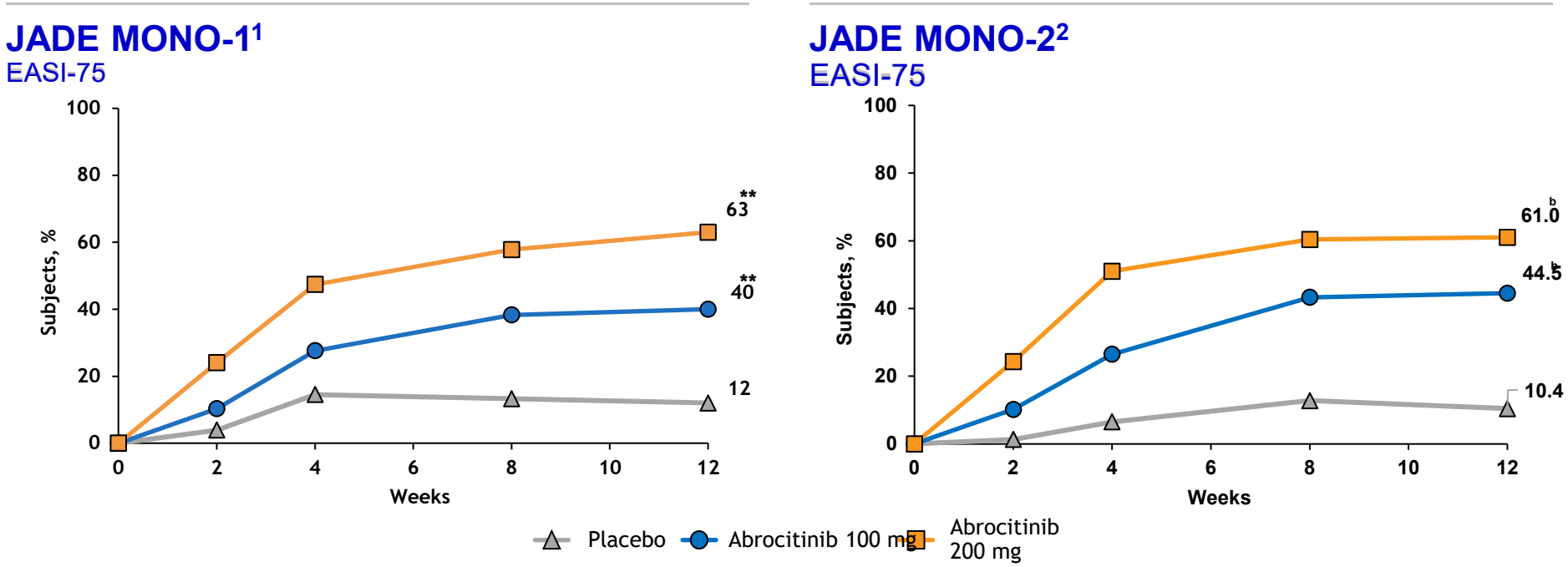
EASI-75 responses for both abrocitinib doses were significantly greater than placebo as early as week 2 and continued to increase until week 12[1]



*P<0.05; **P<0.0001 versus placebo. [b]P < .001 vs placebo.
Conclusion of statistical significance was controlled for multiplicity only at week 12. EASI-75, eczema area and severity index with75% improvement from baseline.

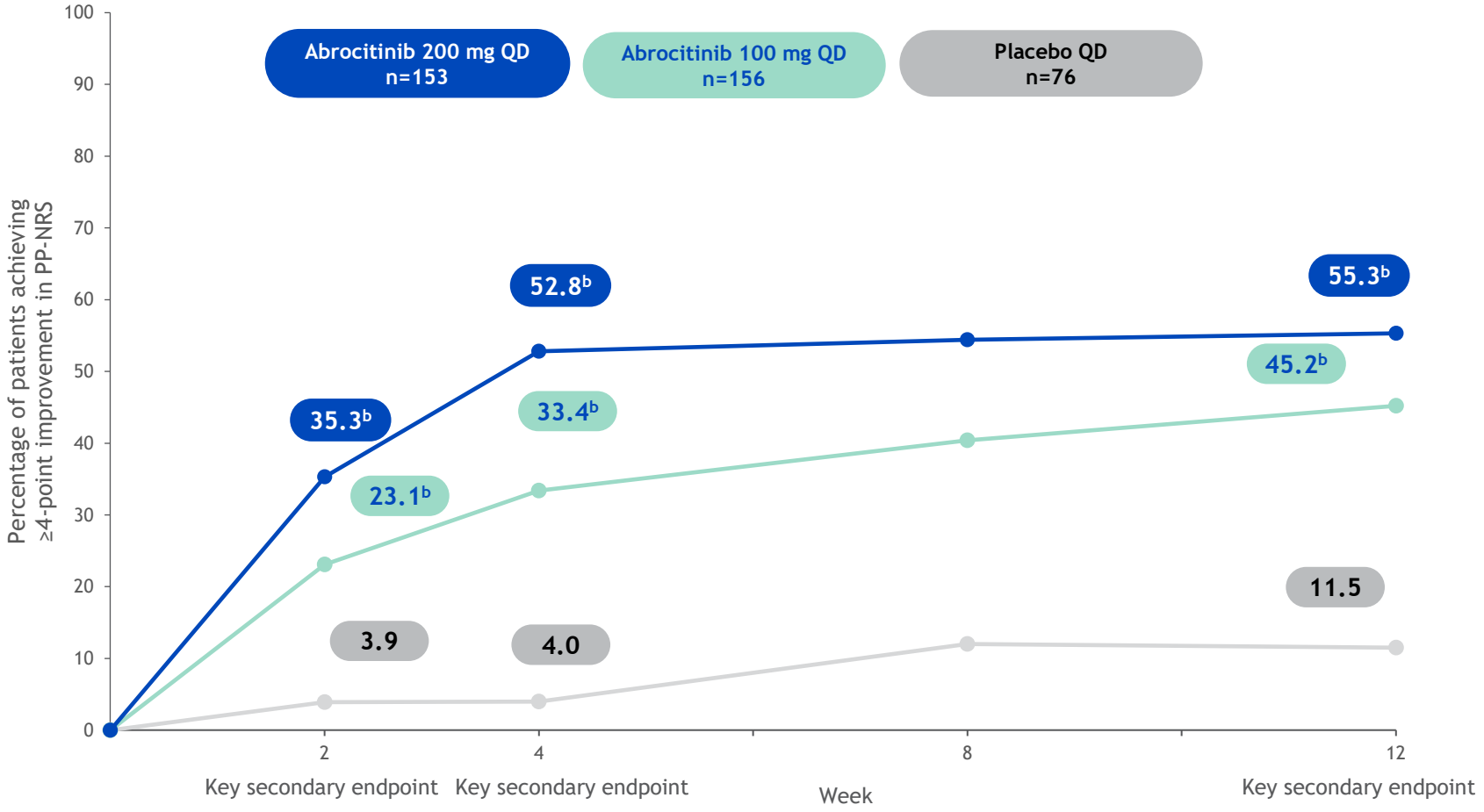
EASI-75=≥75% improvement from baseline in the Eczema Area and Severity Index

[a]Patients in JADE MONO-1 and MONO-2 did not receive medicated topical therapies and rescue treatment was not permitted.[1,2]

1. Simpson EL, et al. *Lancet*. 2020;396(10246):255-266. **2.** Silverberg JI, et al. *JAMA Dermatol*. 2020;156(8):863-873. 3. Data on file. Pfizer Inc, New York, NY.

Itch Relief With Abrocitinib Monotherapy: PP-NRS4 Response vs Placebo[1,a]

JADE MONO-2: PP-NRS4 at weeks 2, 4 and 12 (key secondary endpoints)



Consistent results in JADE MONO-1[2]

- 57%[c] of patients taking Abrocitinib 200 mg, 38%[d] taking Abrocitinib 100 mg, and 15% taking placebo achieved itch relief (PP-NRS4) at Week 12

Differences in absolute PP-NRS scores between both doses of Abrocitinib and placebo were observed within **24 hours** of the first dose of treatment in MONO-2[3]

(−0.7 [95% CI: −0.9 to −0.5] with Abrocitinib 200 mg, −0.6 [95% CI: −0.8 to −0.4] with Abrocitinib 100 mg, and −0.1 [95% CI: −0.4 to 0.2] with placebo; nominal p value <0.05 for both doses vs. placebo)

[b]p≤0.001 vs. placebo.[3]

[a]Patients in JADE MONO-1 and MONO-2 did not receive medicated topical therapies and rescue treatment was not permitted.[2,3]

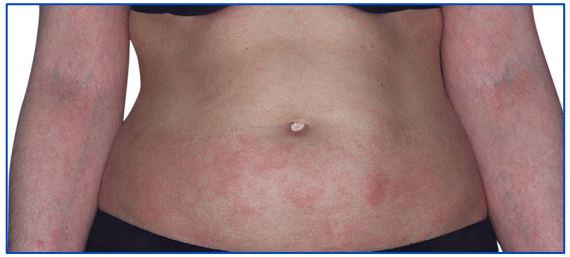
1. Supplement to: Silverberg JI, et al. *JAMA Dermatol*. 2020;156(8):863-873. **2.** Simpson EL, et al. *Lancet*. 2020;396(10246):255-266. 3. Silverberg JI, et al. *JAMA Dermatol*. 2020;156(8):863-873.

Skin Clearance Observed at Week 12 With Abrocitinib as Monotherapy[1,2]

JADE MONO-2

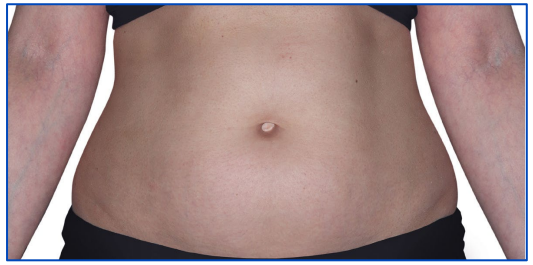
Abdomen

Baseline



IGA: Moderate

Week 12

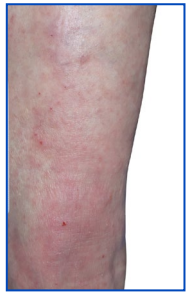


IGA: Almost Clear

Treatment: Abrocitinib: 100 mg QD monotherapy
Sex: F; **Age:** 28

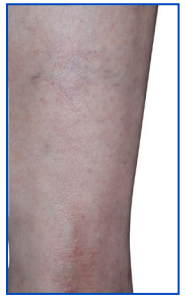
Shin

Baseline



IGA: Moderate

Week 12



IGA: Almost Clear

Treatment: Abrocitinib: 100 mg QD monotherapy
Sex: F; **Age:** 53

Not everyone will respond to treatment with Abrocitinib. Individual results may vary.

Patients in JADE MONO-2 did not receive medicated topical therapies and rescue treatment was not permitted.[2]
Images of patients from JADE MONO-2 with moderate AD at study baseline.
Clinical trial labels have been blurred and background colors and clothing have been modified in photos.

1. Data on file. Pfizer Inc, New York, NY. **2.** Silverberg JI, et al. *JAMA Dermatol*. 2020;156(8):863-873.

JADE COMPARE

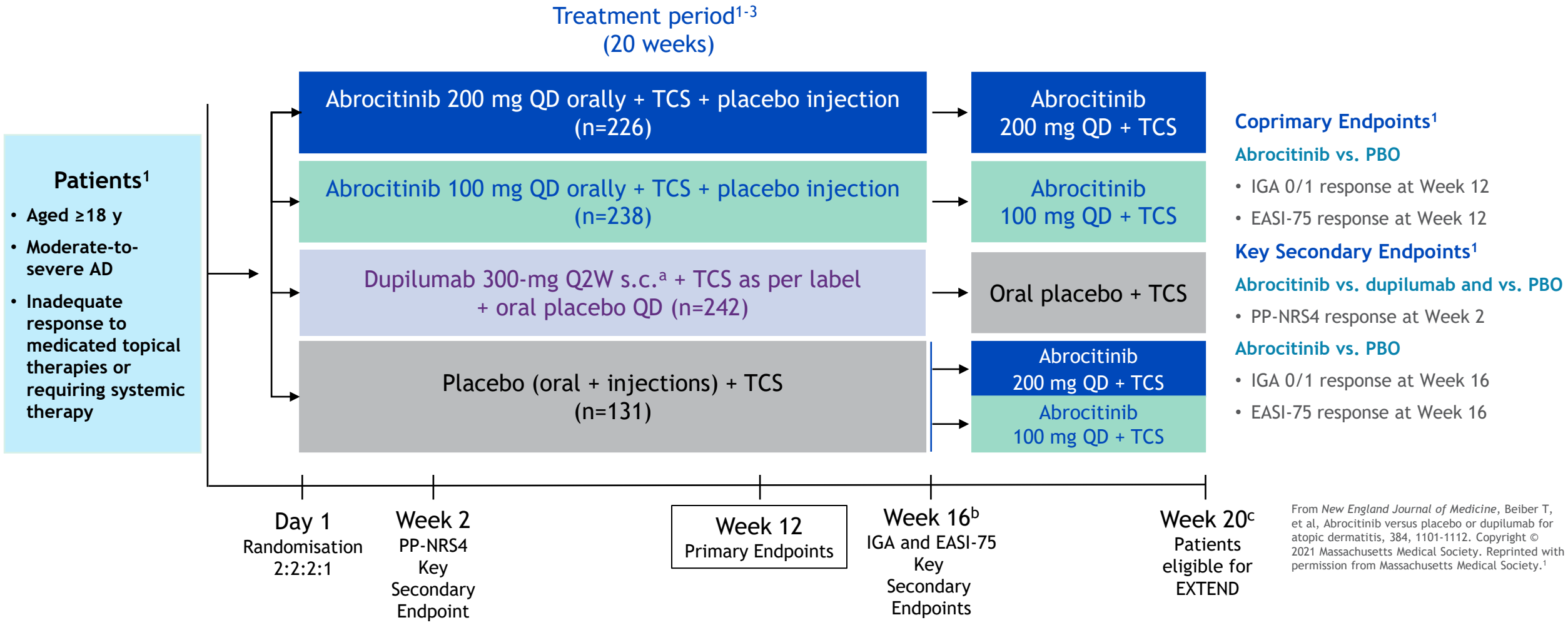
JADE COMPARE (N=837)[1,2]

- Efficacy and safety of Abrocitinib in combination with TCS
- Head-to-head comparison of itch relief with Abrocitinib vs. dupilumab at Week 2

TCS included low-to-medium potency topical corticosteroids and other medicated topicals, which were required per study protocol.

1. Bieber T, et al. *N Engl J Med*. 2021;384(12):1101-1112. 2. Protocol for: Bieber T, et al. *N Engl J Med*. 2021;384(12):1101-1112.

JADE COMPARE: Abrocitinib vs. Placebo as Combination Treatment With TCS and Head-to-Head Comparison of Abrocitinib vs. Dupilumab as Combination Treatment With TCS for Itch Response at Week 2[1]



Coprimary Endpoints[1]

Abrocitinib vs. PBO

- IGA 0/1 response at Week 12
- EASI-75 response at Week 12

Key Secondary Endpoints[1]

Abrocitinib vs. dupilumab and vs. PBO

- PP-NRS4 response at Week 2

Abrocitinib vs. PBO

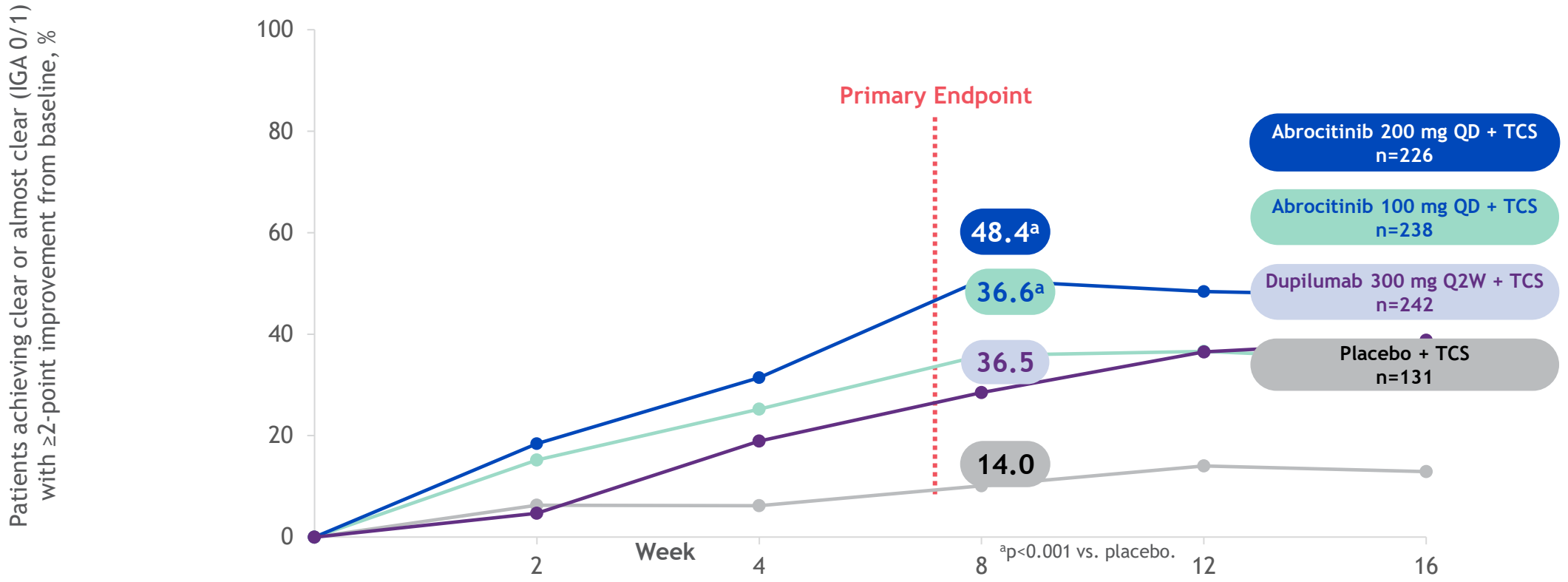
- IGA 0/1 response at Week 16
- EASI-75 response at Week 16

TCS included low-to-medium potency topical corticosteroids and other medicated topicals, which were required per study protocol.[1]
[a]Patients randomised to dupilumab received a loading dose of 600 mg.[1] [b]Dupilumab or its matching placebo was administered for 16 weeks, with the final injection planned for Week 14 to facilitate the washout of dupilumab prior to eligible subjects entering the long-term extension study.[2] [c]At Week 20, eligible patients entered the long-term extension study (JADE EXTEND); ineligible patients entered the 4-week off-treatment follow-up period.[2]

1. Bieber T, et al. *N Engl J Med.* 2021;384(12):1101-1112. **2.** Supplement to: Bieber T, et al. *N Engl J Med.* 2021:384(12):1101-1112. **3.** Protocol for: Bieber T, et al. *N Engl J Med.* 2021;384(12):1101-1112.

Significantly More Patients Had Skin Clearance Response (IGA 0/1) at Week 12 With Abrocitinib + TCS vs. Placebo + TCS

JADE COMPARE (coprimary endpoint)



Methodology and Limitations

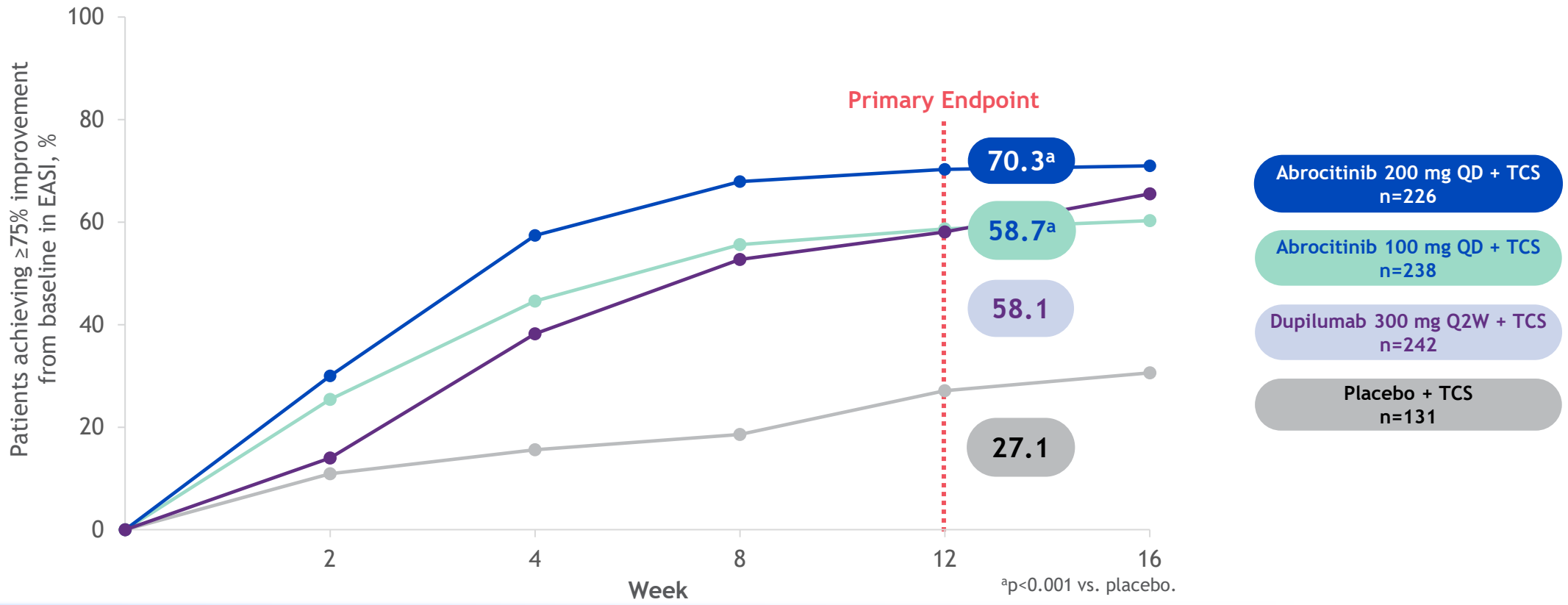
- IGA 0/1 response for Abrocitinib vs. placebo at Weeks 12 and 16 were prespecified, multiplicity-controlled endpoints; all other timepoints were prespecified, non-multiplicity-controlled endpoints
- This study was not designed to evaluate Abrocitinib vs. dupilumab with respect to IGA 0/1 response

TCS included low-to-medium potency topical corticosteroids and other medicated topicals, which were required per study protocol; IGA 0/1=Investigator's Global Assessment score of clear/almost clear.

Bieber T, et al. *N Engl J Med.* 2021;384(12):1101-1112.

Significantly More Patients Had Skin Clearance Response (EASI-75) at Week 12 With Abrocitinib + TCS vs. Placebo + TCS

JADE COMPARE (coprimary endpoint)



Methodology and Limitations

- EASI-75 response for Abrocitinib vs. placebo at Weeks 12 and 16 were prespecified, multiplicity-controlled endpoints; all other timepoints were prespecified, non-multiplicity-controlled endpoints
- This study was not designed to evaluate Abrocitinib vs. dupilumab with respect to EASI-75 response

TCS included low-to-medium potency topical corticosteroids and other medicated topicals, which were required per study protocol.

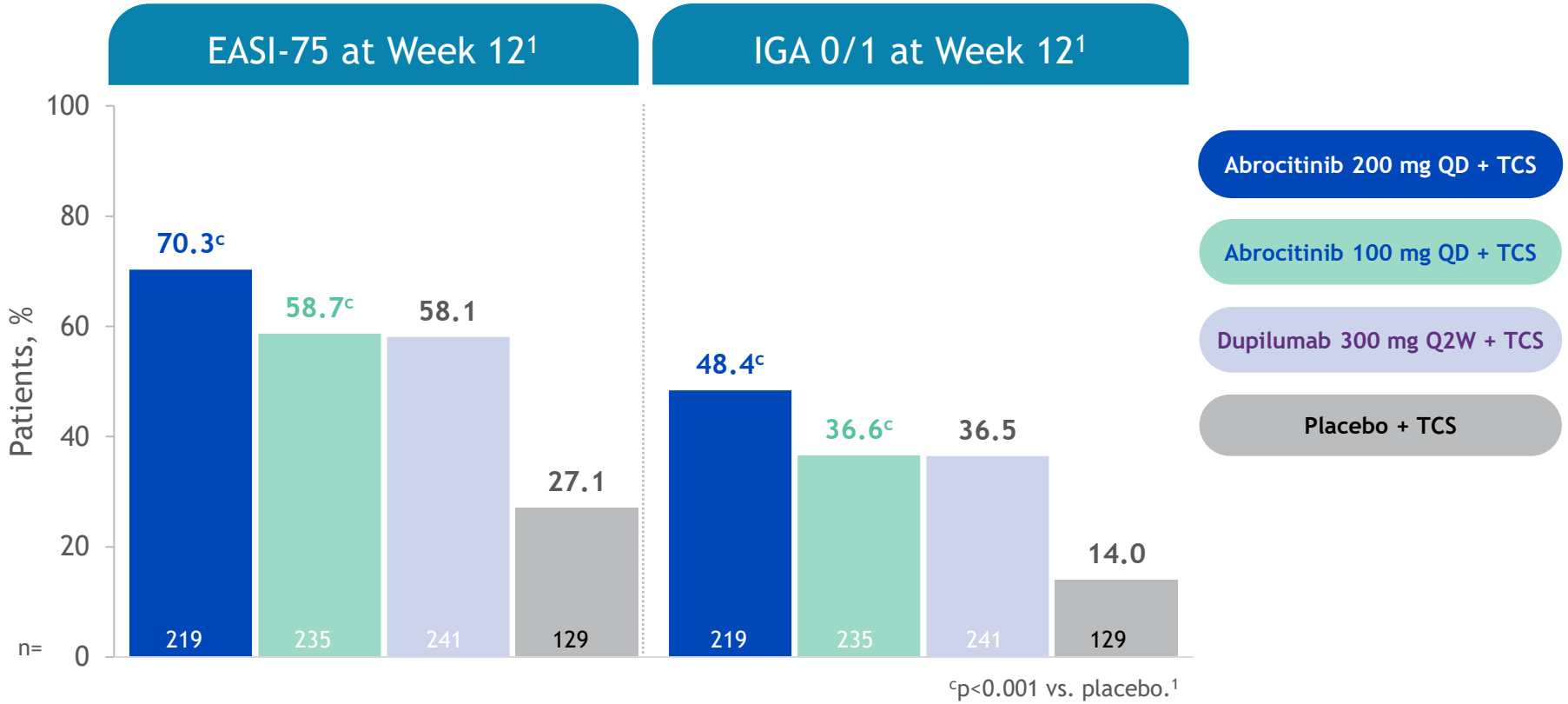
Bieber T, et al. *N Engl J Med.* 2021;384(12):1101-1112.

Significantly More Patients Had Skin Clearance Response (EASI-75 or IGA 0/1) at Week 12 With Abrocitinib + TCS vs. Placebo + TCS[1]

JADE COMPARE: Coprimary endpoints

Study Design[1]

- JADE COMPARE was a 20-week randomised double-blind, double-dummy, placebo-controlled, Phase III study in adult patients with moderate-to-severe AD[a]
- Evaluated efficacy and safety of 2 dosing regimens of Abrocitinib + TCS vs. placebo + TCS
- Patients were randomised 2:2:2:1 at Day 1 to receive Abrocitinib 200 mg QD + TCS, Abrocitinib 100 mg QD + TCS, dupilumab 300 mg Q2W[b] + TCS or placebo + TCS



[c]p<0.001 vs. placebo.[1]

Methodology and Limitations

- This study was not designed to evaluate Abrocitinib vs. dupilumab with respect to EASI-75 or IGA 0/1 response[1]

EASI-75=≥75% improvement from baseline in the Eczema Area and Severity Index; IGA 0/1=Investigator's Global Assessment score of clear/almost clear with ≥2-point improvement from baseline. TCS included low-to-medium potency topical corticosteroids and other medicated topicals, which were required per study protocol.[1]

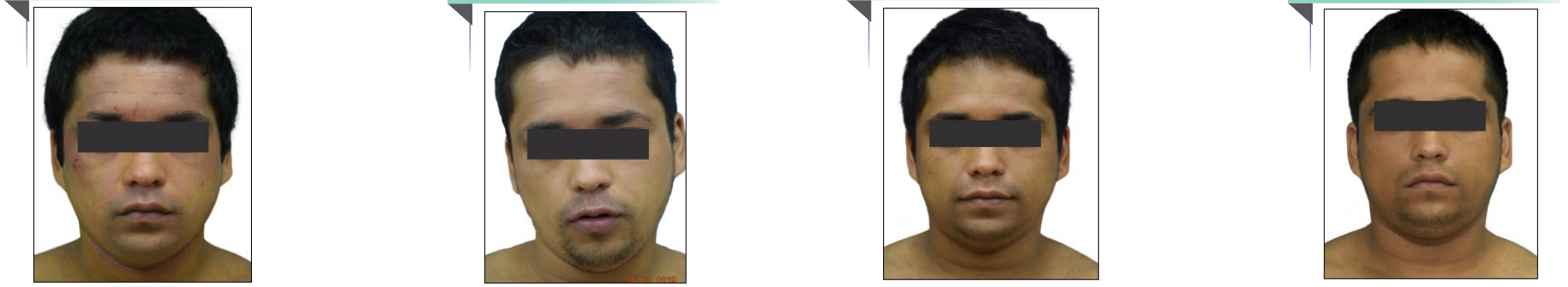
[a]At Week 20, eligible patients entered the long-term extension study (JADE EXTEND); ineligible patients entered the 4-week off-treatment follow-up period.[2] [b]Patients randomised to dupilumab received a loading dose of 600 mg.[1,2] Dupilumab or its matching placebo was administered for 16 weeks, with the final injection planned for Week 14 to facilitate the washout of dupilumab prior to eligible subjects entering the long-term extension study.[2]

1. Bieber T, et al. *N Engl J Med*. 2021;384(12):1101-1112. **2.** Supplement to: Bieber T, et al. *N Engl J Med*. 2021:384(12):1101-1112.

Skin Clearance Response Was Observed as Early as Week 2 and Sustained Through Week 16 With Abrocitinib + TCS[1,2]

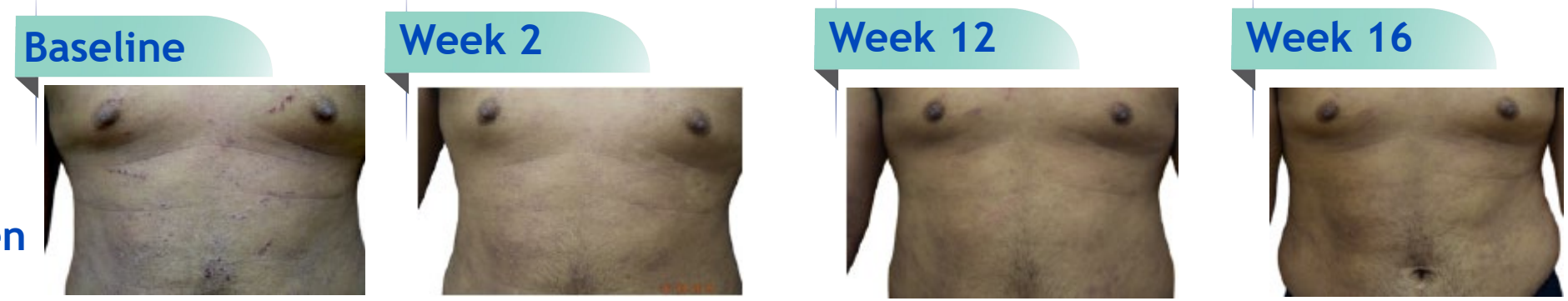
Treatment: Abrocitinib: 200 mg QD + TCS; **Sex:** Male **Age:** 21

Face



IGA: Severe | IGA: Moderate | IGA: Clear | IGA: Clear

Lower chest/ Abdomen



IGA: Severe | IGA: Moderate | IGA: Clear | IGA: Clear

Not everyone will respond to treatment with Abrocitinib. Individual results may vary.

Images of a patient from JADE COMPARE trial with severe AD at study baseline.

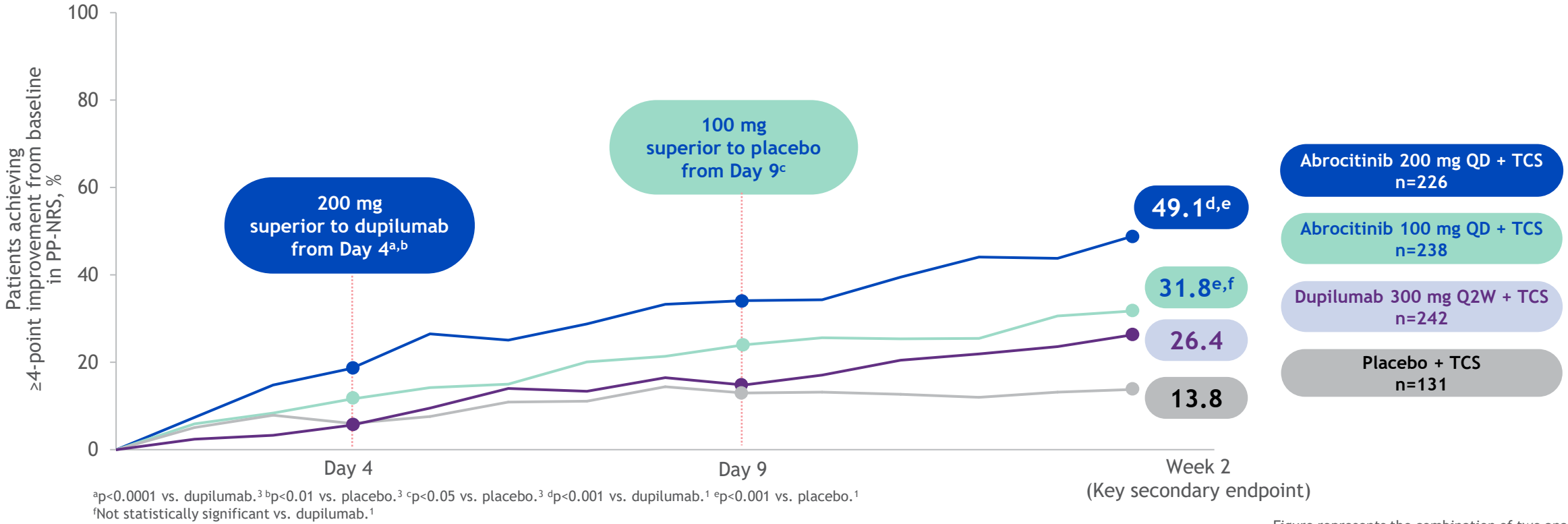
Clinical trial labels have been blurred and background colors and clothes have been modified in photos.

TCS included low-to-medium potency topical corticosteroids and other medicated topicals, which were required per study protocol.[2]

1. Data on file. Pfizer Inc, New York, NY. **2.** Bieber T, et al. *N Engl J Med.* 2021;384(12):1101-1112

A Greater Proportion of Patients Treated With Abrocitinib 200 mg Experienced Itch Relief at Week 2 Compared With Dupilumab or Placebo[1,2]

JADE COMPARE: key secondary endpoint[1]



[a]p<0.0001 vs. dupilumab.[3] [b]p<0.01 vs. placebo.[3] [c]p<0.05 vs. placebo.[3] [d]p<0.001 vs. dupilumab.[1] [e]p<0.001 vs. placebo.[1]
[f]Not statistically significant vs. dupilumab.[1]

Figure represents the combination of two analyses:
1) PP-NRS4 assessment at Week 2 and
2) PP-NRS4 assessment from Day 15 to Day 2

Methodology and Limitations

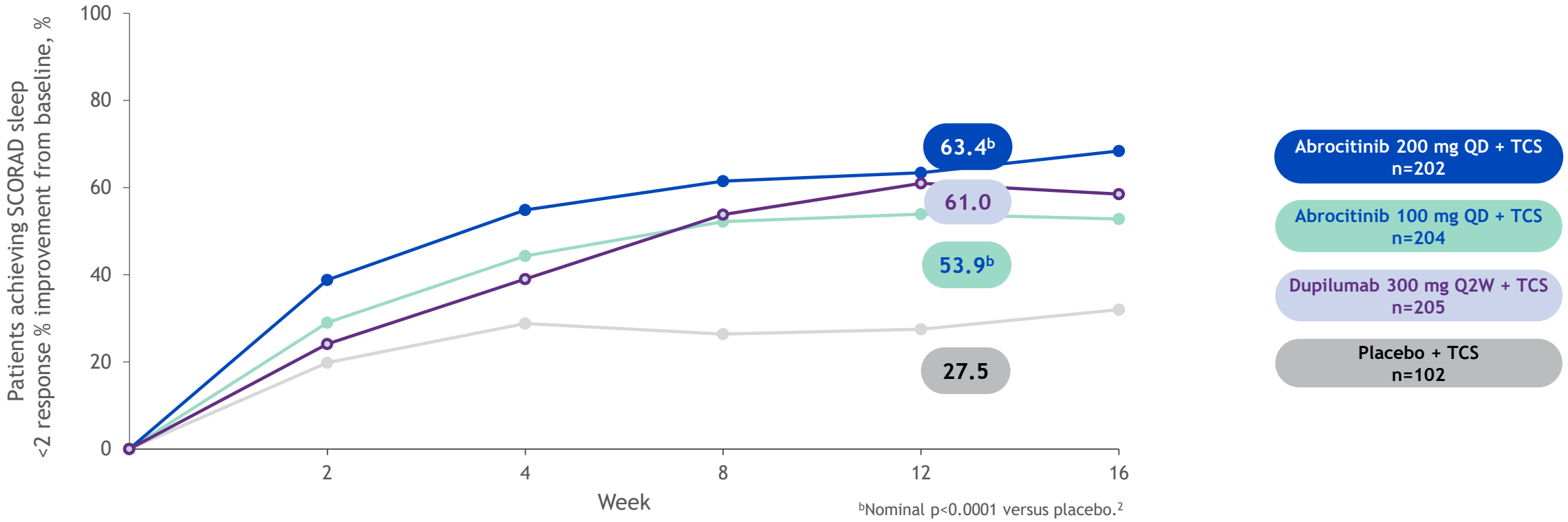
- PP-NRS4 response for Abrocitinib vs. dupilumab and vs. placebo at Week 2 was a prespecified multiplicity-controlled endpoint[1]
- The onset of pruritus relief was assessed through a step-down approach by day from Day 15 to Day 2.[4] Statistical significance was determined at the 5% level prior to step down. Any hypothesis made after the last day for which the comparison was significant was not considered statistically significant[4]
- P values at Day 4 and Day 9 are controlled for multiplicity for the family of PP-NRS4 comparisons[4]

TCS included low-to-medium potency topical corticosteroids and other medicated topicals, which were required per study protocol.[1]

1. Bieber T, et al. *N Engl J Med.* 2021;384(12):1101-1112. **2.** Ständer S, et al. Poster presented at: American Academy of Dermatology Association Virtual Meeting Experience 2021; April 23-25, 2021. **3.** Data on file. Pfizer Inc, New York, NY. **4.** Protocol for: Bieber T, et al. *N Engl J Med.* 2021;384(12):1101-1112.

In a Post Hoc Analysis, Patients Reported Improvement in Sleep With Abrocitinib + TCS at Week 12[1,2]

JADE COMPARE: SCORAD VAS sleep loss <2[a] at Week 12[1,2]



[b]Nominal p<0.0001 versus placebo.[2]

Methodology and Limitations

- SCORAD VAS sleep loss <2 response was a post hoc analysis and the p values are nominal
- The study was not designed to evaluate Abrocitinib vs. dupilumab with respect to SCORAD VAS sleep loss subscale

TCS included low-to-medium potency topical corticosteroids and other medicated topicals, which were required per study protocol.[3]

[a]A SCORAD sleep-loss score of <2 is defined as minimal or no sleep loss.[1]

1. Thyssen JP, et al. *J Eur Acad Dermatol Venereol*. 2022;36(3):434-443. **2.** Supplement to Thyssen JP, et al. *J Eur Acad Dermatol Venereol*. 2022;36(3):434-443. **3.** Bieber T, et al. *N Engl J Med*. 2021;384(12):1101-1112. 4. Supplement to: Bieber T, et al. *N Engl J Med*. 2021:384(12):1101-1112. doi:10.1056/NEJMoa2019380

JADE TEEN

JADE TEEN (N=285)[1]

- Efficacy and safety of Abrocitinib with TCS in adolescents

TCS included low-to-medium potency topical corticosteroids and other medicated topicals, which were required per study protocol.[1,2]

1. Eichenfield LF, et al. [published correction appears in JAMA Dermatol. 2021 Oct 1;157(10):1246]. *JAMA Dermatol*. 2021;157(10):1165-1173. **2.** Supplement to: Eichenfield LF, et al. [published correction appears in JAMA Dermatol. 2021 Oct 1;157(10):1246]. *JAMA Dermatol*. 2021;157(10):1165-1173.

Skin Clearance and Itch Response Was Improved in Adolescents Treated With Abrocitinib + TCS Compared With Placebo[1]

JADE TEEN: Coprimary (IGA 0/1, EASI-75) and key secondary (PP-NRS4) endpoints at Week 12[1]

Study Design[1,2]

- Phase III, randomised, double-blind, placebo-controlled, 12-week clinical trial
- JADE TEEN assessed the safety and efficacy of Abrocitinib + TCS vs. placebo + TCS in adolescents aged 12 to <18 years with moderate-to-severe AD (N=285)
- All patients had history of inadequate response to medicated topical therapy or were eligible for systemic therapies
- Patients were randomised 1:1:1 at Day 1 to receive Abrocitinib 200 mg, Abrocitinib 100 mg or placebo

	Abrocitinib 200 mg QD + TCS n=94	Abrocitinib 100 mg QD + TCS n=95	Placebo + TCS n=96
	Responders, %		
IGA 0/1 with a ≥2-point reduction from baseline[1]	46.2[a]	41.6[a]	24.5
EASI-75[1]	72.0[a]	68.5[a]	41.5
PP-NRS4 response[1]	55.4[a]	52.6	29.8

Methodology and Limitations

- Abrocitinib 100 mg PP-NRS4 response vs. placebo was not statistically significant at Week 4; all subsequent hypotheses for 100 mg were not considered statistically significant, including response at Week 12[3]
- PP-NRS4 is defined as an improvement of ≥4 points from baseline in the severity of PP-NRS[1]

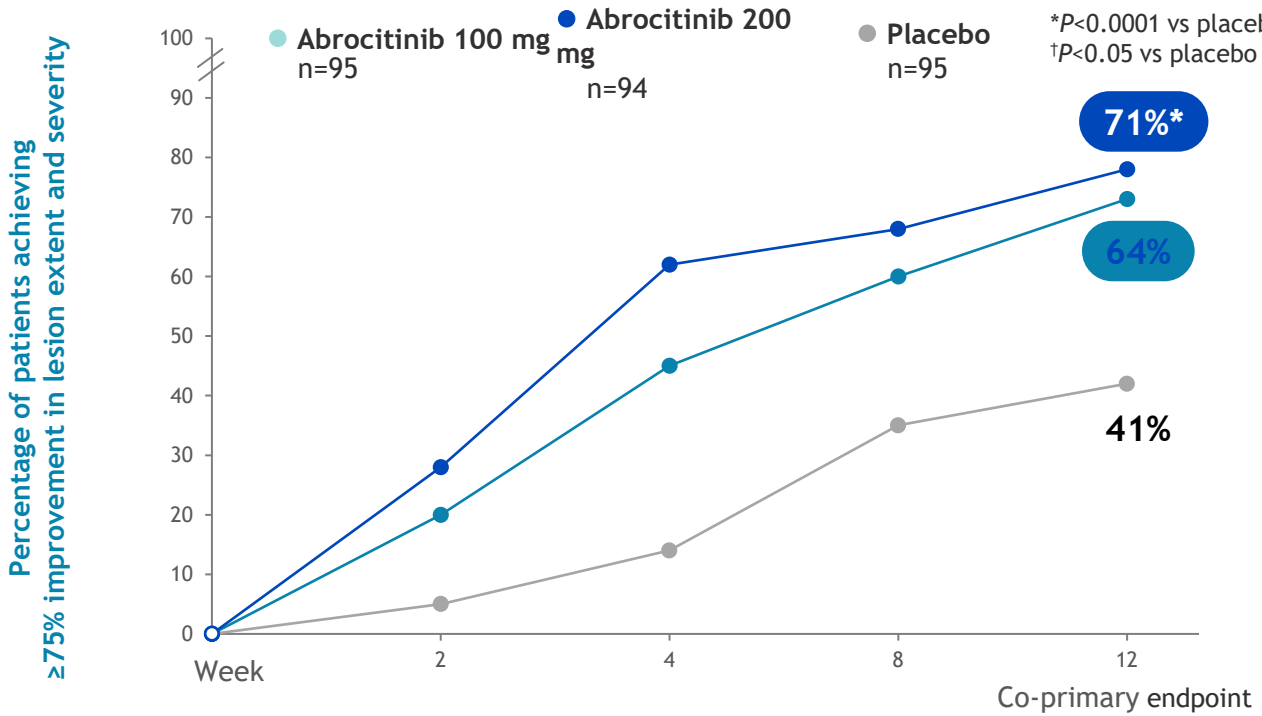
TCS included low-to-medium potency topical corticosteroids and other medicated topicals, which were required per study protocol.[1,4]

[a]Statistically significant, p<0.05, with adjustment for multiplicity versus placebo.[1]

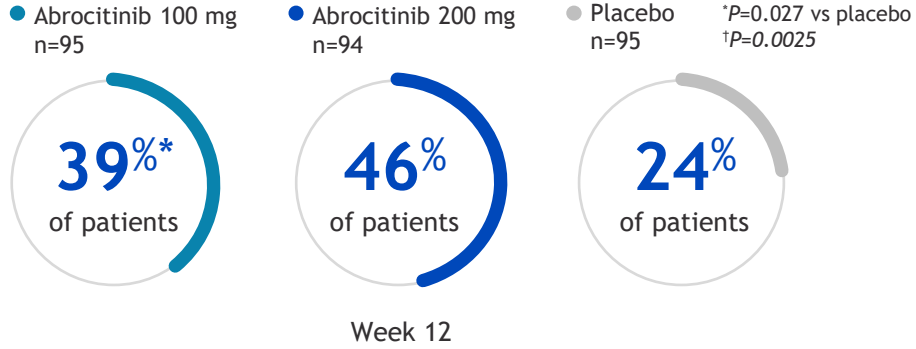
1. Eichenfield LF, et al. [published correction appears in JAMA Dermatol. 2021 Oct 1;157(10):1246]. *JAMA Dermatol*. 2021;157(10):1165-1173. **2.** Cibinqo (Abrocitinib) Singapore Prescribing Information Available From: http://labeling.pfizer.com/ShowLabeling.aspx?id=15308. **3.** Data on file. Pfizer Inc, New York, NY. **4.** Supplement to: Eichenfield LF, et al. [published correction appears in JAMA Dermatol. 2021 Oct 1;157(10):1246]. *JAMA Dermatol*. 2021;157(10):1165-1173.

JADE TEEN - Skin Clearance Results vs Placebo at Week 12 in Pediatric Patients 12 to <18 years

EASI-75 (co-primary endpoint)



IGA 0/1 at week 12 (co-primary endpoint)



~5 in 10 PEDIATRIC PATIENTS achieved CLEAR SKIN with CIBINQO 200 mg

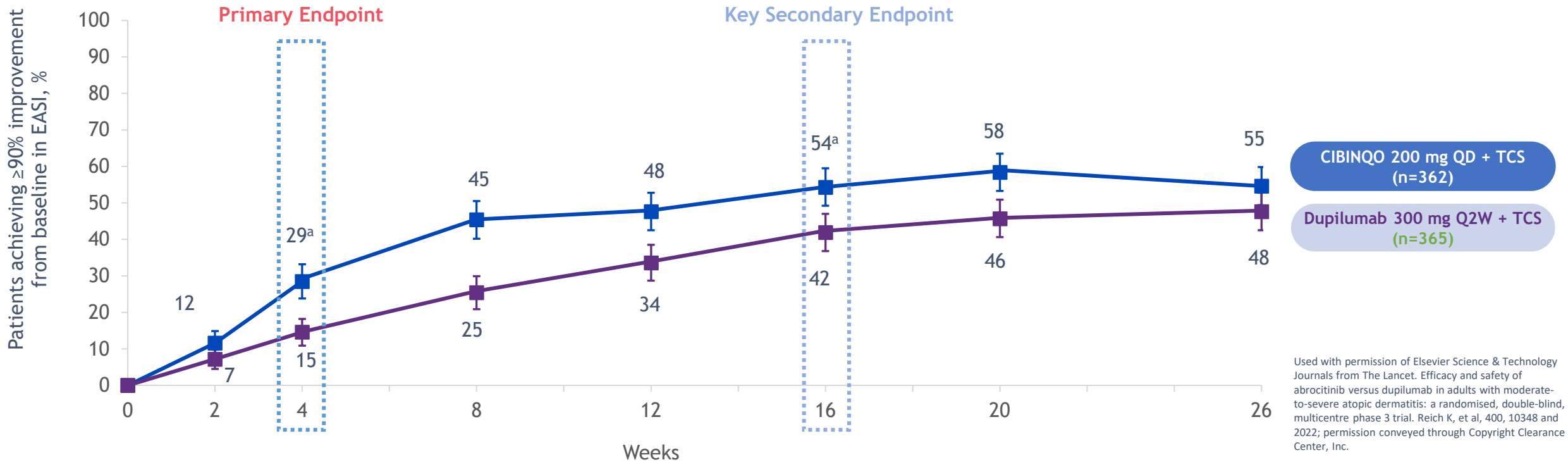
FAS was defined as all randomized subjects who received at least 1 dose of study medication. All missing responses were defined as non-responders.
An IGA responder was defined as achieving IGA 0 or 1 and at least a 2-point improvement from baseline.
Patients were permitted to use emollients during the study.

1. Eichenfield LF, et al. *JAMA Dermatol*. 2021;157(10):1165-1173.

CIBINQO® (abrocitinib) tablets

In JADE DARE, CIBINQO 200 mg + TCS Was Superior to Dupilumab + TCS in Improving Skin Clearance at Week 4 and Week 16

- Primary endpoint: EASI-90 at Week 4
  Key secondary endpoint: EASI-90 at Week 16



Methodology and Limitations

- EASI-90 response for CIBINQO vs. dupilumab at Weeks 4 and 16 were prespecified, multiplicity-controlled endpoints; all other timepoints were prespecified, non-multiplicity-controlled endpoints
- If a patient withdrew from the study or used rescue therapy, then this patient was counted as a nonresponder after that point

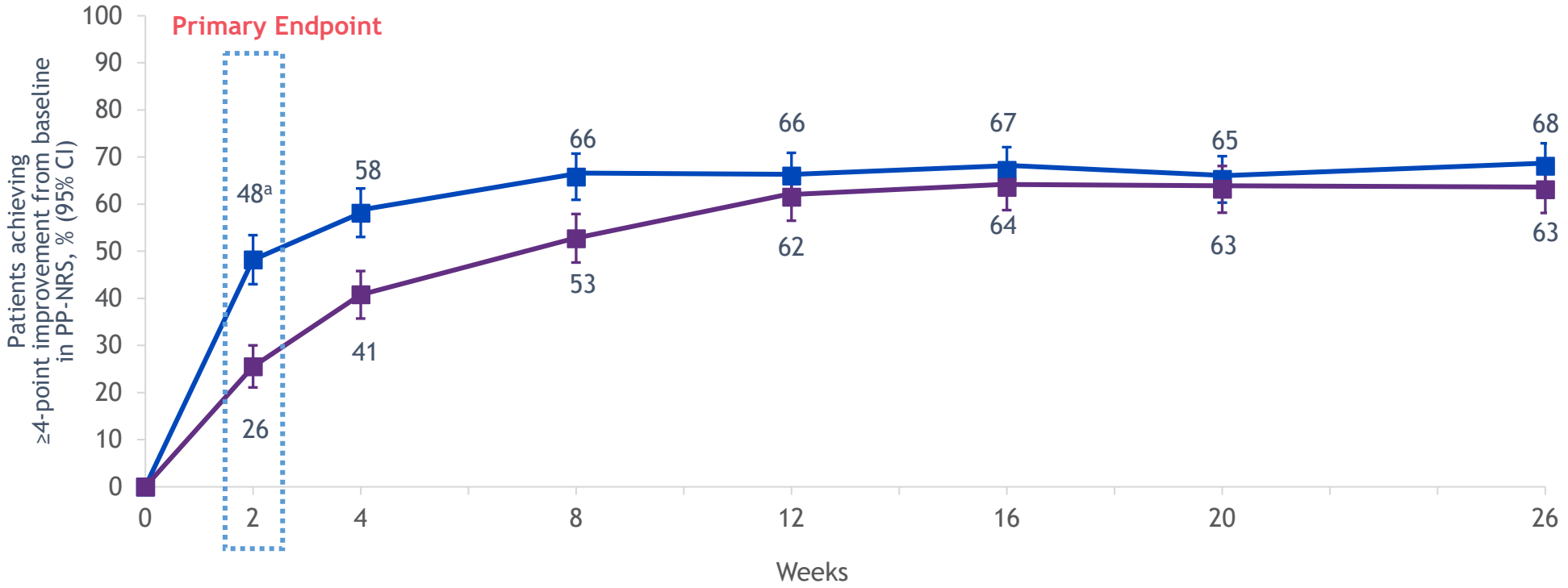
TCS included low-to-medium potency topical corticosteroids and other medicated topicals, which were required per study protocol.

[a]Two-sided p<0.001 vs. dupilumab calculated using the Cochran-Mantel-Haenszel method adjusted for baseline disease severity.

Reich K, et al. *Lancet*. 2022;400(10348):273-282.

In JADE DARE, CIBINQO 200 mg + TCS Was Superior to Dupilumab + TCS in Itch Relief at Week 2

- Primary endpoint: PP-NRS4 at Week 2



CIBINQO 200 mg QD + TCS (n=362)

Dupilumab 300 mg Q2W + TCS (n=365)

Methodology and Limitations

- PP-NRS4 response for CIBINQO vs. dupilumab at Week 2 was a prespecified, multiplicity-controlled endpoint; all other timepoints were prespecified, non-multiplicity-controlled endpoints
- If a patient withdrew from the study or used rescue therapy, then this patient was counted as a nonresponder after that point

TCS included low-to-medium potency topical corticosteroids and other medicated topicals, which were required per study protocol.

[a]Two-sided p<0.0001 vs. dupilumab calculated using the Cochran-Mantel-Haenszel method adjusted for baseline disease severity.

Reich K, et al. *Lancet*. 2022;400(10348):273-282.

In JADE DARE, CIBINQO 200 mg + TCS Demonstrated Fast and Superior Itch Relief in One Day After the First Dose Versus Dupilumab + TCS

- Primary endpoint: PP-NRS4 at Week 2

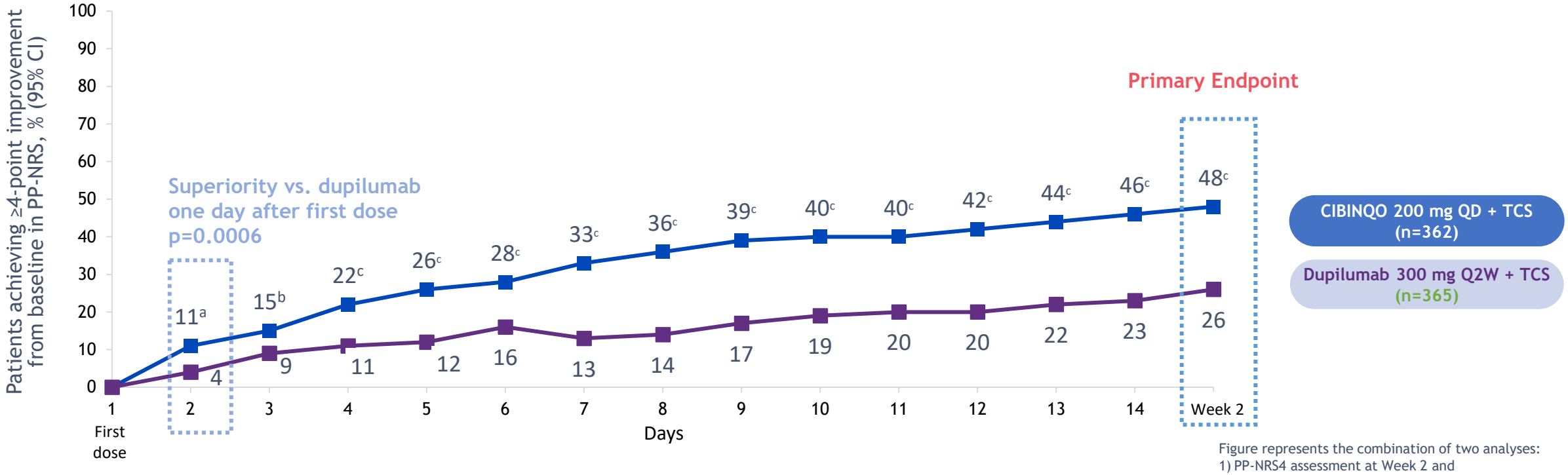


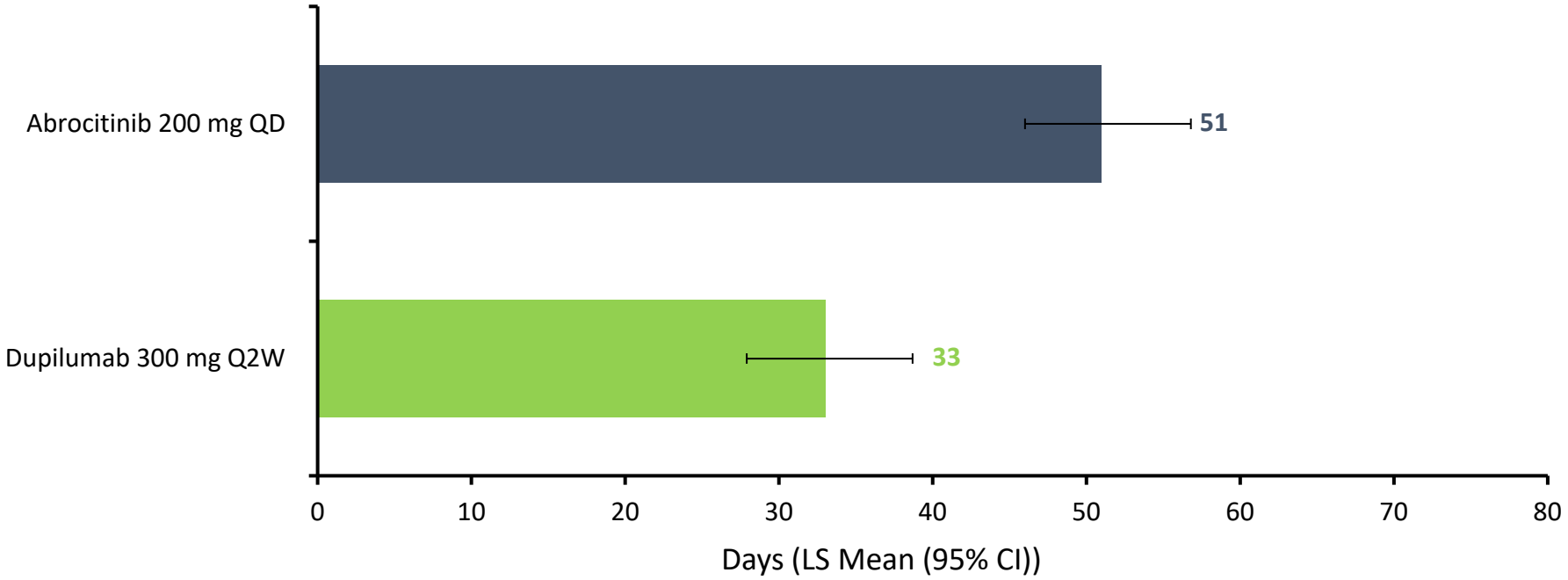
Figure represents the combination of two analyses:
1) PP-NRS4 assessment at Week 2 and
2) PP-NRS4 assessment from Day 15 to Day 1

Methodology and Limitations

- PP-NRS4 response for abrocitinib vs. dupilumab at Week 2 was a primary endpoint controlled for multiplicity
- The onset of pruritus relief was assessed through a step-down approach, day by day, from Week 2 to earlier time points once statistical significance was demonstrated at Week 2, at the 5% level of significance
- *P* value at Day 2 is controlled for multiplicity for the family of PP-NRS4 comparisons

TCS included low-to-medium potency topical corticosteroids and other medicated topicals, which were required per study protocol.
[a]p=0.0006 vs. dupilumab. [b]p=0.0078 vs. dupilumab. [c]p<0.0001 vs. dupilumab.
Reich K, et al. *Lancet.* 2022;400(10348):273-282.

Abrocitinib Was Associated with More Medicated Topical Therapy-Free Days than Dupilumab while Maintaining EASI-90 Response



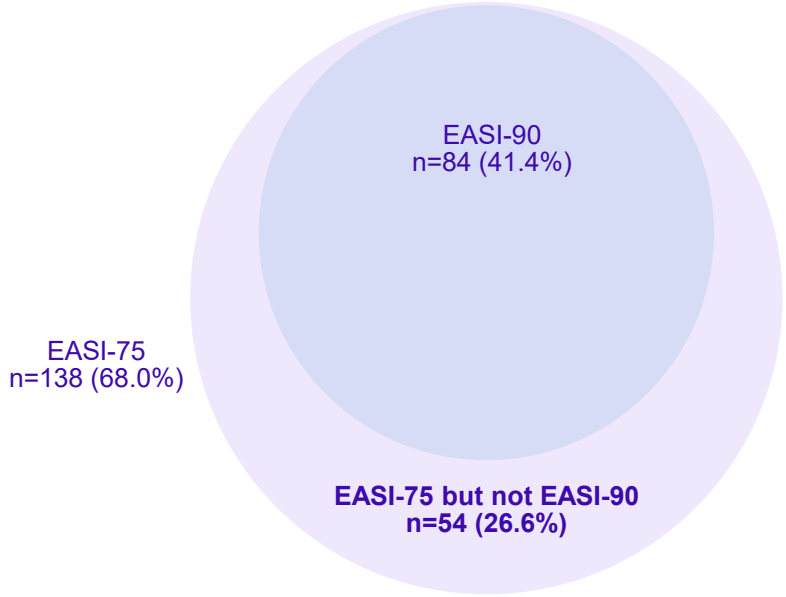
Patients were asked to use standardized topical medicated therapy on active lesions from day 1 onward but could stop 7 days after clear or almost clear skin was achieved and restart upon reoccurrence of active lesions.
Medicated topical background therapy-free days defined as days in which a participant maintains a response of EASI-90 or greater as two consecutive EASI-90 responses, without the use of medicated topical background therapy.
CI, confidence interval; EASI-90, ≥90% improvement from baseline in Eczema Area and Severity Index; LS, least squares; Q2W, once every 2 weeks; QD, once daily.
Reich K, et al. *Lancet.* 2022;400(10348):273–82.

Abrocitinib 200mg + TT more effective than dupilumab in reducing signs of AD[1]
Significant improvement of pruritus vs. dupilumab[1,2]

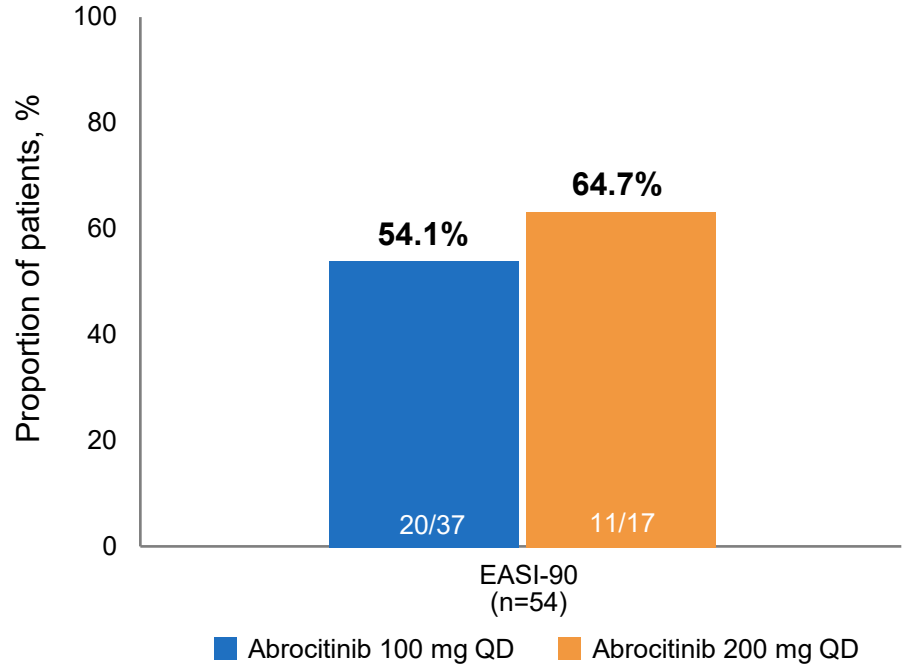
1. Bieber T, et al. JADE COMPARE Investigators. Abrocitinib versus Placebo or Dupilumab for Atopic Dermatitis. N Engl J Med. 2021 Mar 25;384(12):1101-1112. 2.. Reich et al. Efficacy and safety of abrocitinib versus dupilumab in adults with moderate-to-severe atopic dermatitis: a randomised, double-blind, multicentre phase 3 trial. Lancet 2022; 400: 273–82

More Than Half of Prior Dupilumab EASI-75 Responders Achieved an EASI-90 Response with Abrocitinib

Prior dupilumab responders at Week 16 in JADE COMPARE



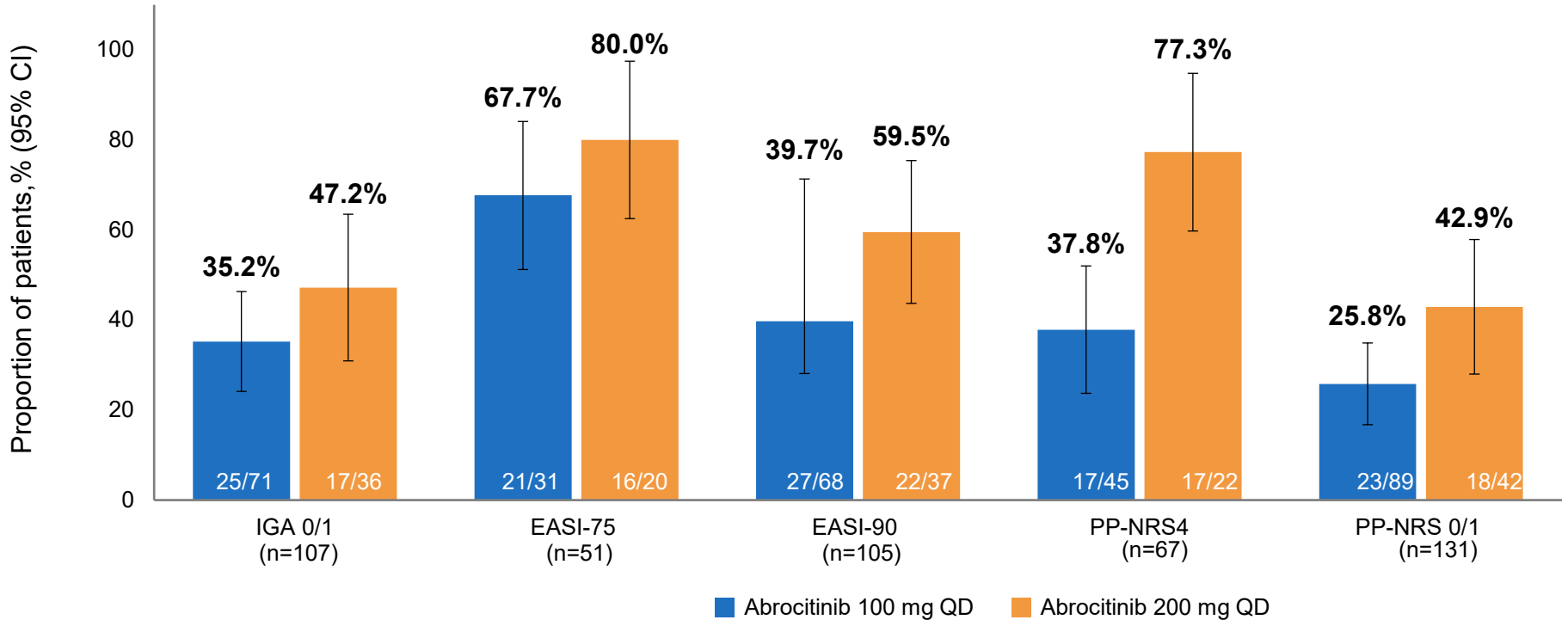
EASI-90 response with abrocitinib at Week 12 in JADE EXTEND among patients who achieved EASI-75 but not EASI-90 with dupilumab at Week 16 in JADE COMPARE



- For Week 12 JADE EXTEND data, numbers in each bar represent the proportion of patients assigned to each treatment arm who achieved an EASI-90 response to abrocitinib 100 mg or 200 mg. The numerator is the number of patients who responded to abrocitinib and the denominator is the number of patients with prior response to dupilumab.
- EASI-75, ≥75% improvement from baseline in Eczema Area and Severity Index; EASI-90, ≥90% improvement from baseline in Eczema Area and Severity Index; QD, once daily.
- Shi VY. et al. *J Am Acad Dermatol.* 2022;87(2):351-358.

Prior Non-response to Dupilumab Did Not Preclude an Efficacy Response with Abrocitinib

Efficacy responses with abrocitinib among prior dupilumab non-responders at Week 12

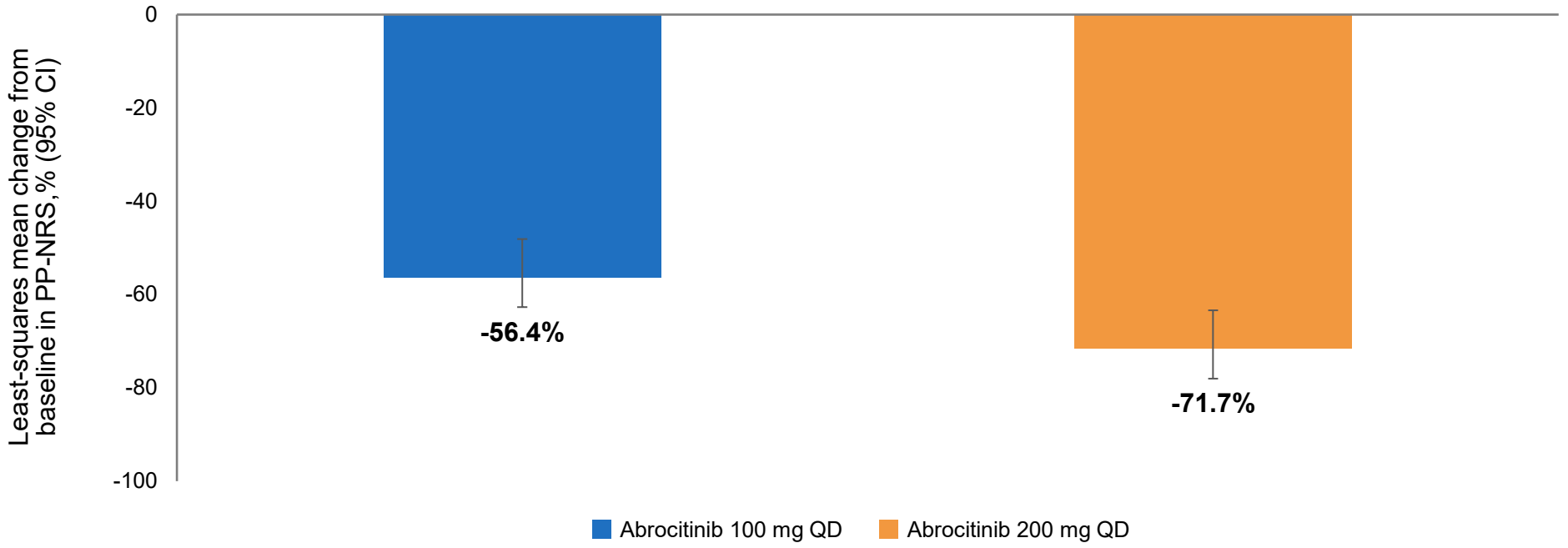


Numbers in each bar represent the proportion of patients assigned to each treatment arm who achieved the indicated response to abrocitinib 100 mg or 200 mg. The numerator is the number of patients who responded to abrocitinib and the denominator is the number of patients who received the indicated dose of abrocitinib.CI, confidence interval; EASI-75, ≥75% improvement from baseline in Eczema Area and Severity Index; EASI-90, ≥90% improvement from baseline in Eczema Area and Severity Index; IGA 0/1, Investigator's Global Assessment
of clear or almost clear with ≥2-grade improvement from baseline; n, number of patients with prior non-response to dupilumab; PP-NRS 0/1, Peak Pruritus Numerical Rating Scale score of 0 or 1; PP-NRS4, ≥4-point improvement from baseline in Peak Pruritus Numerical Rating Scale; QD, once daily. PP-NRS: © Regeneron Pharmaceuticals, Inc., and Sanofi, 2017.

Shi VY. et al. *J Am Acad Dermatol*. 2022;87(2):351-358.

Itch Reduction with Abrocitinib at Week 12 in JADE EXTEND

PP-NRS response with abrocitinib (regardless of dupilumab response status) at Week 12

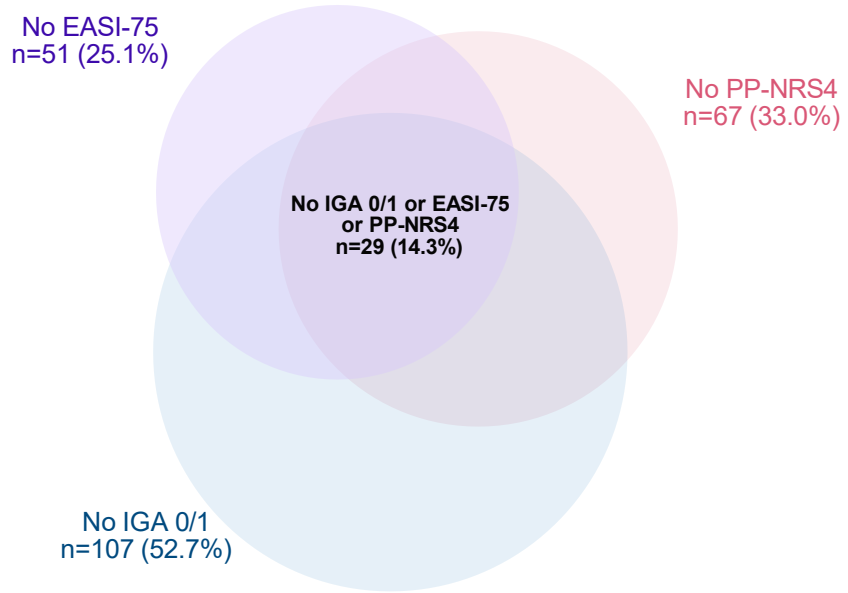


CI, confidence interval; PP-NRS, Peak Pruritus Numerical Rating Scale; QD, once daily.

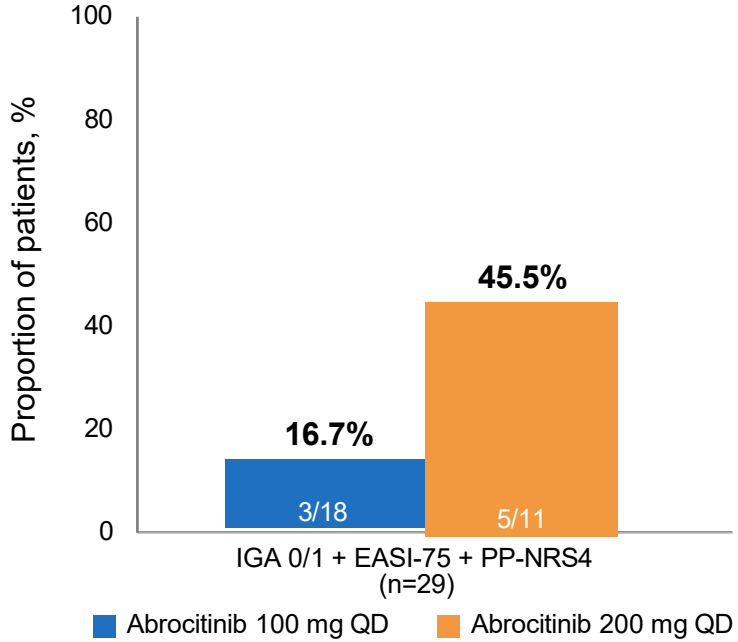
Supplementary appendix to Shi VY, et al. *J Am Acad Dermatol*. 2022;87(2):351-358.

Some Patients Who Were Non-responders to Dupilumab by IGA 0/1, EASI-75 and PP-NRS4 Achieved All These Responses with Abrocitinib

Prior dupilumab non-responders at Week 16 in JADE COMPARE



IGA 0/1, EASI-75 and PP-NRS4 response with abrocitinib at Week 12 in JADE EXTEND among patients who achieved no responses in these domains with dupilumab at Week 16 in JADE COMPARE



EASI-75, ≥75% improvement from baseline in Eczema Area and Severity Index; IGA 0/1, Investigator's Global Assessment of clear or almost clear with ≥2-grade improvement from baseline; n, number of patients with prior non-response to dupilumab; PP-NRS4, ≥4-point improvement from baseline in Peak Pruritus Numerical Rating Scale; QD, once daily. Numbers in each bar represent the proportion of patients assigned to each treatment arm that achieved the indicated response to abrocitinib 100 mg or 200 mg. The numerator is the number of patients who responded to abrocitinib and the denominator is the number of patients who received the indicated dose of abrocitinib.

Safety Profile of Abrocitinib

Abrocitinib has shown a consistent safety profile, with >3,000 patients treated in clinical studies in moderate-to-severe AD[1,a]

[a]Includes patients from a Phase II trial, pivotal and additional Phase III trials, one of which is ongoing.[2]

1. Cibinqo (Abrocitinib) bula, acesso em www.pfizer.com.br/bulas/cibinqo . **2.** Simpson EL, et al. *Am J Clin Dermatol*. 2021;22(5):693-707.

JADE DARE: The Safety and Tolerability Profile of Abrocitinib Was Consistent With Previous Clinical Trials[1]

Summary of AEs[2]

Patients, n (%)	Abrocitinib 200 mg QD + topicals n=362	Dupilumab 300 mg Q2W + topicals n=365
TEAEs	268 (74)	239 (65)
Serious TEAEs	6 (2)	6 (2)
Severe TEAEs[a]	11 (3)	8 (2)
TEAEs leading to study discontinuation	12 (3)	9 (2)
Most frequently reported TEAEs (≥5% of patients in any group)		
Nausea[b]	70 (19)	8 (2)
Headache	47 (13)	24 (7)
Acne or folliculitis	48 (13)	11 (3)
Conjunctivitis	10 (3)	39 (11)

- TEAEs that were serious, severe or led to study discontinuation affected few patients[2]
- Two deaths were in the Abrocitinib 200-mg group[2]
  - One patient died from COVID-19
  - Another patient died due to cardiopulmonary arrest and intracranial haemorrhage
- 6 serious AEs were reported in the dupilumab arm[2]
  - One serious AE of rhabdomyolysis occurred in the dupilumab group

Conjunctivitis was more frequent in the dupilumab group than in the Abrocitinib group[2]

[a]An AE that prevents normal everyday activities.[2]
[b]Oral study medication was to be swallowed whole, with or without food, except on study visit days, which required fasting.

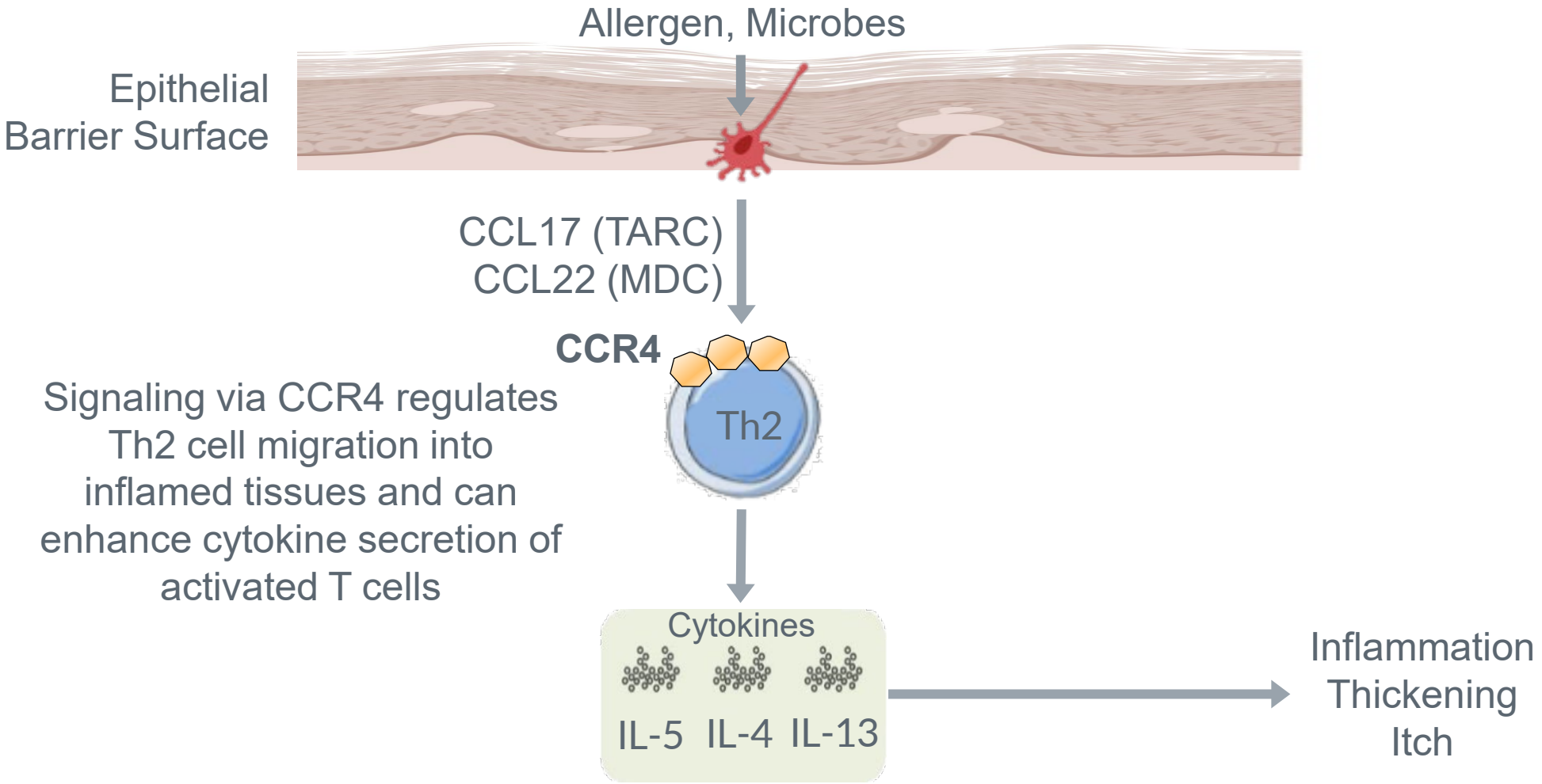
1. Reich K, et al. Presented at EADV 30th Congress; 29 September-2 October 2021. **2.** Reich K, et al. *Lancet*. 2022;400(10348):273-282.

“JAK inhibitors are no longer a potential treatment for AD—they are here, and the future is bright”

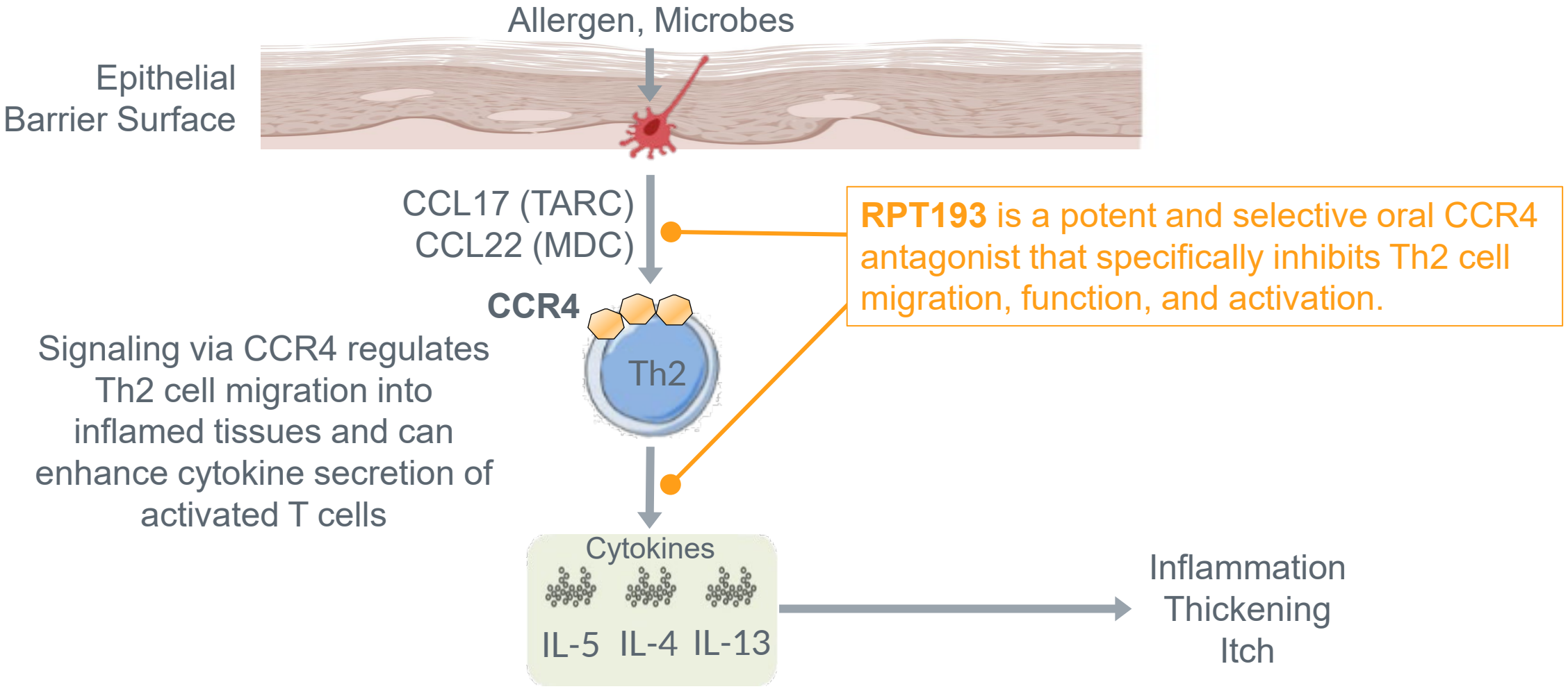
Raj Chovatiya, Amy S. Paller. JAK inhibitors in the treatment of atopic dermatites. Journal of Allergy and Clinical Immunology. Vol 148, (4). 2021. Pages 927-940. doi.org/10.1016/j.jaci.2021.08.009

NEW CHEMICAL ENTITIES

RPT193 Targets Th2 Activity Responsible for Allergic Inflammation in Atopic Dermatitis, Asthma, and Other Diseases



RPT193 Targets Th2 Activity Responsible for Allergic Inflammation in Atopic Dermatitis, Asthma, and Other Diseases



Clinical safety and efficacy of RPT193, an oral CCR4 inhibitor: Results from a randomized, placebo-controlled Phase 1b monotherapy trial in patients with moderate-to-severe atopic dermatitis

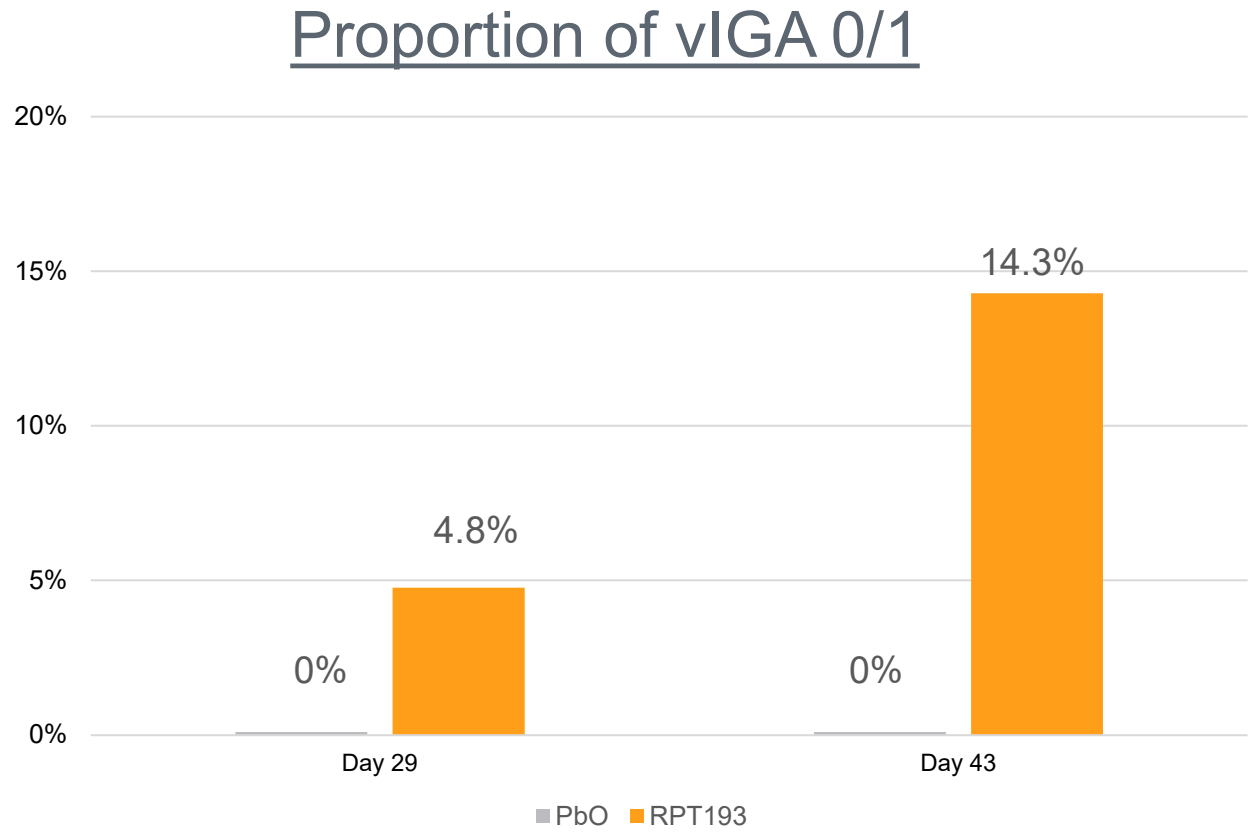
Robert Bissonnette[1], Mark Lee[2], Janet DuBois[3], Joshua Rulloda[4], Nadine Lee[4], Daniel Johnson[4], David Wustrow[4], Jasmina Jankicevic[4], William Ho[4], Laurence Cheng[4], Emma Guttman-Yassky[5]

EADV Late-Breaker Abstract #2746

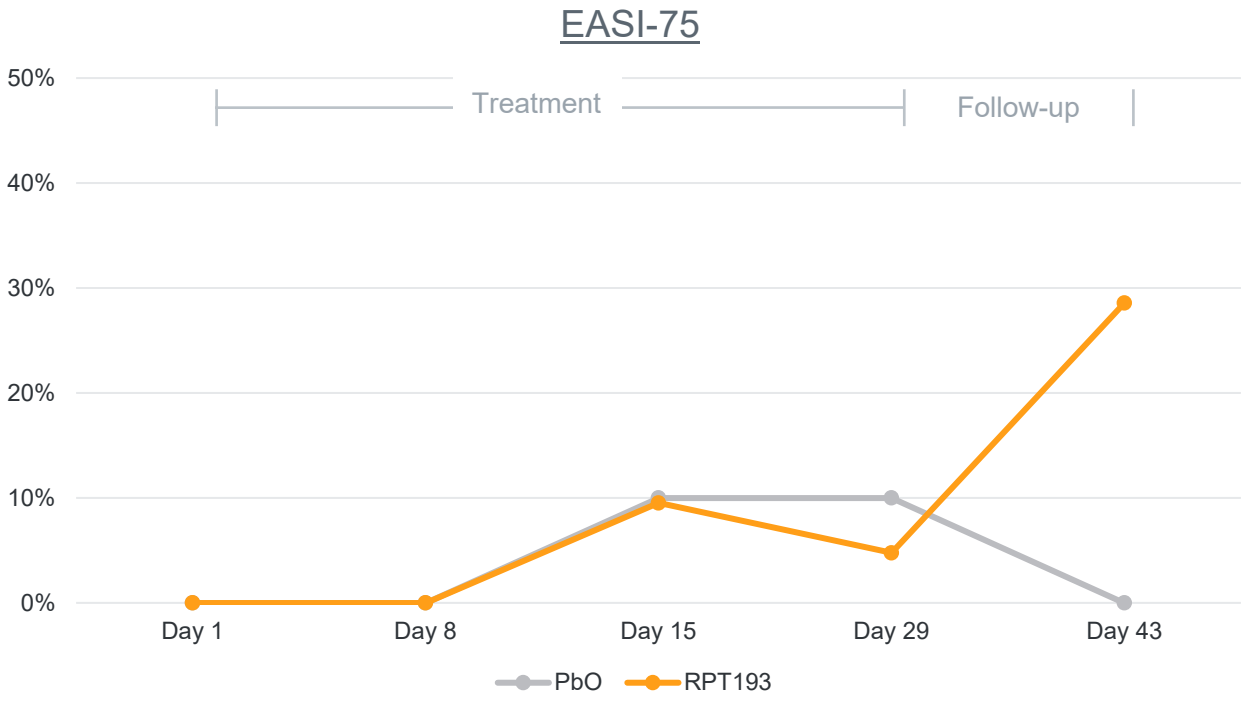
30 September 2021

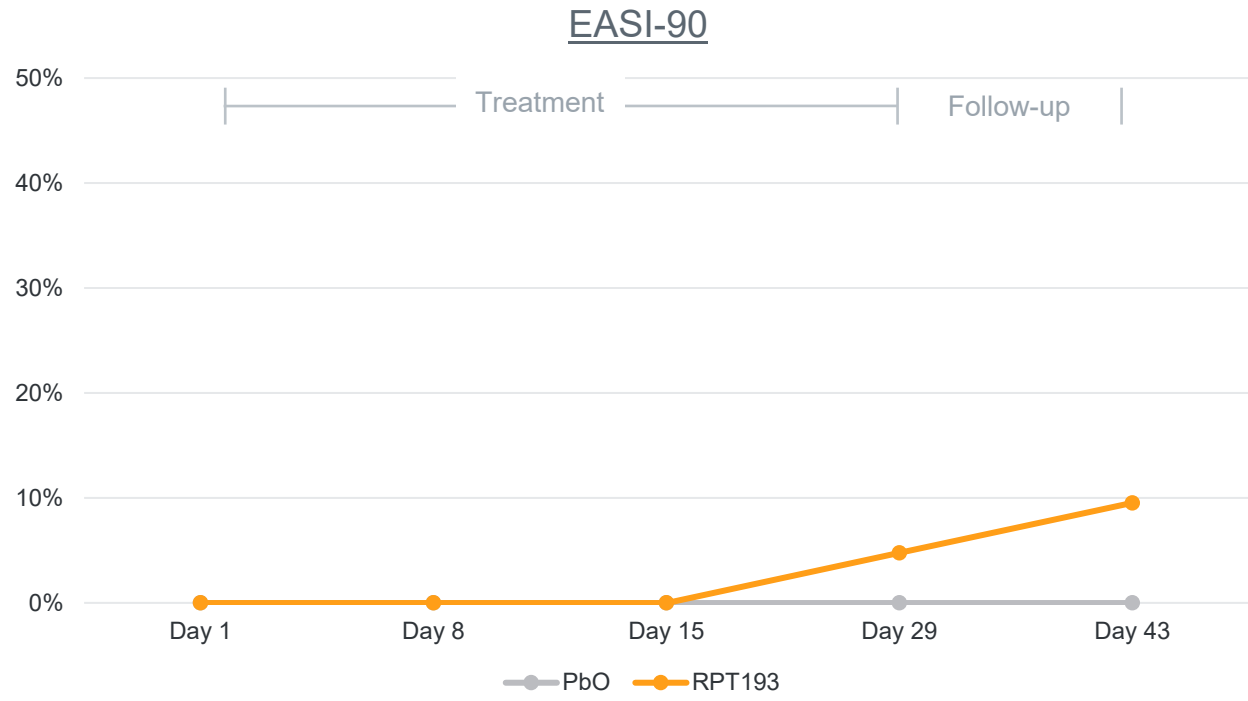
[1]Innovaderm Research Inc., Montreal, Quebec, Canada, [2]Progressive Clinical Research, San Antonio, TX, USA, [3]DermResearch, Inc., Austin, TX, USA, [4]RAPT Therapeutics, Inc., South San Francisco, CA, USA, [5]Icahn School of Medicine at Mount Sinai, New York, NY, USA

RPT193: vIGA 0/1 (Clear/Almost Clear at Day 29 and Day 43)



RPT193: EASI-75 and EASI-90

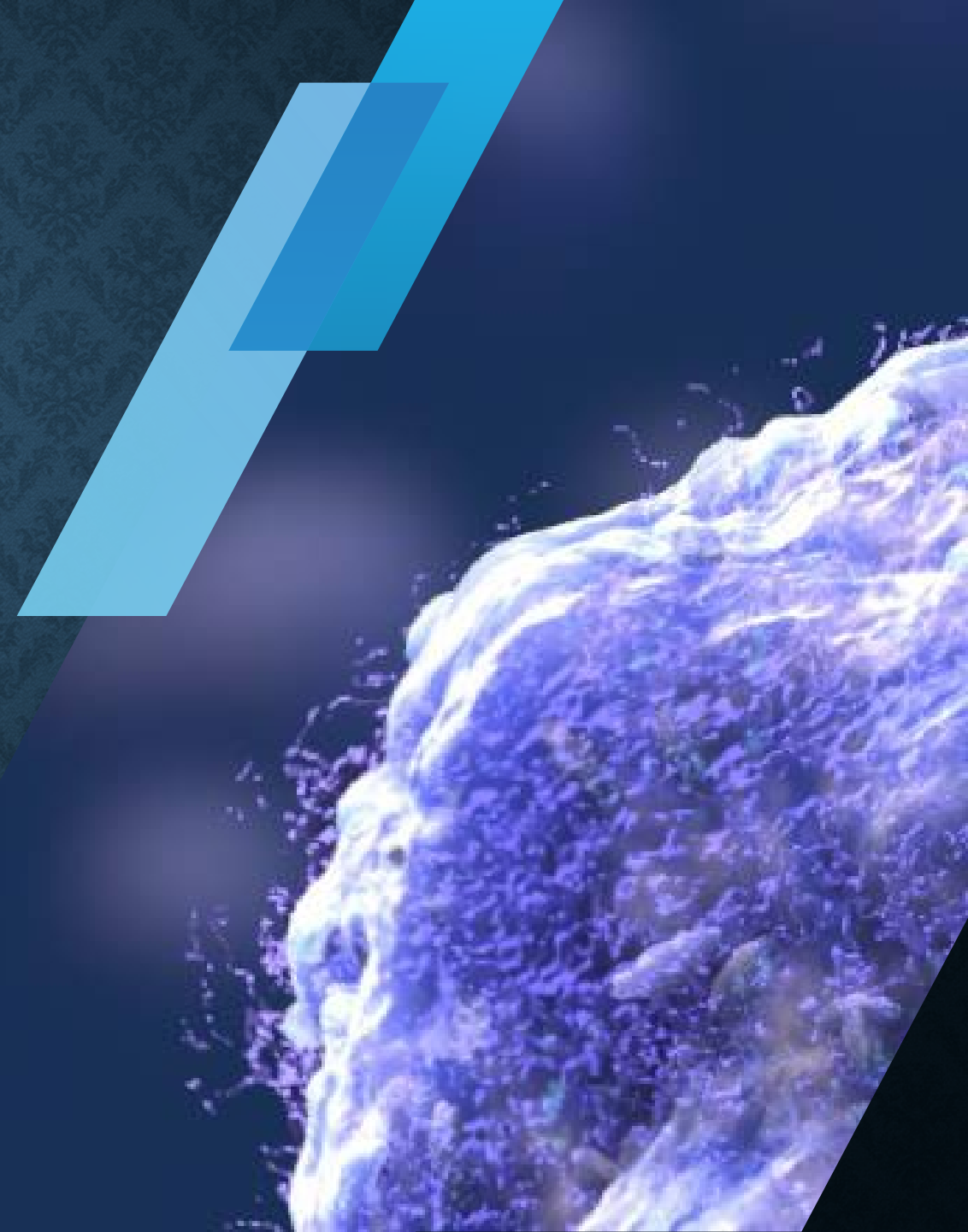




Etrasimod, a Novel, Oral, Selective Sphingosine 1-Phosphate Receptor Modulator, Improves Patient- and Clinician- Reported Outcomes in Adults With Moderate-to-Severe Atopic Dermatitis in a Randomized, Double-Blind Placebo-Controlled Phase 2 Study (ADVISE)

- *Emma Guttman-Yassky, Robert Bissonnette, Leon Kircik, Dedee Murrell, Andrew Selfridge, Kris Liu, Gurpreet Ahluwalia and*
- *Jonathan Silverberg*

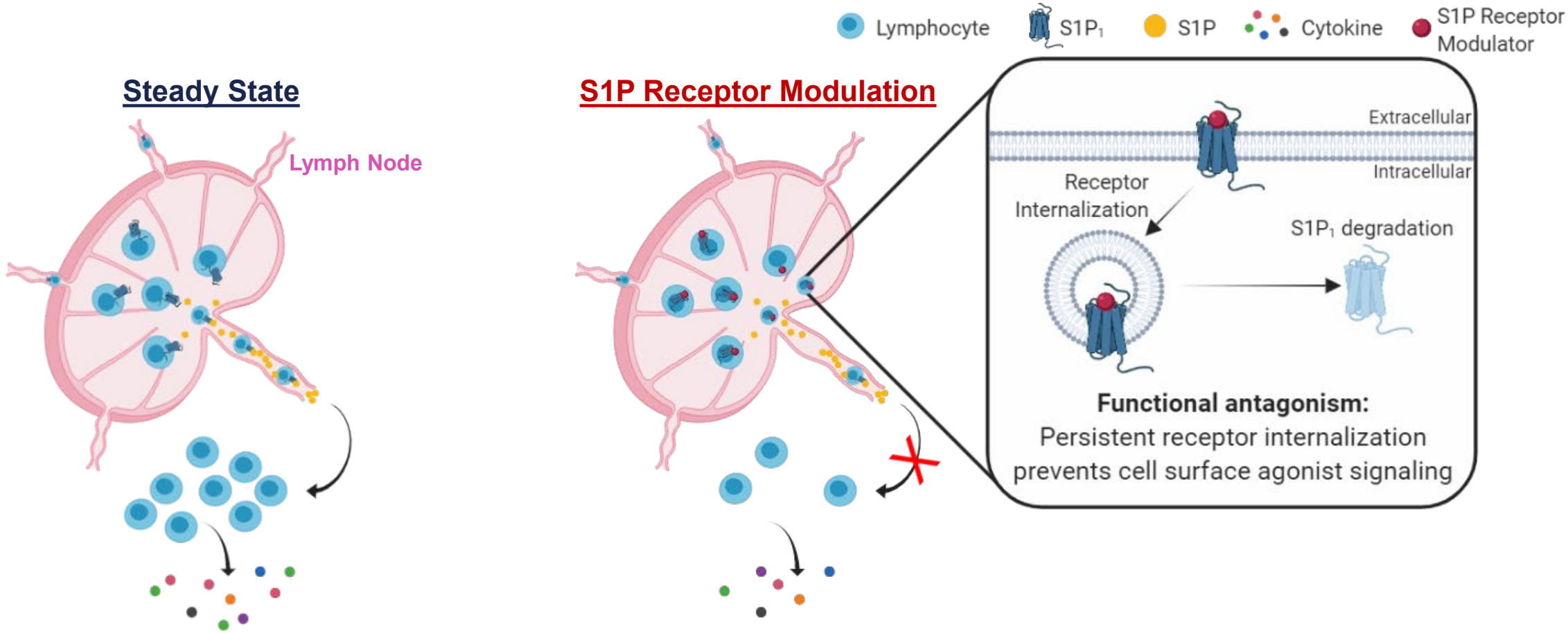
- **AAD VMX 2021**
- **April 24, 2021**



Etrasimod is an investigational drug, not approved for use by any health authority. This information is not intended to promote or recommend etrasimod for any use.

S1P Receptor Modulation is a Potential Novel MOA in Atopic Dermatitis

$S1P_1$ Functional Antagonism Selectively Reduces Migration of Lymphocytes From Lymph Nodes[1,2]

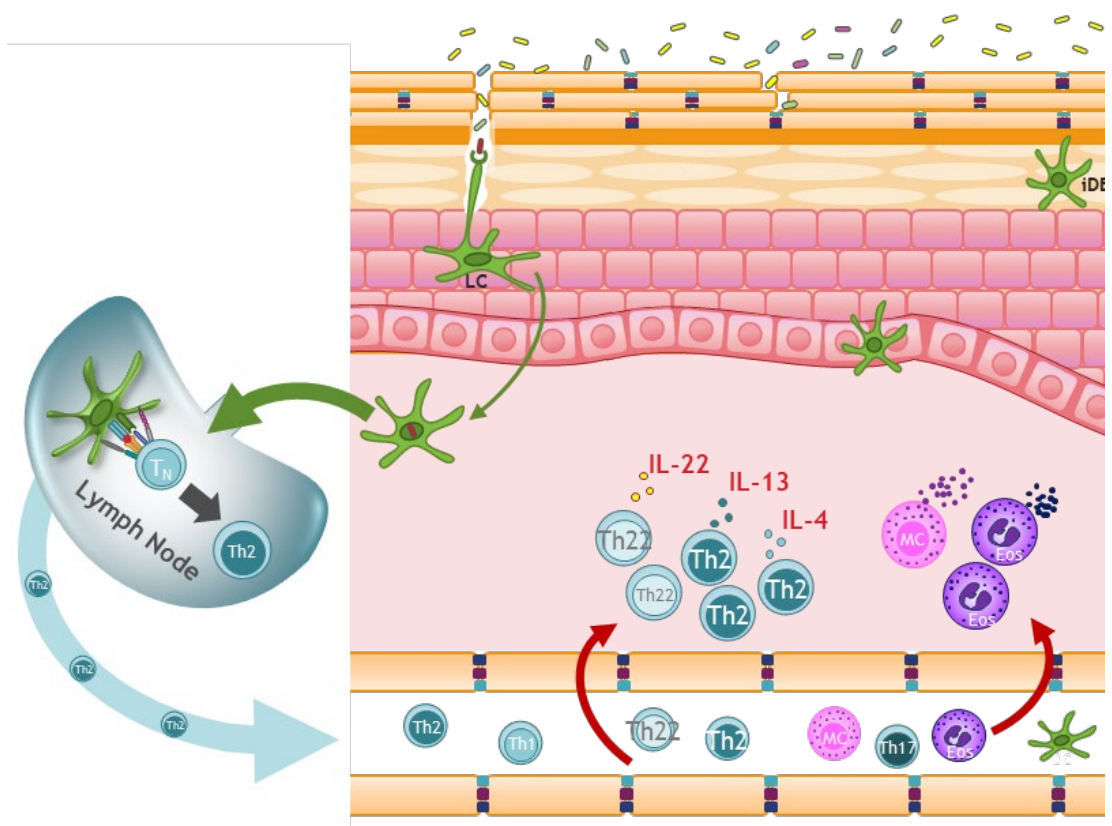


- **Circulating lymphocytes exit lymph nodes ➔ traffic to tissues ➔ cause inflammation & tissue damage**
- **Reduced egress ➔ fewer circulating lymphocytes ➔ decreased inflammation & tissue damage**
- **Immune surveillance maintained**

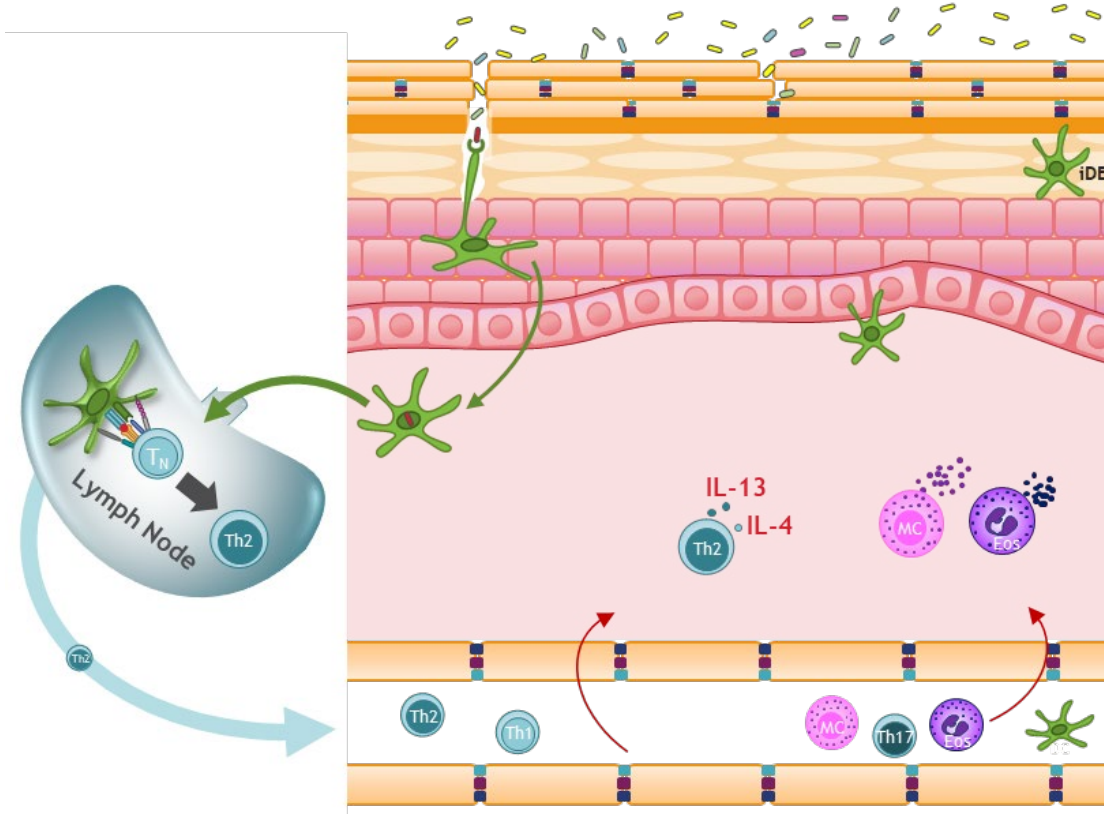
1. Peyrin-Biroulet L et al. *Autoimmune Rev*. 2017;16:495-503. **2.** Olivera P et al. *Gut*. 2017;66:199-209.

Etrasimod[1], a Selective $S1P_{1,4,5}$ Receptor Modulator, Reduces Lymphocyte Trafficking and may Decrease Skin Inflammation in AD

Barrier defects, altered microbiota, and T cell mediated inflammation drive AD pathology[a]



Etrasimod reduces the trafficking of T cells, which may lead to improved skin inflammation[b]

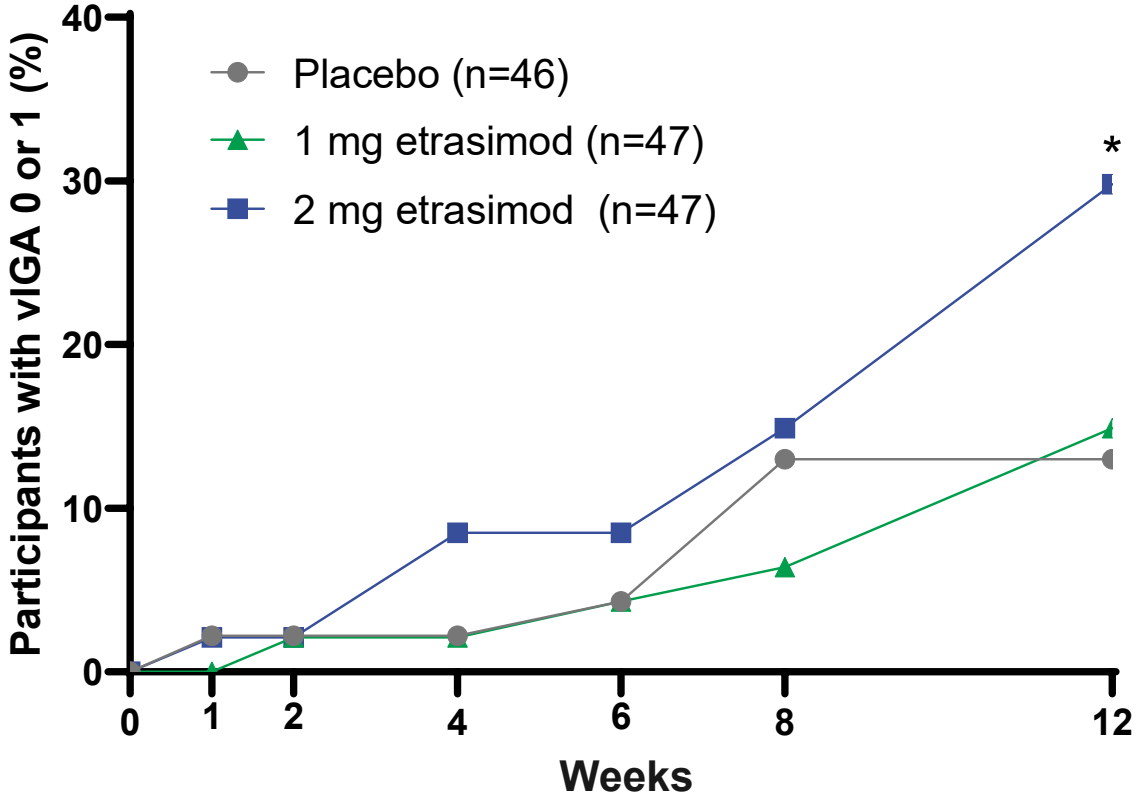


1. Etrasimod is an investigational drug and is not currently approved for use

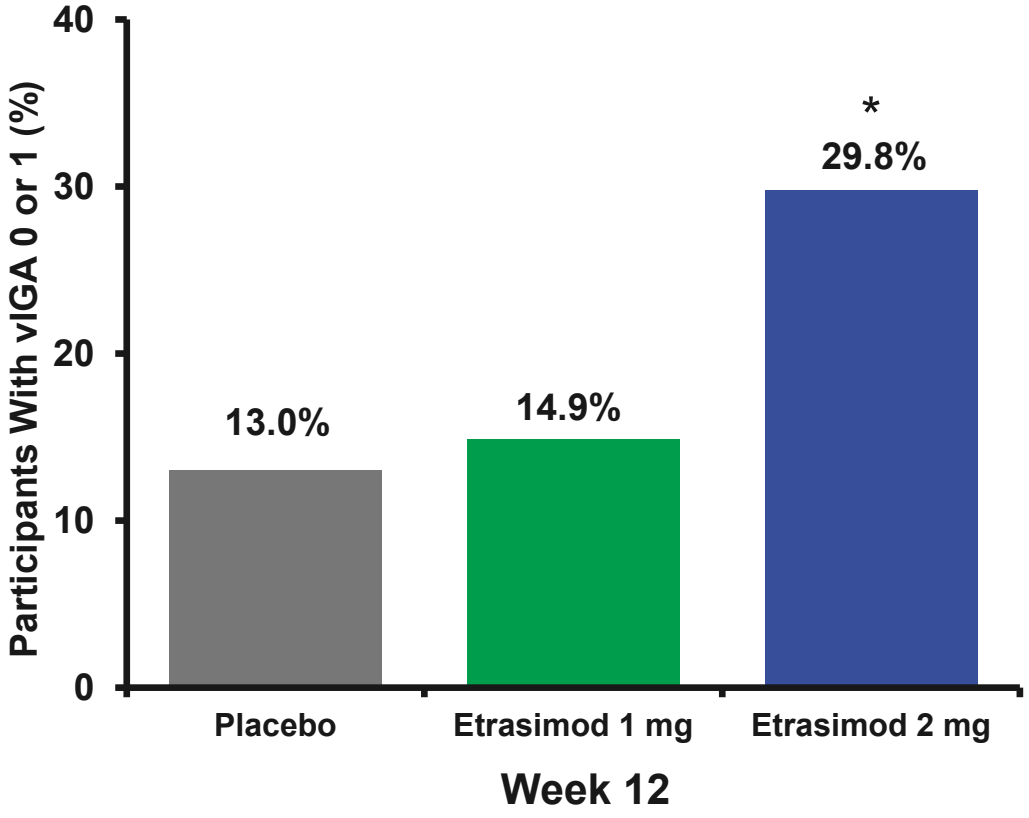
a: Guttman-Yassky E, et al. *JACI* 2011; 127, 6: 1420-1432.; b: Japtok et al. Allergo J Int 2014; 23: 54–9

Proportion of Participants Achieving vIGA Success Over Time and at Week 12

vIGA 0 or 1 and reduction from baseline of ≥2 points



FAS, CMH, NRI



FAS, CMH, NRI

* *P*<0.05 vs placebo.

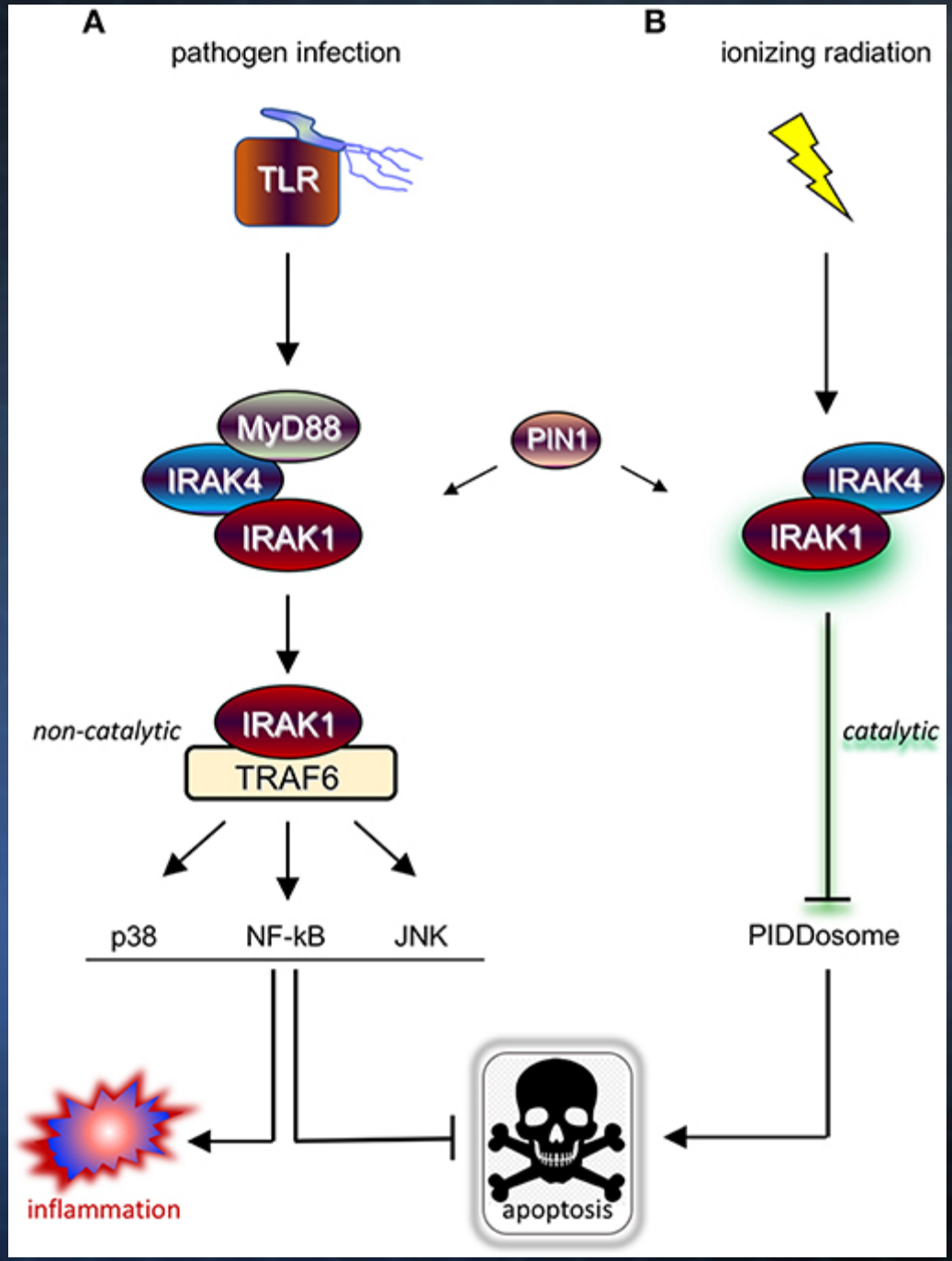
CMH, Cochran-Mantel-Haenszel; FAS, Full Analysis Set; NRI, non-responder imputation; vIGA, validated Investigator Global Assessment.

Review

Interleukin-1 receptor-associated kinase 4 (IRAK4) inhibitors: an updated patent review (2016-2018)

William T. McElroy

Pages 243-259 | Received 15 Dec 2018, Accepted 18 Mar 2019, Accepted author version posted online: 27 Mar 2019, Published online: 29 Mar 2019


A
pathogen infection
B
ionizing radiation
TLR
MyD88
IRAK4
IRAK1
PIN1
IRAK4
IRAK1
non-catalytic
IRAK1
TRAF6
catalytic
p38
NF-kB
JNK
PIDDosome
inflammation
apoptosis

- IRAK4 is the most proximal kinase in the Toll-like receptor (TLR)/IL-1R signaling cascade. Activation of the cascade triggers assembly of the myddosome complex and the downstream production of proinflammatory cytokines. Human and rodent genetics support the role of IRAK4 in the immune response.
- Over a dozen pharmaceutical companies have reported the discovery of IRAK4 inhibitors. Many of the reported compounds are potent enzyme inhibitors. IRAK4 inhibitors have been found to be active in a broad range of cellular and *in vivo* models.
- The work disclosed in patent applications over the last several years has led to multiple IRAK4 inhibitors being advanced to the clinic. Pfizer has enrolled patients in a phase II trial for RA.
- Emerging data suggests IRAK4 inhibition may offer a therapeutic benefit in the treatment of cancer. Aurigene and Curis have reported the start of a clinical trial evaluating IRAK4 inhibition for non-Hodgkin lymphoma.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