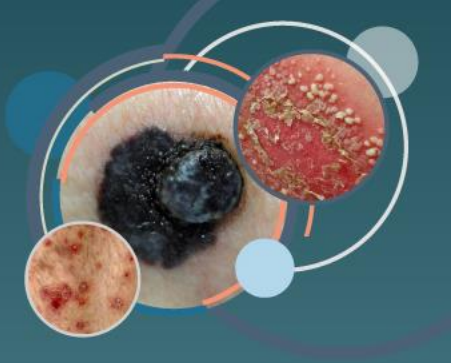
SCUOLA DERMATOLOGICA
SERGIO CHIMENTI
ROMA 17-18 Maggio 2024
Roma Eventi - Piazza di Spagna - Via Alibert 5A, 00187 Roma
1° INCONTRO 2024
YES or NO CONTEST
Dermatology Update



Marco Galluzzo

Ruolo dei farmaci anti-JAK nella dermatite atopica

1. I membri della «JAK family» sono 3?

1. **Sì**
2. **No**

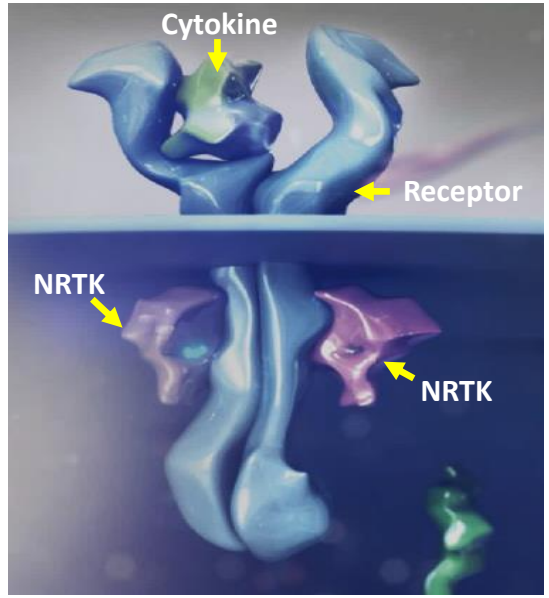
2. Le JANUS chinasi sono delle proteine transmembrana?

1. **Sì**
2. **No**

PER RISPONDERE collegati con il tuo smartphone a: meeter.it/yon

Nonreceptor Tyrosine Kinases (NRTKs)

- NRTKs: cytoplasmic enzymes associated with membrane receptors which regulate their activity[1]

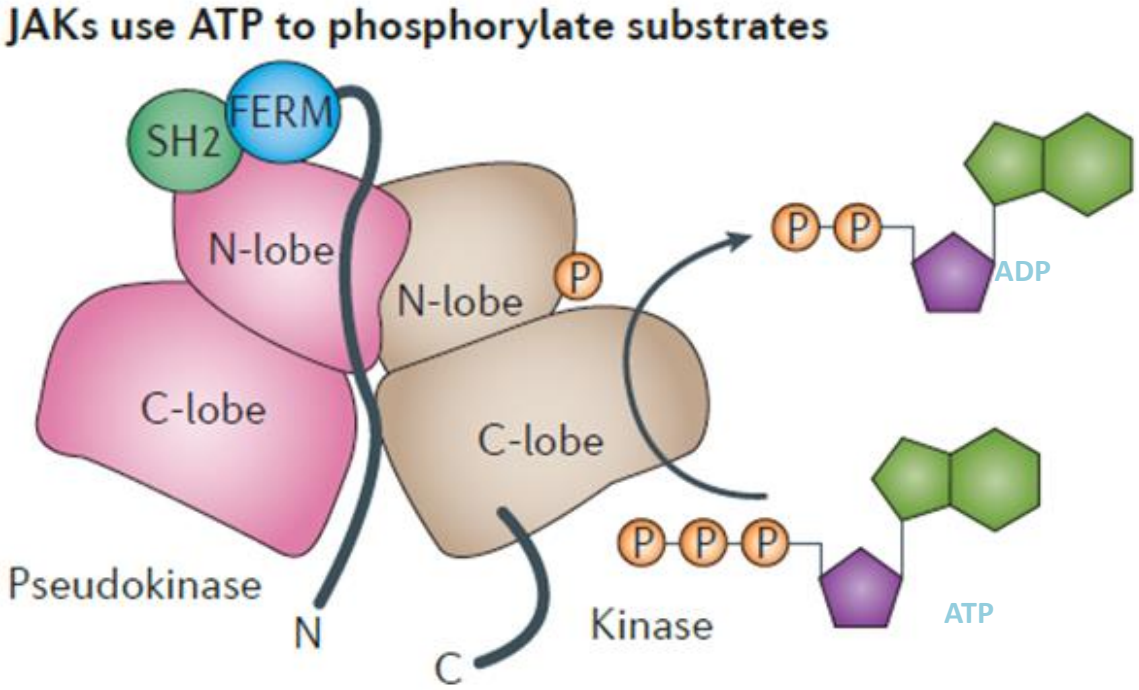


- Only 5 NRTKs have a **pseudokinase** and **kinase domain** present in the same protein:
  - GCN2, a serine threonine kinase
  - 4 members of the **JANUS Kinase family** (**JAK1, JAK2, JAK3, TYK2**)

- They are involved in cell growth, survival, development, and differentiation of a variety of cells but are critically important for immune cells and hematopoietic cells.

1. *Neet and Hunter. Genes Cells 1996;1(2):147-69. 2 . Hubbard and Till. Annu Rev Biochem 2000;69:373-98. 3.Pesu et al. Immunol Rev 2008;223:132-42. 4. Haan C et al. In: Jak-Stat Signaling: From Basics to Disease, 2012*

JANUS KINASE STRUCTURE



IANUS

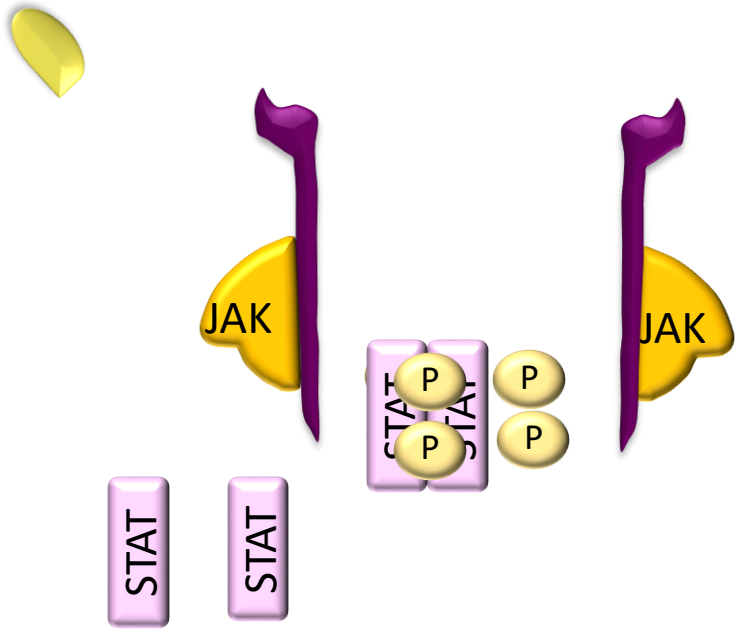
D.M.Schwartz, et al. Nature Reviews Rheumatology. Vol.12 .JANUARY 2016

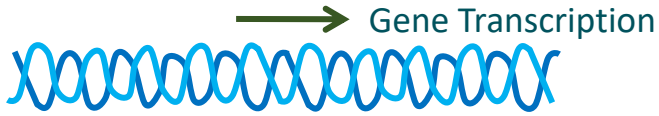
Binding of Cytokine Receptors by Cytokines Activates JAK Pathways Signaling

1 Cytokine binding to its cell surface receptor leads to receptor polymerization and activation of associated JAKs

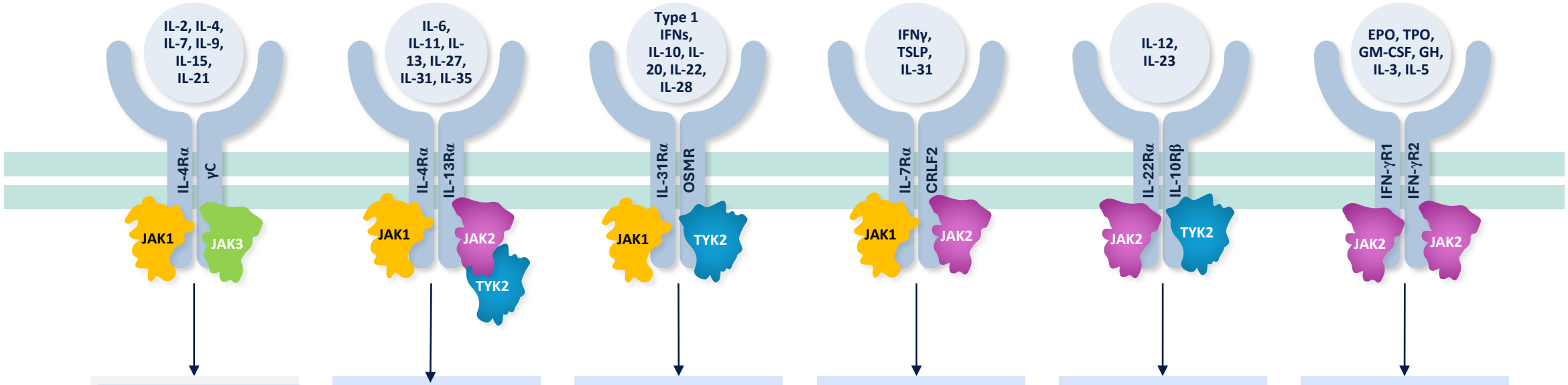
2 Activated JAKs phosphorylate the receptors that dock STATs

3 Activated JAKs phosphorylate STATs, which dimerize and move to the nucleus to activate new gene transcription





JAKs work in pairs and play a role in a diverse range of biologic functions, so selective inhibition is a central principle in therapeutic intervention



- Growth/maturation lymphoid cells
- Lymphocyte proliferation and homeostasis
- Differentiation/ homeostasis of T cells, NK cells
- B cell class switching
- Inflammation

- Naïve T cell differentiation
- T cell homeostasis
- Inflammation
- Granulopoiesis

- Anti-viral
- Inflammation
- Anti-tumor

- Anti-viral
- Inflammation
- Anti-mycobacterial

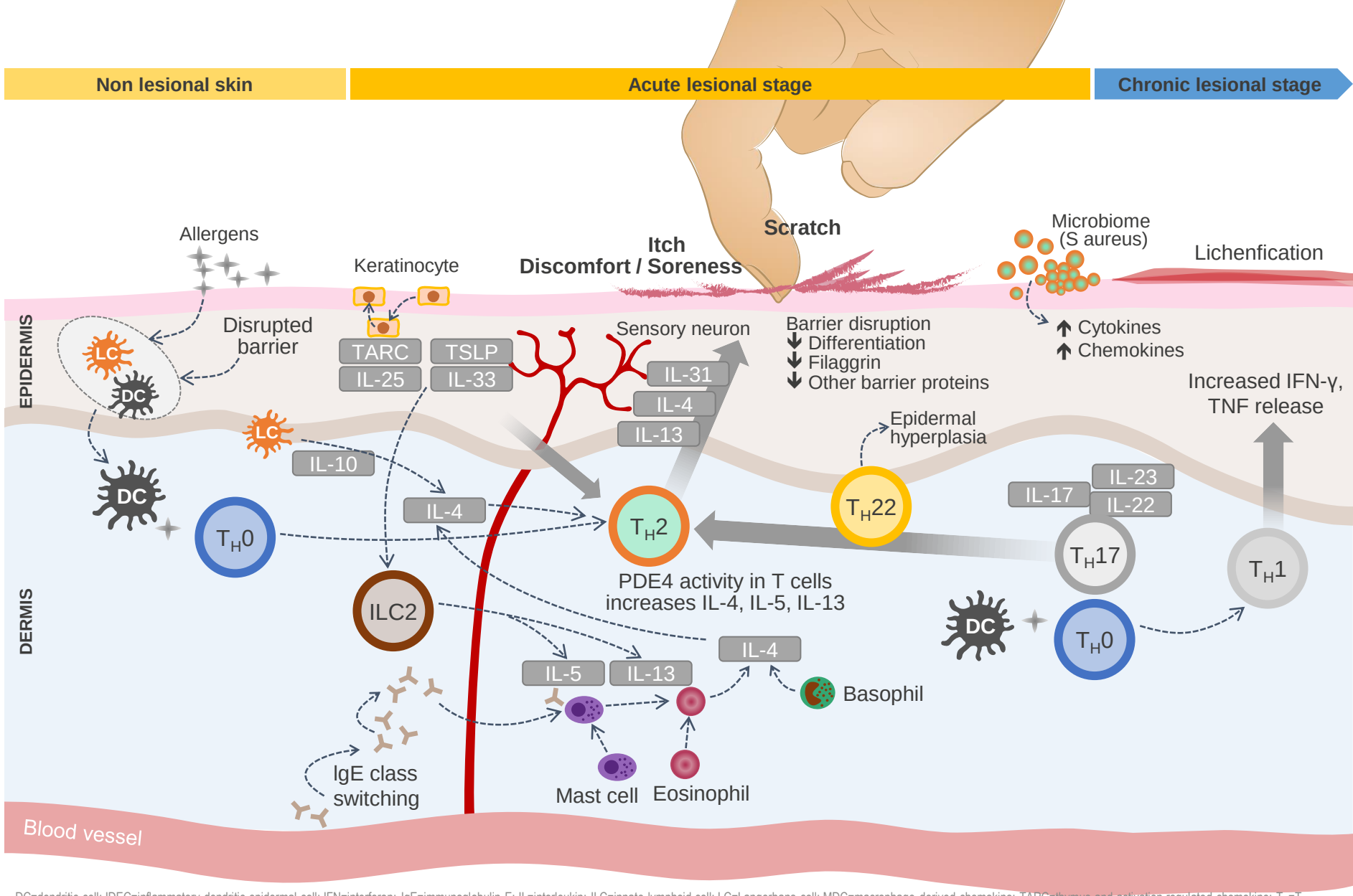
- Innate immunity
- Differentiation/ proliferation of Th17 cells
- Inflammation

- Erythro-/ myelopoiesis
- Megakaryocyte/ platelet production
- Growth
- Mammary development

γC, gamma chain; CRLF2, cytokine receptor-like factor 2; EPO, erythropoietin; GH, growth hormone; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFNγ, interferon gamma; IL, interleukin; JAK, Janus kinase; NK, natural killer; OSMR, oncostatin M receptor; Th, T helper cell; TPO, thrombopoietin; TSLP, thymic stromal lymphopoietin; TYK, tyrosine kinase

1. Clark JD, et al. J Med Chem 2014;57:5023–38; 2. Cornelissen C, et al. Eur J Cell Bio 2012;91:552–66; 3. Lou H, et al. J Immunol 2017;198:2543–55; 4. Klonowska J, et al. Int J Mol Sci 2018;19:3086; 5. Bieber T, et al. Nat Rev Drug Discov 2021;20:1–20; 6. Wolk K, et al. J Interferon Cytokine Res 2010;30:617–28

Atopic dermatitis is caused by a complex dysregulation of many immune pathways



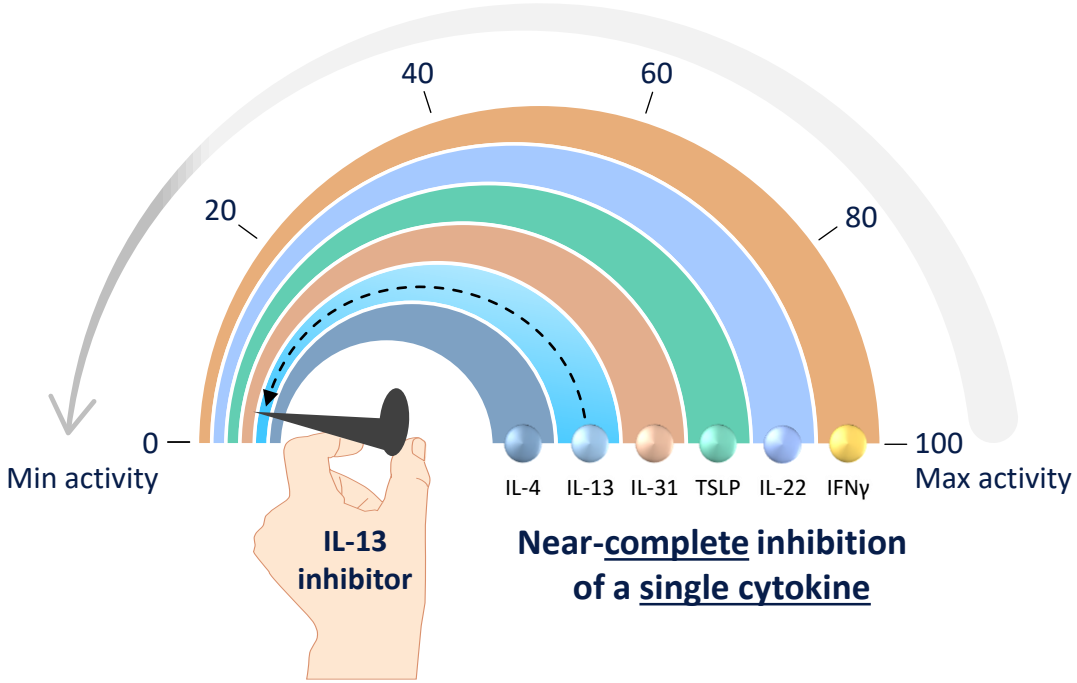
DC=dendritic cell; IDEC=inflammatory dendritic epidermal cell; IFN=interferon; IgE=immunoglobulin E; IL=interleukin; ILC=innate lymphoid cell; LC=Langerhans cell; MDC=macrophage-derived chemokine; TARC=thymus and activation-regulated chemokine; T_H=T-helper cell; TRM=T resident memory; TSLP=thymic stromal lymphopoietin.

Figure recreated from Bieber T, et al. *J Eur Acad Dermatol Venereol.* 2022;36(9):1432-1449.

Therapeutic paradigm for incomplete JAK inhibition in AD[a]

Biologics

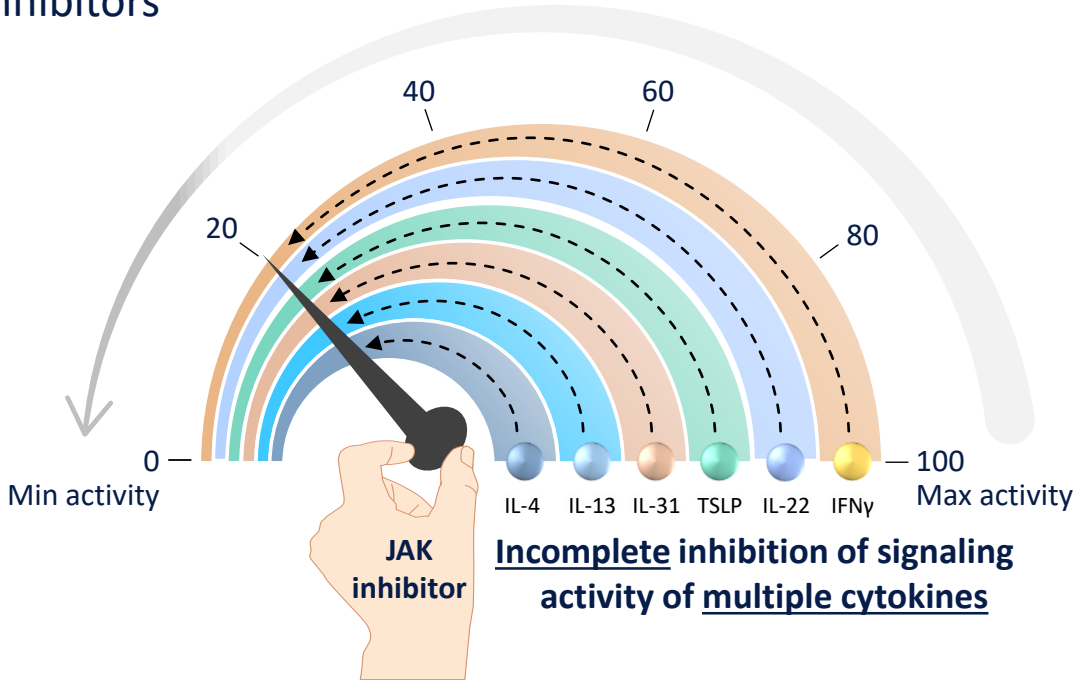
"Biologics generally act by binding to individual cytokines or receptors and nearly **completely inhibiting an individual cytokine** for prolonged periods of time"[1]



Near-complete inhibition of a single cytokine

JAK inhibitors

"JAK signaling is downstream of multiple cytokines ….and therefore, efficacy can be observed at doses that **partially and reversibly modulate the signaling of multiple pathways**"[1]

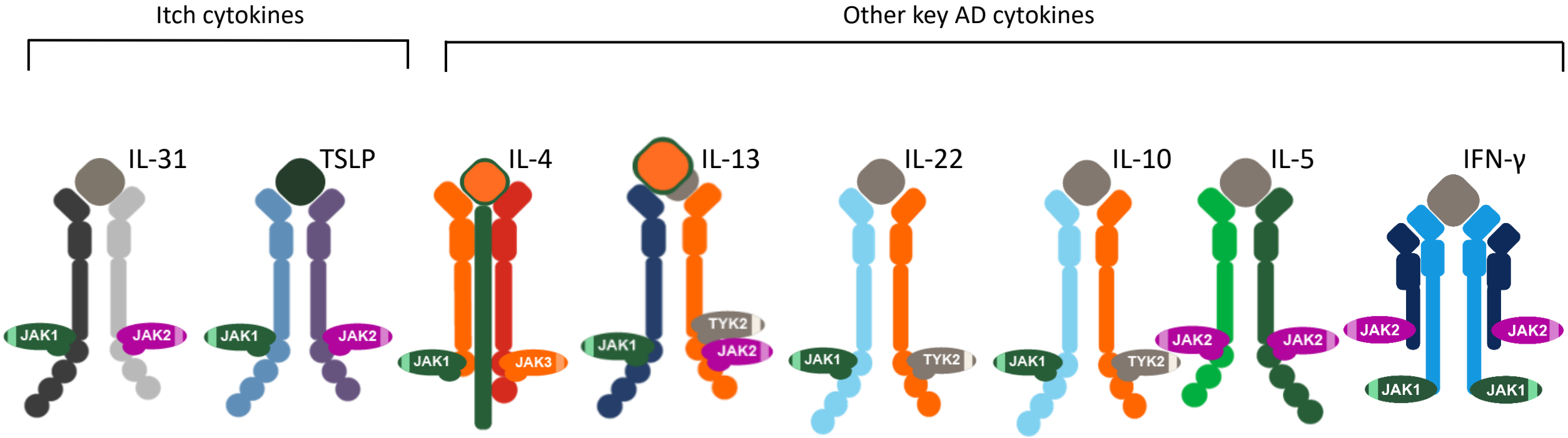


Incomplete inhibition of signaling activity of multiple cytokines

[a]Conceptual schematic, not based on data
AD, atopic dermatitis; IFNγ, interferon gamma; IL, interleukin; JAK, Janus kinase; TSLP, thymic stromal lymphopoietin

1. Clark JD, et al. J Med Chem 2014;57:5023–38

Cytokines involved in Atopic Dermatitis use the JAK/STAT pathway

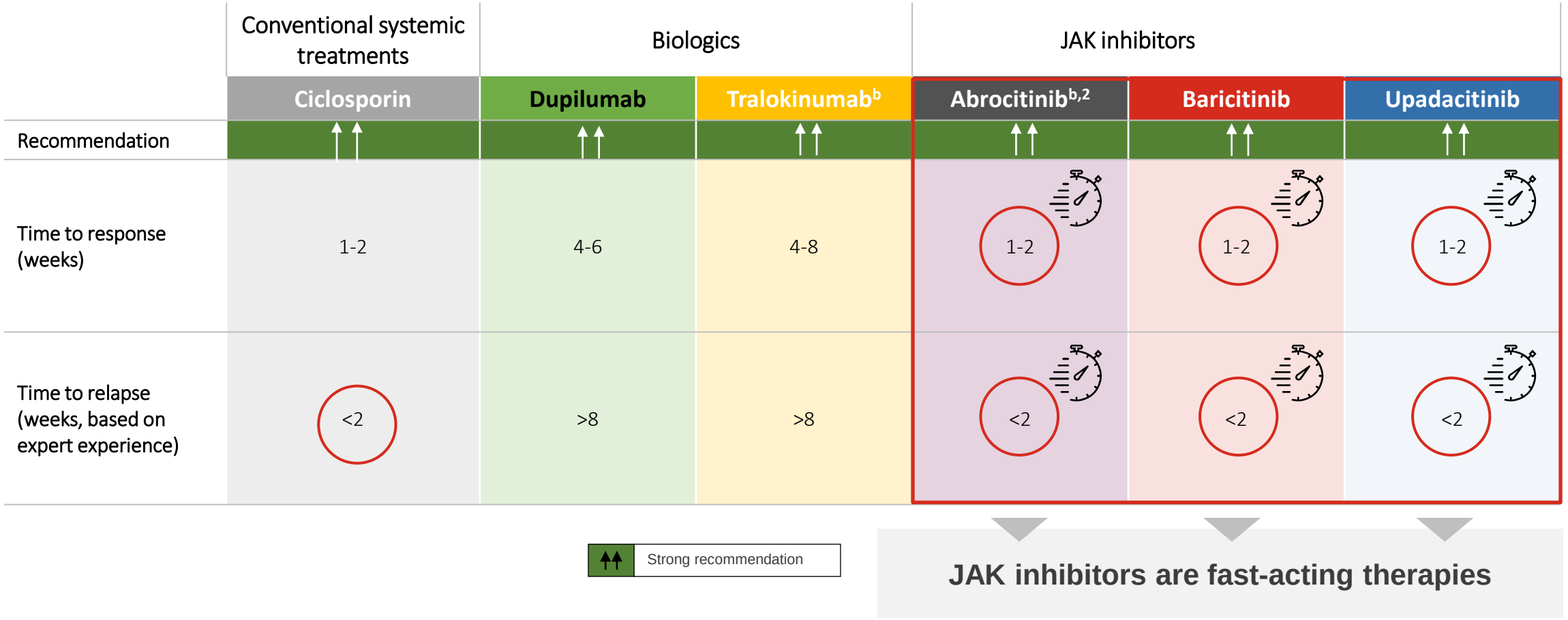


Ex vivo JAKi assays

AD=atopic dermatitis; IL=interleukin; JAK=Janus kinase; TSLP=thymic stromal lymphopoietin; TYK=tyrosine kinase.

1. Chen L, et al. Clin Exp Immunol. 2004;138:375-87; 2. Guttman-Yassky E et al. Curr Opin Immunol. 2017;48:68-73; 3. O'Shea JJ and Plenge R. Immunity. 2012;36(4):542-50.

Systemic drugs with strong recommendation for patients with atopic dermatitis who are candidates for systemic therapy[a,1]



[a]Based on expert's opinion from Wollenberg A, et al. J Eur Acad Dermatol Venereol. 2022 Sep;36(9):1409–1431. No head-to-head studies have been conducted; [b]Abrocitinib and Tralokinumab are not approved in AD in Brazil
AD=atopic dermatitis; JAK=Janus kinase 1. Wollenberg A, et al. *J Eur Acad Dermatol Venereol*. 2022;36(9):1409–1431. 2. EDF. EuroGuideDerm. Dec 2022. https://guidelines.edf.one//uploads/attachments/clbm6smyq07z30d3qmqdl2aiy-5-overview-tables-dec-2022.pdf

3. JAK inibitori : Uguali ma diversi?

1. **Sì**
2. **No**

Drug-Drug-Interaction Profiles Differ between JAK Inhibitors CYP450 Enzymes

	Baricitinib[1]	Upadacitinib[2]	Abrocitinib[3]
Metabolization via CYP450 enzymes	<10% by CYP3A4	Mainly via CYP3A4	~53% by CYP2C19 ~30% by CYP2C9 ~11% by CYP3A4 ~6% by CYP2B6
Relevance for CYP450 drug interactions	No	**Yes** CYP3A4 inducers or inhibitors can affect upadacitinib exposure	Yes CYP2C19 and CYP2C9 inhibitors or inducers can affect abrocitinib exposure
Examples for CYP450 inducers/inhibitors		CYP3A4 inhibitors: • Clarithromycin • Ketokonazole • Itraconazole • Posaconazole • Voriconazole • Grapefruit CYP3A4 inducers: • Rifampicin • Phenytoin	CYP2C19/CYP2C9 inhibitors: • Fluvoxamine • Fluoxetine • Fluconazole CYP2C19/CYP2C9 inducers: • Rifampicin • Apalutamide • Enzalutamide • Efavirenz • Phenytoin
Examples of diseases, in which listed **CYP450 inducers/inhibitors might be used**		• Bacterial infections[4] • Fungal infections[5-8] • Tuberculosis[9] • Epilepsy[10]	• Depression[11,12] • Obsessive compulsive disorder[11,12] • Fungal infections[13] • Tuberculosis[9] • Prostate cancer[14, 15] • HIV[16] • Epilepsy[10]

1. Baricitinib. Summary of product characteristics. Eli Lilly. 2. upadacitinib. Summary of product characteristics. Abbvie. 3. abrocitinib. Summary of product characteristics. Pfizer. .4-12 SmPC Clarithromycin, Ketoconazole, Itraconazole, Posaconazole, Rifampicin, Phenytoin, Fluvoxamine, Fluconazole, Apalutamide, Enzalutamide, Efavirenz.

Tolerability across oral JAK inhibitors in AD
PBO-controlled period of JAK inhibitor atopic dermatitis clinical trial programs

BARI integrated safety (16 weeks)[1,2]

Data presented as n (adjusted %)	PBO (N=743)	BARI 2-mg (N=576)	BARI 4-mg (N=489)
Nausea	8 (0.8)	14 (1.8)	4 (0.8)
Vomiting	8 (0.9)	5 (0.7)	3 (0.6)
Headache	28 (3.3)	37 (5.9)	35 (6.3)
Acne	7 (0.7)	8 (1.2)	9 (1.4)

ABR integrated safety (12-16 weeks)[3]

Data presented as n (%)	PBO (N=342)	ABR 100-mg (N=608)	ABR 200-mg (N=590)
Nausea	7 (2.0)	37 (6.1)	86 (14.6)
Vomiting	3 (0.9)	9 (1.5)	19 (3.2)
Headache	12 (3.5)	36 (5.9)	46 (7.8)
Acne	0	10 (1.6)	28 (4.7)

UPA integrated safety (16 weeks)[4,5]

Data presented as n (%)	PBO (N=902)	UPA 15-mg (N=899)	UPA 30-mg (N=906)
Nausea	5 (0.6)	24 (2.7)	24 (2.6)
Vomiting	NA	NA	NA
Headache	39 (4.3)	50 (5.6)	57 (6.3)
Acne	20 (2.2)	86 (9.6)	137 (15.1)

Data shown side by side for illustrative purposes only, head-to-head studies in atopic dermatitis are not available

ABR, abrocitinib; BARI, baricitinib; JAK, Janus kinase; NA=not available; PBO, placebo; UPA, upadacitinib

1. Bieber T, et al. J Eur Acad Dermatol Venereol. 2020;35:476-85; 2. Kircik L, et al., poster presented at EADV 2021 3. Simpson EL, et al. Am J Clin Dermatol. 2021 Sep;22(5):693-707; 4. Guttman-Yassky E et al. Presented at AAD VMX 2021. Poster 27082: 5. https://www.ema.europa.eu/en/documents/variation-report/rinvoq-h-c-004760-x-0006-g-epar-assessment-report-variation_en.pdf

4. Una dose di 30 mg di upadacitinib una volta al giorno può essere appropriata per i pazienti con un alto carico di malattia che non sono a rischio aumentato di TEV, MACE e tumore maligno

1. **Sì**
2. **No**

Upadacitinib: Inibitore JAK1

Indicazioni terapeutiche

Dermatite atopica, Artrite reumatoide, Artrite psoriasica, Spondiloartrite assiale non radiografica, Spondilite anchilosante (SA, spondiloartrite assiale radiografica), Colite ulcerosa, Malattia di Crohn

Upadacitinib è indicatore nel trattamento della dermatite atopica da moderata a severa negli adulti e negli adolescenti di età pari o superiore a 12 anni eleggibili alla terapia sistemica .

Posologia

Dermatite atopica

Adulti

- **La dose raccomandata di upadacitinib è di 15 mg o 30 mg una volta al giorno in base alle caratteristiche cliniche del singolo paziente.**
  - Una dose di 15 mg è raccomandata per i pazienti a rischio aumentato di TEV, MACE e tumore maligno
  - Una dose di 30 mg una volta al giorno può essere appropriata per i pazienti con un alto carico di malattia che non sono a rischio aumentato di TEV, MACE e tumore maligno o per i pazienti con una risposta inadeguata alla dose di 15 mg una volta al giorno.
  - **Per la terapia di mantenimento deve essere considerata la dose efficace più bassa.**
  - **Per i pazienti di età ≥ 65 anni, la dose raccomandata è di 15 mg una volta al giorno.**

Adolescenti (da 12 a 17 anni di età)

Per gli adolescenti di peso pari o superiore a 30 kg, la dose raccomandata di upadacitinib è di 15 mg una volta al giorno

Terapie topici concomitanti:

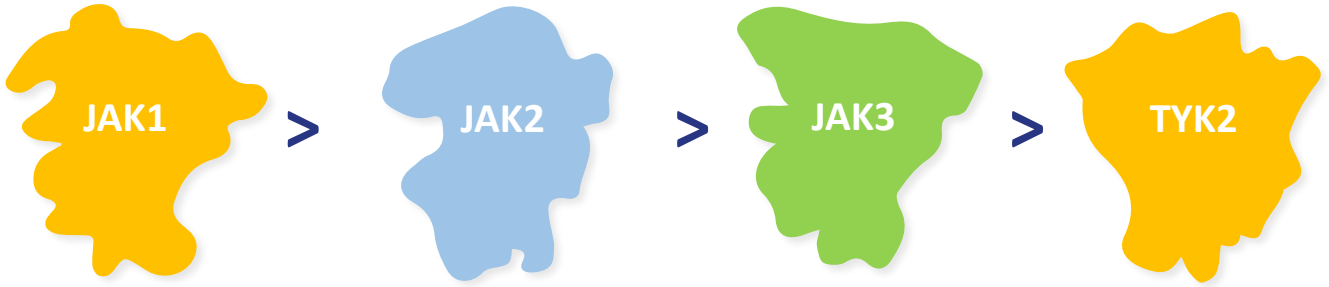
Upadacitinib può essere usato con o senza corticosteroidi topici. Gli argomenti inibitori della calcineurina possono essere usati nelle aree sensibili come il viso, il collo e le aree intertriginose e genitali.

È necessario in considerazione l'interruzione del trattamento con upadacitinib in qualsiasi paziente che non mostri nessuna evidenza di beneficio terapeutico dopo 12 settimane di trattamento.

UPADACITINB: RCP 20.12.2023

Upadacitinib demonstrates the highest selectivity for JAK1 over other JAK isoforms in engineered cellular assays[1]

Upadacitinib is a selective and reversible JAK inhibitor. Upadacitinib preferentially inhibits signaling by JAK1 or JAK1/3, with functional selectivity over cytokine receptors that signal via pairs of JAK2[2]



	JAK1	JAK2	JAK3	TYK2
Increased selectivity of upadacitinib for JAK1 versus other JAK isoforms[a]	NA	42 × more selective for JAK1 vs JAK2	133 × more selective for JAK1 vs JAK3	194 × more selective for JAK1 vs TYK2

- [a]Relative JAK inhibitory activity assessed in engineered cellular assays
JAK, Janus kinase; NA, not applicable; TYK, tyrosine kinase

1. Parmentier JM, et al. BMC Rheumatol 2018;2:23–34
2. RINVOQ SmPC.

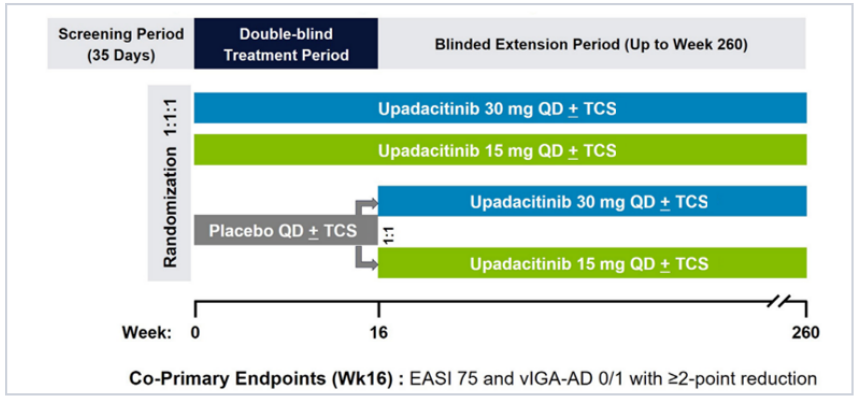
Upadacitinib long term efficacy up to 140 weeks

Study Design

Study Design

- Patients were randomized 1:1:1 to receive oral upadacitinib (UPA) 15 mg, UPA 30 mg, or placebo once daily alone (Measure Up 1 and 2) or with concomitant topical corticosteroids (AD Up).
- At Week 16, patients receiving UPA 15 mg or 30 mg during the double-blinded period continued their assigned treatment, whereas patients receiving placebo were re-randomized 1:1 to receive either UPA 15 mg or 30 mg for up to 260 weeks. **(Figure 1)**
- Efficacy analyses were conducted in the intention-to-treat (ITT) population defined as all adolescent and adult patients randomized at baseline, including subjects from the main studies and the adolescent substudies. Safety analyses included all patients who received at least 1 dose of study drug. The data cutoff was defined as the date when all subjects reached week 140.
- Observed Case (OC) approach was used, which included all observed data up to the study drug discontinuation and did not impute missing data.

Figure 1. Measure Up 1, Measure Up 2, and AD Up Study Design



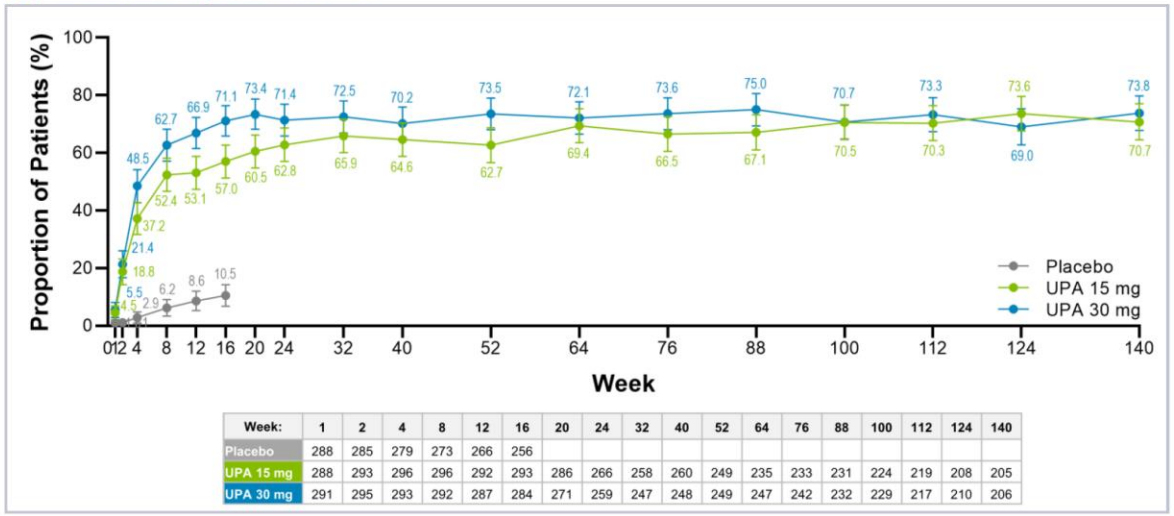
Silverberg JI - Presented at European Academy of Dermatology and Venereology (EADV) Congress 2023, Berlin, Germany

QD, once-daily; TCS, topical corticosteroids; EASI, Eczema Area and Severity Index; vIGA-AD, Validated Investigator Global Assessment Scale for Atopic Dermatitis

Results: EASI 90 across 140 weeks

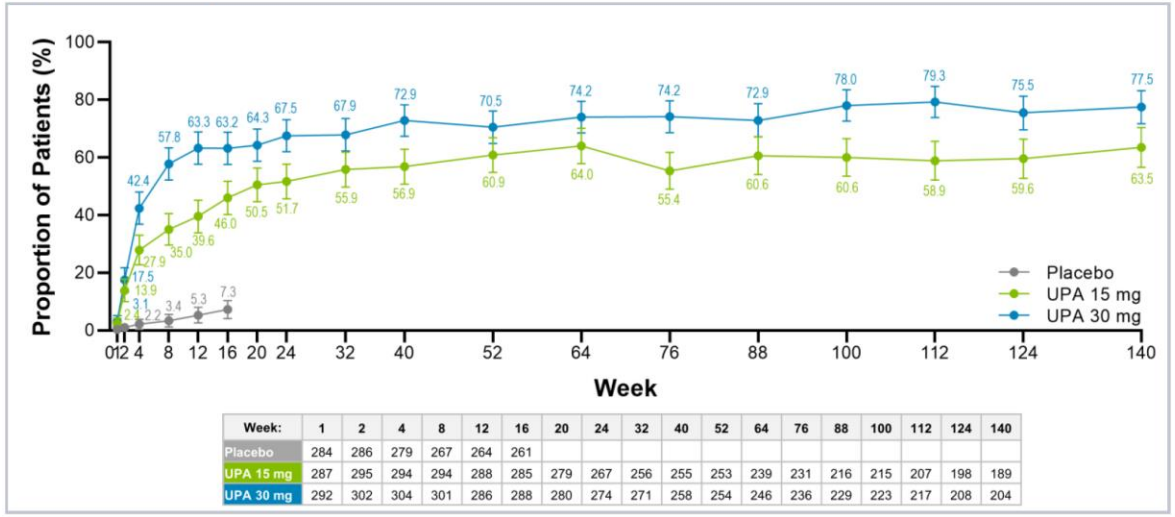
Figure 3. Proportion of patients achieving EASI 90 across 140 weeks in (a) Measure Up 1, (b) Measure Up 2, and (c) AD Up

(a) Measure Up 1: EASI 90



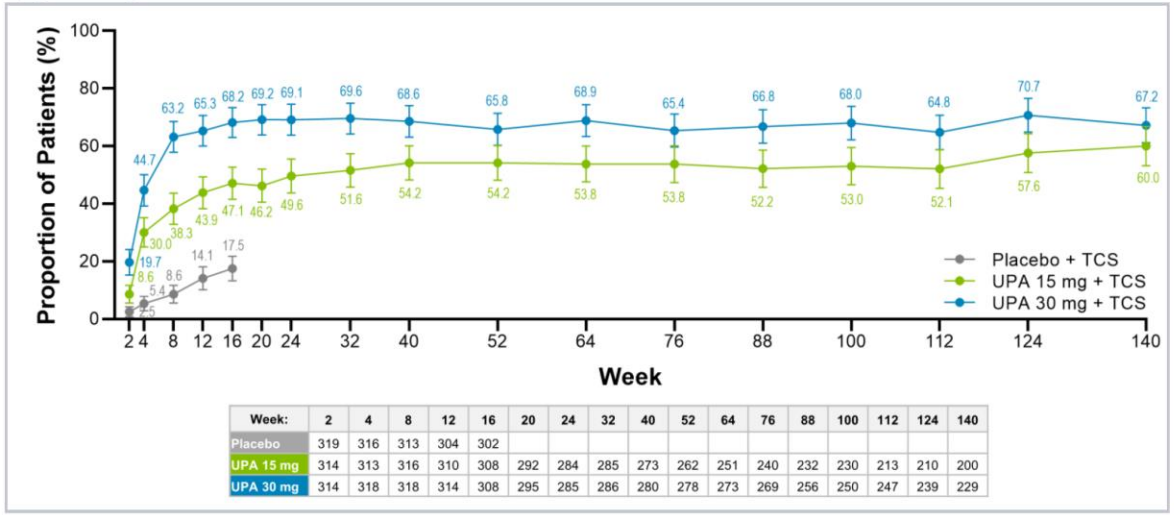
Week:	1	2	4	8	12	16	20	24	32	40	52	64	76	88	100	112	124	140
Placebo	288	285	279	273	266	256												
UPA 15 mg	288	293	296	296	292	293	286	266	258	260	249	235	233	231	224	219	208	205
UPA 30 mg	291	295	293	292	287	284	271	259	247	248	249	247	242	232	229	217	210	206

(b) Measure Up 2: EASI 90



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	274	271	258	254	246	236	229	223	217	208	204

(c) AD Up: EASI 90



Week:	2	4	8	12	16	20	24	32	40	52	64	76	88	100	112	124	140
Placebo	319	316	313	304	302												
UPA 15 mg	314	313	316	310	308	292	284	285	273	262	251	240	232	230	213	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*)

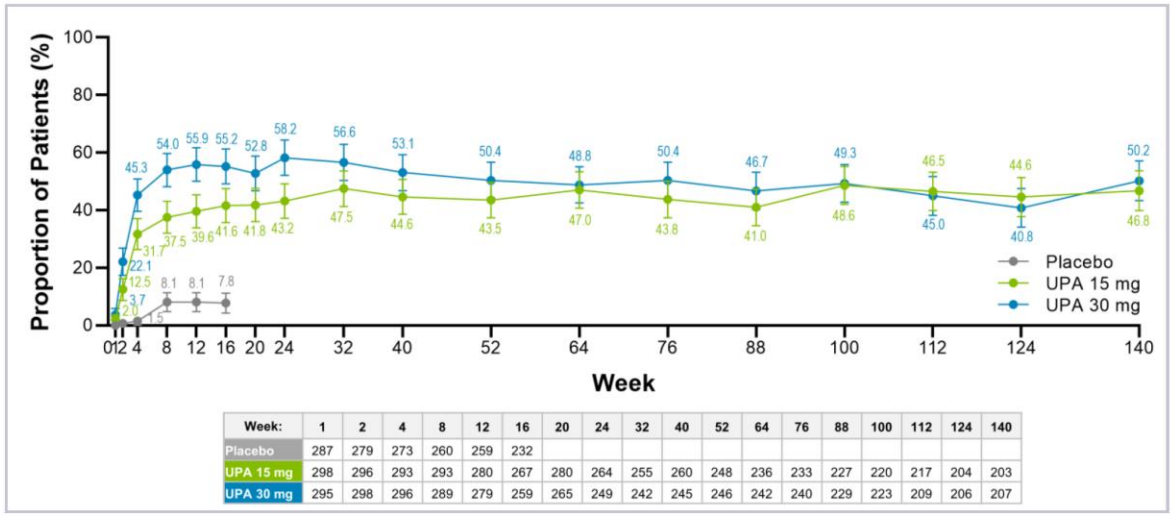
Silverberg JI, et al. Oral presentation. EADV 11−14 October 2023, Berlin, Germany

UPA, upadacitinib; TCS, topical corticosteroids; EASI, Eczema Area and Severity Index

Results: WP-NRS 0/1 across 140 weeks

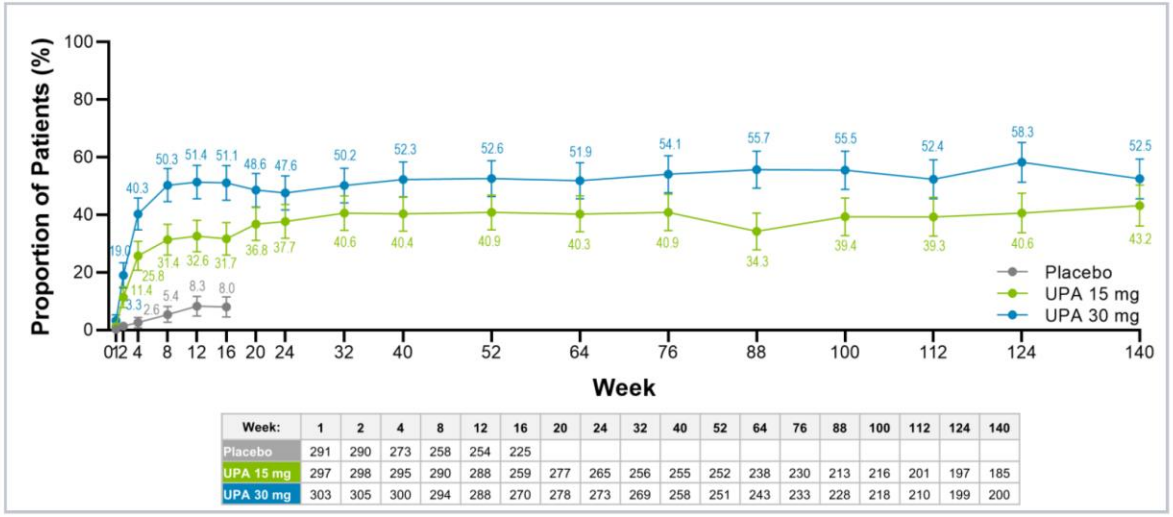
Figure 6. Proportion of patients achieving WP-NRS 0/1 across 140 weeks in (a) Measure Up 1, (b) Measure Up 2, and (c) AD Up

(a) Measure Up 1: WP-NRS 0/1



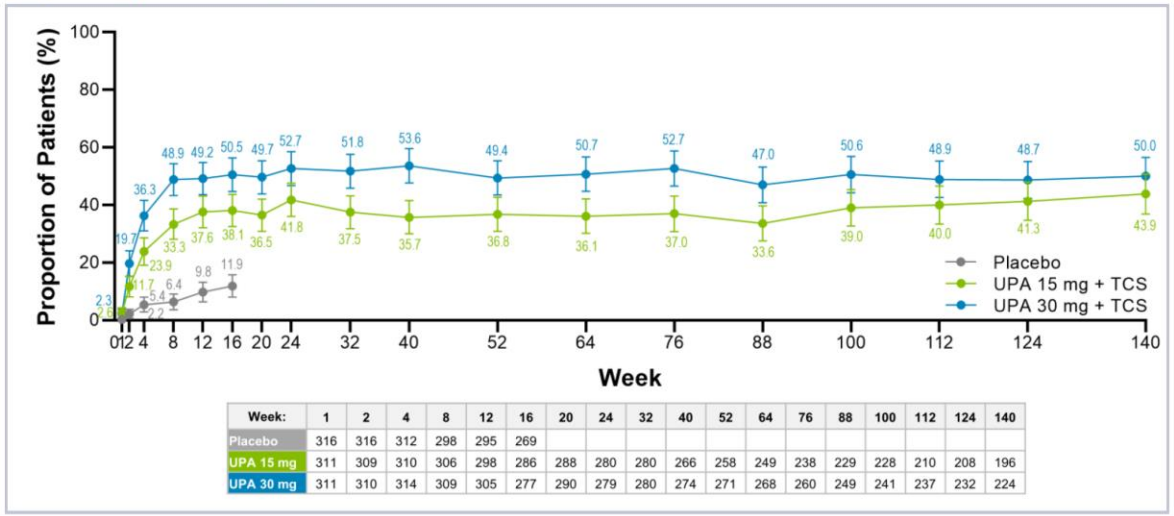
Week:	1	2	4	8	12	16	20	24	32	40	52	64	76	88	100	112	124	140
Placebo	287	279	273	260	259	232												
UPA 15 mg	298	296	293	293	280	267	280	264	255	260	248	236	233	227	220	217	204	203
UPA 30 mg	295	298	296	289	279	259	265	249	242	245	246	242	240	229	223	209	206	207

(b) Measure Up 2: WP-NRS 0/1



Week:	1	2	4	8	12	16	20	24	32	40	52	64	76	88	100	112	124	140
Placebo	291	290	273	258	254	225												
UPA 15 mg	297	298	295	290	288	259	277	265	256	255	252	238	230	213	216	201	197	185
UPA 30 mg	303	305	300	294	288	270	278	273	269	258	251	243	233	228	218	210	199	200

(c) AD Up: WP-NRS 0/1



Week:	1	2	4	8	12	16	20	24	32	40	52	64	76	88	100	112	124	140
Placebo	316	316	312	298	295	269												
UPA 15 mg	311	309	310	306	298	286	288	280	280	266	258	249	238	229	228	210	208	196
UPA 30 mg	311	310	314	309	305	277	290	279	280	274	271	268	260	249	241	237	232	224

- 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*)

Silverberg JI, et al. Oral presentation. EADV 11−14 October 2023, Berlin, Germany

UPA, upadacitinib; TCS, topical corticosteroids; WP-NRS, Worst Pruritus Numerical Rating Scale

Results: Safety Tables

Table 2. Most Frequently Reported Treatment-Emergent Adverse Events (≥5 events/100 patient years in any treatment group)

Events per 100 Patient-Years (E/100 PY)	Measure Up 1		Measure Up 2		AD Up	
	UPA 15 mg (N=432) PY=1238.2	UPA 30 mg (N=432) PY=1270.6	UPA 15 mg (N=431) PY=1178.6	UPA 30 mg (N=442) PY=1258.5	UPA 15 mg + TCS (N=474) PY=1295.8	UPA 30 mg + TCS (N=472) PY=1429.9
COVID-19	10.1	11.0	9.9	11.5	11.9	11.8
Upper respiratory tract infection	9.9	10.2	7.8	4.8	8.5	8.5
Acne	6.1	12.0	8.2	9.5	7.8	10.6
Nasopharyngitis	7.4	9.0	4.5	5.7	17.9	12.5
Dermatitis atopic	8.3	5.4	8.0	5.2	9.4	6.4
Blood CPK increased	5.1	7.6	7.1	8.1	6.0	8.0
Oral herpes	2.3	5.7	2.8	5.2	6.1	7.0
Headache	4.0	3.4	6.9	5.4	4.6	4.5
Herpes simplex	3.0	3.2	3.7	2.1	5.5	3.8
Herpes zoster	2.6	4.3	2.5	3.7	2.5	5.9

Silverberg JI, et al. Oral presentation. EADV 11−14 October 2023, Berlin, Germany

Upadacitinib safety data up to 5 years of exposure in AD: baseline patient characteristics

Table 1. Patient Baseline Safety Characteristics: AD Phase 3 Long-Term Safety Set (Up to 5 years; Measure UP 1/Measure UP 2/AD UP[1])

	AD: Phase 3 Long-Term (Up to 5 Years) MEASURE UP 1/MEASURE UP 2/AD UP[1]	
	UPA 15 mg (N=1337)	UPA 30 mg (N=1346)
Presence of CV Risk Factor†; n (%)	721 (53.9)	684 (50.8)
Tobacco/nicotine use; n (%)	418 (31.3)	419 (31.1)
History of hypertension; n (%)	149 (11.1)	126 (9.4)
History of CV event; n (%)	71 (5.3)	71 (5.3)
Diabetes mellitus; n (%)	26 (1.9)	27 (2.0)
Elevated LDL-C (≥130 mg/dL); n (%)	197 (15.0)	185 (14.0)
Low HDL-C (< 40 mg/dL); n (%)	177 (13.3)	168 (12.6)
Age ≥ 50 with ≥ 1 CV risk factor†; n (%)	179 (13.4)	208 (15.5)
Number of CV Risk Factors†; n (%)		
0	616 (46.1)	662 (49.2)
1	484 (36.2)	448 (33.3)
2	173 (12.9)	175 (13.0)
3	50 (3.7)	49 (3.6)
4+	14 (1.0)	12 (0.9)
BMI ≥ 30 kg/m^2; mean (%)	252 (18.9)	258 (19.3)
History of VTE; n (%)	4 (0.3)	6 (0.4)
Oral contraceptive use; n (%)[2]	105 (17.7) n= 593	129 (22.1) n=585

†CV risk factors included CV event, hypertension, diabetes mellitus, tobacco/nicotine use (current and former), elevated LDL-C, lowered HDL-C; [1]AbbVie Data on file ABVRRTI 77022; [2]Percentage of oral contraceptive use is % of all females.
AD, atopic dermatitis; UPA, upadacitinib; CV, cardiovascular; BMI, body mass index; VTE, venous thromboembolic events (VTE was defined as deep vein thrombosis and pulmonary embolism).

Bunick C, et al. Poster 115-1000533 presented at Revolutionizing Atopic Dermatitis (RAD) Virtual Conference; December 10, 2023

Upadacitinib safety data up to 5 years of exposure in AD: treatment-emergent AESIs

Table 3. 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

Overall, the safety profile observed in patients with AD treated with UPA was similar to the safety profile in patients with RA.

Adverse reaction rates observed in clinical trials may not fully characterize the risks of UPA. Certain adverse events may require longer-term patient exposure to ascertain risk.

MACE was defined as CV death, non-fatal MI, and non-fatal stroke. VTE was defined as deep vein thrombosis and pulmonary embolism. AE, adverse events; CV, cardiovascular events; UPA, upadacitinib; PY, patient-years. [1] Excluding tuberculosis/herpes zoster, [2] Rates shown are n/100 PY=number of subjects with at least one event per 100 PY, [3] Adjudicated.

Bunick C, et al. Poster 115-1000533 presented at Revolutionizing Atopic Dermatitis (RAD) Virtual Conference; December 10, 2023

Upadacitinib safety data up to 5 years of exposure in AD: incidence rates/background rates

Figure 4. 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)

Bunick C, et al. Poster 115-1000533 presented at Revolutionizing Atopic Dermatitis (RAD) Virtual Conference; December 10, 2023

	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)

Figure 5. 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

	AL BASALE	ENTRO 12 SETTIMANE DA INIZIO TERAPIA	IN SEGUITO, VALUTARE IN BASE ALLA GESTIONE ROUTINARIA DEL PAZIENTE E ALLE LINEE GUIDA	NON INIZIARE O INTERROMPERE LA TERAPIA
EMOGLOBINA	✓	✓	✓	<8 g/dL
NEUTROFILI	✓	✓	✓	<1 x 10^9/L
LINFOCITI	✓	✓	✓	<0.5 x 10^9/L
TRANSAMINASI (AST/ALT)	✓		✓	Aumento di AST/ALT indicativo di danno epatico da farmaco
LIPIDI		✓ (a 12 settimane)	✓	
TUBERCOLOSI	✓		✓	Segni e sintomi di TB attiva
EPATITI VIRALI (HBV, HCV)	✓		✓	Segni e sintomi di epatite virale
ESCLUDERE INFEZIONI GRAVI/ OPPORTUNISTICHE	✓		✓	Segni e sintomi di infezione grave/opportunisitica
ESAME PERIODICO DELLA CUTE (in particolare nei pz con aumentato rischio di neoplasia cutanea)	✓		✓	
RISCHIO TEV	✓		✓	Segni e sintomi di TEV

5. La dose iniziale raccomandata di baricitinib per il trattamento della dermatite atopica moderata-grave dell'adulto è 2 mg una volta al giorno?

1. **Sì**
2. **No**

6. Baricitinib è l'unico anti-JAK approvato da EMA per il trattamento della dermatite atopica a partire dai 2 anni di età

1. **Sì**
2. **No**

7. I best responders al trattamento con baricitinib alla settimana 16 sono quei pazienti con un NRS prurito <7 ed un BSA>40% al baseline

1. **Sì**
2. **No**

Baricitinib posology

4 mg

once daily

Recommended starting dose

2 mg

once daily

Recommended for:

- patients aged ≥ 65 years*
- patients at higher risk of major adverse cardiovascular events (MACE) and malignancy*
- patients at higher risk of venous thromboembolism (VTE)
- patients with a history of chronic or recurrent infections

is also recommended for:

- patients with creatinine clearance 30–60 mL/min
- patients taking organic anion transporter 3 inhibitors with a strong potential, such as probenecid

Dose adaptability:

2 mg → 4 mg

A dose of **4 mg once daily** may be considered for patients who don't achieve adequate control of disease activity with 2 mg once daily dose

4 mg → 2 mg

A dose of **2 mg once daily** should be considered for patients who have achieved sustained control of disease activity with 4 mg once daily and are eligible for dose tapering

Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit after **8 weeks of treatment**.

* Baricitinib should only be used in these patients if no suitable treatment alternatives are available Baricitinib SMPC.

Baricitinib: Selective inhibition of JAK1 and JAK2

- Baricitinib is a selective and reversible inhibitor of JAK1 and JAK2

Isolated enzyme assays				
	JAK1	JAK2	JAK3	TYK2
IC_{50} values (nM)	5.9	5.7	>400	53

- Baricitinib modulates cell signaling pathways through partial inhibition of JAK1 and JAK2 enzymatic activity, thereby reducing the phosphorylation and activation of STAT proteins

IC_{50}=half maximal inhibitory concentration; JAK=janus kinase; STAT=signal transducer and activator of transcription; TYK=tyrosine kinase

Baricitinib [SmPC]. Utrecht, The Netherlands: Eli Lilly Nederland B.V., 2017

Laboratory monitoring before and during baricitinib therapy

	Before treatment initiation	During routine patient management	Monitoring at Week 12
Tuberculosis screening	✓[a]		
Hepatitis screening in accordance with clinical guidelines	✓		
Full blood count (ALC, ANC, Hb)	✓	✓	
Hepatic transaminases (ALT, AST)	✓	✓	
Lipids			✓[b]

Avoid initiation or interrupt treatment with baricitinib if:

- ALC <0.5 x 10^9 cells/L
- ANC <1 x 10^9 cells/L
- Hb levels <8 g/dL
- Liver enzyme elevations and suspected drug-induced liver injury
- Active infection

Treatment can be initiated or restarted after levels return above specified values, drug-induced liver injury diagnosis is excluded, or infection is controlled.

[a]Baricitinib should not be given to patients with active tuberculosis, anti-tuberculosis therapy should be prior to initiation of treatment in patients with previously untreated latent tuberculosis; [b]12 weeks after initiation of treatment and thereafter according to international clinical guidelines for hyperlipidemia.

ALC=absolute lymphocyte count; ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate transaminase; Hb=hemoglobin; MACE=major adverse cardiovascular event; VTE=venous thromboembolism.

Baricitinib [SmPC]. Utrecht, The Netherlands: Eli Lilly Nederland B.V., 2023.

Summary of adverse events

	Placebo-controlled (to week 16)			2-mg and 4-mg extended (up to 3.9 years)		All-BARI-AD (up to 3.9 years)
	PBO (N=743)	BARI 2-mg (N=576)	BARI 4-mg (N=489)	BARI 2-mg (N=584)	BARI 4-mg (N=497)	All-BARI-AD (N=2636)
Total PY of exposure	211.8	169.1	147.1	727.1	800.1	4628.4
Any TEAE; n (%) **[IR]**	388 (43.2) **[234.7]**	347 (49.3) **[281.4]**	300 (51.0) **[300.1]**	428 **[214.7]**	407 **[216.3]**	2040 **[145.8]**
Serious AEs; n (%) **[IR]**	21 (2.3) **[8.0]**	10 (1.4) **[4.4]**	14 (2.3) **[7.7]**	33 **[4.2]**	58 **[7.9]**	237 **[5.2]**
Interruption of study drug due to AE; n (%) **[IR]**	14 (1.6) **[5.4]**	27 (3.4) **[11.6]**	26 (4.6) **[15.8]**	77 **[11.2]**	81 **[11.7]**	410 **[9.6]**
Discontinuation of study drug due to AE; n (%) **[IR]**	13 (1.4) **[4.6]**	10 (1.5) **[4.7]**	15 (2.1) **[6.5]**	22 **[2.7]**	37 **[4.6]**	158 **[3.4]**
Death; n (%) **[IR]**	0	0	0	0	0	4 **[0.1]**

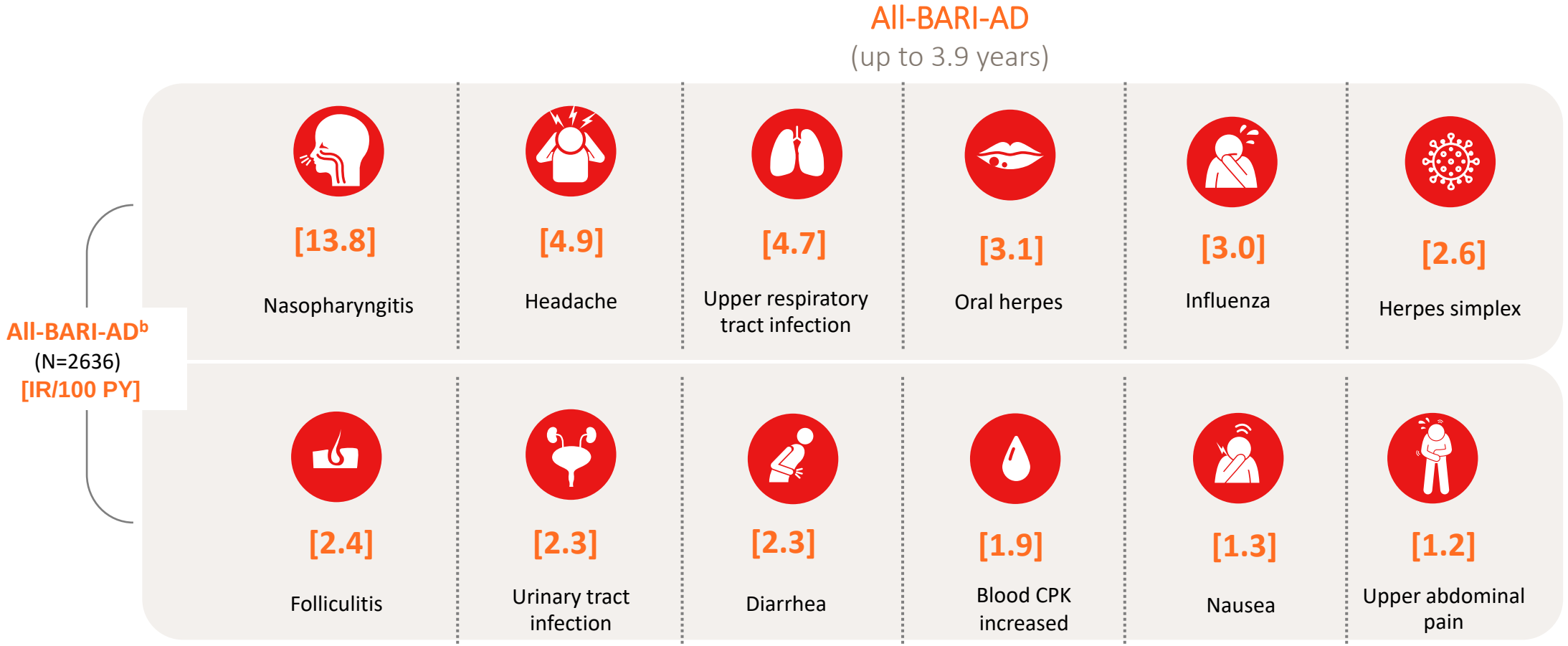
Data are presented as n (adjusted %) [adjusted IR] for the 16-week placebo-controlled period, [adjusted IR] for 2-mg vs 4-mg extended datasets, and [IR] for All-BARI-AD

Note: All-BARI-AD includes BARI 1-mg, 2-mg, and 4-mg.AD=atopic dermatitis; AE=adverse event; BARI=baricitinib; IR=incidence rate; n=number of patients in specified category; N=number of patients in the analysis population; PBO=placebo; PY=patient-years; TEAE=treatment-emergent adverse event

Bieber T et al 2022. *J Dermatolog Treat.* 2023:34(1):2161812

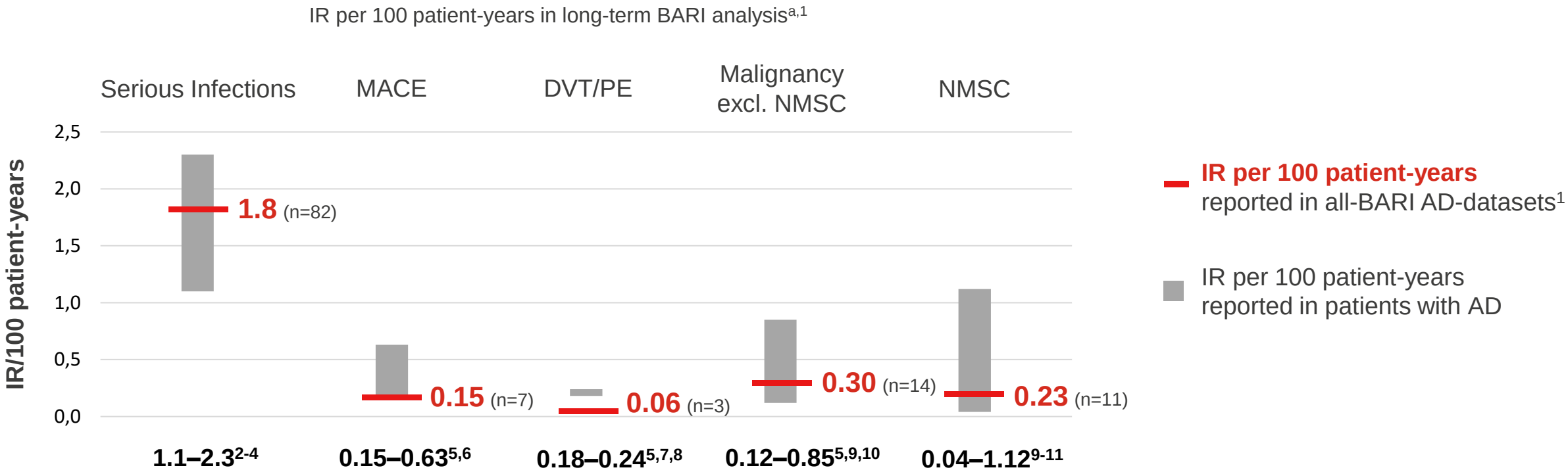
Integrated baricitinib safety over a median of 1.6 and up to 3.9 years of atopic dermatitis treatment

Most common[a] TEAEs in the PBO-controlled datasets



[a]TEAE occurring in ≥2% of patients in any group in the PBO-controlled dataset bAll-BARI-AD includes BARI 1-mg, 2-mg, and 4-mg.
AD=atopic dermatitis; BARI=baricitinib; CPK=creatinine phosphokinase; IR=incidence rate; n=number of patients in specified category; N=number of patients in the analysis population; PBO=placebo; PY=patient-years; TEAE=treatment-emergent adverse event. Bieber T, et al. *J Dermatolog Treat*. 2023;34(1):2161812

Rates of events of special interest reported with baricitinib generally reflect the underlying risk of the atopic dermatitis patient population



Baricitinib IRs of serious infections, MACE, DVT/PE and malignancies were **within the background rates in AD**

[a]Rates in patients treated with ≥1 dose of baricitinib across 8 clinical trials; 2,636 patients received baricitinib for 4,628 patient-years of exposure (median exposure, 588 days; maximum exposure, 3.9 years).
AD=atopic dermatitis; DVT=deep vein thrombosis; IR=incidence rate; MACE=major adverse cardiovascular event; n=number of patients in the specified category; NMSC=nonmelanoma skin cancer; PE=pulmonary embolism.

1. Bieber T, et al. Oral presentation at: *EADV 2022*. Abstract 1346. 2. Bieber T et al. *J Eur Acad Dermatol Venereol.* 2021;35(2):476-485 3. Wan J, et al. *Br J Dermatol.* 2022;186:664-672. 4. Simpson EL, et al. *Am J Clin Dermatol.* 2021;22(5):693-707. 5. Bieber T. et al. *Adv Ther.* 2022;39(11):4910-4960. 6. Andersen et al. *J Allergy Clin Immunol.* 2016;138(1):310-312.e3. 7. Meyers KJ, et al. *Dermatol Ther (Heidelb).* 2021;11(3):1041-1052. 8. Schneeweiss MC, et al. *JAMA Dermatol.* 2021;157(7):805-816.9. Arana A, et al. *Br J Dermatol.* 2010;163(5):1036-1043. 10. Mansfield KE, et al. *JAMA Dermatol.* 2020;156(10)1086-1097. 11. Rubbert-Roth A, et al. *RMD Open.* 2016;2(1): e000213.

Baricitinib: Inibitore JAK1/JAK2

Indicazioni terapeutiche

Dermatite atopica, artrite reumatoide, alopecia areata, artrite idiopatica giovanile

Baricitinib è indicato per il trattamento della dermatite atopica da moderata a severa nei pazienti adulti e in pazienti pediatrici di età pari e superiore ai 2 anni che sono candidati ad una terapia sistemica.

Posologia

Dermatite atopica

Adulti

La dose raccomandata di baricitinib è 4 mg una volta al giorno.

- Una dose di 2 mg una volta al giorno è raccomandata per pazienti ad alto rischio di TEV, MACE e neoplasia maligna, per pazienti di età ≥ 65 anni e per i pazienti con storia di infezioni croniche o ricorrenti.
- Una dose di 4 mg una volta al giorno può essere considerata per pazienti che non abbiano raggiunto un controllo adeguato dell'attività della malattia con una dose di 2 mg una volta al giorno.
- Una dose di 2 mg una volta al giorno deve essere presa in considerazione per i pazienti che hanno raggiunto un controllo persistente dell'attività di malattia con un dosaggio di 4 mg una volta al giorno e sono eleggibili per una riduzione della dose

Bambini e adolescenti (di età pari o superiore a 2 anni)

- La dose raccomandata di baricitinib è di 4 mg una volta al giorno per pazienti di peso pari o superiore a 30 kg.
- Per i pazienti di peso compreso tra 10 e meno di 30 kg, la dose raccomandata è 2 mg una volta al giorno.
- Una riduzione a metà della dose deve essere presa in considerazione per i pazienti che hanno raggiunto un controllo persistente dell'attività di malattia con la dose raccomandata e sono eleggibili per una riduzione graduale della dose.

Terapie topiche concomitanti:

Baricitinib può essere usato con o senza corticosteroidi topici. L'efficacia di baricitinib può essere aumentata quando somministrato con corticosteroidi topici. L'uso di inibitori topici della calcineurina è consentito, ma dovrebbe essere limitato alle sole aree sensibili, come viso, collo, pieghe e genitali.

E' necessario considerare l'interruzione del trattamento nei pazienti che non manifestino evidenza di beneficio terapeutico dopo 8 settimane di terapia.

BARICITINIB: RCP 30.10.2023

Adv Ther
https://doi.org/10.1007/s12325-023-02528-8

ORIGINAL RESEARCH

Baseline Body Surface Area and Itch Severity Define Response to Baricitinib in Patients with Moderate-to-Severe Atopic Dermatitis at Week 16

Jacob P. Thyssen · Marjolein de Bruin-Weller · Antonio Costanzo · Susanne Grond · Christopher Schuster · Chunyuan Liu · Maria Jose Rueda · Yun-Fei Chen · Andreas Pinter · Thomas Bieber

The objective of this post-hoc analysis was to identify and characterize patients who are likely to benefit most from baricitinib 4-mg, using a machine learning approach on data from the Phase 3 TCS combination therapy trial BREEZE-AD7, and to propose a clinical tailoring approach which accounts for unique AD phenotypes.

Response to BARI 4-mg at Week 16 was defined as achieving:

- EASI75
- EASI75 or Itch NRS ≥4-point improvement from baseline

Baseline Variables Included in the Machine Learning Model to Predict EASI75 and EASI75/Itch 4-Point Response[1]

BREEZE AD7 TCS Combo

Demographic variables

Male/female
Baseline age
Race
Baseline BMI

Disease characteristic variables

AD disease duration
Atopic comorbidity (yes/no)
Prior systemic therapy (yes/no)
Prior cyclosporine use (yes/no)
Tobacco use (yes/no)
Alcohol use (yes/no)

Disease severity variables

Baseline EASI
Baseline Head/Neck EASI score
Baseline BSA derived from EASI
Baseline SCORAD

Patient-reported outcomes

Baseline POEM
Baseline DLQI
Baseline Itch NRS

Laboratory parameters

Baseline eosinophil count
Baseline IgE levels

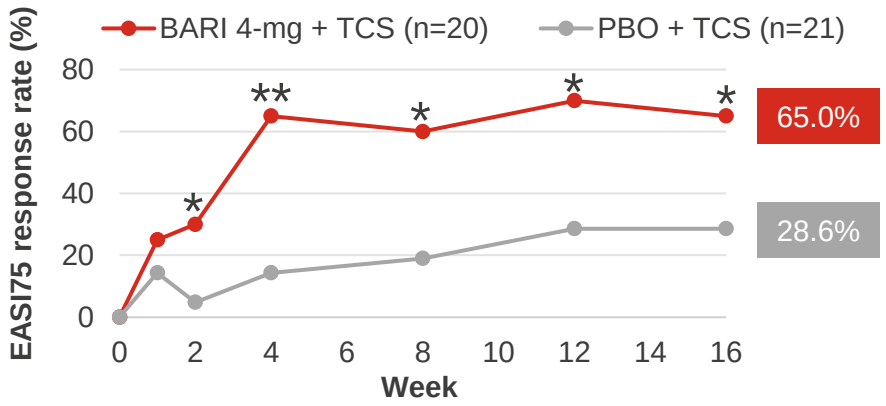
AD=Atopic Dermatitis; BMI=Body Mass Index; BSA=Body Surface Area; DLQI=Dermatology Life Quality Index; EASI=Eczema Area and Severity Index; EASI75=≥75% Improvement in Eczema Area and Severity Index; IgE=Immunoglobulin E; NRS=Numerical Rating Scale; POEM=Patient Orientated Eczema Measure; SCORAD=SCORing of Atopic Dermatitis.

1. Thyssen JP, et al. Adv Ther 2023.

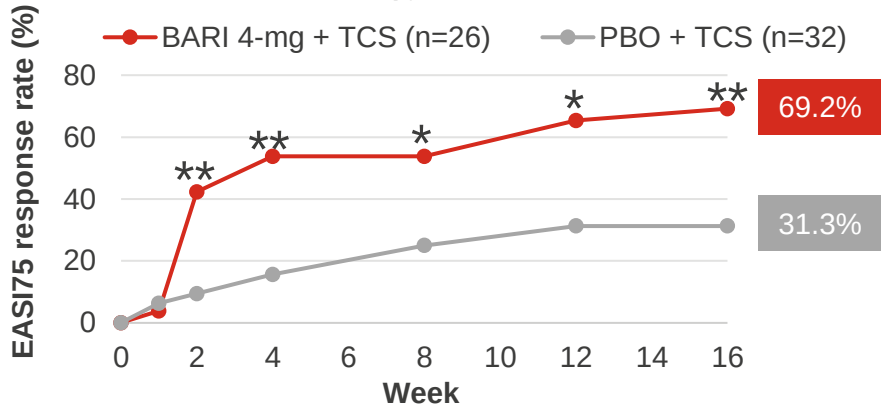
EASI75 Response Rate over 16 Weeks Across Identified BSA/Itch NRS Subgroups[1]

BREEZE AD7 TCS Combo

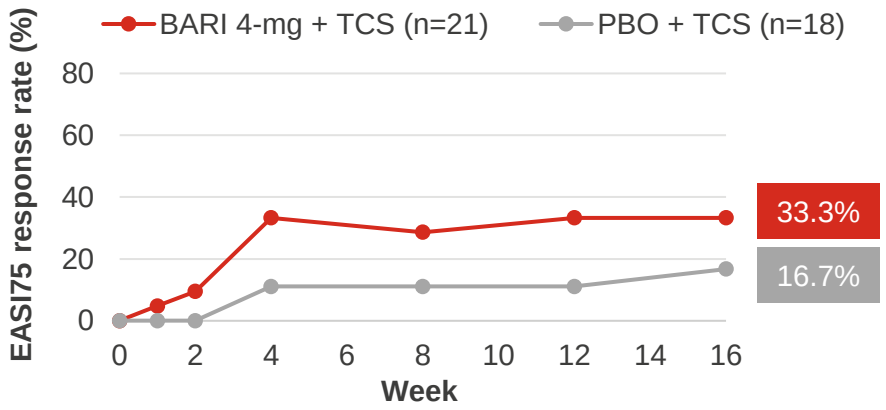
BSA 10–40% / Itch NRS <7



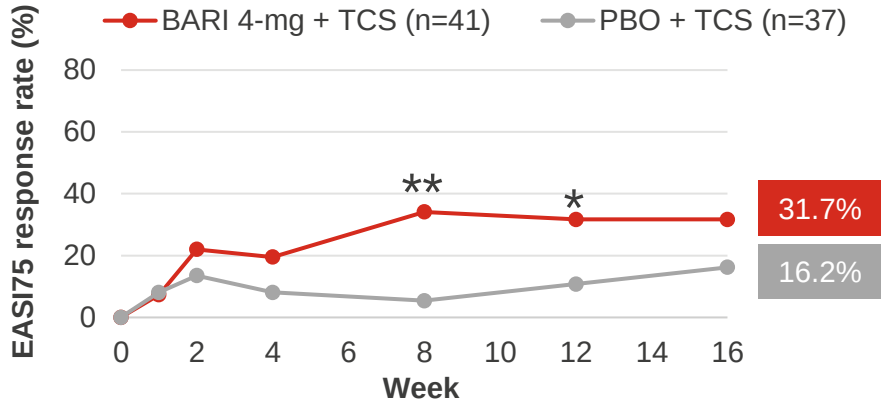
'Itch-dominant' BSA 10–40% / Itch NRS ≥7



BSA >40% / Itch NRS <7



BSA >40% / Itch NRS ≥7



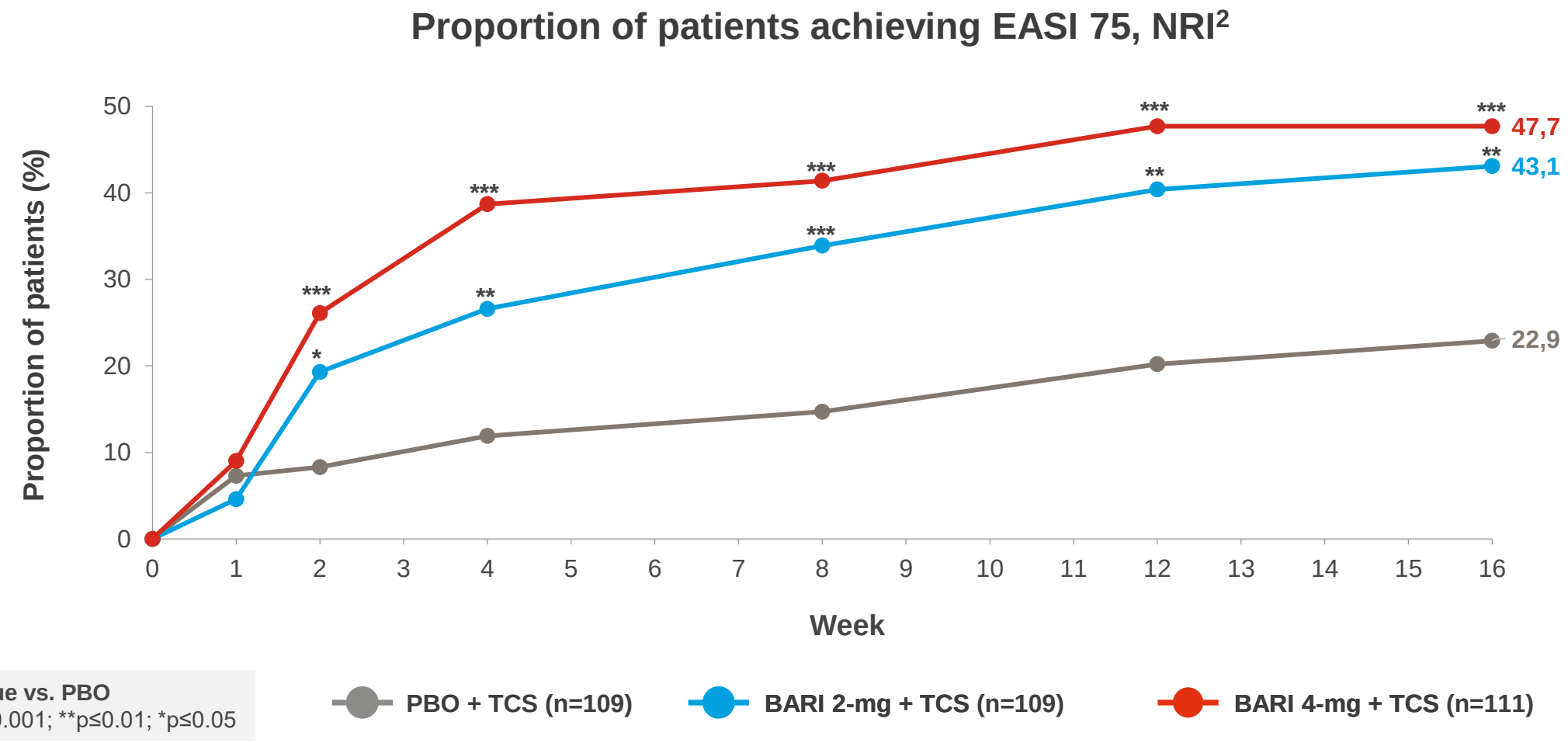
*p<0.05; **p<0.01 all compared to PBO.

BARI=Baricitinib; BSA=Body Surface Area; EASI75=≥75% Improvement in Eczema Area and Severity Index; n=Number; NRS=Numerical Rating Scale; PBO=Placebo; TCS=Topical Corticosteroids.

1. Thyssen JP, et al. Adv Ther 2023.

Patient need: “get better skin quickly”[1]
Baricitinib 4-mg demonstrated higher proportion of EASI 75 score vs placebo within two weeks

BREEZE AD7 TCS-IR



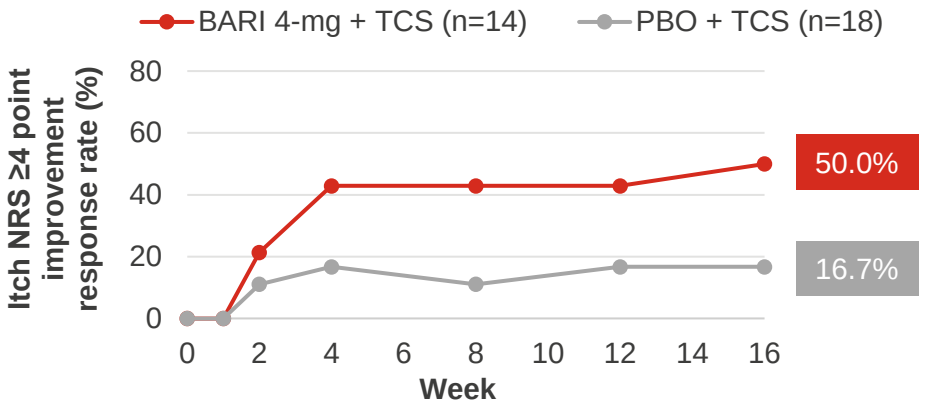
BARI=baricitinib; EASI 75=eczema area and severity index ≥75% reduction; IR=inadequate responder; NRI=nonresponder imputation; PBO=placebo; TCS=topical corticosteroid

1. Augustin M, et al. *J Eur Acad Dermatol Venereol.* 2020;34(1):142–52. 2. Reich K, et al. *JAMA Dermatol.* 2020;156(12):1333–43.

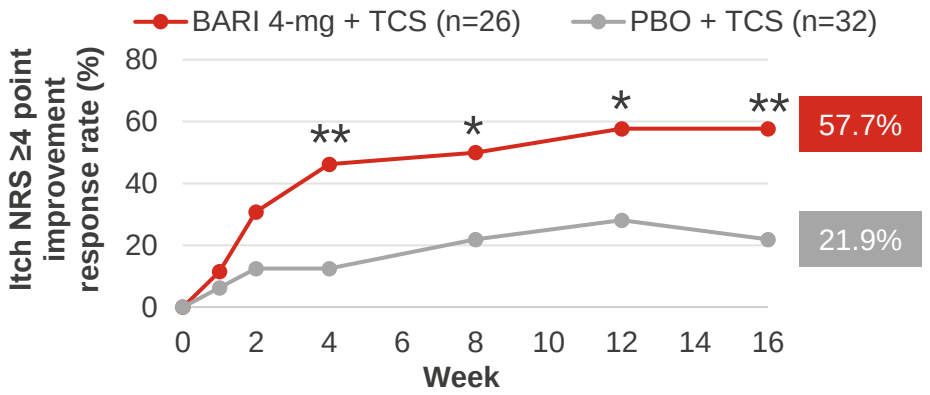
Itch NRS ≥4-Point Improvement Response Rate over 16 Weeks Across Identified BSA/Itch NRS Subgroups[1]

BREEZE AD7 TCS Combo

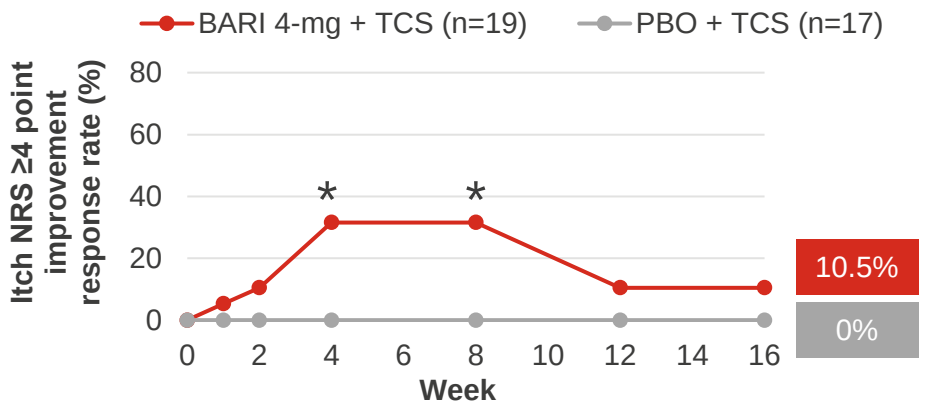
BSA 10–40% / Itch NRS <7



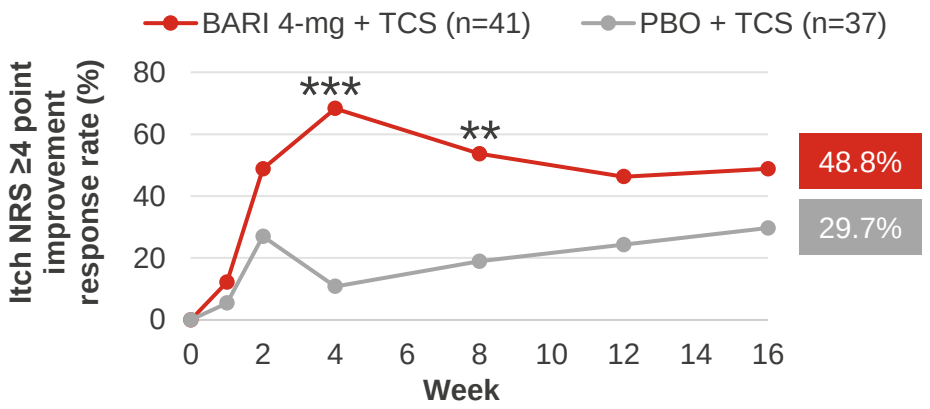
'Itch-dominant' BSA 10–40% / Itch NRS ≥7



BSA >40% / Itch NRS <7



BSA >40% / Itch NRS ≥7



*p<0.05; **p<0.01; ***p<0.001 all compared to PBO.
BARI=Baricitinib; BSA=Body Surface Area; n=Number; NRS=Numerical Rating Scale; PBO=Placebo; TCS=Topical Corticosteroids.

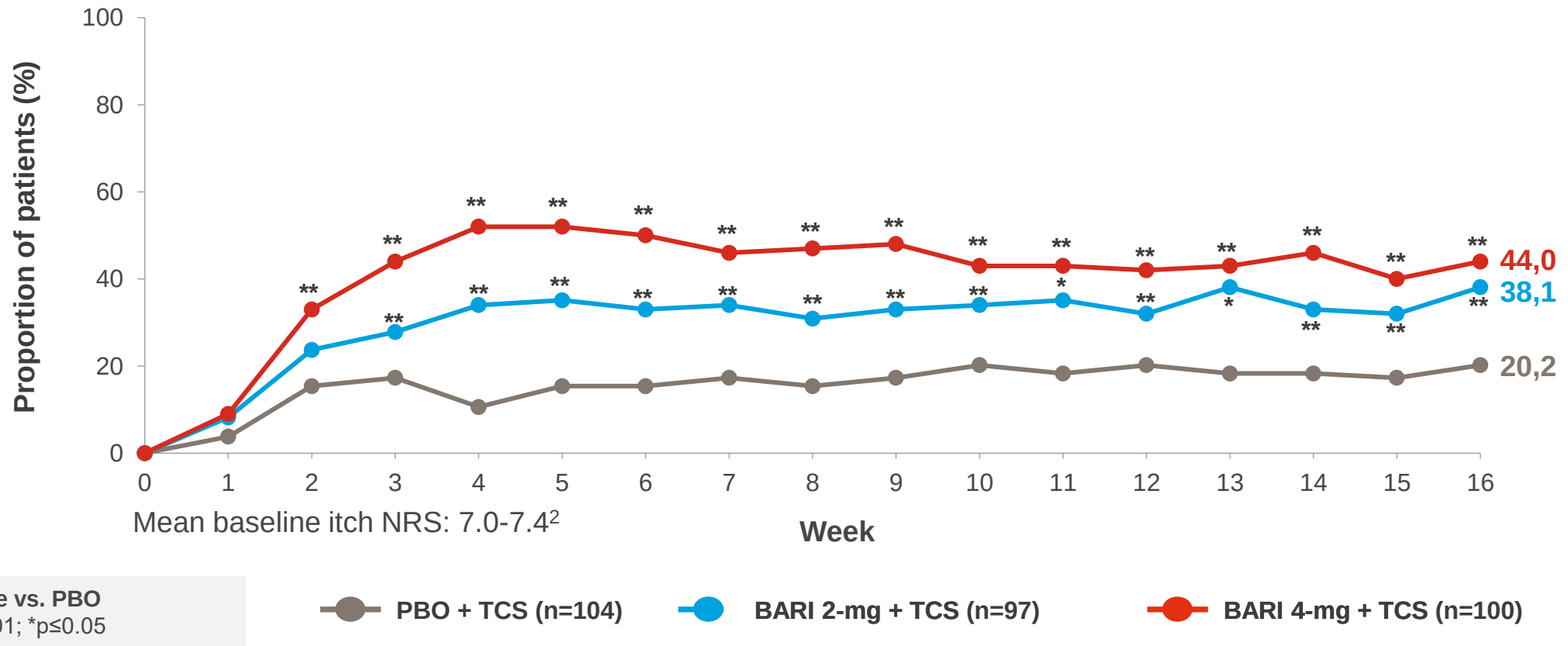
1. Thyssen JP, et al. Adv Ther 2023.

Patient need: “be free of itching”[1]

Baricitinib 4-mg demonstrated clinically meaningful improvements in itch severity

BREEZE AD7 TCS-IR

Proportion of patients with itch NRS ≥4-point improvement from baseline, NRI[2]



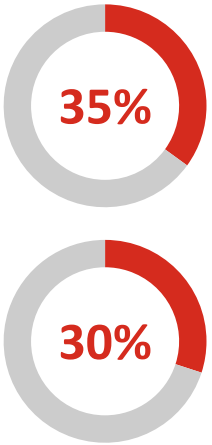
BARI=baricitinib; IR=inadequate responder; n=number of patients in the specified category; NRI=non-responder imputation; NRS=numeric rating scale; PBO=placebo; TCS=topical corticosteroid

1. Augustin M, et al. *J Eur Acad Dermatol Venereol.* 2020;34(1):142–52; 2. Reich K, et al. *JAMA Dermatol.* 2020;156(12):1333–43

‘Itch-Dominant’ Phenotype Characteristics[1]

‘Itch-dominant’ subgroup

BSA 10–40% / Itch NRS ≥7



of patients had **EASI >21**, reflecting severe AD with EASI values reaching up to 30.5

Mean BSA affected by AD

21 **Mean EASI**

15 **Mean DLQI**

8 **Mean Itch NRS**

Patients with Itch NRS ≥7 tended to have higher scores for DLQI in addition to higher values for ADSS Item 2 and HADS

AD=Atopic Dermatitis; ADSS=Atopic Dermatitis Sleep Scale; BARI=Baricitinib; BSA=Body Surface Area; DLQI=Dermatology Life Quality Index; EASI=Eczema Area and Severity Index; HADS=Hospital Anxiety and Depression Scale; NRS=Numerical Rating Scale.

1. Thyssen JP, et al. Adv Ther 2023.

Efficacy And Safety of Baricitinib In Combination With Topical Corticosteroids In Pediatric Patients With Moderate-to-severe Atopic Dermatitis With An Inadequate Response To Topical Corticosteroids: Results From A Phase 3, Randomized, Double-blind, Placebo-controlled Study (BREEZE-AD PEDS)

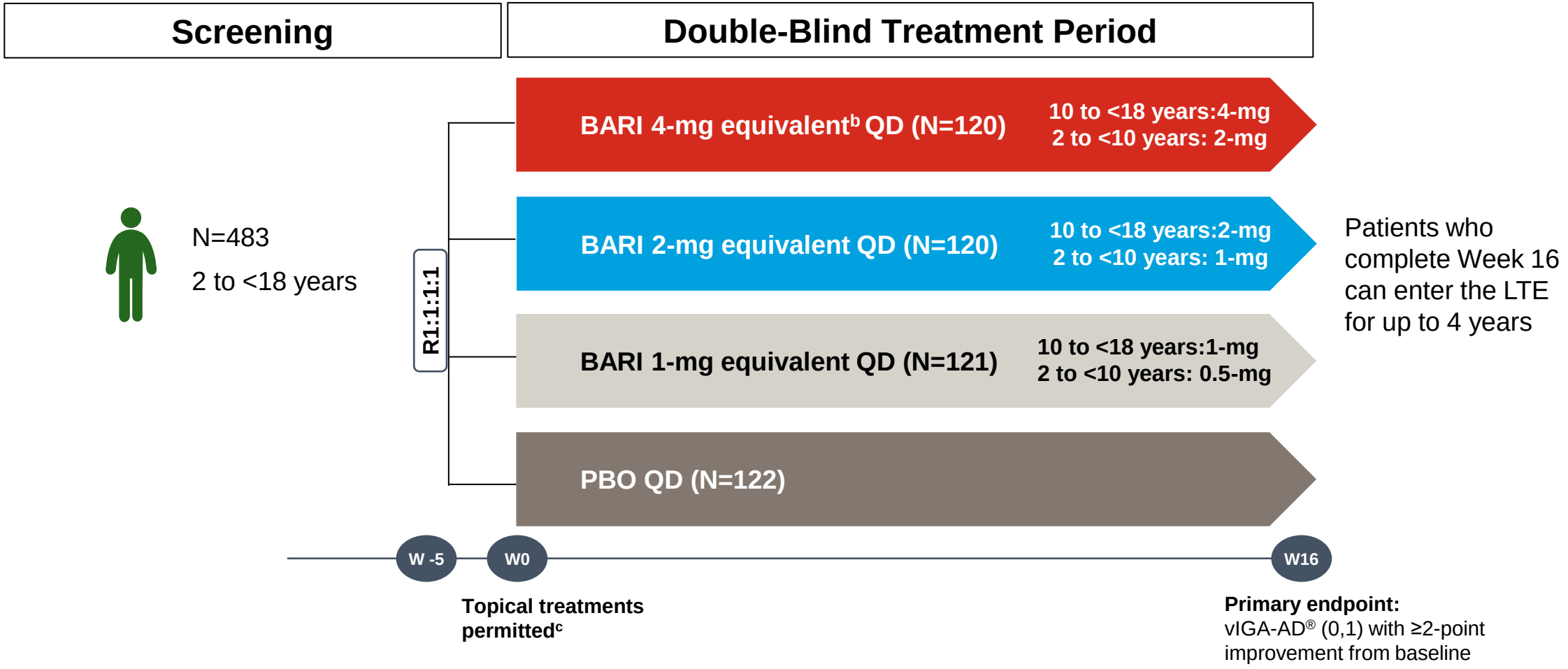
Torrelo A[1], Rewerska B[2], Galimberti M[3], Paller A[4], Yang CY[5,6], Prakash A[7], Zhu D[7], Filho MAGP[7], Wu WS[7], Eichenfield LF[8]

[1]Department of Dermatology, Hospital Infantil Universitario Niño Jesús, Madrid, Spain; [2]Diamond Clinic, Kraków, Poland; [3]Dermatology Service, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; [4]Departments of Dermatology and Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [5]Department of Dermatology, New Taipei Municipal TuCheng Hospital, New Taipei City, Taiwan, [6]Department of Dermatology, Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan; [7]Eli Lilly and Company, Indianapolis, IN, USA; [8]University of California San Diego and Rady Children's Hospital, San Diego, CA, USA

Torrelo A, et al. *Br J Dermatol.* 2023;ljad096. doi:10.1093/bjd/ljad096.

Methods

Study Design[a], BREEZE-AD-PEDS - Randomized, Double-blind, Placebo-controlled Study



[a]Figure does not present full study, only the double-blind, placebo-controlled period is shown; [b]Prior PK results showed that PK exposure at BARI 4-mg in 10 to <18-year-old patients was comparable to exposure in adults with AD treated with BARI 4-mg, and PK exposure at BARI 2-mg in 2 to <10-year-old patients was comparable to exposure in adults with AD treated with BARI 4-mg[2]; [c]Use of low- and medium-potency TCS, and TCNI, and PDE-4 inhibitor was permitted as background treatment. Full list of abbreviations and references are available in the speaker notes.

Outcome Measures

- **Primary objective of the study:**
  - demonstrate the superiority of each dose of BARI (1-mg, 2-mg, and 4-mg equivalents) plus TCS versus PBO plus TCS in the treatment of patients with moderate-to-severe AD, as measured by the proportion of patients achieving a vIGA-AD of 0/1 with ≥2- point improvement at week 16
- **Key secondary objectives of the study:**
  - compare the efficacy of BARI doses with PBO in improvement of signs and symptoms of AD through 16 weeks as measured by EASI, SCORAD and Itch NRS, a PRO in patients aged ≥10 years
- **Other endpoints included assessment of:**
  - itch severity in patients aged 2 to <10 made by the parent/caregiver using the PRISM, effect on sleep in patients aged ≥10 years using the ADSS, TCS use over 16 weeks, and
  - Other measures include: PGI-S-AD, Skin Pain NRS in patients aged ≥10 years, POEM, PROMIS for depression and anxiety, DFI, CDLQI/IDQol, WPAI-AD-CG and EQ-5D-Y
- Clinical laboratory tests, vital signs, growth assessments, physical examination and AEs were evaluated at scheduled study visits

AD=Atopic Dermatitis; ADSS=Atopic Dermatitis Sleep Scale; AE=Adverse Event; BARI=Baricitinib; CDLQI/IDQol=Children's Dermatology Life Quality Index/Infant's Dermatitis Quality of Life Index; DFI=Dermatitis Family Impact; EASI=Eczema Area and Severity Index; EQ-5D-Y=European Quality of Life-5 Dimensions-Youth version; NRS=Numeric Rating Scale; PBO=Placebo; PGI-S-AD=Patient Global Impression of Severity–Atopic Dermatitis; POEM=Patient-oriented Eczema Measure; PRISM=Parent-reported Itch Severity Measure; PROMIS=Patient-reported Outcomes Measurement Information System; SCORAD=SCORing Atopic Dermatitis; TCS=Topical Corticosteroid; WPAI-AD-CG=Work Productivity and Activity Impairment Questionnaire: Atopic Dermatitis-Caregiver; vIGA=validated Investigator's Global Assessment™. Torrelo A, et al. *Br J Dermatol.* 2023;ljad096. doi:10.1093/bjd/ljad096.

Baseline Patient Demographics

	PBO (N=122)	BARI 1-mg equivalent (N=121)	BARI 2-mg equivalent (N=120)	BARI 4-mg equivalent (N=120)
Age, years	11.8 (4.0)	12.4 (4.1)	11.8 (3.7)	11.9 (3.8)
Patients aged ≥10 years, n (%)	88 (72.1)	88 (72.7)	86 (71.7)	88 (73.3)
Patient aged 2 to <10 years, n (%)	34 (27.9)	33 (27.3)	34 (28.3)	32 (26.7)
Patient aged 2 to <6 years, n (%)	14 (41.2)	9 (27.3)	8 (23.5)	9 (28.1)
Patient aged 6 to <10 years, n (%)	20 (58.8)	24 (72.7)	26 (76.5)	23 (71.9)
Female, n (%)	64 (52.5)	62 (51.2)	63 (52.5)	53 (44.2)
Race, n (%)				
White	94 (77.0)	94 (77.7)	93 (77.5)	88 (73.3)
Asian	16 (13.1)	18 (14.9)	18 (15.0)	21 (17.5)
Black	3 (2.5)	2 (1.7)	5 (4.2)	4 (3.3)
Geographic Region, n (%)				
Europe	46 (37.7)	46 (38.0)	43 (35.8)	46 (38.3)
Japan	9 (7.4)	10 (8.3)	10 (8.3)	9 (7.5)
Rest of the World[a]	67 (54.9)	65 (53.7)	67 (55.8)	65 (54.2)

Data are presented as mean (SD) unless otherwise indicated . [a]Rest of the world included Argentina, Australia, Israel, Russia, Taiwan, Brazil, India, and Mexico. BARI=Baricitinib; SD=Standard Deviation. Torrelo A, et al. *Br J Dermatol.* 2023;ljad096. doi:10.1093/bjd/ljad096.

Baseline Disease Characteristics

	PBO (N=122)	BARI 1-mg equivalent (N=121)	BARI 2-mg equivalent (N=120)	BARI 4-mg equivalent (N=120)
Age at AD diagnosis, years	2.6 (3.6)	2.6 (3.9)	2.5 (3.5)	3.0 (4.0)
Duration since AD diagnosis, years	9.2 (4.4)	9.8 (5.1)	9.4 (4.2)	9.0 (4.1)
vIGA-AD[a], n (%)				
3	74 (60.7)	75 (62.5)	74 (61.7)	75 (62.5)
4	48 (39.3)	45 (37.5)	46 (38.3)	45 (37.5)
EASI Score	27.0 (10.3)	26.6 (10.0)	26.8 (9.0)	25.3 (9.5)
% BSA affected by AD	41.3 (19.1)	42.4 (19.5)	41.2 (16.8)	40.4 (17.7)
Itch NRS Score[b]	4.9 (2.5)	5.7 (2.4)	5.7 (2.6)	5.7 (2.7)
SCORAD	61.5 (11.9)	63.6 (12.7)	62.4 (11.8)	60.7 (13.1)
Prior TCNI use, n (%)	98 (80.3)	107 (88.4)	102 (85.0)	105 (86.7)
Prior TCS use, n (%)	122 (100)	119 (98.3)	120 (100)	117 (97.5)
Prior systemic therapy, n (%)	53 (43.4)	47 (38.8)	56 (46.7)	49 (40.8)
POEM	14.5 (6.8)	15.5 (7.1)	15.7 (7.2)	15.1 (6.9)
CDLQI[c]	8.4 (5.5)	9.3 (6.5)	9.3 (6.5)	8.7 (6.3)
IDQOL[d]	14.3 (7.3)	23.0 (3.6)	10.0 (n/a)	11.0 (1.4)

Data are presented as mean (SD) unless otherwise indicated. [a]One patient in the BARI 1 mg equivalent dose group was inadvertently randomized and discontinued from the study prior to receiving the first dose of study drug and was included in the intent-to-treat population but not the safety population, and not all baseline efficacy measures were collected. [b]Measured for patients aged ≥10. [c]Measured for patients aged 4 to <18 years. [d]Measured for patients aged 2 to <4 years. AD=Atopic Dermatitis; BARI=Baricitinib; BSA=Body Surface Area; CDLQI=Children's Dermatology Life Quality Index; EASI=Eczema Area and Severity Index; IDQOL=Infant's Dermatitis Quality of Life Index; NRS=Numeric Rating Scale; PBO=Placebo; POEM, Patient Oriented Eczema Measure; SCORAD=Scoring Atopic Dermatitis; SD=Standard Deviation; TCNI=Topical Calcineurin Inhibitor; TCS=Topical Corticosteroid; vIGA-AD=Validated Investigator's Global Assessment for Atopic Dermatitis. Torrelo A, et al. *Br J Dermatol.* 2023;ljad096. doi:10.1093/bjd/ljad096.

Safety Summary (1/2)

	PBO (N=122)	BARI 1-mg equivalent (N=120)	BARI 2-mg equivalent (N=120)	BARI 4-mg equivalent (N=120)
Any TEAE	61 (50.0)	60 (50.0)	63 (52.5)	61 (50.8)
TEAE severity				
Mild	33 (27.0)	36 (30.0)	40 (33.3)	36 (30.0)
Moderate	22 (18.0)	22 (18.3)	22 (18.3)	23 (19.2)
Severe	6 (4.9)	2 (1.7)	1 (0.8)	2 (1.7)
Serious adverse events	5 (4.1)	2 (1.7)	1 (0.8)	1 (0.8)
Study drug discontinuation due to AE	2 (1.6)	1 (0.8)	0	1 (0.8)
Infections	35 (28.7)	36 (30.0)	32 (26.7)	31 (25.8)

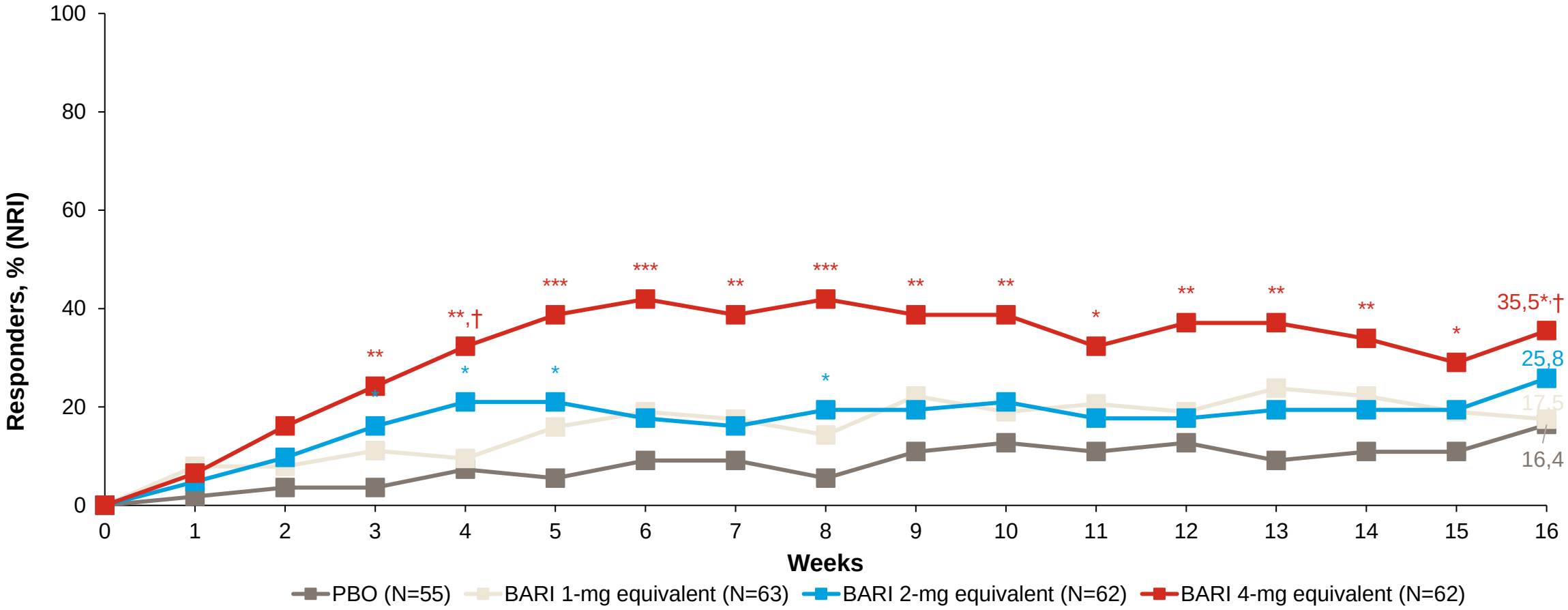
Data are presented as n (%). AE=Adverse Event; BARI=Baricitinib; PBO=Placebo; TEAE=Treatment-emergent Adverse Event. Torrelo A, et al. *Br J Dermatol.* 2023;ljad096. doi:10.1093/bjd/ljad096.

Safety Summary (2/2)

	PBO (N=122)	BARI 1-mg equivalent (N=120)	BARI 2-mg equivalent (N=120)	BARI 4-mg equivalent (N=120)
TEAEs reported in ≥2% of patients who received BARI 4-mg equivalent dose[a]				
Abdominal pain	3 (2.5)	3 (2.5)	5 (4.2)	6 (5.0)
Acne	5 (4.1)	3 (2.5)	4 (3.3)	6 (5.0)
Headache	10 (8.2)	7 (5.8)	11 (9.2)	6 (5.0)
Diarrhea	2 (1.6)	1 (0.8)	2 (1.7)	5 (4.2)
Nasopharyngitis	6 (4.9)	4 (3.3)	5 (4.2)	5 (4.2)
Upper respiratory tract infection	1 (0.8)	3 (2.5)	4 (3.3)	5 (4.2)
Upper Abdominal Pain	1 (0.8)	2 (1.7)	2 (1.7)	4 (3.3)
Bronchitis	1 (0.8)	6 (5.0)	1 (0.8)	3 (2.5)
COVID-19	4 (3.3)	5 (4.2)	5 (4.2)	3 (2.5)
Decreased appetite	0	0	0	3 (2.5)
Gastroenteritis	0	0	2 (1.7)	3 (2.5)

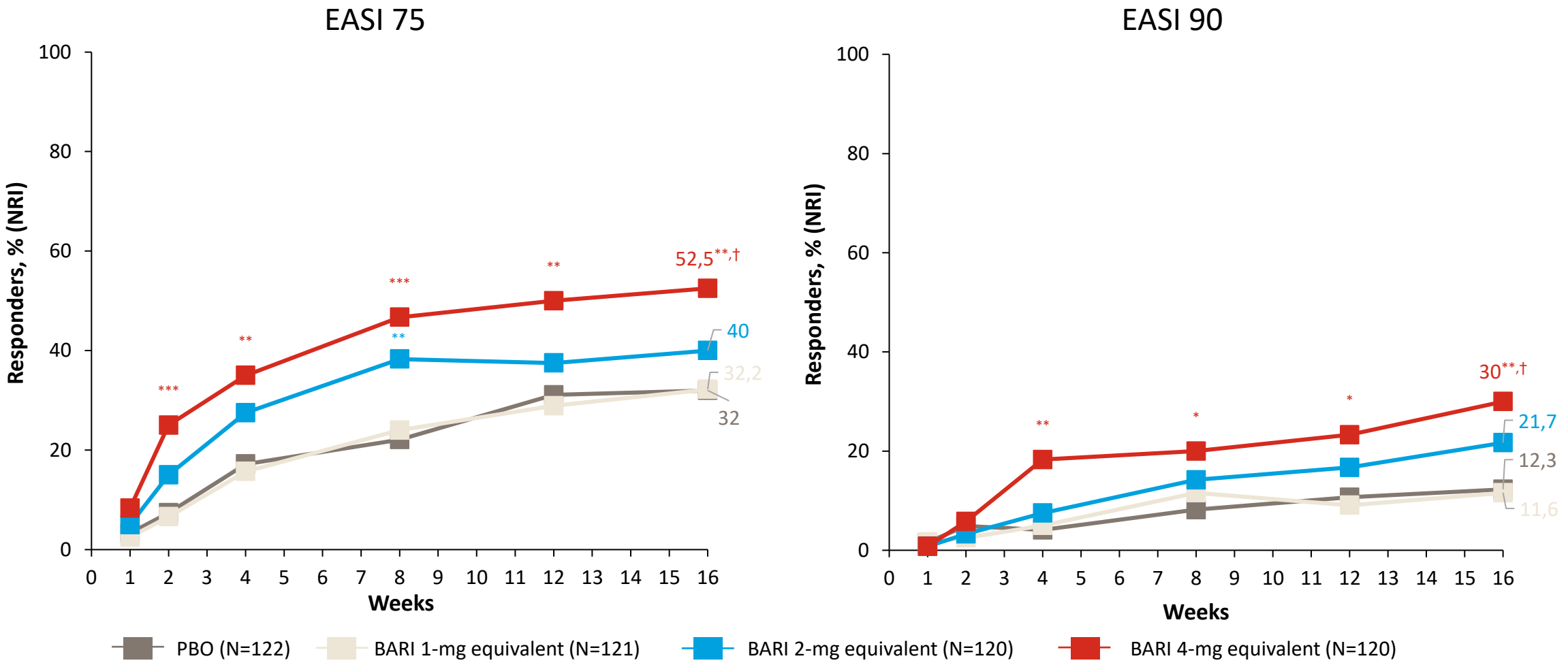
Data are presented as n (%). Note: There were no venous thromboembolic events, arterial thrombotic events, major adverse cardiovascular events, gastrointestinal perforations, malignancies, cases of tuberculosis, or confirmed opportunistic infections. [a]Nausea was reported in < 2% of patients receiving the BARI 4 mg equivalent dose [one (0.8%) patient in the PBO group, no (0%) patients in the BARI low-dose group, two (1.7%) patients in the BARI medium-dose group, two (1.7%) patients in the BARI high-dose group]; conjunctivitis was reported in < 2% of patients receiving the BARI 4 mg equivalent dose [two (1.6%) patients in the PBO group, no (0%) patients in the BARI low-dose group, one (0.8%) patient in the BARI medium-dose group, one (0.8%) patient in the BARI high-dose group]. BARI=Baricitinib; PBO=Placebo; TEAE=Treatment-emergent Adverse Event. Torrelo A, et al. *Br J Dermatol. 2023;ljad096. doi:10.1093/bjd/ljad096.*

Itch NRS with ≥ 4-point Improvement for Patients Aged ≥10 years



* p<.05; ** p<.01; *** p<.001 vs. placebo; †Statistically significant with multiplicity adjustment. BARI=Baricitinib; NRI=Nonresponder Imputation; NRS=Numeric Rating Scale; PBO=Placebo. Torrelo A, et al. *Br J Dermatol.* 2023;ljad096. doi:10.1093/bjd/ljad096.

EASI 75 and EASI 90



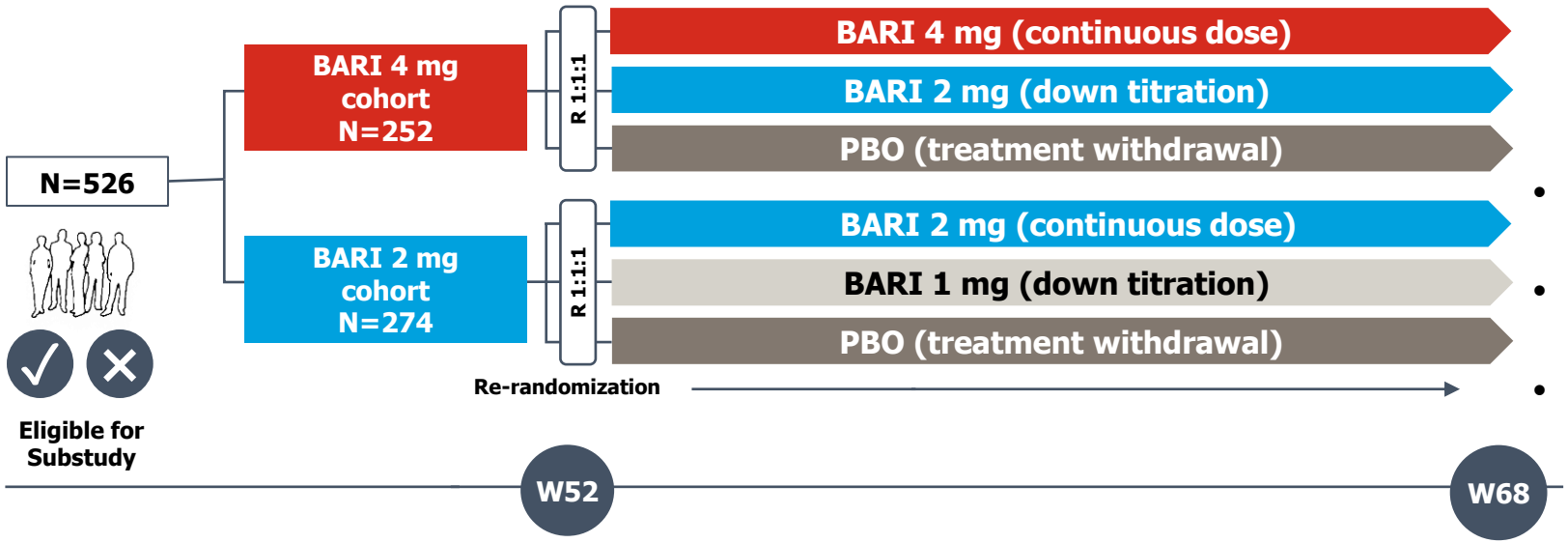
* p<.05; ** p<.01; *** p<.001 vs. placebo; †Statistically significant with multiplicity adjustment. BARI=Baricitinib; EASI=Eczema Area and Severity Index; NRI=Non-responder Imputation; PBO=Placebo. Torrelo A, et al. *Br J Dermatol.* 2023;ljad096. doi:10.1093/bjd/ljad096.

Br J Dermatol 2023; **188**:208–217
https://doi.org/10.1093/bjd/ljac057
Advance access publication date: 17 November 2022

BJD
British Journal of Dermatology
Clinical Trial

Efficacy of downtitration or treatment withdrawal compared with continuous dosing after successful treatment with baricitinib in patients with moderate-to-severe atopic dermatitis in a randomized substudy from the long-term extension study BREEZE-AD3

Kristian Reich,[1] Eric Simpson,[2] Andreas Wollenberg,[3,4] Robert Bissonnette,[5] Masatoshi Abe,[6] Tracy Cardillo,[7] Jonathan Janes,[7] Luna Sun,[7] Sherry Chen[8] and Jonathan I. Silverberg[9]

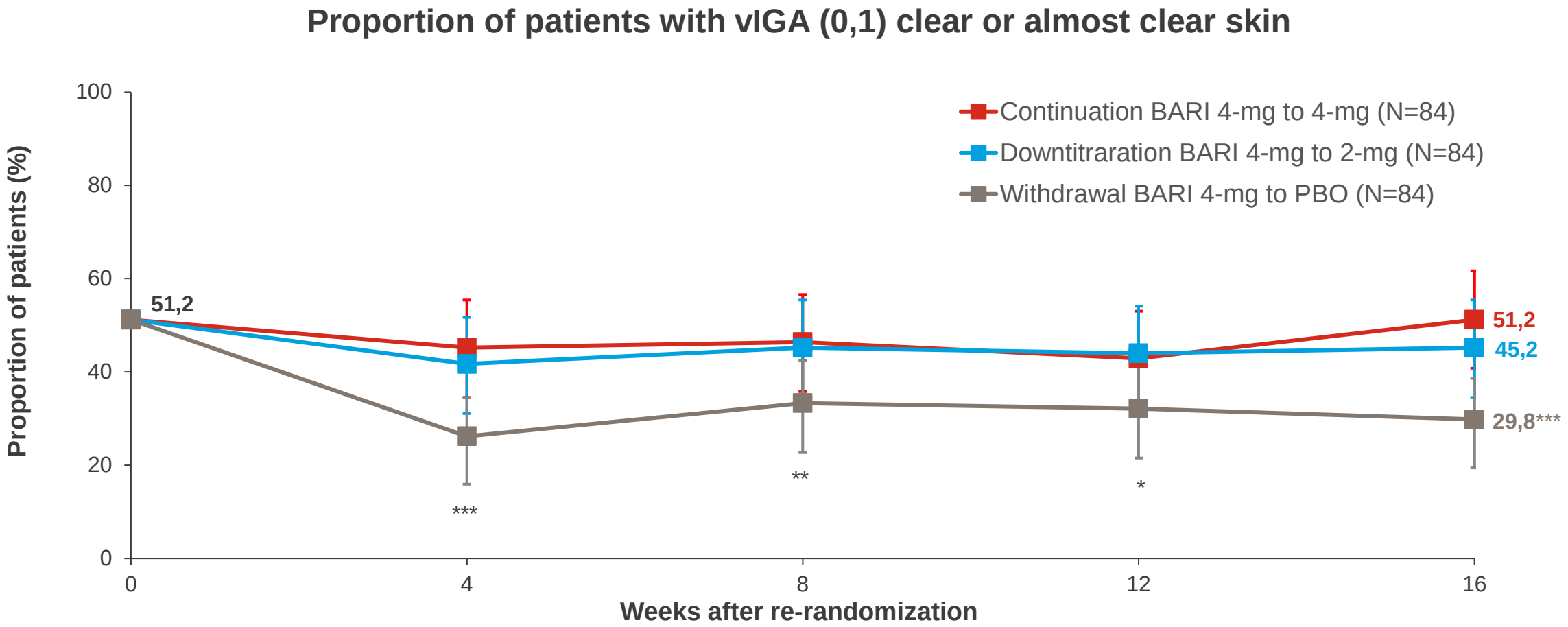


- The ongoing double-blind, phase III, longterm extension trial BREEZE-AD3 (NCT03334435) investigates the maintenance of efficacy and safety in patients who responded to baricitinib treatment in BREEZE-AD1, BREEZE-AD2 and BREEZE-AD7.
- To determine the feasibility of a flexible dosing regimen with baricitinib, a substudy of BREEZE-AD3 was designed to evaluate the maintenance of response with downtitration (from baricitinib 4 mg to 2 mg or from baricitinib 2 mg to 1 mg) or treatment withdrawal (placebo) compared with continuous dosing with baricitinib 4 mg or 2 mg.
- At Week 52 of BREEZE-AD3, substudy eligibility was assessed and re-randomization occurred.
- Outcomes were evaluated 16 weeks after re-randomization
- Relapsing patients (vIGA-AD™ ≥3), were readministered their original baricitinib dose

Many patients who reduced dosage or were switched to placebo maintained response in clear or nearly clear skin

vIGA-AD 0,1 response through 16 weeks after re-randomization

BREEZE AD3 LTE



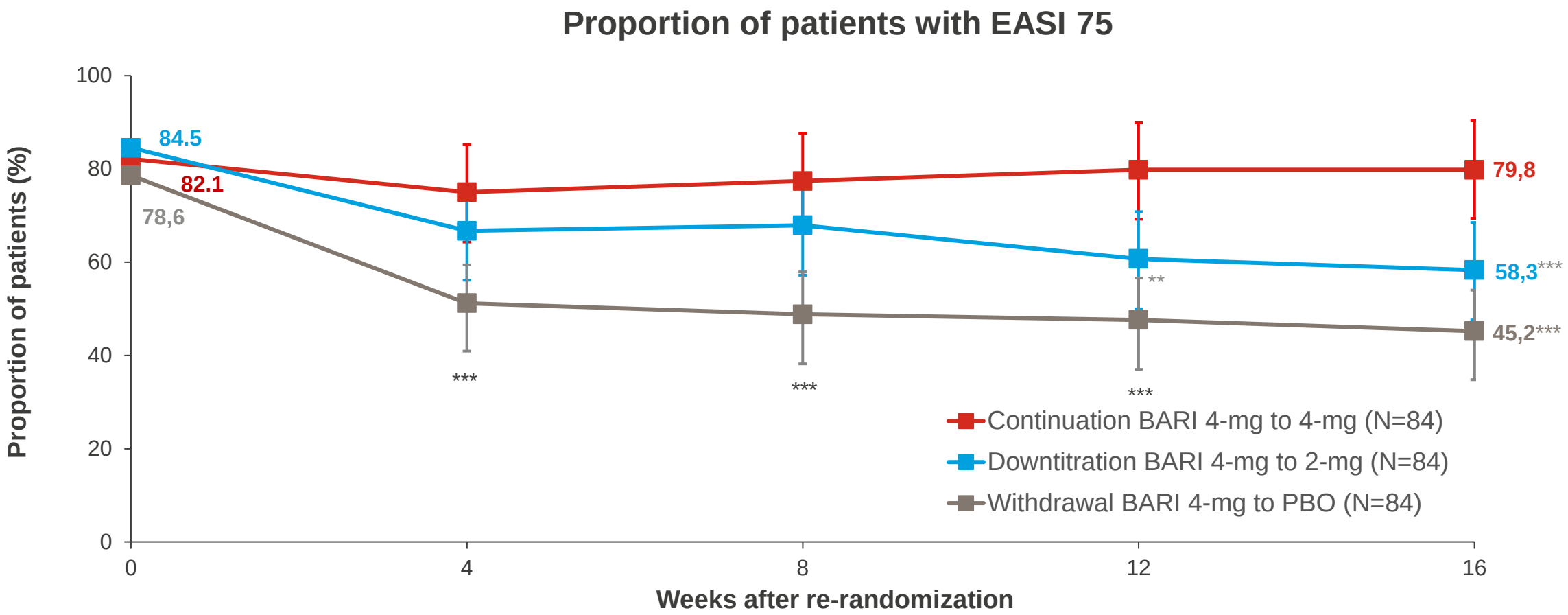
*p ≤0.05; **p ≤0.01; ***p ≤0.001 vs. 4-mg. Note: The analyses included patients that met substudy criteria including vIGA-AD 0/1/2 at substudy baseline. Data after treatment readministration or treatment discontinuation were considered as missing for the treatment withdrawal or downtitration groups, and data after treatment discontinuation were considered missing for those in the continuous dosing group; LOCF was used for missing data imputation.
BARI=baricitinib; LTE=long-term extension; N=number of patients in the analysis population; PBO=placebo; vIGA-AD=validated investigator global assessment - atopic dermatitis

Reich K, et al. *Br J Dermatol.* 2023;188(2):208-217.

Many patients who reduced dosage or were switched to placebo maintained response in skin improvement

EASI 75 response through 16 weeks after re-randomization

BREEZE AD3 LTE



**p ≤0.01; ***p ≤0.001 vs. 4-mg. Note: The analyses included patients that met substudy criteria including vIGA-AD 0/1/2 at substudy baseline. Data after treatment readministration or treatment discontinuation were considered as missing for the treatment withdrawal or downtitration groups, and data after treatment discontinuation were considered missing for those in the continuous dosing group; LOCF was used for missing data imputation.
BARI=baricitinib; EASI-75=75% improvement from baseline in the eczema area and severity index; LTE=long-term extension; N=number of patients in the analysis population; PBO=placebo; vIGA-AD=validated investigators global assessment - atopic dermatitis

Reich K, et al. *Br J Dermatol.* 2023;188(2):208-217.

8. L’inefficacia primaria di abrocitinib può essere dichiarata dopo 12 settimane di trattamento insoddisfacente?

1. **Sì**
2. **No**

Abrocitinib: Inibitore JAK1

Indicazioni terapeutiche

Abrocitinib è indicato per il trattamento della dermatite atopica da moderata a severa negli adulti e negli adolescenti di età pari o superiore a 12 anni candidati alla terapia sistemica.

Posologia e modo di somministrazione

Il trattamento deve essere iniziato e seguito da un operatore sanitario esperto nella diagnosi e nel trattamento della dermatite atopica.

Posologia

- **La dose iniziale raccomandata è di 100 mg o 200 mg una volta al giorno in base alle caratteristiche del singolo paziente**
- Una dose iniziale di 100 mg una volta al giorno è raccomandata per i pazienti a più alto rischio di TEV, MACE e tumori maligni (vedere paragrafo 4.4).
- Se il paziente non risponde adeguatamente a 100 mg una volta al giorno, la dose può essere aumentata a 200 mg una volta al giorno.
- **Una dose di 200 mg una volta al giorno potrebbe essere appropriata per i pazienti che non sono a più alto rischio di TEV, MACE e tumori maligni con elevato carico di malattia o per i pazienti con una risposta inadeguata a 100 mg una volta al giorno.** Dopo aver raggiunto il controllo della malattia, la dose deve essere ridotta a 100 mg una volta al giorno.
- Se il controllo della malattia non viene mantenuto dopo la riduzione della dose, può essere preso in considerazione il ritorno a 200 mg una volta al giorno.
- Negli adolescenti (da 12 a 17 anni) di peso compreso tra 25 kg e < 59 kg, si raccomanda una dose iniziale di 100 mg una volta al giorno. Se il paziente non risponde adeguatamente a 100 mg una volta al giorno, la dose può essere aumentata a 200 mg una volta al giorno.
- Negli adolescenti che pesano almeno 59 kg, potrebbe essere appropriata una dose iniziale di 100 mg o 200 mg una volta al giorno.
- **Per il mantenimento deve essere considerato la *dose efficace più bassa* .**

Anziani

- Per i pazienti di età pari o superiore a 65 anni, la dose raccomandata è di 100 mg una volta al giorno

Abrocitinb può essere utilizzato con o senza terapie topiche per la dermatite atopica.

L'interruzione del trattamento deve essere presa in considerazione nei pazienti che non mostra evidenza di beneficio dopo *24 settimane* .

ABROCITINIB: RCP 05.04.2024

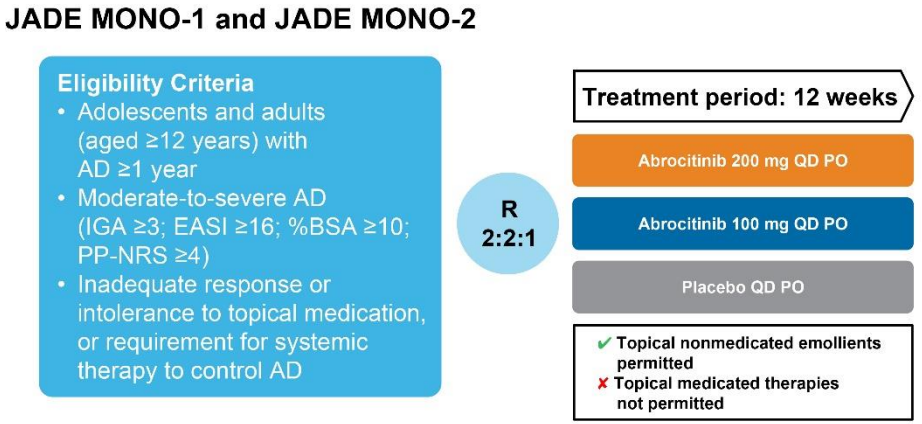
Received: 10 February 2023 | Accepted: 2 June 2023
DOI: 10.1111/jdv.19280

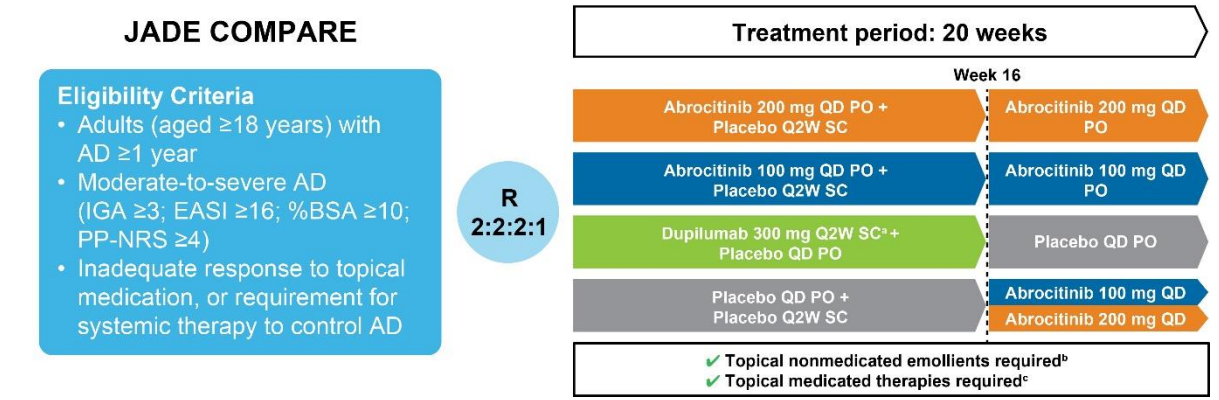
ORIGINAL ARTICLE

Abrocitinib efficacy and safety in patients with moderate-to-severe atopic dermatitis: Results from phase 3 studies, including the long-term extension JADE EXTEND study

Kristian Reich[1,2] | Jonathan I. Silverberg[3] | Kim A. Papp[4,5] | Mette Deleuran[6] | Norito Katoh[7] | Bruce Strober[8,9] | Lisa A. Beck[10] | Marjolein de Bruin-Weller[11] | Thomas Werfel[12] | Fan Zhang[13] | Pinaki Biswas[14] | Marco D. DiBonaventura[14] | Gary Chan[13] | Susan Johnson[15] | Saleem A. Farooqui[16] | Urs Kerkmann[17] | Claire Clibborn[18]

- JADE EXTEND (NCT03422822) is an ongoing, phase 3, long-term extension (LTE) study of oral abrocitinib 200 mg or 100 mg once daily (QD) in adolescent (12 to <18 years of age) and adult (≥18 years of age) patients with moderate-to-severe AD enrolled from qualifying abrocitinib phase 3 studies.





- These analyses focus on patients enrolled in JADE EXTEND after completing the full treatment period of abrocitinib or placebo in the qualifying studies JADE MONO-1, JADE MONO-2 or JADE COMPARE.
- Patients who discontinued from the qualifying studies or received dupilumab in JADE COMPARE and subsequently received abrocitinib in JADE EXTEND are not included.
- For patients randomized to the placebo arm in the qualifying studies, the date of first dose of abrocitinib is considered Day 1, which could be at entry to JADE EXTEND.

Baseline demographics and clinical characteristics of the full LTE population

	Abrocitinib 100 mg QD, *N* = 595	Abrocitinib 200 mg QD, *N* = 521
Age, median (IQR), years	32 (23–45)	32 (23–45)
Age group, years		
12–<18	57 (9.6)	50 (9.6)
≥18	538 (90.4)	471 (90.4)
Male, *n* (%)	340 (57.1)	277 (53.2)
Duration of AD, median (IQR), years	21.2 (11.0–31.5)	19.9 (10.7–31.5)
%BSA affected		
Mean (SD)	48.6 (22.8)	49.5 (23.4)
Median (IQR)	43.9 (31.0–66.0)	46.0 (30.0–67.7)
IGA, *n* (%)		
Moderate (3)	384 (64.5)	322 (61.8)
Severe (4)	211 (35.5)	199 (38.2)
EASI		
Mean (SD)	29.6 (12.4)	30.9 (13.2)
Median (IQR)	25.5 (19.8–37.4)	27.0 (20.2–38.8)
PP-NRS		
Mean (SD)	7.1 (1.7)	7.2 (1.7)
Median (IQR)	7.0 (6.0–8.0)	7.0 (6.0–8.0)

Note: Baseline was defined as the baseline visit from the qualifying study.

Abbreviations: %BSA, percentage of body surface area; AD, atopic dermatitis; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; IQR, interquartile range; LTE, long-term extension; PP-NRS, Peak Pruritus Numerical Rating Scale; QD, once daily; SD, standard deviation.

As of the 22 April 2020 data cut-off,
~70% and ~45% of patients in the full LTE population received abrocitinib for ≥36 weeks and ≥48 weeks, respectively

Abrocitinib exposure in the full LTE population

Patients, *n* (%)	Abrocitinib 100 mg QD, *N* = 595	Abrocitinib 200 mg QD, *N* = 521
<12 weeks	12 (2.0)	2 (0.4)
≥12 to <24 weeks	75 (12.6)	58 (11.1)
≥24 to <36 weeks	97 (16.3)	90 (17.3)
≥36 to <48 weeks	146 (24.5)	134 (25.7)
≥48 weeks	265 (44.5)	237 (45.5)

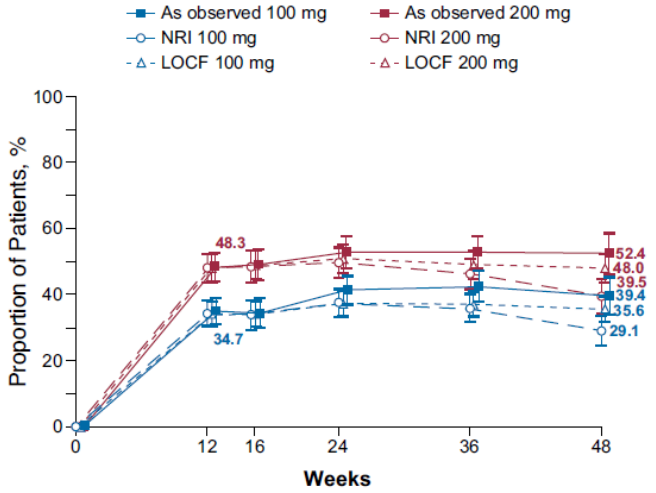
Note: For patients who received placebo in the qualifying studies, duration of exposure refers to abrocitinib treatment duration only. The 14 patients who received <12 weeks of abrocitinib treatment at the time of data cut-off were randomized to the placebo arm in the qualifying studies (JADE MONO-1, *n* = 5; JADE MONO-2, *n* = 5; JADE COMPARE, *n* = 4).

Abbreviation: LTE, long-term extension; QD, once daily.

Reich K, Silverberg JI, Papp KA et al. J Eur Acad Dermatol Venereol. 2023 Oct;37(10):2056-2066.

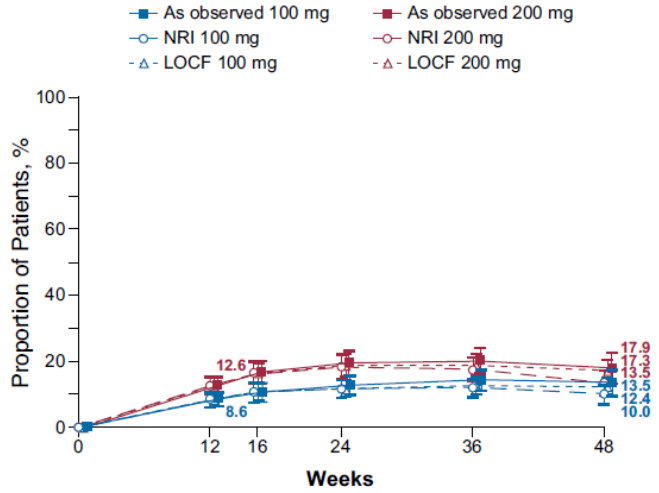
EFFICACY

(a)



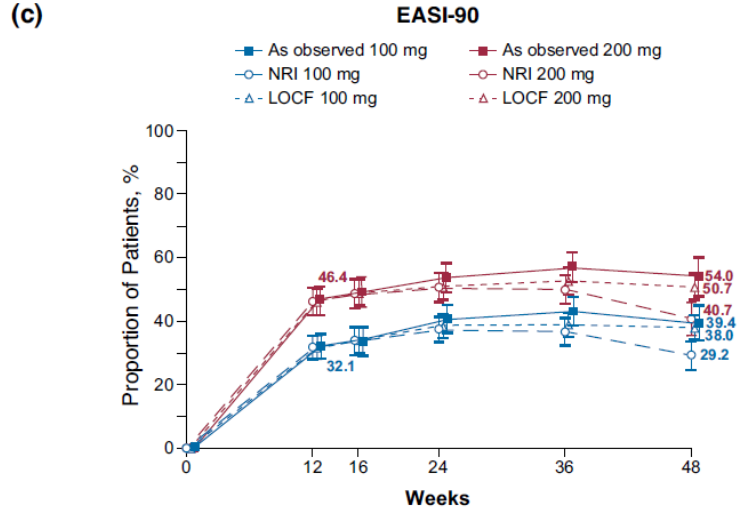
As observed, n					
Abrocitinib 100 mg QD	595	582	439	493	434	287
Abrocitinib 200 mg QD	521	509	437	434	400	250

(d)



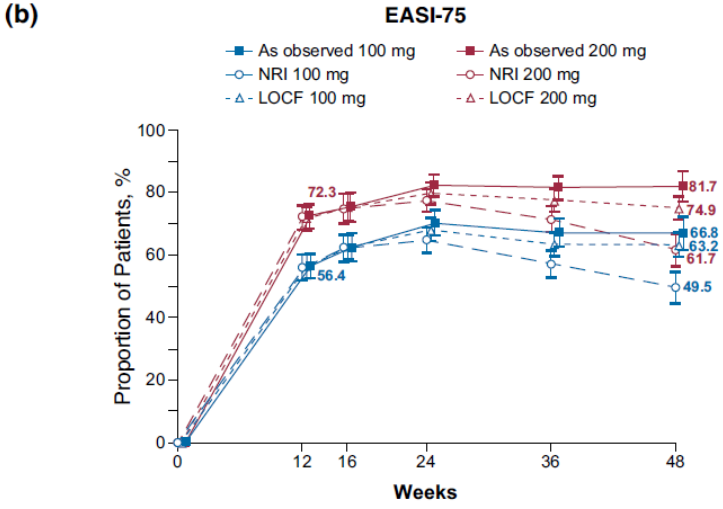
As observed, n					
Abrocitinib 100 mg QD	595	583	443	497	438	289
Abrocitinib 200 mg QD	521	509	436	435	401	252

(c)



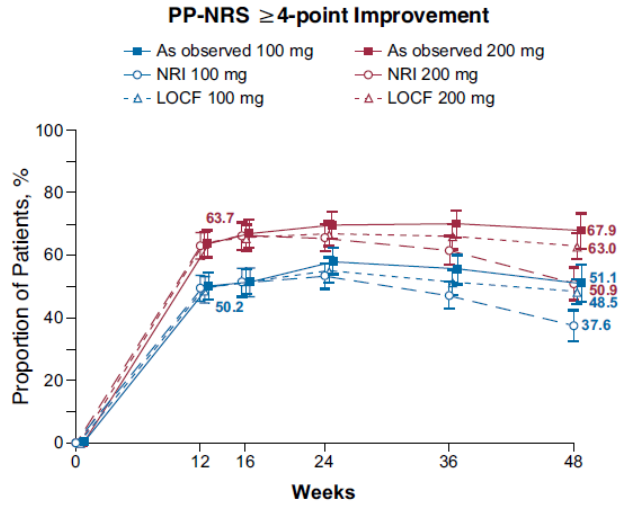
As observed, n					
Abrocitinib 100 mg QD	595	583	443	497	438	289
Abrocitinib 200 mg QD	521	509	436	435	401	252

(b)



As observed, n					
Abrocitinib 100 mg QD	595	583	443	497	438	289
Abrocitinib 200 mg QD	521	509	436	435	401	252

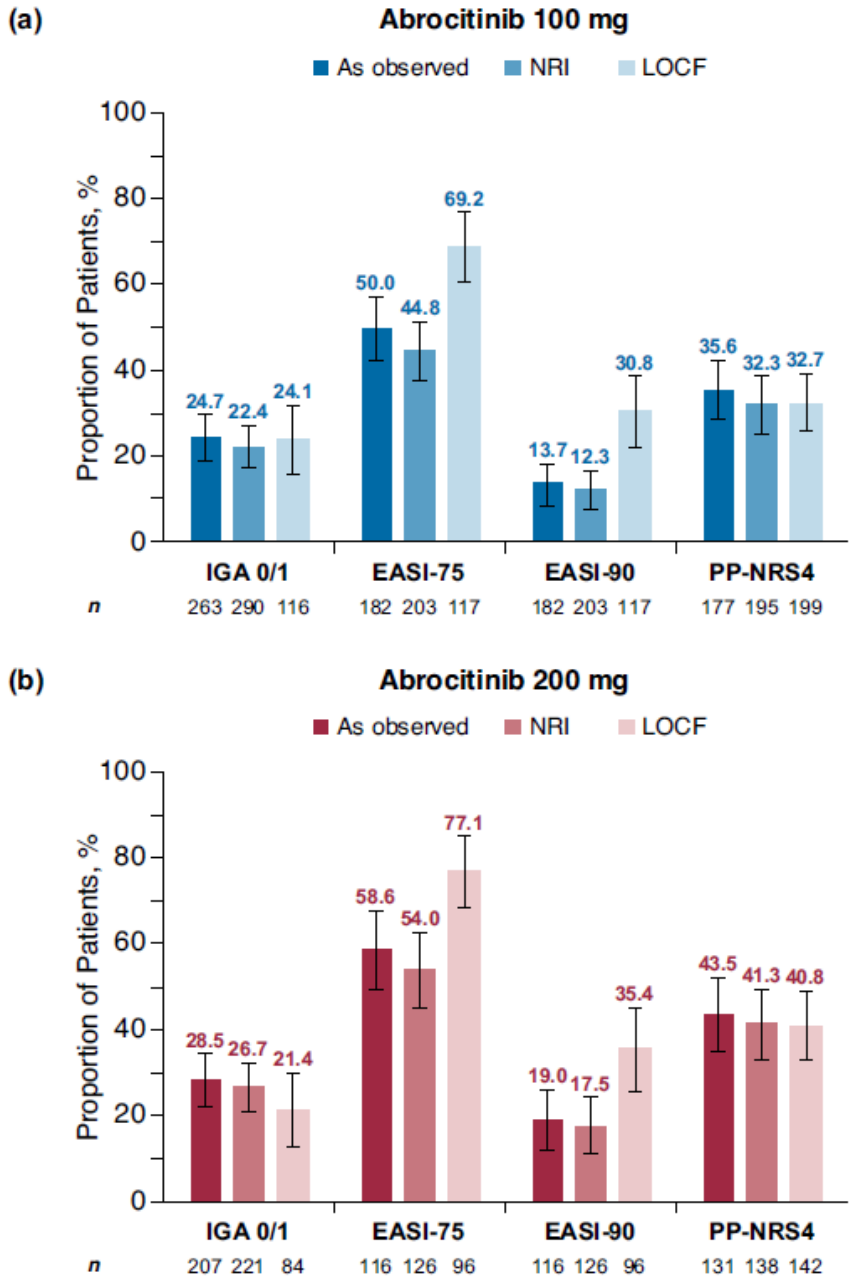
(e)



As observed, n					
Abrocitinib 100 mg QD	594	540	429	488	431	280
Abrocitinib 200 mg QD	521	485	426	435	398	246

Long-term efficacy among Week 12 responders/non-responders

- For the all-abrocitinib LTE population, the majority of patients achieving IGA 0/1, EASI-75, EASI-90, or ≥4-point improvement in PP-NRS severity response at Week 12 of abrocitinib treatment sustained this response at Week 48
- Among patients who did not meet the response criteria for IGA 0/1, EASI-75 or ≥4-point improvement in PP-NRS severity at Week 12 of abrocitinib treatment, substantial proportions met response criteria at Week 24



Reich K, Silverberg JI, Papp KA et al. J Eur Acad Dermatol Venereol. 2023 Oct;37(10):2056-2066.

SAFETY

In the full LTE population, TEAEs were reported in 82.0% and 75.5% of patients who received abrocitinib 200 mg and 100 mg, respectively; nasopharyngitis, atopic dermatitis, nausea and upper respiratory tract infection were the most frequent.

Serious TEAEs occurred in 7.1% and 4.7% of patients and TEAEs leading to study discontinuation in 9.4% and 6.9% of patients receiving abrocitinib 200 mg and 100 mg, respectively.

Patients, *n* (%)	Abrocitinib 100 mg QD, *N* = 595	Abrocitinib 200 mg QD, *N* = 521
TEAEs	449 (75.5)	427 (82.0)
Serious TEAEs	28 (4.7)	37 (7.1)
Severe TEAEs	40 (6.7)	40 (7.7)
TEAEs leading to study discontinuation	41 (6.9)	49 (9.4)
TEAEs leading to study drug discontinuation but continued study[a]	3 (0.5)	5 (1.0)
Deaths	0 (0)	1 (0.2)
TEAEs occurring in ≥5% of either treatment group		
Nasopharyngitis	110 (18.5)	89 (17.1)
Atopic dermatitis	96 (16.1)	56 (10.7)
Nausea	34 (5.7)	78 (15.0)
Upper respiratory tract infection	65 (10.9)	69 (13.2)
Headache	34 (5.7)	48 (9.2)
Acne	19 (3.2)	40 (7.7)
Blood creatine phosphokinase increased	28 (4.7)	29 (5.6)
Herpes simplex	19 (3.2)	27 (5.2)

9. Secondo una recente consensus italiana, i JAK inhibitors dovrebbero essere utilizzati come I linea di trattamento nei pazienti con coinvolgimento di aree sensibili, oppure con storia di AKC ricorrenti?

1. **Sì**
2. **No**

Heads Up Study Design

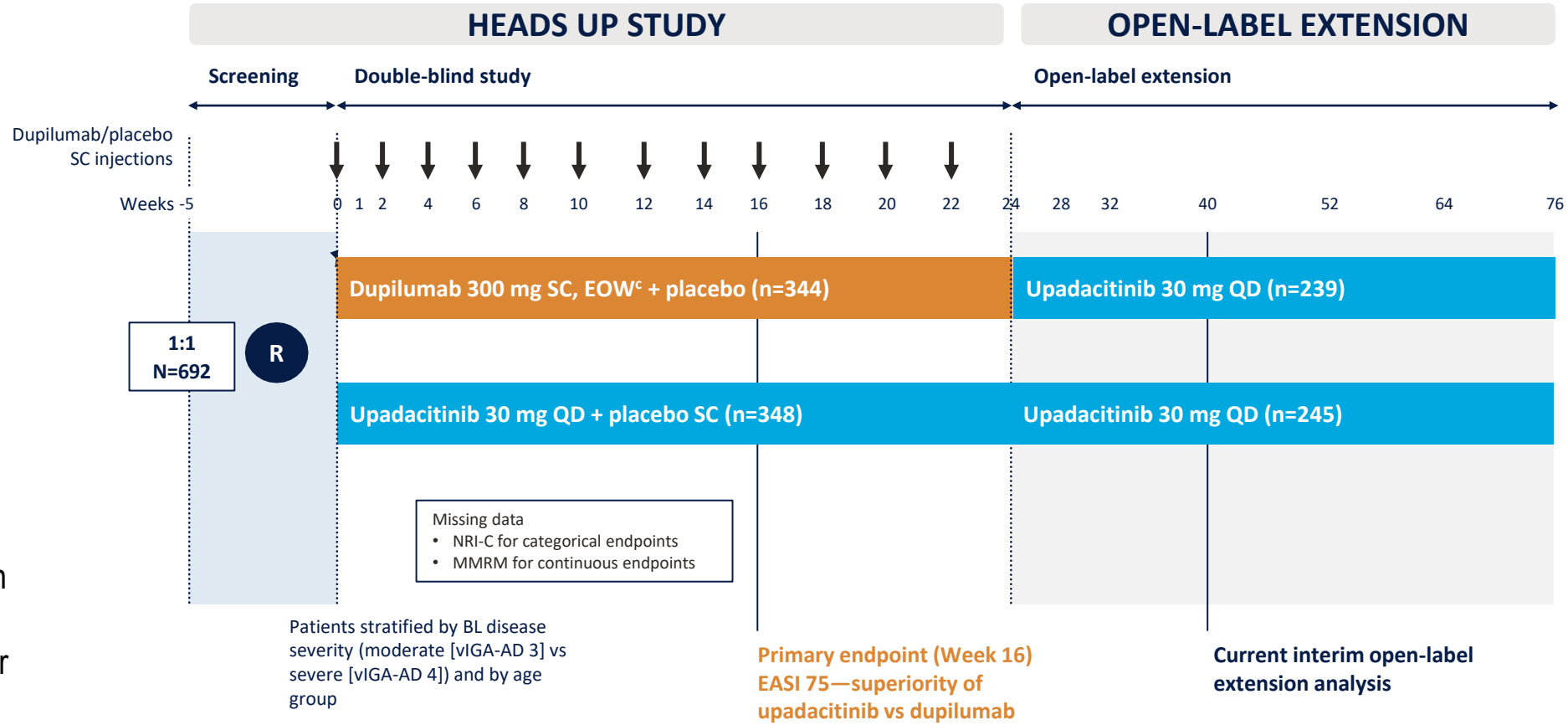
Objective is to assess efficacy and safety of upadacitinib vs dupilumab in adults with moderate-to-severe AD who are candidates for systemic therapy

Key inclusion criteria

- 18-75 years with chronic AD[a]
- AD symptoms for ≥3 years
- ≥10% BSA, EASI ≥16, and vIGA-AD ≥3
- BL weekly average of daily Worst Pruritus NRS ≥4

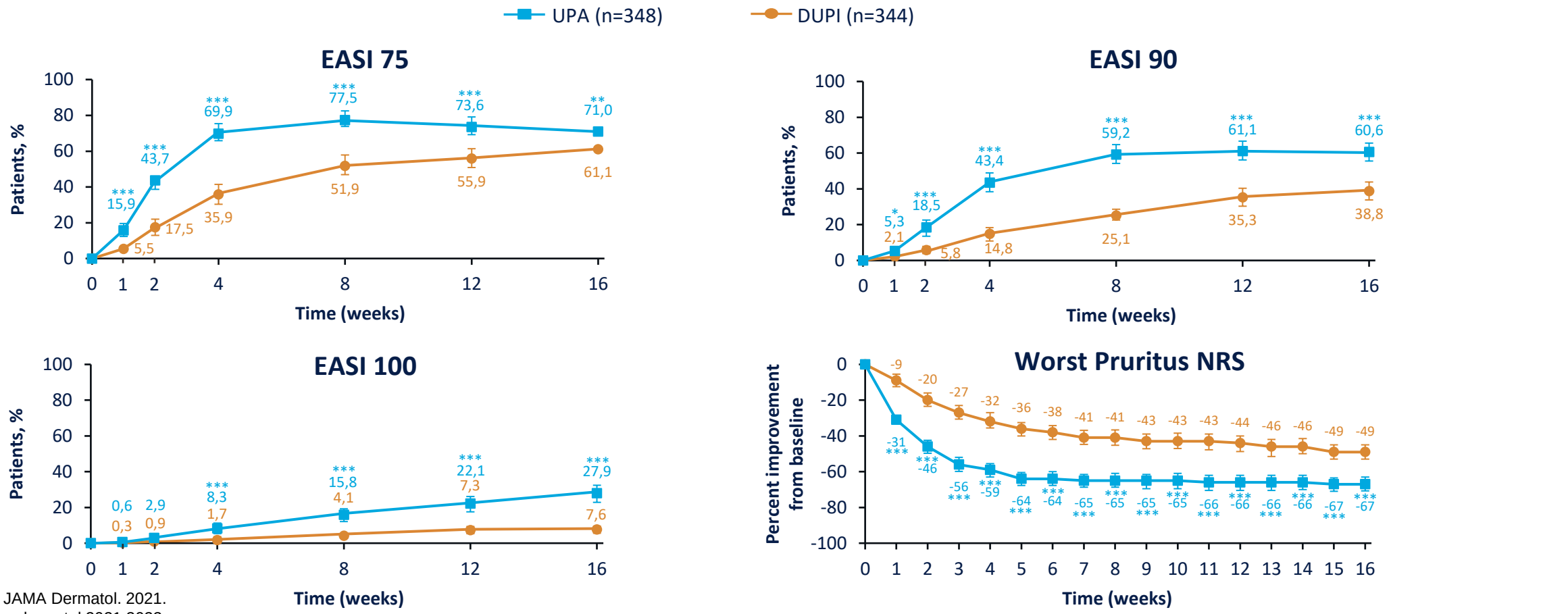
Key exclusion criteria

- Topical treatments within 7 days prior to BL[b]
- Systemic therapy for AD within 4 weeks prior to BL
- Prior exposure to dupilumab or JAK inhibitors



Blauvelt A, et al. JAMA Dermatol. 2021. doi: 10.1001/jamadermatol.2021.3023.

HEADS UP: EASI 75/90/100 and Worst Pruritus NRS over 16 weeks[a]

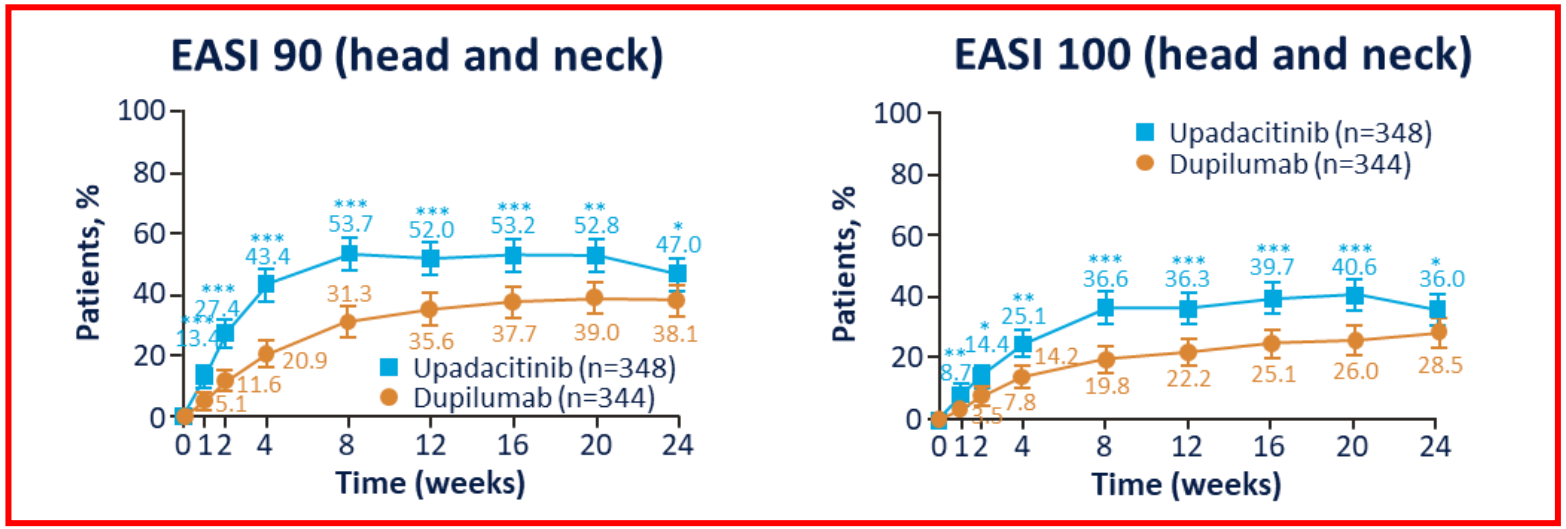


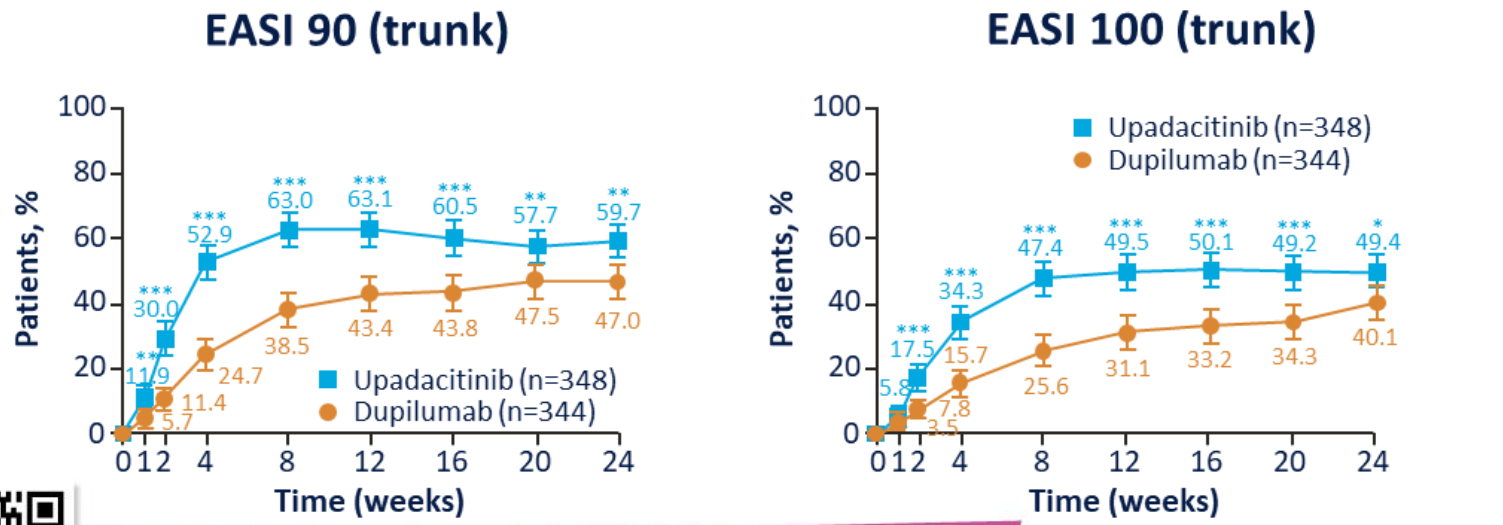
Blauvelt A, et al. JAMA Dermatol. 2021. doi: 10.1001/jamadermatol.2021.3023.

UPA met the primary endpoint and all key secondary endpoints vs dupilumab in the Heads Up study[1,2]

*p≤0.05; **p≤0.01; ***p≤0.001; error bars indicate 95% confidence interval; [a]Percent improvement in Worst Pruritus NRS from baseline vs dupilumab at Weeks 1, 4, and 16 were ranked secondary endpoints, as were EASI 90, EASI 100, and proportion of subjects achieving ≥4-point improvement in Worst Pruritus NRS from baseline at Week 16. Missing data were handled using NRI-C for categorical endpoints and MMRM for continuous endpoints.
DUPI, dupilumab; EASI 75/90/100, ≥75%/90%/100% reduction in Eczema Area and Severity Index; EOW, every other week; MMRM, mixed-effect model repeat measurement; NRI-C, non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19; NRS, numeric rating scale

Skin clearance through Week 24 (EASI 90 and 100): Head and neck, trunk[a]





*p≤0.05; **p≤0.01; ***p≤0.001 (nominal)
[a]Intent-to-treat population; NRI-C
DUPI, dupilumab; EASI 75/90/100, ≥75%/≥90%/100% improvement in Eczema Area and Severity Index; NRI-C, non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19

Clin Exp Dermatol. 2023 Apr 27;48(5):558-559. doi: 10.1093/ced/llad040.

Successful response to upadacitinib in the treatment of atopic dermatitis lesions involving sensitive and visible areas resistant to dupilumab treatment

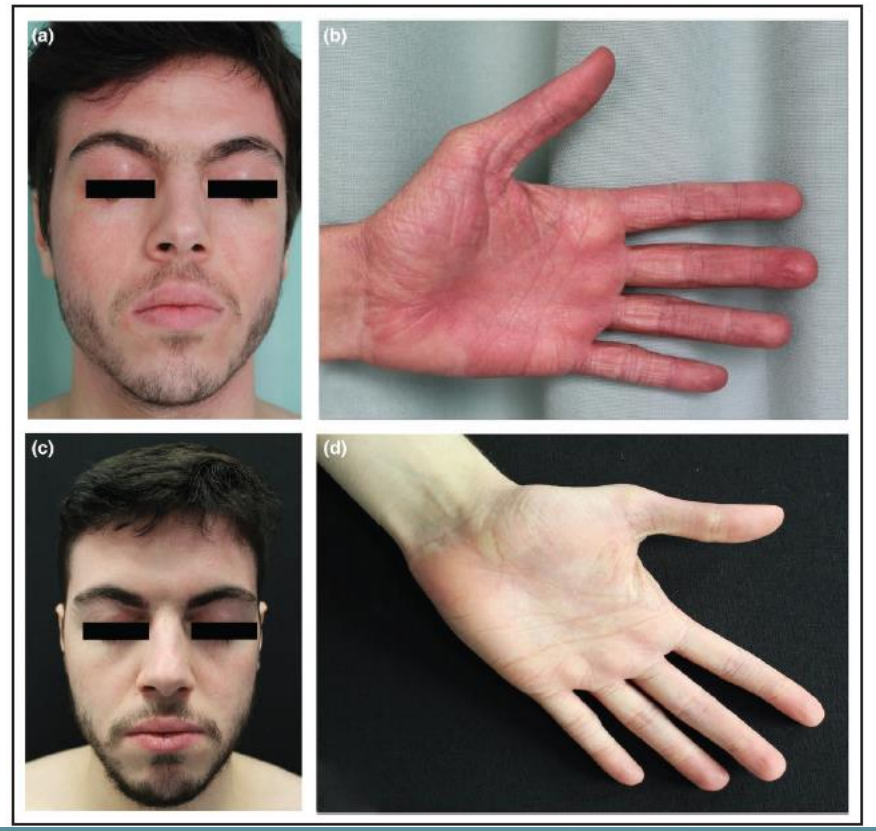
Niccolò Gori [1 2], Elena Ippoliti [1 2], Flaminia Antonelli [1 2], Ketty Peris [1 2], Andrea Chiricozzi [1 2]

Eight patients had **withdrawn from dupilumab** treatment (median therapy duration: 11.5 months) because of **inefficacy** with persistency of eczematous lesions in different body areas including the **head and neck** (six patients), **hands** (three patients) and **genitalia** (two patients) and were then **treated with upadacitinib.**

5/8 patients achieved a **complete clearance** of AD lesions located on visible body areas after **4 weeks** of treatment with a long-term response maintained through 52 weeks.

In **3 patients** a **minimal residual disease** (absolute **EASI ≤ 1**) on the head and neck area persisted from week 4 throughout the 52 weeks of observation, albeit residual AD lesions did not have an impact either on symptoms or the patients' quality of life (DLQI 0–1).

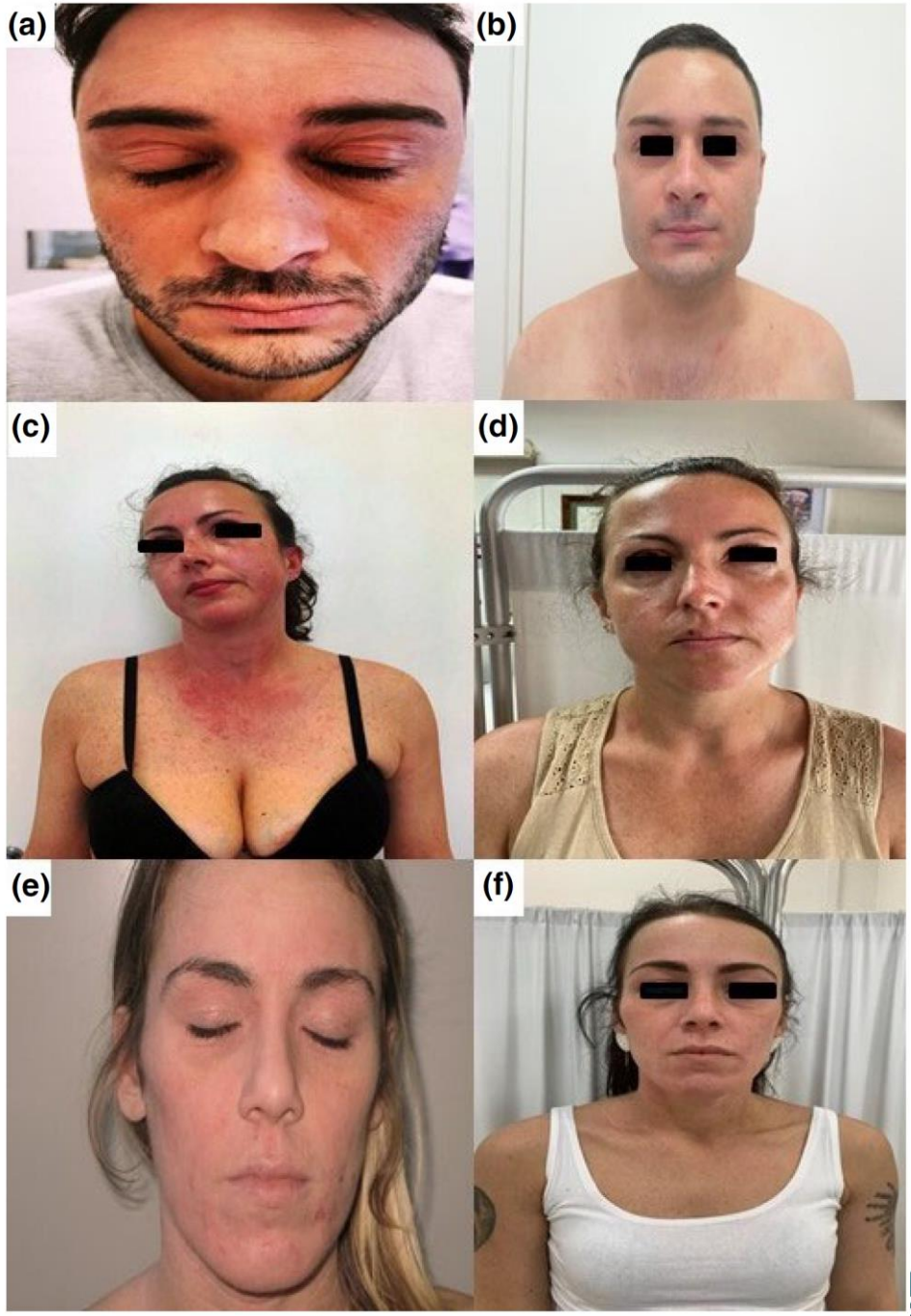
4/8 patients experienced at least one adverse event, including acneiform eruptions (*n* = 2), molluscum contagiosum infection (*n* = 1) and transient increase of phosphor–creatine kinase (*n* = 2). **No patients withdrew treatment because of the occurrence of adverse events,** although a **dose adjustment from 30 to 15 mg** was necessary for one patient.



Case Reports > J Eur Acad Dermatol Venereol. 2022 Feb;36(2):e150-e152. doi: 10.1111/jdv.17705. Epub 2021 Sep 30.

Face atopic dermatitis resistant to dupilumab: a case series of three patients successfully treated with upadacitinib

G Licata [1], A Gambardella [1], V Tancredi [1], G Calabrese [1], A De Rosa [1], R Alfano [2], G Argenziano [1]



(a) Face atopic dermatitis with periorbital eczema in patient treated with dupilumab.
(b) Clinical improvement **after 1 month** of upadacitinib.

(c) Face and neck eczema under dupilumab.
(d) Clinical resolution **after 2 months** of upadacitinib.

(e) Face and periorbital eczema in a 23-year-old woman previously treated with dupilumab.
(f) Face and periorbital eczema resolution **after 4 weeks** with upadacitinib.

Ocular Adverse Events in Patients With Atopic Dermatitis Treated With Upadacitinib: A Real-Life Experience

Federica Gelato, MD,* Luca Mastorino, MD,* Pietro Quaglino, MD,* Giovanni Cavaliere, MD,* Michela Ortoncelli, MD,* and Simone Ribero, MD, PhD*

Among the patients in the study, **14** had developed dupilumab-associated conjunctivitis during dupilumab treatment.

Of these, only 2 patients had a positive history of allergic conjunctivitis.

All of these patients developed symptoms **within 8 months** of starting treatment with dupilumab, in particular 7 patients within the first 4 months of dupilumab treatment.

All 14 patients had **complete resolution** of ocular symptoms **after the switch to upadacitinib** within the 1-month follow-up visit.

Gelato F, Mastorino L, Quaglino P, Cavaliere G, Ortoncelli M, Ribero S. Ocular Adverse Events in Patients With Atopic Dermatitis Treated With Upadacitinib: A Real-Life Experience. Dermatitis. 2023 Sep-Oct;34(5):445-447.

Received: 15 September 2023 | Revised: 7 January 2024 | Accepted: 21 February 2024

DOI: 10.1002/ski2.354

CASE REPORT

SKIN HEALTH AND DISEASE Open Access

Dupilumab-associated ocular surface disease or atopic keratoconjunctivitis not improved by dupilumab? Upadacitinib may clarify the dilemma: A case report

Marco Galluzzo[1,2] | Lorenzo Tofani[1,2] | Sara Spelta[3] | Alessandra Micera[4] | Luca Bianchi[1,2] | Marco Coassin[3] Antonio Di Zazzo[3]

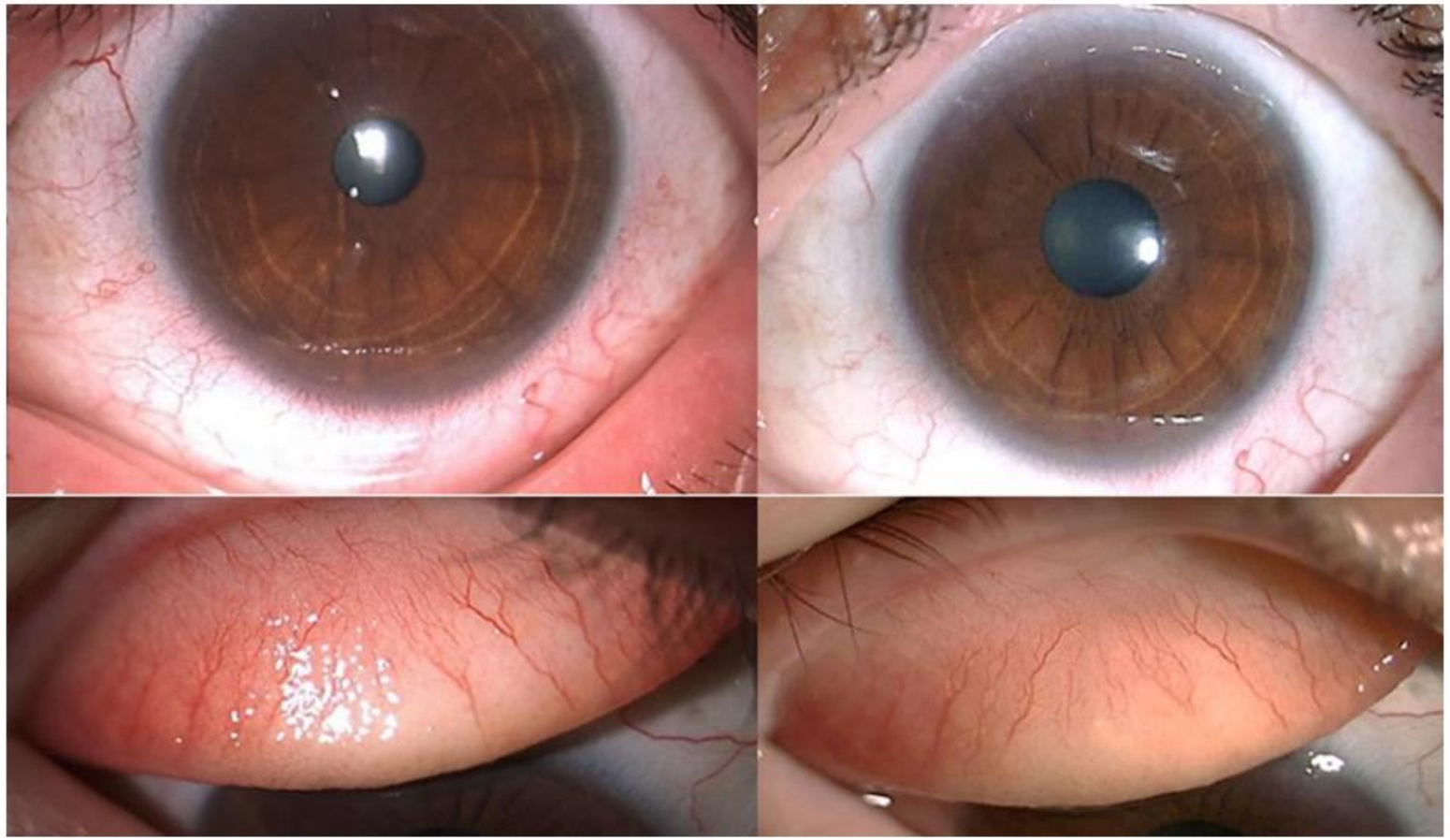


FIGURE 3 Ocular involvement in atopic dermatitis (AD). The figure shows ocular signs of atopic keratoconjunctivitis (AKC) in a patient previously treated with dupilumab (on the left): conjunctival hyperaemia, mucous filaments, increased tear meniscus, tarsal papillary reaction. On the right, the improvement of hyperaemia and papillary reaction after 12 weeks of treatment with upadacitinib.

Received: 20 October 2022 | Accepted: 16 January 2023
DOI: 10.1111/jdv.18922

JEADV JOURNAL OF THE EUROPEAN ACADEMY OF DERMATOLOGY & VENEREOLOGY

REVIEW ARTICLE

Expert consensus on the systemic treatment of atopic dermatitis in special populations

D. N. Adam[1,2,3] | M. J. Gooderham[3,4] | J. R. Beecker[3,5,6,7] | C. H. Hong[3,8,9] | C. S. Jack[10,11] | V. Jain[3,12] | P. Lansang[1,13,14] | C. W. Lynde[1,3,15] | K. A. Papp[3,16] | V. H. Prajapati[3,17,18,19,20,21] | I. Turchin[3,22,23] | J. Yeung[1,3,13,14]

Type 2 comorbidities: Ocular surface disease

5. Th2 blockade with IL-4 and/or IL-13 inhibitors in patients with AD increases incidence of OSD; however, this increased incidence is not observed when these medications are used in other conditions including asthma, CRSwNP and EoE.
   100% agreement
6. Although OSD may be induced or exacerbated by Th2 blockade with biologics, most cases are mild-to-moderate and do not warrant drug discontinuation.
   100% agreement
7. There is no evidence that MTX, CsA, MMF, AZA, or JAKis increase the incidence of OSD.
   100% agreement
8. When choosing a systemic treatment option for patients with a history of severe OSD, the treating dermatologist could consider starting with a JAKi or traditional systemic agent. If initiating an IL-4 and/or IL-13 inhibitor, consider an ophthalmology assessment prior to commencement of treatment.
   92% agreement

Management of Patients Affected by Moderate-to-Severe Atopic Dermatitis with JAK Inhibitors in Real-World Clinical Practice: An Italian Delphi Consensus

Luigi Gargiulo · Luciano Ibba · Piergiorgio Malagoli · Anna G. Burroni · Andrea Chiricozzi · Paolo Dapavo · Silvia M. Ferrucci · Massimo Gola · Maddalena Napolitano · Michela Ortoncelli · Maria T. Rossi · Claudio Sciarrone · Antonio Costanzo · Alessandra Narcisi

Received: January 19, 2024 / Accepted: February 28, 2024

Table 1 Summary of the Delphi consensus process for statements regarding the use of JAK inhibitors in clinical practice

Statement	Expert agreement first round (%)	Second round reformulation	Expert agreement second round (%)	Included in final recommendations
1 First-line JAK inhibitor may be preferred over biologic (anti-IL-4/13 or anti-IL-13) in the patient with moderate-severe atopic dermatitis with prevalent involvement of sensitive areas (e.g., face/neck, hands, genitalia)	100.00			Yes
3 JAK inhibitor may be a viable alternative, even in the first line, in patients with different clinical phenotypes of AD (nummular-like atopic dermatitis, prurigo nodularis-like, generalized inflammatory, psoriasiform)	83.33			Yes

Gargiulo L, Ibba L, Malagoli P, Burroni AG, Chiricozzi A, Dapavo P, Ferrucci SM, Gola M, Napolitano M, Ortoncelli M, Rossi MT, Sciarrone C, Costanzo A, Narcisi A. Management of Patients Affected by Moderate-to-Severe Atopic Dermatitis with JAK Inhibitors in Real-World Clinical Practice: An Italian Delphi Consensus. Dermatol Ther (Heidelb). 2024 Mar 21.

Table 1 Summary of the Delphi consensus process for statements regarding the use of JAK inhibitors in clinical practice

Statement	Expert agreement first round (%)	Second round reformulation	Expert agreement second round (%)	Included in final recommendations
4 JAK inhibitor may be preferred first-line over biologic (anti-IL-4/13 or anti-IL-13) in patients with concomitant psoriasis or an AD–psoriasis overlap pattern	83.33			Yes
6 In patients who have a history of recurrent conjunctivitis at baseline, JAK inhibitors may be preferred over dupilumab	100.00			Yes

Gargiulo L, Ibba L, Malagoli P, Burroni AG, Chiricozzi A, Dapavo P, Ferrucci SM, Gola M, Napolitano M, Ortoncelli M, Rossi MT, Sciarrone C, Costanzo A, Narcisi A. Management of Patients Affected by Moderate-to-Severe Atopic Dermatitis with JAK Inhibitors in Real-World Clinical Practice: An Italian Delphi Consensus. Dermatol Ther (Heidelb). 2024 Mar 21.

Grazie

Dott.ssa Marina Talamonti
Dott.ssa Claudia Paganini
Dott.ssa Virginia Maffei
Dott.ssa Angela Fico
Dott.ssa Antonia Rivieccio
Dott. Alfredo Belcastro
Dott. Lorenzo Savastano