SCUOLA DERMATOLOGICA
SERGIO CHIMENTI
Roma, 1-2 Dicembre 2023 YES or NO CONTEST 3° INCONTRO
Dermatology Update

Andrea Chiricozzi

Gestione clinica della dermatite atopica con farmaci anti-JAK (upadacitinib, abrocitinib, baricitinib)

Discosures

- In the last 3 years I have been board member and/or speaker and/or scientific advisor for:
  - AbbVie
  - Almirall
  - Boehringer Ingelheim
  - Bristol Myers Squibb
  - Galderma
  - Leo Pharma
  - Lilly
  - Janssen
  - Novartis
  - Sanofi Genzyme
  - UCB pharma

JAK inhibitors in AD

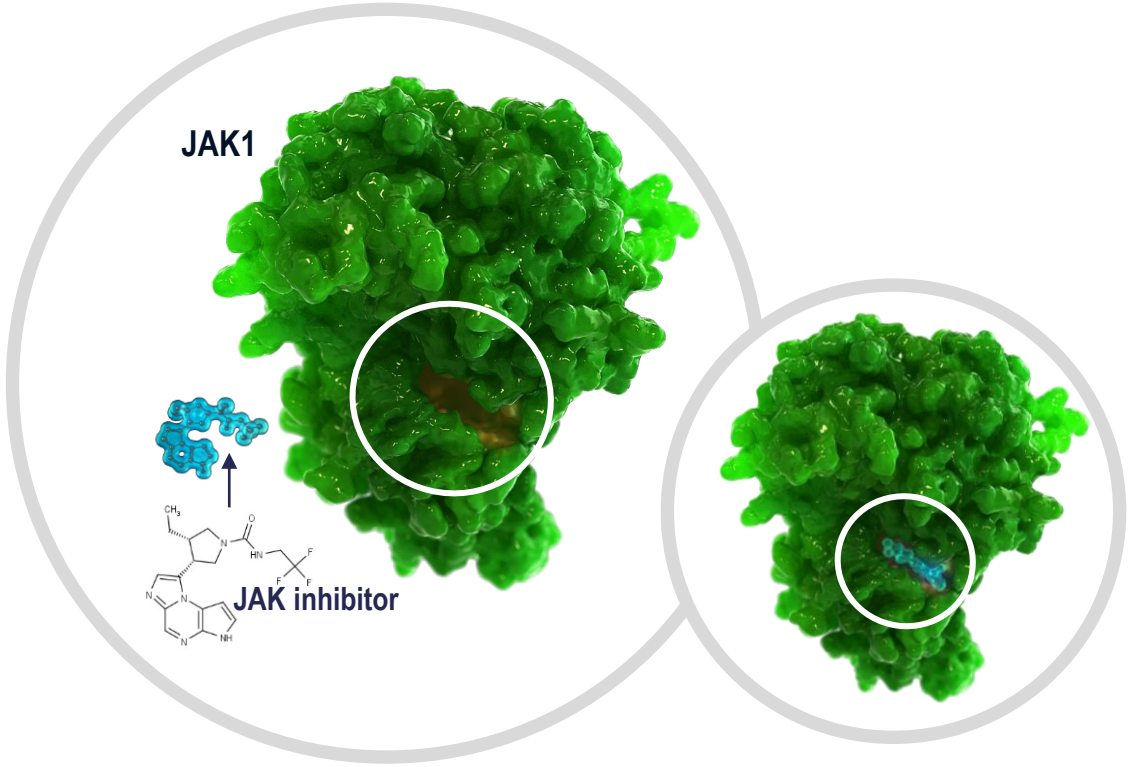
Table 1. List of novel JAK inhibitors investigated for the treatment of atopic dermatitis, describing their main targets and formulations.

Drug	Main target	Formulation
Ruxolitinib	JAK1, JAK2	Topical
Delgocitinib	Pan-JAK	Topical
Tofacitinib (Not in scope for AD)	Pan-JAK	Topical/Oral
Baricitinib	JAK1, JAK2	Oral
Upadacitinib	JAK1	Oral
Abrocitinib	JAK1	Oral

EMA-approved for the treatment of AD

Calabrese L, Chiricozzi A, De Simone C, Fossati B, D'Amore A, Peris K. Pharmacodynamics of Janus kinase inhibitors for the treatment of atopic dermatitis. Expert Opin Drug Metab Toxicol. 2022 May;18(5):347-355. doi: 10.1080/17425255.2022.2099835. Epub 2022 Jul 12. PMID: 35796377.

Advanced medicinal engineering was used to exploit subtle structural differences between the JAK isoforms to design JAK inhibitors with high selectivity



The subtle differences of the ATP-binding pocket between the JAK isoforms were leveraged in order to engineer a molecule with **high affinity** and **high selectivity** for the **JAK1, JAK2, JAK3, and/or TYK2** molecules

ATP, adenosine triphosphate; JAK, Janus kinase; UPA, upadacitinib.

1. Parmentier JM, et al. BMC Rheum 2018;2:23–34

JAK isoform selectivity assessed by *in vitro* assays

Isolated enzyme assays

IC_{50} values (nM)	JAK1	JAK2	JAK3	TYK2	Concluded relative selectivity
Baricitinib[1]	5.9	5.7	>400	53	JAK1 & JAK2
Abrocitinib[2]	29	803	>10000	1253	JAK1
Tofacitinib[3]	15.1	77.4	55.0	489	Pan-JAK
Upadacitinib[4]	47	120	2304	4690	JAK1

IC_{50} describes the concentration needed to inhibit 50% of enzyme activation[3]

A **low IC_{50}** value implies **higher potency**[3]

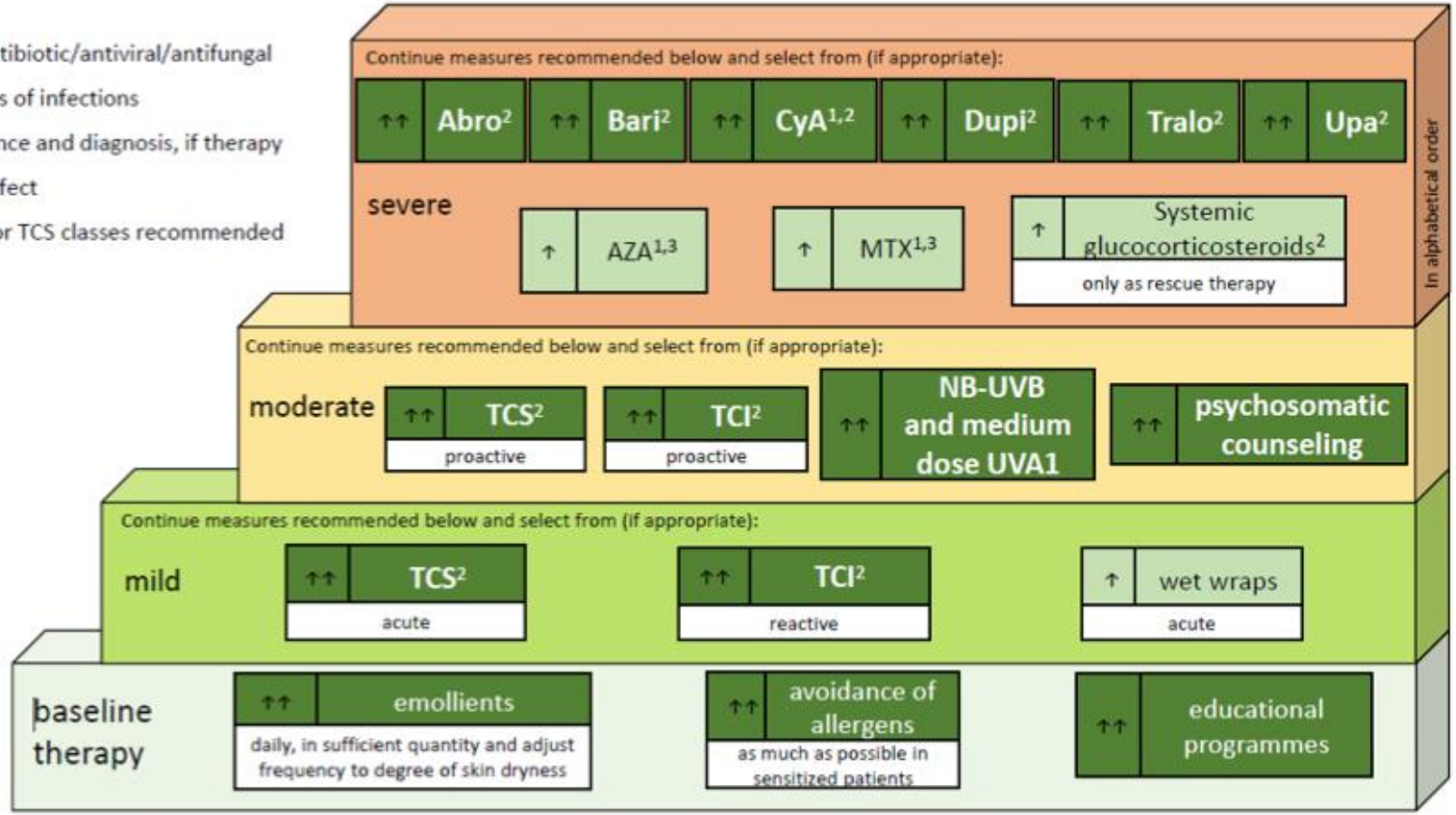
JAK isoform selectivity is defined by the **relative** differences between IC_{50}s for JAK isoforms[3]

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

1. Olumiant [SmPC]. Utrecht, the Netherlands: Eli Lilly Nederland B.V, 2017; 2. Vazquez ML, J Med Chem. 2018;61(3):1130-1152; 3. Choy EH. Rheumatology 2019;58:953-62; 4. Parmentier JM et al. BMC Rheum 2018;2:23;

EuroGuiDerm Guideline on Atopic Eczema
Stepped-care plan for adults with atopic eczema

- Add antiseptic/antibiotic/antiviral/antifungal treatment in cases of infections
- Consider compliance and diagnosis, if therapy has insufficient effect
- Refer to table 3 for TCS classes recommended



[1] refer to guideline text for restrictions, [2] licensed indication, [3] off-label treatment
↑↑ (dark green) strong recommendation for the use of an intervention / ↑ (light green) weak recommendation for the use of an intervention
For definitions of disease severity, acute, reactive, proactive see section 'VII' and section 'Introduction to systemic treatment' of the EuroGuiDerm Atopic Eczema Guideline
Abro= abrocitinib; AZA=azathioprine; Bari=baricitinib; CyA=ciclosporin; Dupi=dupilumab; MTX=methotrexate; TCI=topical calcineurin inhibitors; TCS= topical corticosteroids; Tralo=tralokinumab; Upa=upadacitinib; UVA1=ultraviolet A1; NB-UVB=narrow-band ultraviolet B

>75%
13/15

Table 1: General recommendations for systemic drugs for AE adult patients, who are candidates for systemic treatment (for details see corresponding chapter)

	Conventional systemic treatments			Biologics		JAK-inhibitors			Rescue therapy
	Ciclosporin	**Methotrexate**	**Azathioprine**	**Dupilumab**	**Tralokinumab**	**Abrocitinib**	**Baricitinib**	**Upadacitinib**	**Systemic corticosteroids**
Recommendation	↑↑	↑	↑	↑↑	↑↑	↑↑	↑↑	↑↑	↑
Dose for adults[1]	licensed ≥ 16 years; standard dosage adults: 2.5-5 mg/kg per day in two single doses	off-label; commonly used dosage adults: initial dose: 5-15 mg/ per week; maximum dose: 25 mg/ week	off-label; commonly used dosage adults: 1-3 mg/kg per day	licensed ≥ 6 years; adults: initially 600 mg s.c. day 1 followed by 300 mg Q2W	licensed for adults; initially 600 mg s.c. day 1 followed by 300 mg Q2W; consider Q4W dosing at week 16 in those achieving clear or almost clear skin	licensed for adults; dosage adults: 200 mg per day, reduction to 100 mg per day possible, depending on treatment response; age ≥ 65: 100 mg per day; the lowest effective dose for maintenance should be considered	licensed for adults; dosage adults: 4 mg per day, reduction to 2 mg per day possible, depending on treatment response	licensed ≥ 12 years; dosage adults: 15 or 30 mg per day based on individual patient presentation; age ≥ 65: 15 mg per day; the lowest effective dose for maintenance should be considered	general unspecific licence for adults and children for steroid responsive skin disease; dosage maximum: 1 mg/kg per day
Time to response (weeks)[2]	1-2	8-12	8-12	4-6	4-8	1-2	1-2	1-2	1-2
Time to relapse (weeks, based on expert experience)[2]	<2	>12	>12	>8	> 8	<2	<2	<2	<2
Monitoring	complete blood count, renal and liver profile, blood pressure,	complete blood count, renal and liver profile, PIIINP if available, screen for chronic infections	complete blood count, renal and liver profile, TPMT activity if available, screen for chronic infections	not required	not required	complete blood count, lipid profile, liver profile	complete blood count, lipid profile, liver profile	complete blood count, lipid profile, liver profile	not required for short-term treatment, consider blood glucose and testing for adrenal gland suppression with high doses/longer-term treatment
Selection of most relevant adverse events	serum creatinine↑, blood pressure ↑	nausea, fatigue, liver enzymes ↑, myelotoxicity	gastrointestinal disturbances, idiosyncratic hypersensitivity reactions, hepatotoxicity, myelotoxicity	Conjunctivitis, upper respiratory tract infections, arthralgia	upper respiratory tract infections; conjunctitivitis	upper respiratory tract infections,, increase in LDL cholesterol; thrombocytopenia, increased creatine phosphokinase, nausea and abdominal pain herpes virus infections, acne	upper respiratory tract infections,, increase in LDL cholesterol; thrombocytosis, nausea and abdominal pain herpes virus infections, acne	upper respiratory tract infections, acne; headache, anaemia and neutropenia, CK elevation, increase in LDL cholesterol, nausea and abdominal pain herpes virus infections	skin atrophy, weight gain, sleep disturbance, mood changes, hyperglycaemia or new onset diabetes, peptic ulcers/gastritis, osteoporosis

[1] SmPC, [2]expert experience, ↑ rise, AE- atopic eczema; GL – guideline, LDL – low density lipoprotein, PIIINP - Procollagen III N-Terminal Propeptide, TPMT – Thiopurine-S-Methyltransferase

Symbols	Implications (adapted from GRADE [1])
↑↑	We believe that all or almost all informed people would make that choice.
↑	We believe that most informed people would make that choice, but a substantial number would not.
0	We cannot make a recommendation.
↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not.
↓↓	We believe that all or almost all informed people would make a choice against that choice.
	No recommendation.

Upadacitinib

Selective JAK-1 inhibitor

Upadacitinib Phase 3 trial program in AD

	Measure Up 1 and Measure Up 2		AD Up	Heads Up
	Monotherapy vs placebo[1]		Combination (+ TCS) vs placebo[2]	Monotherapy vs dupilumab[3]
Trial	**NCT03569293**	**NCT03607422**	**NCT03568318**	**NCT03738397 (Phase 3b)**
Population	**Moderate-to-severe AD** Candidates for systemic therapy or have recently required systemic therapy for AD Adults and adolescents (≥12 years), adults (≥18 years) only in Heads Up vIGA-AD ≥3, EASI ≥16, BSA involvement ≥10%, Worst Pruritus NRS ≥4			
Trial duration	16 weeks (followed by long-term extension)			24 weeks (followed by open-label 52-week extension: NCT04195698[4])
Sample size	n=847	n=836	n=901	n=692
Comparator	Placebo		Placebo + TCS	Dupilumab
Treatment arms	Upadacitinib 15 mg QD Upadacitinib 30 mg QD Placebo QD		Upadacitinib 15 mg QD + TCS Upadacitinib 30 mg QD + TCS Placebo QD + TCS	Upadacitinib 30 mg QD Dupilumab 300 mg EOW
Primary endpoints	**16 weeks**			
	vIGA-AD 0/1 (% patients) EASI 75 (% patients)		vIGA-AD 0/1 (% patients) EASI 75 (% patients)	EASI 75 (% patients)

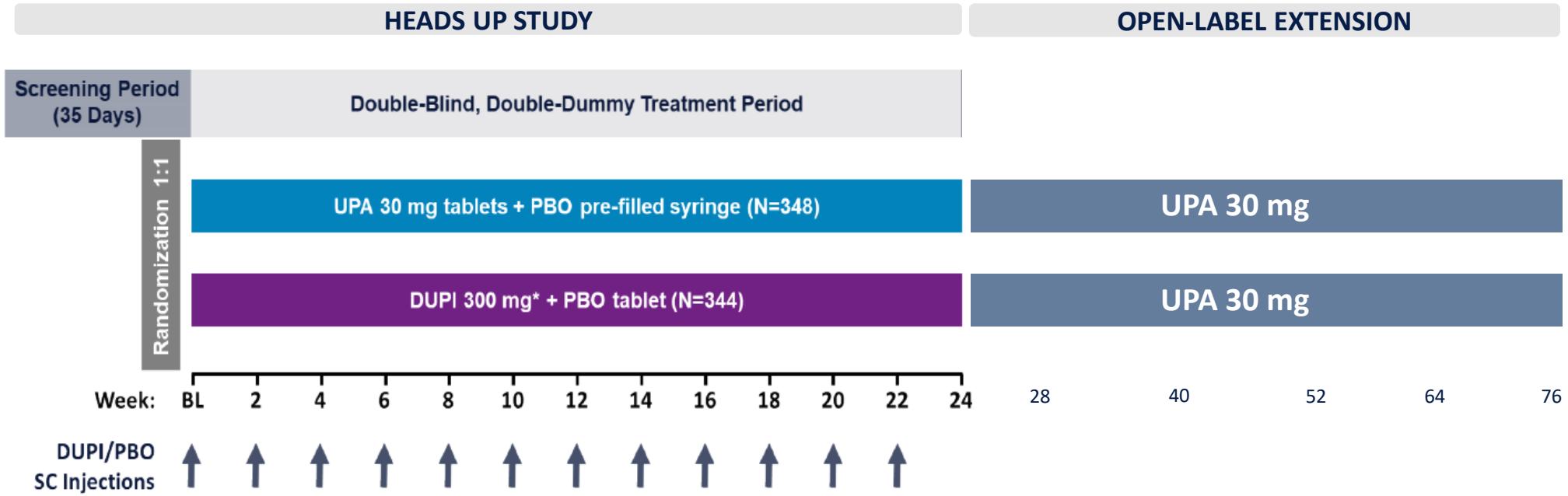
Upadacitinib met the primary and all key secondary endpoints vs placebo in Measure Up 1, 2, and AD Up, and of superiority vs dupilumab in Heads Up

AD, atopic dermatitis; BSA, body surface area; EASI, Eczema Area and Severity Index; EASI 75, ≥75% improvement in EASI; EOW, every other week; NRS, numeric rating scale; QD, once daily; TCS, topical corticosteroid; vIGA-AD, validated Investigator's Global Assessment for AD

1. Guttman-Yassky E, et al. Lancet 2021;397:2151–68; 2. Reich K, et al. Lancet 2021;397:2169–81; 3. Blauvelt A, et al. ISAD 2021 (PT-29); 4. ClinicalTrials.gov. NCT04195698. Available at: https://clinicaltrials.gov/ct2/show/NCT04195698 (last accessed June 2021).

Study design[1]

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

[a] Diagnosis of AD according to the Hanifin and Rajka criteria (≥3 of 4 major features and ≥3 of 23 minor features)[2]
[b] Exception of topical emollients. [c] Dupilumab 300 mg SC injection was administered EOW starting at the Week 2 visit and until the Week 22 visit, after an initial dose of 600 mg at the BL visit.

1. Blauvelt A, et al. JAMA Dermatol 2021;157:1047–55
2. Hanifin JM, Rajka G. Acta Derm Venereol Suppl (Stockh) 1980;92:44–47

Primary and secondary end point

End point	Time point
Primary end point	
Achievement of EASI75[a]	Week 16
Secondary end points in order of ranking	
% Change from baseline in worst pruritus NRS[b]	Week 16
Achievement of EASI100[a]	Week 16
Achievement of EASI90[a]	Week 16
% Change from baseline in Worst Pruritus NRS[b]	Week 4
Achievement of EASI75[a]	Week 2
% Change from baseline in Worst Pruritus NRS[b]	Week 1
Worst Pruritus NRS improvement ≥4 points[a,c]	Week 16

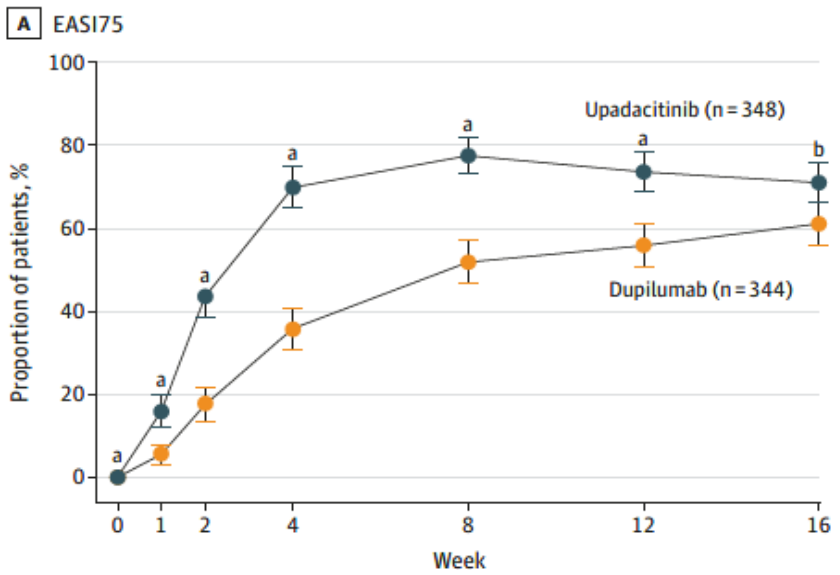
This study met

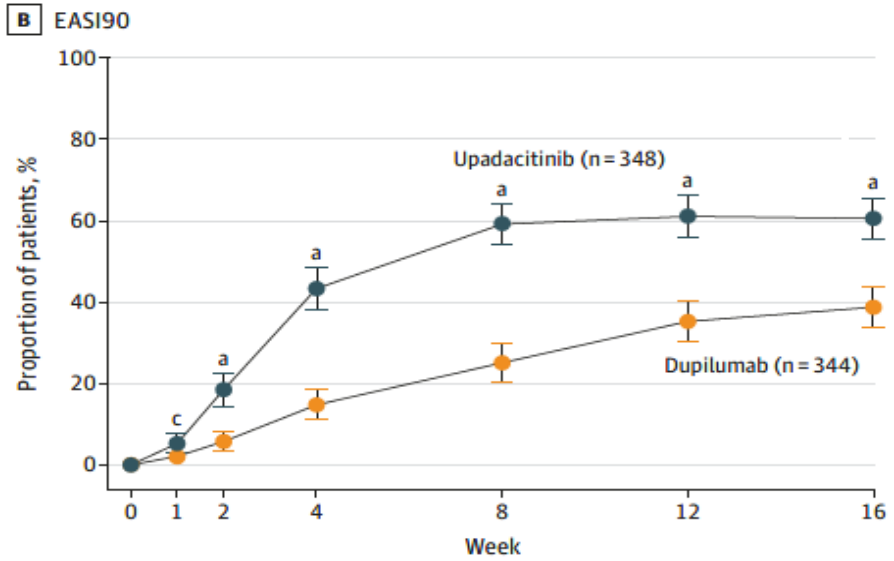
- the primary end point of EASI75 at week 16
- and all ranked secondary end points,

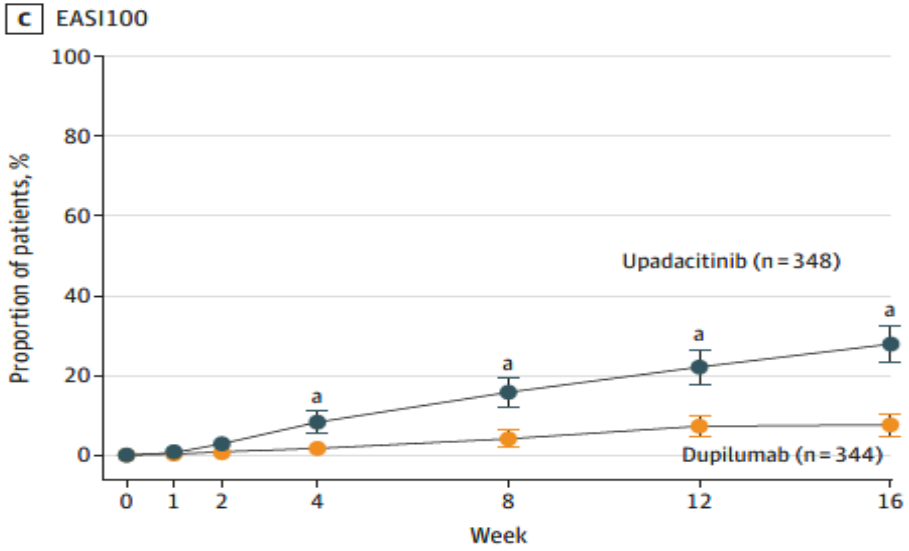
demonstrating **superiority of upadacitinib vs dupilumab** for the treatment of adults with moderate-to-severe AD.

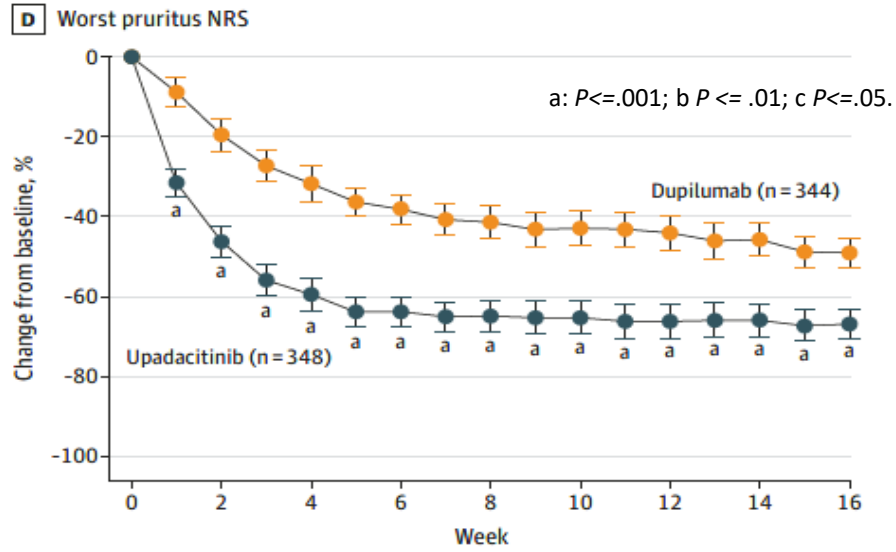
Blauvelt A, et al. JAMA Dermatol 2021;157:1047–55

Efficacy of upadacitinib vs dupilumab in adults with moderate-to-severe atopic dermatitis









a: *P*<=.001; b *P* <= .01; c *P*<=.05.

Blauvelt A, et al. JAMA Dermatol 2021;157:1047–55

American Journal of Clinical Dermatology (2023) 24:953–961
https://doi.org/10.1007/s40257-023-00798-0

ORIGINAL RESEARCH ARTICLE

Long-term Effectiveness and Safety of Upadacitinib for Atopic Dermatitis in a Real-world Setting: An Interim Analysis Through 48 Weeks of Observation

Andrea Chiricozzi · Michela Ortoncelli · Donatella Schena · Niccolò Gori · Silvia Mariel Ferrucci · Graziella Babino, et al. *[full author details at the end of the article]*

Table 1 Clinical and demographic characteristics of the study population

Patient characteristics	
Total population	146 patients
Male/female *n*, (%)	89 (61)/57 (39)
Mean age (± SD)	37.83 (± 14.4)
Mean BMI (± SD)	24.0 (± 4.1)
Median age at the onset of disease (25–75 percentile)	3 (1–13.2)
Atopic comorbidities	
Allergic rhinitis *n*, (%)	50/146 (34.2)
Asthma *n*, (%)	39/146 (26.7)
Allergic conjunctivitis *n*, (%)	29/146 (23.3)
Chronic rhinosinusitis with nasal polyposis *n*, (%)	1/146 (0.7)
Food allergy *n*, (%)	15/146 (10.3)
Family history of atopic conditions including AD	19/146 (13.0)
Previous treatments	
CsA *n*, (%)	110/146 (75.3)
Dupilumab *n*, (%)	136/146 (93.2)
Oral corticosteroids *n*, (%)	62/146 (42.5)
Methotrexate *n*, (%)	15/146 (10.3)
Phototherapy *n*, (%)	11/146 (7.5)
Azathioprine *n*, (%)	11/146 (7.5)
Tralokinumab *n*, (%)	2/146 (1.7)

AD atopic dermatitis, *BMI* body mass index, *CsA* cyclosporine, *SD* standard deviation

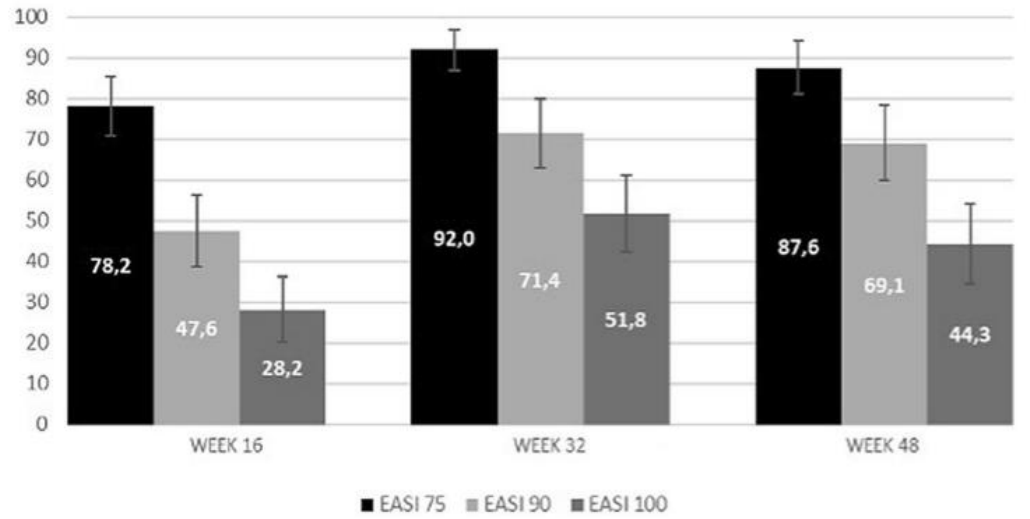


Fig. 1 Percentages of upadacitinib-treated patients achieving Eczema Area and Severity Index (EASI) 50, EASI 75, EASI 90, and EASI 100 responses through 48 weeks of treatment

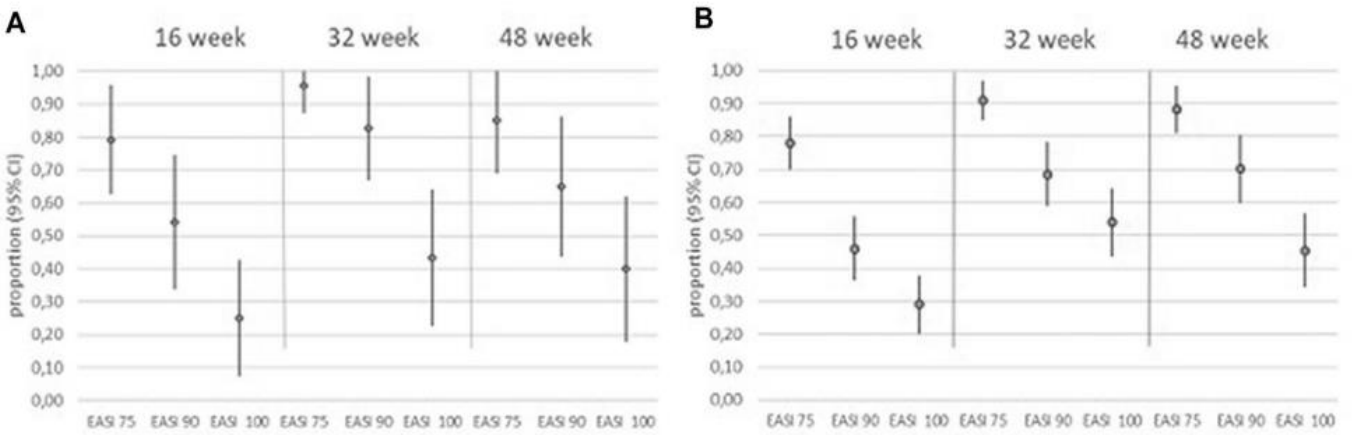


Fig. 2 Treatment response was similar between 15 mg versus 30 mg upadacitinib dosage. EASI 75, EASI 90, and EASI 100 responses in patients treated with an initial dose of 15 mg (**A**) or 30 mg (**B**) upadacitinib. *EASI* Eczema Area and Severity Index

Upadacitinib was initially prescribed at the dos- age of 30 mg daily in 118 of 146 (80.8%) patients and 15 mg daily in 28/146 (19.2%) patients. The two patient sub- cohorts did not differ in terms of baseline disease severity (Table 2). Dose variation was observed in 38 of 146 patients (26%) for a total of 48 treatment courses. Dose reduction from 30 to 15 mg was frequently prescribed

Safety

Item	
Total n. of AEs	29
Number of pts with at least one AE	17.8% (26/146)
AEs causing drug discontinuation	4
Infections	31.0% (9/29)
Blood test abnormalities	22.6% (7/29)
Folliculitis/acne	3.4% (5/146)
Herpes Zoster reactivation	1
Herpes simplex infection	1
Thrombophlebitis	3

Chiricozzi A, et al. Am J Clin Dermatol 2023

Overall TEAEs (Treatment-Emergent Adverse Events) Through End of Monitoring Period*

TEAEs through end of monitoring period*, n (%)	DUPI 300 mg (N = 344)	UPA 30 mg (N = 348)
Adverse event (AE)	230 (66.9)	270 (77.6)
AE with reasonable possibility of being drug-related[a]	129 (37.5)	170 (48.9)
Severe AE	15 (4.4)	31 (8.9)
Serious AE (SAE)	7 (2.0)	14 (4.0)
SAE with reasonable possibility of being drug-related[a]	4 (1.2)	5 (1.4)
AE leading to discontinuation of study drug	4 (1.2)	11 (3.2)
AE leading to death[b]	0	1 (0.3)
TEAEs Reported by ≥5% in Either Treatment Group		
Acne[h]	11 (3.2)	64 (18.4)
Dermatitis atopic	32 (9.3)	37 (10.6)
Upper respiratory tract infection	17 (4.9)	26 (7.5)
Blood CPK increased	11 (3.2)	26 (7.5)
Nasopharyngitis	27 (7.8)	23 (6.6)
Folliculitis	4 (1.2)	22 (6.3)
Urinary tract infection	15 (4.4)	19 (5.5)
Headache	23 (6.7)	17 (4.9)
Conjunctivitis	35 (10.2)	5 (1.4)

- The most frequently reported AE with upadacitinib was acne; all acne events were mild · moderate in severity, and primarily involved the face and trunk
- Conjunctivitis was the most commonly-reported AE for dupilumab
- No acne or conjunctivitis events were serious or led to study drug discontinuation

*Through 30 days following the last dose of upadacitinib or 84 days following the last dose of dupilumab, regardless of any study drug interruption

Blauvelt A, et al. JAMA Dermatol 2021;157:1047–55

Overall TEAEs (Treatment-Emergent Adverse Events) Through End of Monitoring Period*

Adverse Events of Special Interest	DUPI 300 mg (N = 344)	UPA 30 mg (N = 348)
Serious infections	2 (0.6)	4 (1.1)
Opportunistic infection, excluding tuberculosis (TB) and herpes zoster[c]	0	3 (0.9)
Herpes zoster	4 (1.2)	12 (3.4)
Active TB	0	0
Non-melanoma skin cancer (NMSC)[d]	1 (0.3)	0
Malignancy, excluding NMSC[e]	0	1 (0.3)
Lymphoma	0	0
Hepatic disorder[f]	5 (1.5)	12 (3.4)
Adjudicated gastrointestinal perforations	0	0
Anemia[g]	1 (0.3)	8 (2.3)
Neutropenia[g]	2 (0.6)	6 (1.7)
Lymphopenia[g]	0	2 (0.6)
Creatine phosphokinase (CPK) elevation	11 (3.2)	26 (7.5)
Renal dysfunction	1 (0.3)	1 (0.3)
Adjudicated major adverse cardiovascular events (MACE)	0	0
Adjudicated venous thromboembolic events (VTE)	0	0

- Rates of serious infection, eczema herpeticum, herpes zoster, and laboratory-related AEs were higher for upadacitinib
- Each of the serious infections was reported in a single patient; no eczema herpeticum or herpes zoster event was serious; most herpes zoster events involved a single dermatome
- Most hepatic disorders were asymptomatic transaminase elevations; mild or moderate in severity; none were serious
- Rates of anemia, neutropenia, and CPK elevation were higher among upadacitinib-treated patients; no events were serious or led to study drug discontinuation
- No cases of adjudicated VTEs or MACEs, active TB, or gastrointestinal perforation were reported in either treatment group

Blauvelt A, et al. JAMA Dermatol 2021;157:1047–55

Integrated safety analysis out to 52 weeks: Treatment-emergent adverse events and exposure-adjusted event rates during upadacitinib administration[a]

	Week 16			Week 52	
Events (events/100 PY)	**UPA 15 mg (n=557) PY=167.9**	**UPA 30 mg (n=567) PY=169.9**	**PBO (n=559) PY=156.0**	**UPA 15 mg (n=797) PY=953.3**	**UPA 30 mg (n=811) PY=978.2**
Any TEAE	870 (518.1)	1082 (637.0)	710 (455.2)	2402 (252.0)	2951 (301.7)
Serious AEs	13 (7.7)	17 (10.0)	18 (11.5)	65 (6.8)	83 (8.5)
AEs leading to discontinuation of study drug	17 (10.1)	22 (13.0)	24 (15.4)	43 (4.5)	70 (7.2)
Deaths	0	0	0	0	1[b] (0.1)
Most frequently reported TEAEs (≥10 events/100 PY in any treatment group at any time point)					
Acne	56 (33.4)	94 (55.3)	12 (7.7)	125 (13.1)	199 (20.3)
URTI	47 (28.0)	65 (38.3)	37 (23.7)	116 (12.2)	112 (11.4)
Nasopharyngitis	41 (24.4)	58 (34.1)	40 (25.6)	94 (9.9)	107 (10.9)
Headache	38 (22.6)	42 (24.7)	26 (16.7)	71 (7.4)	66 (6.7)
Blood CPK increased	28 (16.7)	30 (17.7)	13 (8.3)	67 (7.0)	109 (11.1)
Oral herpes	12 (7.1)	25 (14.7)	5 (3.2)	31 (3.3)	69 (7.1)
Diarrhea	18 (10.7)	19 (11.2)	14 (9.0)	32 (3.4)	34 (3.5)
Folliculitis	10 (6.0)	19 (11.2)	8 (5.1)	33 (3.5)	39 (4.0)
Neutropenia	4 (2.4)	18 (10.6)	2 (1.3)	10 (1.0)	28 (2.9)
Cough	16 (9.5)	17 (10.0)	9 (5.8)	45 (4.7)	28 (2.9)
Dermatitis atopic	17 (10.1)	8 (4.7)	56 (35.9)	85 (8.9)	52 (5.3)
Nausea	18 (10.7)	16 (9.4)	4 (2.6)	22 (2.3)	27 (2.8)

The most frequently reported AEs (≥10 events/100 PY in any group) were acne, URTI, nasopharyngitis, and CPK elevation

The safety profile of UPA through Week 52 generally remained unchanged from that observed during the 16-week, placebo-controlled treatment period

[a]Combined data from Measure Up 1 and Measure Up 2 studies (safety population). [b]One death (myocardial infarction related to COVID-19 infection) occurred on study Day 309 (28 days after last study drug dose) in a 67-year-old man treated with UPA 30 mg in Measure Up 1; the patient had cardiovascular disease risk factors, including type 2 diabetes mellitus, hypertension, obesity, and hypercholesterolemia. AE, adverse event; CPK, creatine phosphokinase; PBO, placebo; PY, patient-year; TEAE, treatment-emergent AE; UPA, upadacitinib; URTI, upper respiratory tract infection

Simpson EL, et al. DERM 2021 Presentation

Integrated safety analysis out to 52 weeks: Adverse events of special interest during upadacitinib administration[a]

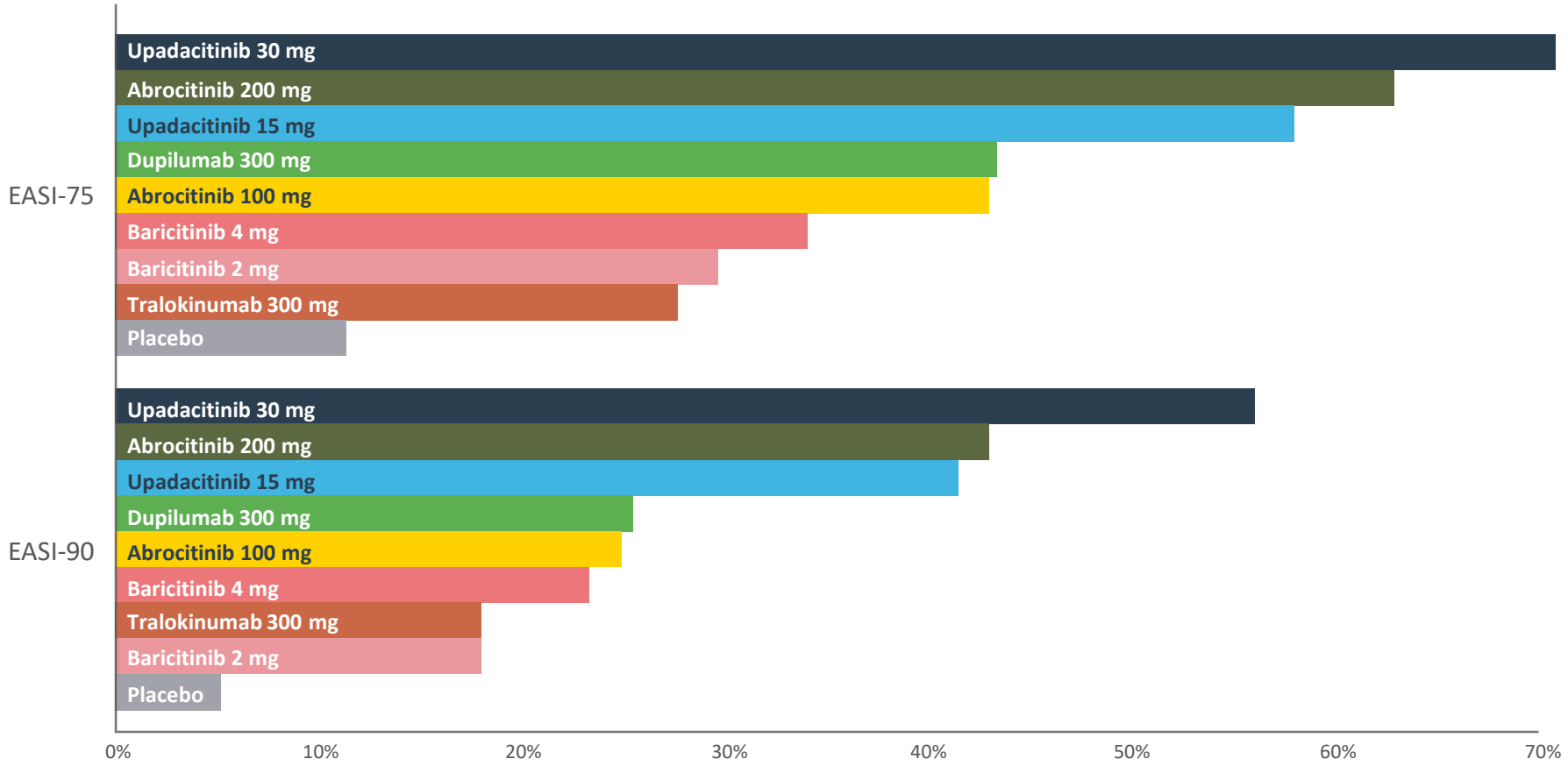
Events (events/100 PY)	Week 16			Week 52	
	UPA 15 mg (n=557) PY=167.9	UPA 30 mg (n=567) PY=169.9	PBO (n=559) PY=156.0	UPA 15 mg (n=797) PY=953.3	UPA 30 mg (n=811) PY=978.2
Serious infections	3 (1.8)	4 (2.4)	3 (1.9)	21 (2.2)	35 (3.6)
Opportunistic infection excluding tuberculosis and herpes zoster	5 (3.0)	4 (2.4)	4 (2.6)	18 (1.9)	20 (2.0)
Eczema herpeticum[b]	5 (3.0)	4 (2.4)	4 (2.6)	18 (1.9)	19 (1.9)
Herpes zoster	11 (6.6)	9 (5.3)	2 (1.3)	34 (3.6)	53 (5.4)
Active tuberculosis	0	0	0	1 (0.1)	1 (0.1)
NMSC	3 (1.8)	1 (0.6)	0	4 (0.4)	4 (0.4)
Malignancy other than NMSC	0	3 (1.8)	0	2 (0.2)	5 (0.5)
Lymphoma	0	1 (0.6)	0	0	1 (0.1)
Hepatic disorder	8 (4.8)	15 (8.8)	7 (4.5)	56 (5.9)	94 (9.6)
Adjudicated GI perforations	0	0	0	0	0
Anemia	3 (1.8)	10 (5.9)	3 (1.9)	15 (1.6)	37 (3.8)
Neutropenia	6 (3.6)	22 (13.0)	3 (1.9)	16 (1.7)	34 (3.5)
Lymphopenia	3 (1.8)	3 (1.8)	4 (2.6)	7 (0.7)	9 (0.9)
CPK elevation	28 (16.7)	30 (17. 7)	13 (8.3)	67 (7.0)	109 (11.1)
Renal dysfunction	0	0	0	0	3 (0.3)
Adjudicated MACE	0	0	0	1 (0.1)	0
Adjudicated venous thromboembolic event	0	0	1 (0.6)	1 (0.1)	1 (0.1)

[a]Data from Measure Up 1 and Measure Up 2 studies (safety population). [b]Eczema herpeticum or Kaposi's varicelliform eruption

CPK, creatine phosphokinase; GI, gastrointestinal; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; PBO, placebo; PY, patient-year; UPA, upadacitinib

Simpson EL, et al. DERM 2021 Presentation

Comparison with network metanalysis



È stata condotta una revisione sistematica della letteratura in accordo con il Cochrane Handbook for Systematic Reviews of Interventions 2019, il National Institute for Health and Care Excellence Guide to the Methods of Technology Appraisal 2013 e il Centre for Reviews and Dissemination Guidance for Undertaking Reviews in Health Care. La ricerca sistematica della letteratura è stata condotta su dati registrati fino a Maggio 2021 ed è stata disegnata per identificare tutti gli studi clinici randomizzati controllati di fase 3 o 4 valutando le terapie mirate negli adulti con dermatite atopica moderata-severa che presentavano una risposta inadeguata ai cortisonici per uso topico e al trattamento con gli inibitori della calcineurina o per i quali i trattamenti topici non erano consigliabili da un punto di vista medico. Questa analisi ha anche escluso studi con pazienti che hanno ricevuto cortisonici per uso topico o inibitori della calcineurina in combinazione con le terapie mirate per la dermatite atopica. Nell'analisi sono stati inclusi dati provenienti da 11 studi clinici randomizzati controllati con placebo che hanno incluso 6254 pazienti e 5 terapie mirate (abrocitinib, baricitinib, dupilumab, tralokinumab, e upadacitinib).

Abbreviazioni: NMA, Network Meta-Analysis; EASI, area dell'eczema e indice di gravità; EASI75, proporzione di pazienti che raggiunge un miglioramento del 75% nel punteggio EASI;

EASI90, proporzione di pazienti che raggiunge un miglioramento del 90% nel punteggio EASI

Silverberg JI et al. Dermatol Ther (Heidelb) (2022); 12:1181–1196

Resolution of skin lesions (IGA 0/1) and improvement of itch (ΔNRS≥4)

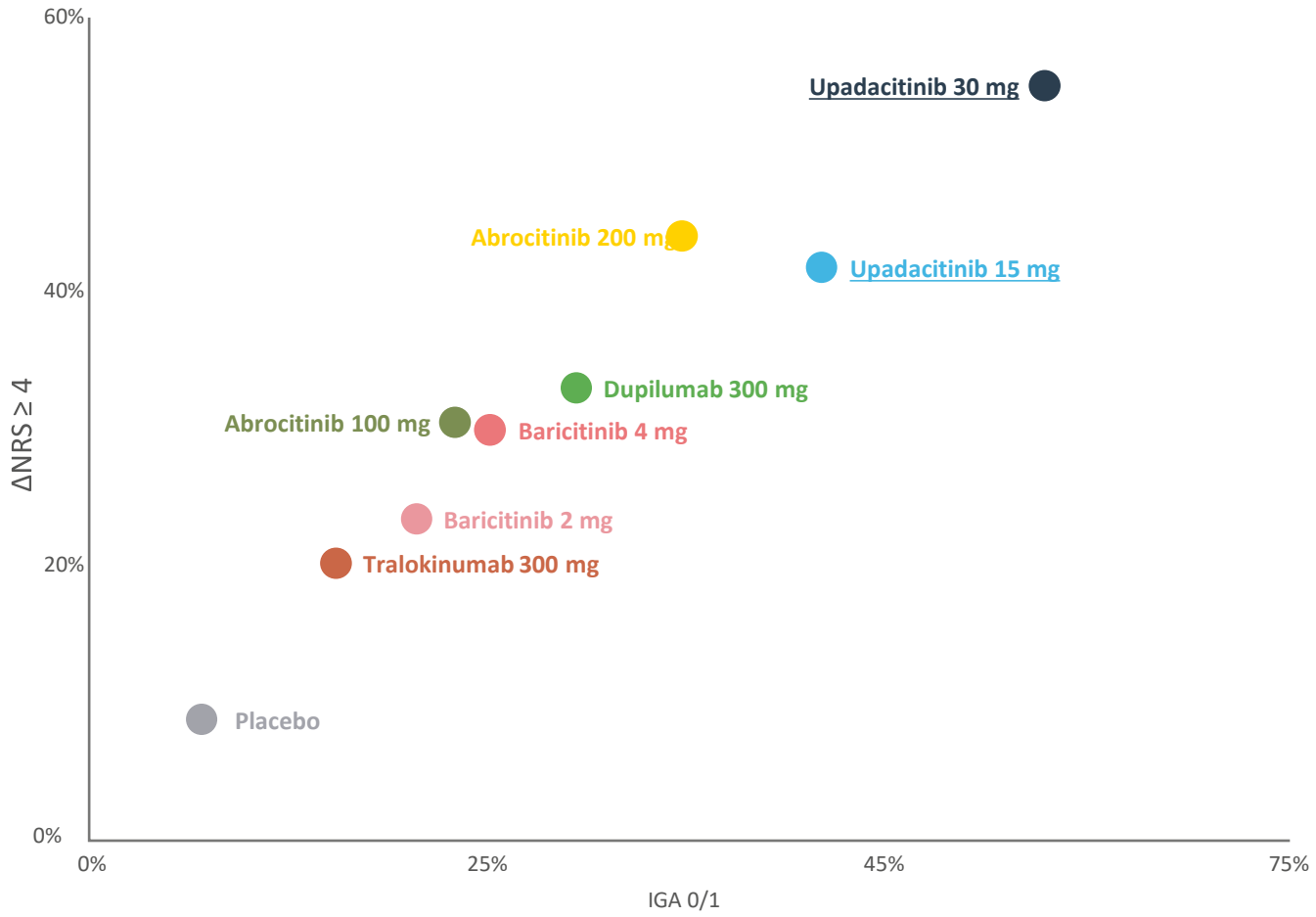


Figura adattata da fig 2. Stime del tasso di risposta assoluto per IGA 0/1 vs NRS ≥ 4 per la dermatite atopica moderata-severa (timepoint dell'endpoint primario)

È stata condotta una revisione sistematica della letteratura in accordo con il Cochrane Handbook for Systematic Reviews of Interventions 2019, il National Institute for Health and Care Excellence Guide to the Methods of Technology Appraisal 2013 e il Centre for Reviews and Dissemination Guidance for Undertaking Reviews in Health Care. La ricerca sistematica della letteratura è stata condotta su dati registrati fino a Maggio 2021 ed è stata disegnata per identificare tutti gli studi clinici randomizzati controllati di fase 3 o 4 valutando le terapie mirate negli adulti con dermatite atopica moderata-severa che presentavano una risposta inadeguata ai cortisonici per uso topico e al trattamento con gli inibitori della calcineurina o per i quali i trattamenti topici non erano consigliabili da un punto di vista medico. Questa analisi ha anche escluso studi con pazienti che hanno ricevuto cortisonici per uso topico o inibitori della calcineurina in combinazione con le terapie mirate per la dermatite atopica. Nell'analisi sono stati inclusi dati provenienti da 11 studi clinici randomizzati controllati con placebo che hanno incluso 6254 pazienti e 5 terapie mirate (abrocitinib, baricitinib, dupilumab, tralokinumab, e upadacitinib).

Abbreviazioni: NMA, Network Meta-Analysis; ΔNRS ≥ 4, riduzione ≥ 4 punti rispetto al basale del Numerical Rating Scale del prurito; IGA, Investigator's Global Assessment for Atopic Dermatitis.

Silverberg JI et al. Dermatol Ther (Heidelb) (2022) 12:1181–1196

Dermatology

Atopic Dermatitis – Research Article

Dermatology
DOI: 10.1159/000519361

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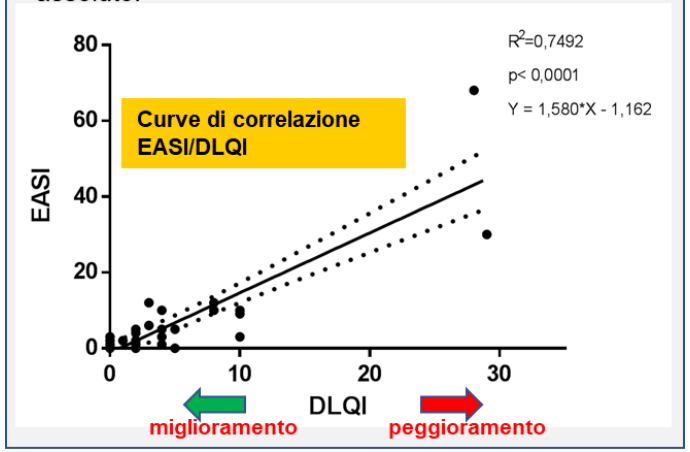
Published online: October 28, 2021

Therapeutic Impact and Management of Persistent Head and Neck Atopic Dermatitis in Dupilumab-Treated Patients

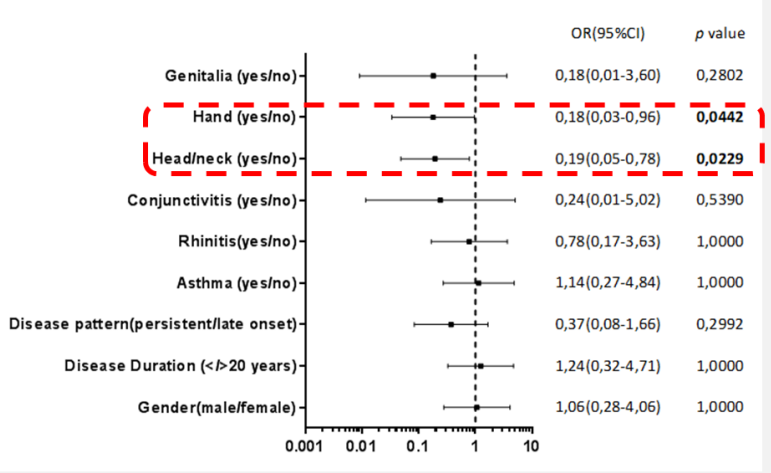
Andrea Chiricozzi[a, b] Niccolò Gori[b] Lucia Di Nardo[b] Flaminia Antonelli[a, b] Cristiano Caruso[c] Giacomo Caldarola[a] Laura Calabrese[a, b] Cristina Guerriero[a] Clara De Simone[a, b] Ketty Peris[a, b]

[a]Dermatologia, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy; [b]Dermatologia, Università Cattolica del Sacro Cuore, Rome, Italy; [c]Allergy Unit, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy

Il punteggio EASI è correlato positivamente con il punteggio DLQI, identificando il punteggio DLQI 0-1 (alcun impatto della malattia sulla QoL) come predittore altamente significativo di EASI ≤1 assoluto.

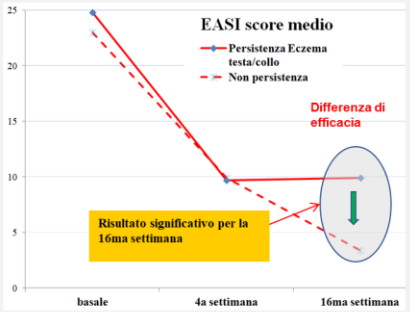


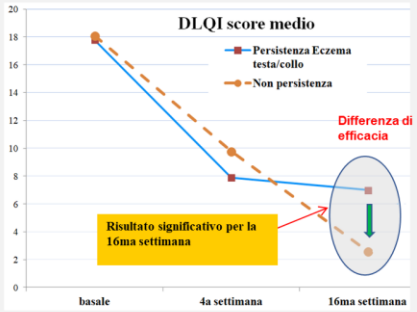
Si è cercato di definire i fattori predittivi di base (siti corporei colpiti, sesso, pattern di malattia, comorbidità atopiche, durata della malattia) che influenzano la risposta al trattamento, in particolare la probabilità di ottenere una risposta completa o quasi completa in termini di EASI≤1 (figura sottostante). Gli unici fattori predittivi significativi sono stati le localizzazioni testa/collo e mani, mentre altri fattori non sono stati trovati significativamente associati ad una risposta inferiore.



I pazienti con persistenza testa/collo hanno mostrato una risposta **significativamente inferiore** rispetto ai pazienti senza persistenza testa/collo della DA in termini di riduzione del punteggio sia EASI che DLQI

I soggetti con coinvolgimento testa/collo DA al basale erano il 61% (25/41), mentre le lesioni eczematose residue in quest'area sono state rilevate nel 43,9% (18/41) alla settimana 4, il 41,5% (17/41) alla settimana 16, e il 14,6% (4/27) alla settimana 32.





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

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

[1] Dermatologia, Dipartimento Universitario di Medicina e Chirurgia Traslazionale, Università Cattolica del Sacro Cuore, Rome, Italy.

[2] Dermatologia, Dipartimento Scienze Mediche e Chirurgiche, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy.

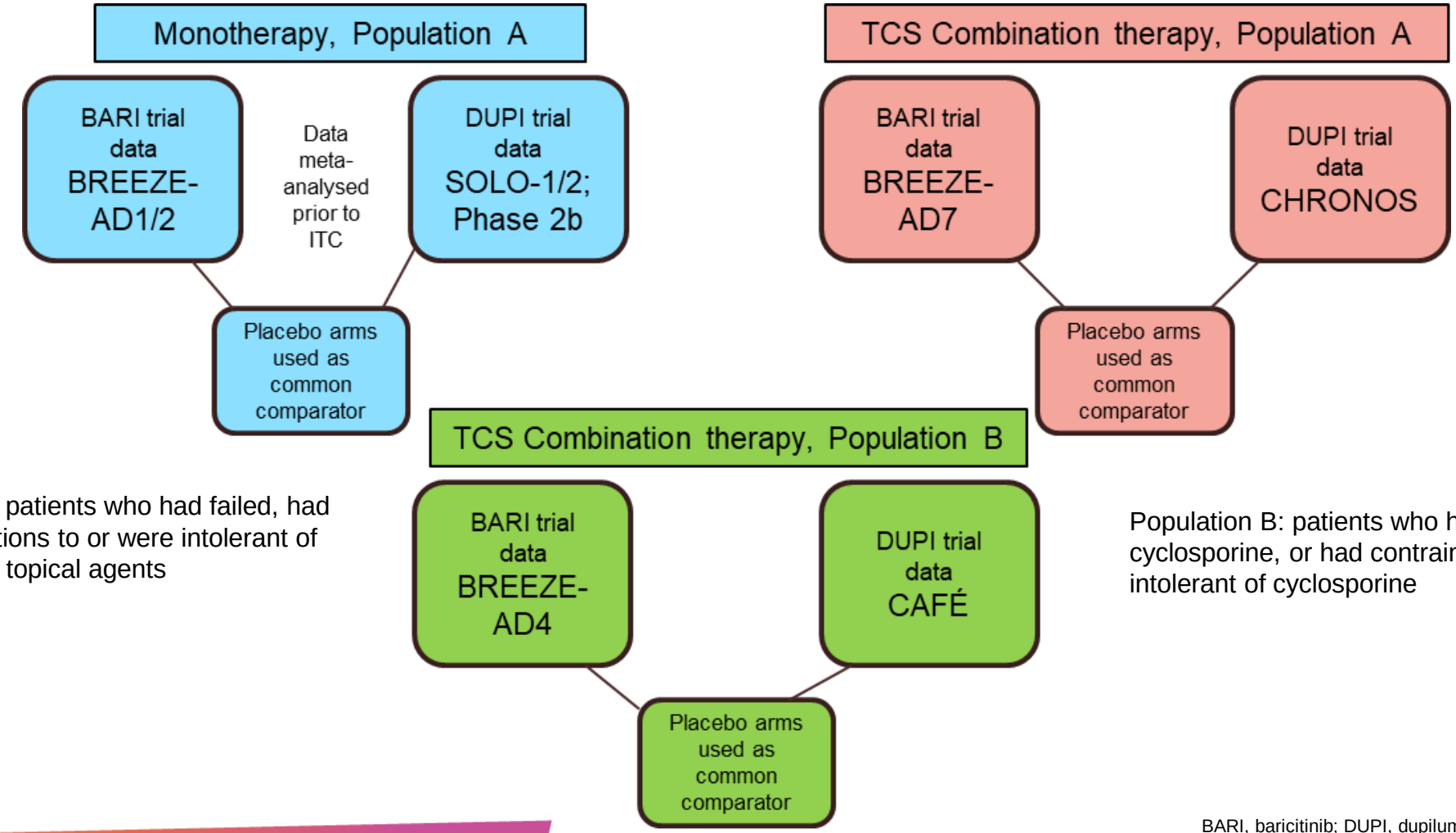
Article *in* Clinical and Experimental Dermatology · February 2023

Baricitinib

JAK-1/2 inhibitor
Dermatological indications: atopic dermatitis and alopecia areata

Indirect Treatment Comparison of Baricitinib versus Dupilumab in Adults with Moderate-to-Severe Atopic Dermatitis

Marjolein S De Bruin-Weller,[1] Esther Serra-Baldrich,[2] Sebastien Barbarot,[3] Afaf Raibouaa,[4] Helmut Petto,[4] Jean-Philippe Capron,[4] Susanne Grond,[4] Thomas Werfel[5]



Population A: patients who had failed, had contraindications to or were intolerant of topical agents

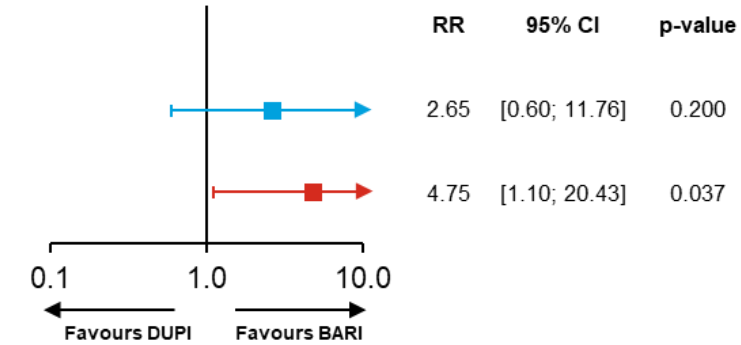
Population B: patients who had in addition failed cyclosporine, or had contraindications to or were intolerant of cyclosporine

BARI, baricitinib; DUPI, dupilumab; TCS, topical corticosteroid

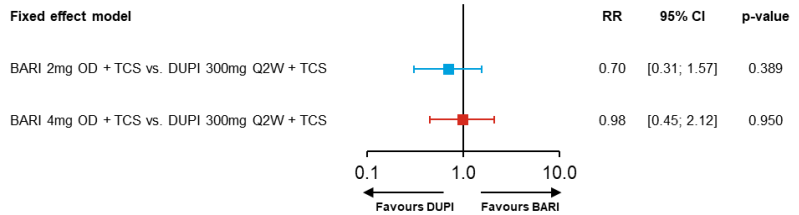
BARI vs DUPI for Itch NRS ≥4-point improvement at Week 2

- In Population A, Itch NRS ≥ 4-point improvement at week 2 significantly favoured BARI 4 mg monotherapy vs DUPI monotherapy when indirectly compared
- No other significant between-treatment differences were observed in any population or for any treatment regimen

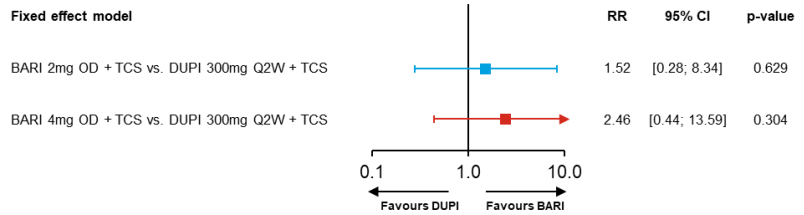
Monotherapy (patients who had failed, had contraindications to or were intolerant of topical agents



TCS Combination Therapy (patients who had failed, had contraindications to or were intolerant of topical agents)



TCS Combination Therapy (patients who had in addition failed cyclosporine, or had contraindications to or were intolerant of cyclosporine)

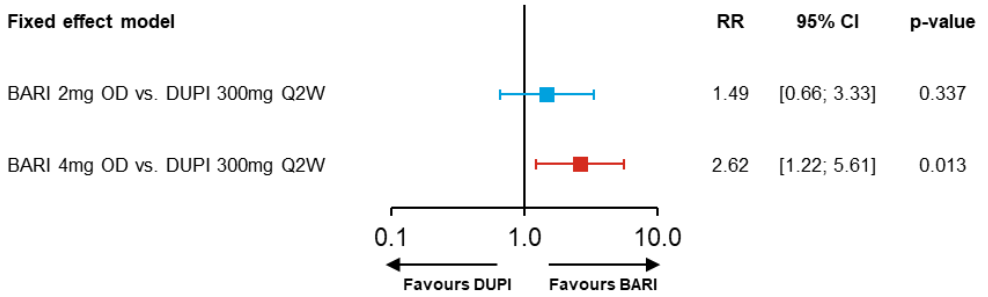


BARI, baricitinib; CI, confidence interval; DUPI, dupilumab; NRS, numeric rating scale; OD, once daily; RR, risk ratio; TCS, topical corticosteroid; Q2W, every 2 weeks

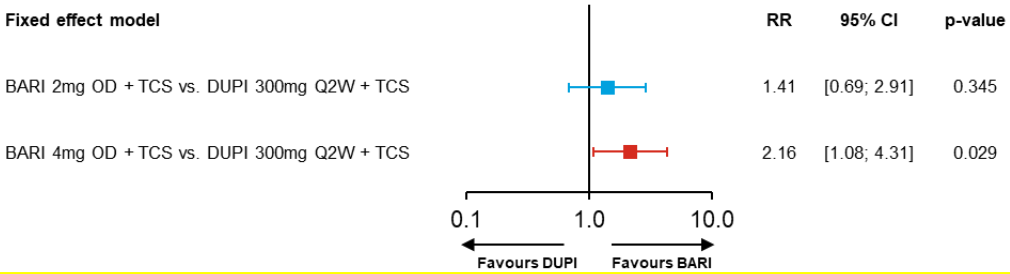
BARI vs DUPI for Itch NRS ≥4-point improvement at Week 4

- In Population A, Itch NRS ≥ 4-point improvement at week 4 significantly favoured BARI 4 mg vs DUPI both as monotherapy and as TCS combination therapy when indirectly compared
- No significant between-treatment differences were observed between BARI 2 mg vs DUPI in Population A or between BARI 4 mg vs DUPI in Population B

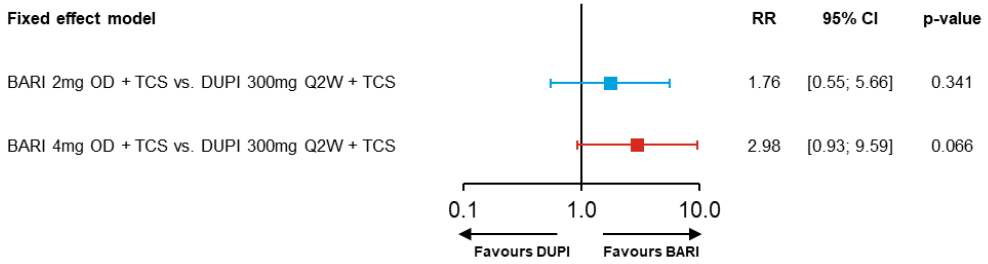
Monotherapy (patients who had failed, had contraindications to or were intolerant of topical agents



TCS Combination Therapy (patients who had failed, had contraindications to or were intolerant of topical agents)



TCS Combination Therapy (patients who had in addition failed cyclosporine, or had contraindications to or were intolerant of cyclosporine)

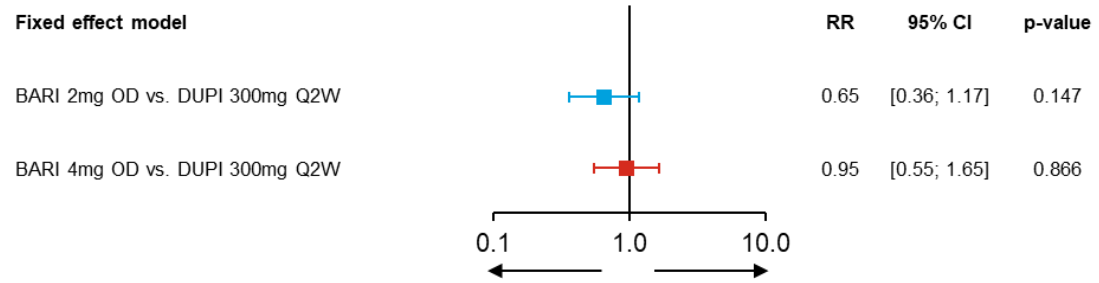


BARI, baricitinib; CI, confidence interval; DUPI, dupilumab; NRS, numeric rating scale; OD, once daily; RR, risk ratio; TCS, topical corticosteroid; Q2W, every 2 weeks

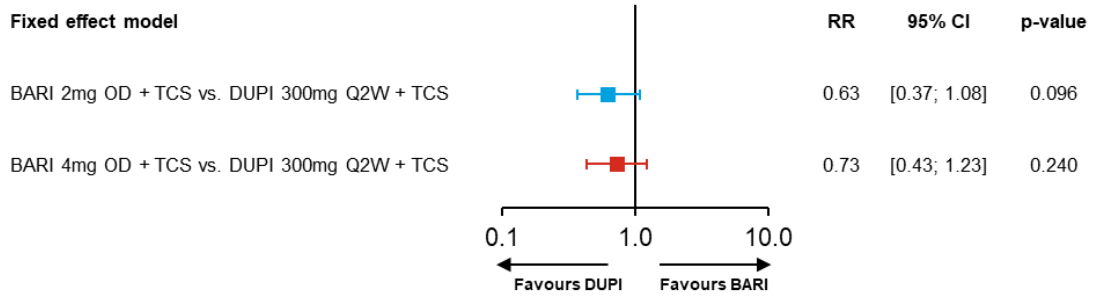
BARI vs DUPI for **Itch NRS ≥4-point improvement at Week 16**

- There were no statistically significant differences between BARI and DUPI as either monotherapy or TCS combination therapy when indirectly comparing Itch NRS ≥ 4-point improvement at week 16

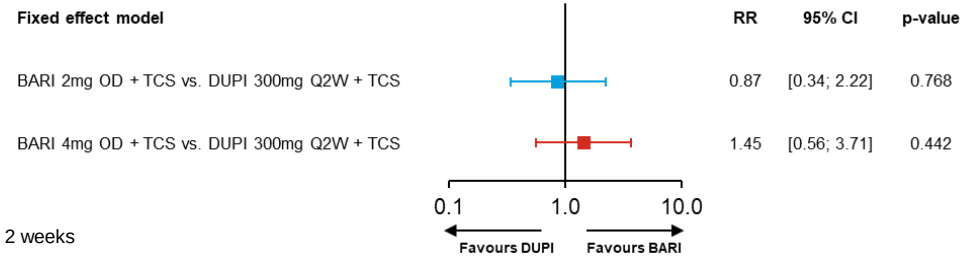
Monotherapy (patients who had failed, had contraindications to or were intolerant of topical agents



TCS Combination Therapy (patients who had failed, had contraindications to or were intolerant of topical agents)



TCS Combination Therapy (patients who had in addition failed cyclosporine, or had contraindications to or were intolerant of cyclosporine)

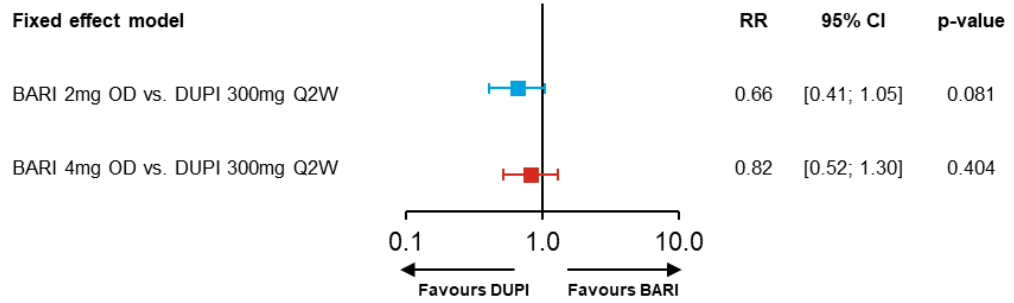


BARI, baricitinib; CI, confidence interval; DUPI, dupilumab; NRS, numeric rating scale; OD, once daily; RR, risk ratio; TCS, topical corticosteroid; Q2W, every 2 weeks

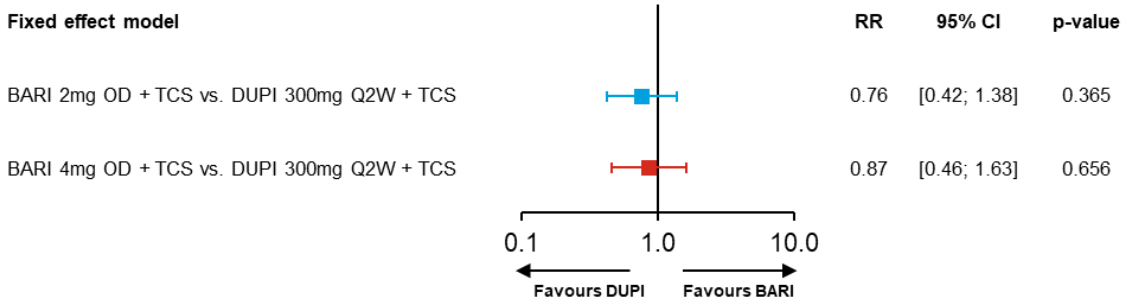
BARI vs DUPI for EASI75 at Week 16

- There were no statistically significant differences between BARI and DUPI in either monotherapy or TCS combination therapy when indirectly comparing EASI75 outcomes at week 16

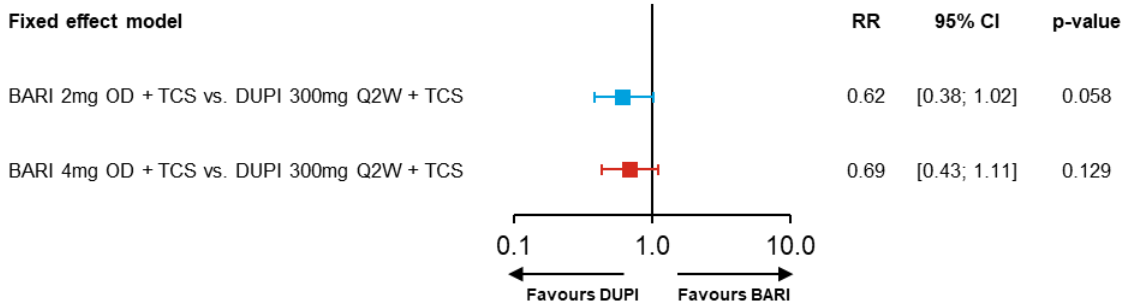
Monotherapy (patients who had failed, had contraindications to or were intolerant of topical agents



TCS Combination Therapy (patients who had failed, had contraindications to or were intolerant of topical agents)



TCS Combination Therapy (patients who had in addition failed cyclosporine, or had contraindications to or were intolerant of cyclosporine)



BARI, baricitinib; CI, confidence interval; DUPI, dupilumab; NRS, numeric rating scale; OD, once daily; RR, risk ratio; TCS, topical corticosteroid; Q2W, every 2 weeks

Adv Ther (2023) 40:3574–3587
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

Adv Ther (2023) 40:3574–3587

Patients with moderate-to-severe atopic dermatitis and body surface area affecting 10–40% and severe itch were characterized as likely to benefit most from baricitinib 4-mg topical corticosteroid combination therapy

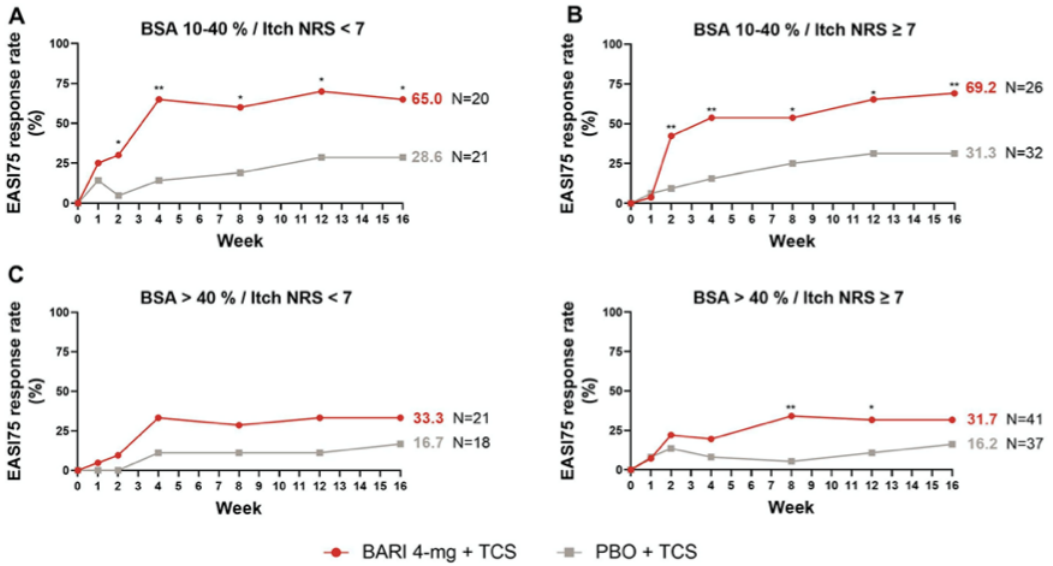


Fig. 2 EASI75 response rate over 16 weeks across identified BSA/Itch NRS subgroups. Proportion of patients achieving a 75% improvement in EASI score with **A** BSA 10–40%/Itch NRS < 7, **B** BSA 10–40%/Itch NRS ≥ 7 (itch-dominant phenotype), **C** BSA > 40%/Itch NRS < 7, and **D** BSA > 40%/Itch NRS ≥ 7. *p*-values are based on Fisher's exact test. $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$. *BARI* baricitinib, *BSA* body surface area, *EASI* Eczema Area and Severity Index, *EASI75* ≥ 75% improvement in Eczema Area and Severity Index, *NRS* numerical rating scale, *N* number, *PBO* placebo, *TCS* topical corticosteroid

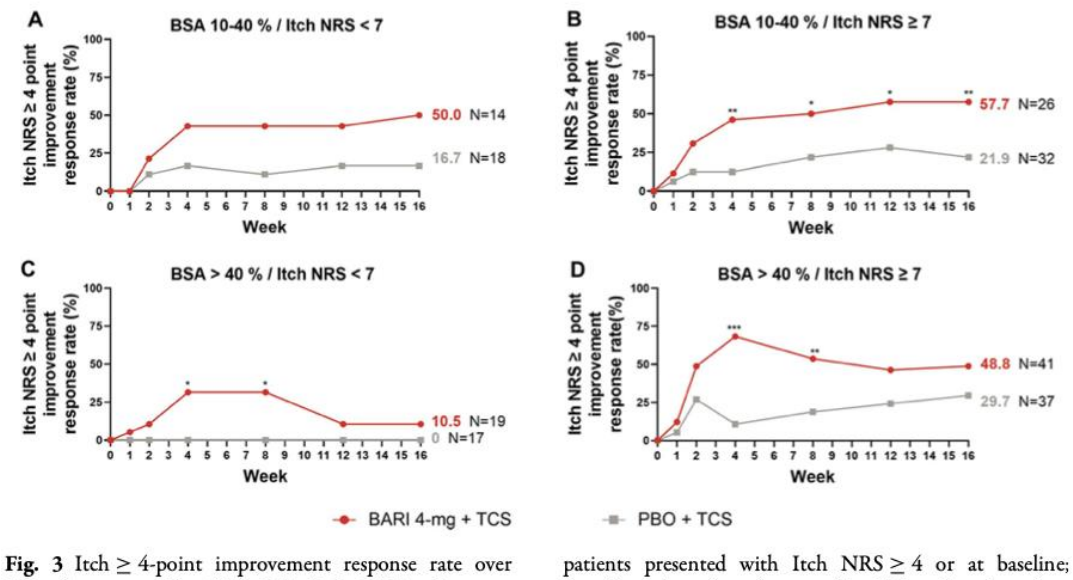


Fig. 3 Itch ≥ 4-point improvement response rate over 16 weeks across identified BSA/Itch NRS subgroups. Proportion of patients achieving a ≥ 4-point improvement in Itch NRS with **A** BSA 10–40%/Itch NRS < 7, **B** BSA 10–40%/Itch NRS ≥ 7 (itch-dominant phenotype), **C** BSA > 40%/Itch NRS < 7, and **D** BSA > 40%/Itch NRS ≥ 7. Itch 4-point improvement was assessed in patients presented with Itch NRS ≥ 4 or at baseline; therefore, the *n* for subgroups (**A**, **C**) is reduced. *p*-values are based on Fisher's exact test. $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$. *BARI* baricitinib, *BSA* body surface area, *NRS* Numerical Rating Scale, *N* number, *PBO* placebo, *TCS* topical corticosteroid

Clin Exp Dermatol 2023; **48**:881–888
https://doi.org/10.1093/ced/llad129
Advance access publication date: 10 April 2023

CED
Clinical and Experimental Dermatology
Original Article

Early improvements in signs and symptoms predict clinical response to baricitinib in patients with moderate-to-severe atopic dermatitis

Thomas Bieber,[1,2] Jacob P. Thyssen,[3] Alan D. Irvine,[4] Yuichiro Tsunemi,[5] Yun-Fei Chen,[6] Luna Sun,[6] Andrea Schloebe,[6] Elisabeth Riedl[6] and Michael J. Cork[7]

What does this study add?

- This study identified a ≥ 50% reduction in Eczema Area and Severity Index (EASI 50) score or ≥ 3-point improvement in Itch Numeric Rating Scale (NRS ≥ 3) and validated Investigator Global Assessment for AD (vIGA-AD) ≤ 2 or Itch NRS ≥ 3 at week 4 or 8 after treatment initiation as reliable predictors of clinical response to baricitinib, both as monotherapy and in combination with topical corticosteroids, at week 16.
- Early predictor analysis can inform therapeutic decision-making for physicians and optimize the benefit/risk ratio for patients with AD who initiate treatment with baricitinib.

Dermatol Ther (Heidelb) (2022) 12:137–148
https://doi.org/10.1007/s13555-021-00640-7

ORIGINAL RESEARCH

Clinical Tailoring of Baricitinib 2 mg in Atopic Dermatitis: Baseline Body Surface Area and Rapid Onset of Action Identifies Response at Week 16

Jonathan I. Silverberg · Mark Boguniewicz · Jill Waibel · Jamie Weisman · Lindsay Strowd · Luna Sun · Yuxin Ding · Meghan Feely · Fabio P. Nunes · Eric L. Simpson

At week 16, EASI75 and vIGA-AD (0,1) were achieved by 37.5% and 31.7% of baricitinib 2-mg-treated patients with baseline BSA 10–50% compared with 9.5% and 4.8% with BSA>50%.
Early response in skin inflammation or itch at week 4 was associated with corresponding EASI75, vIGA-AD (0,1), and Itch > or equal than 4 of 55.4%, 48.2%, and 39.3% at week 16, while early response at week 8 was associated with 66.7%, 56.1%, and 42.1% of patients achieving these endpoints

Drug Evaluation

Immunotherapy

Infectious adverse events in patients with atopic dermatitis treated with baricitinib

Flaminia Antonelli[‡,1,2], Dalma Malvaso[‡,1,2], Giacomo Caldarola[1,2], Clara De Simone[1,2], Ketty Peris[1,2] & Andrea Chiricozzi*[,1,2]

Plain language summary: Baricitinib is a drug taken by mouth, currently approved for the treatment of moderate-to-severe atopic dermatitis in adults who are candidates for systemic therapy, a medication that is designed to be absorbed into the bloodstream and work throughout the body. Baricitinib is available as 2- and 4-mg tablets and has been shown to improve the cutaneous manifestations, such as dry and cracked skin, redness and symptoms of atopic dermatitis, especially itchiness. Baricitinib is generally well tolerated. The most common adverse events that have emerged from clinical trials include headache, nausea and high cholesterol. Another reported side effect is an increased risk of infections, mainly of mild-to-moderate severity, especially upper respiratory tract infections such as nasopharyngitis (inflammation of the nose and throat) and reactivation of herpes zoster, a virus that causes a painful rash on one side of the body, and herpes simplex, which causes clustered blisters usually on the lips or genitals. There is still a lack of data from real-world experience, which will be important for the development of a more precise profile of patients who may benefit from this treatment.

CLINICAL TRIAL

BJD
British Journal of Dermatology

Efficacy and safety of baricitinib in combination with topical corticosteroids in patients with moderate-to-severe atopic dermatitis with inadequate response, intolerance or contraindication to ciclosporin: results from a randomized, placebo-controlled, phase III clinical trial (BREEZE-AD4)*

Thomas Bieber,[1] Kristian Reich,[2] Carle Paul,[3] Yuichiro Tsunemi,[4] Matthias Augustin,[5] Jean-Philippe Lacour,[6] Pierre-Dominique Ghislain,[7] Yves Dutronc,[8] Ran Liao,[8] Fan E. Yang,[8] Dennis Brinker,[8] Amy M. DeLozier,[8] Eric Meskimen,[8] Jonathan M. Janes,[8] and Kilian Eyerich[9] on behalf of the BREEZE-AD4 study group

Table 4 Summary of safety through week 52 in BREEZE-AD4

	PBO (N = 93)	Bari 1-mg (N = 93)	Bari 2-mg (N = 185)	Bari 4-mg (N = 92)
Treatment-emergent adverse events	62 (66·7)	68 (73·1)	149 (81·0)	82 (89·1)
Mild	33 (35·5)	29 (31·2)	72 (39·1)	38 (41·3)
Moderate	21 (22·6)	31 (33·3)	65 (35·3)	37 (40·2)
Severe	8 (8·6)	8 (8·6)	12 (6·5)	7 (7·6)
Serious adverse events	5 (5·4)	7 (7·5)	9 (4·9)	10 (10·9)
Discontinuation from study treatment owing to adverse event	2 (2·2)	1 (1·1)	10 (5·4)	3 (3·3)
Death	0	0	0	0
Major adverse cardiovascular events (adjudicated)	0	0	1 (0·5)	0
Common treatment-emergent adverse events[a]				
Nasopharyngitis	14 (15·1)	16 (17·2)	38 (20·7)	34 (37·0)
Herpes simplex[b]	7 (7·5)	7 (7·5)	17 (9·2)	14 (15·2)
Influenza	2 (2·2)	3 (3·2)	14 (7·6)	14 (15·2)
Headache	8 (8·6)	8 (8·6)	14 (7·6)	10 (10·9)
Back pain	5 (5·4)	6 (6·5)	6 (3·3)	6 (6·5)
Diarrhoea	3 (3·2)	2 (2·2)	9 (4·9)	6 (6·5)
Upper abdominal pain	3 (3·2)	2 (2·2)	7 (3·8)	5 (5·4)
Conjunctivitis	1 (1·1)	1 (1·1)	3 (1·6)	5 (5·4)
Erysipelas	1 (1·1)	0	4 (2·2)	5 (5·4)
Urinary tract infection	0	1 (1·1)	5 (2·7)	5 (5·4)
CPK elevation[c]	16 (17·6)	21 (22·8)	47 (25·7)	27 (29·3)
Increase to grade ≥ 3	2 (2·2)	4 (4·3)	5 (2·8)	2 (2·2)
Treatment-emergent infections	37 (39·8)	52 (55·9)	110 (59·8)	67 (72·8)
Opportunistic infections	0	0	2 (1·1)	1 (1·1)
Herpes zoster	0	4 (4·3)	6 (3·3)	3 (3·3)
Serious infections	2 (2·2)	2 (2·2)	5 (2·7)	4 (4·3)
Tuberculosis	0	0	0	0
Skin infections requiring antibiotic treatment	8 (8·6)	12 (12·9)	24 (13·0)	10 (10·9)
Adverse events of special interest				
Deep vein thrombosis	0	0	0	0
Pulmonary embolism	0	0	0	0
Gastrointestinal perforations	0	0	0	0
NMSC	1 (1·1)	0	1 (0·5)	0
Malignancies other than NMSC	1 (1·1)	0	0	0

Bari, baricitinib; CPK, creatine phosphokinase; CTCAE, Common Terminology for Adverse Events. NMSC, nonmelanoma skin cancer; PBO, placebo. Data are presented as n (%). [a]Common treatment-emergent adverse events are defined as events occurring in ≥ 5% of patients in the baricitinib 4 mg + TCS treatment group. [b]Includes preferred terms of oral herpes, herpes simplex, eczema herpeticum, genital herpes simplex, genital herpes, and Kaposi varicelliform eruption as defined in the medical dictionary for regulatory activities.

Abrocitinib

Selective JAK-1 inhibitor

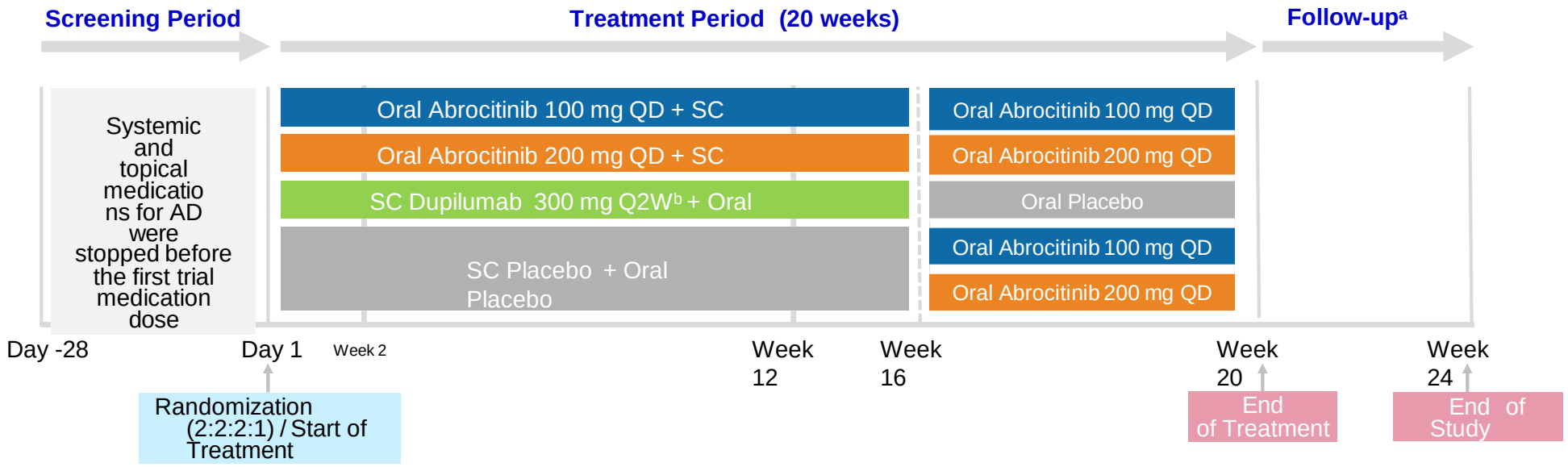
JADE COMPARE[1,2]

Co-primary Endpoints[a]

- IGA response at **Week 12** (abrocitinib versus placebo)
- EASI-75 response at **Week 12** (abrocitinib versus placebo)

Key Secondary Endpoints

- Itch response at **Week 2** (abrocitinib versus dupilumab)
- IGA response at **Week 16** (abrocitinib versus placebo)
- EASI-75 response at **Week 16** (abrocitinib versus placebo)



[a]Subjects discontinuing early from treatment, or who were otherwise ineligible for the long-term extension study [JADE EXTEND (NCT03422822) in which subjects may continue to receive abrocitinib treatment (48 weeks)] underwent a 4-week follow-up off-treatment period in JADE COMPARE. [b]As per label.
AD, atopic dermatitis; QD, once daily; Q2W, every 2 weeks; SC, subcutaneous.

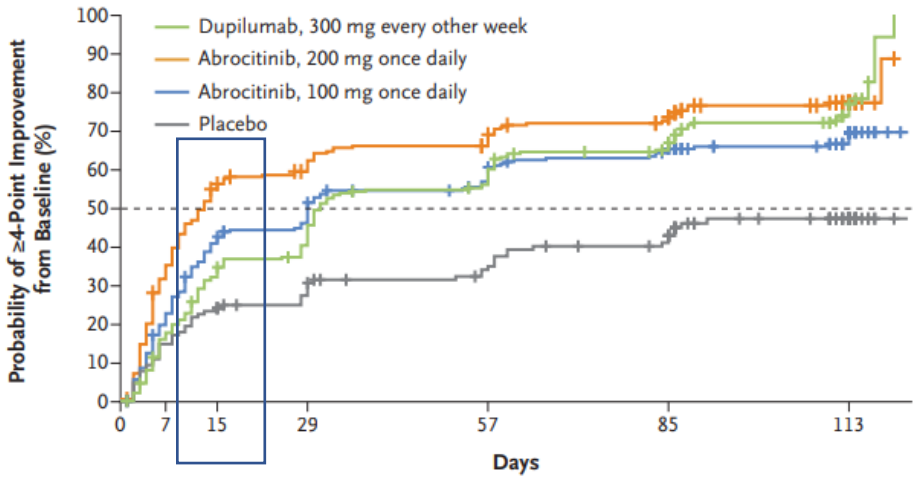
1. Bieber T, Simpson EL, Silverberg JI, et al. Abrocitinib versus placebo or dupilumab for atopic dermatitis. *N Engl J Med*. 2021;384:1101–12.
2. Supplementary appendix to Bieber T, Simpson EL, Silverberg JI, et al. Abrocitinib versus placebo or dupilumab for atopic dermatitis. *N Engl J Med.* 2021;384:1101-12.

JADE COMPARE

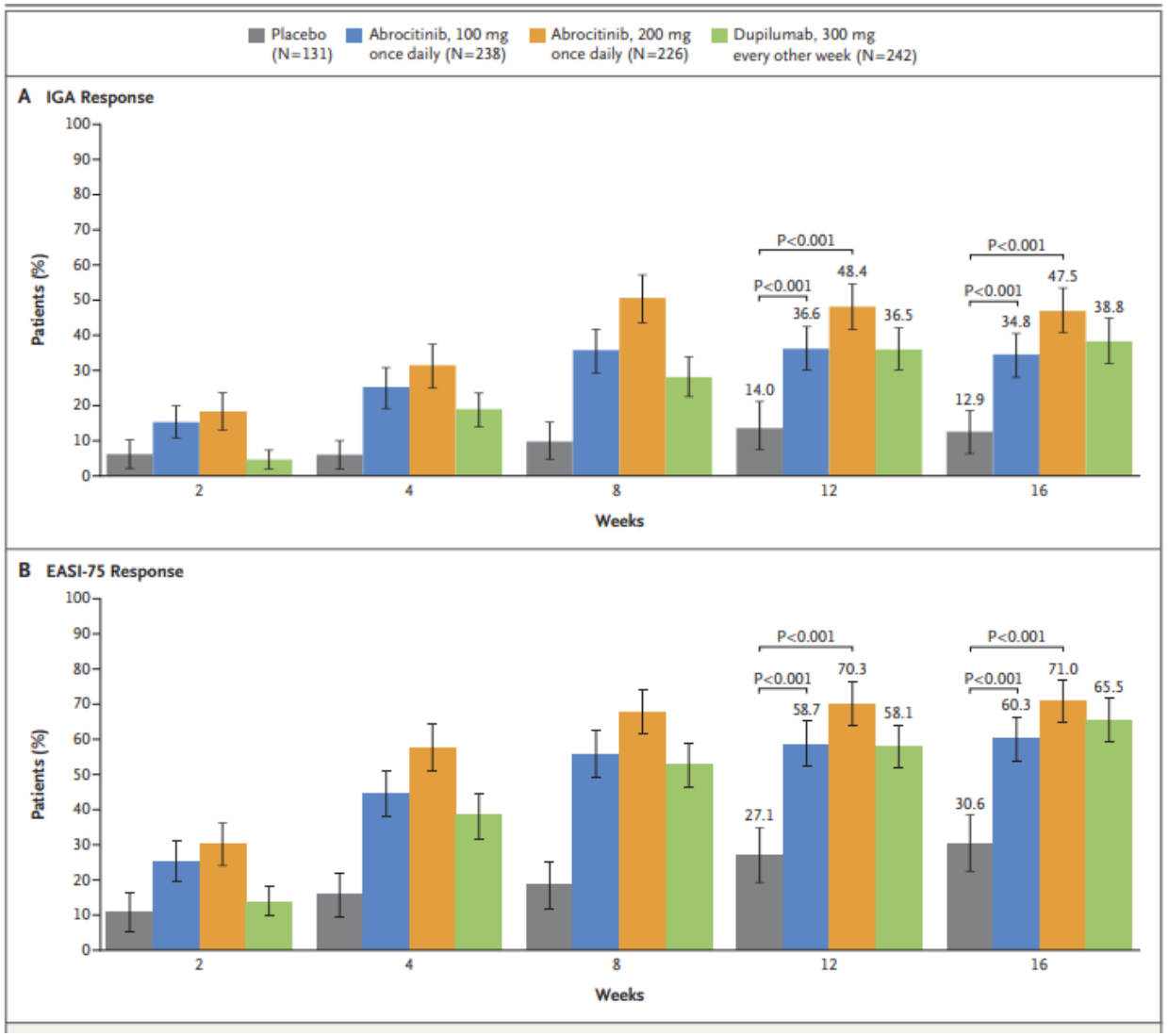
Abrocitinib versus Placebo or Dupilumab for Atopic Dermatitis

JADE COMPARE was a Phase III randomized, double-blind, double-dummy, placebo-controlled, parallel group, multicenter study designed to evaluate the efficacy and safety of abrocitinib (100 mg and 200 mg) **and dupilumab in comparison with placebo in adults with moderate-to-severe AD on background topical therapy**

Median Time to Itch Response.

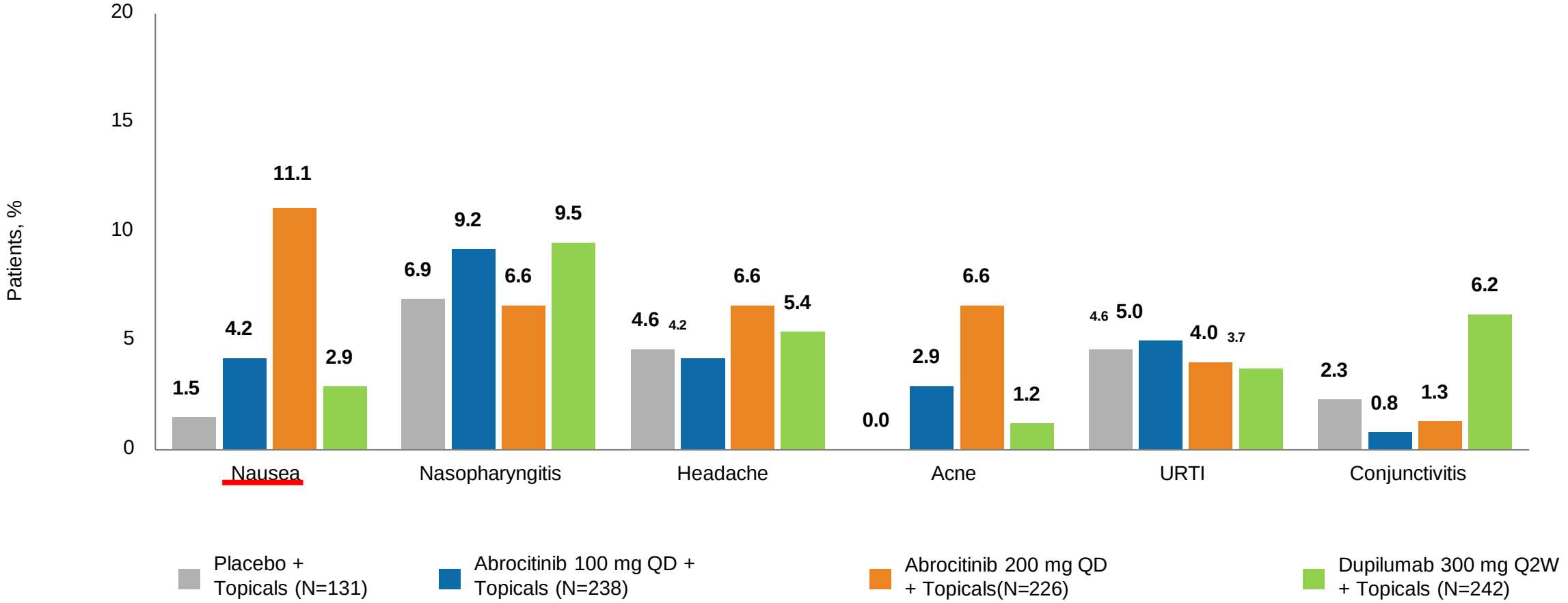


No. at Risk							
Dupilumab, 300 mg every other week	240	199	160	137	99	73	42
Abrocitinib, 200 mg once daily	226	153	100	86	70	53	24
Abrocitinib, 100 mg once daily	236	187	137	122	93	74	44
Placebo	130	110	99	89	76	65	29



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

Adverse Events Reported in ≥5% of Patients in Any Group



QD, once daily; Q2W, every 2 weeks; URTI, upper respiratory tract infection.

1. Bieber T, Simpson EL, Silverberg JI, et al. Abrocitinib versus placebo or dupilumab for atopic dermatitis. *N Engl J Med*. 2021;384:1101–12.
2. Supplementary appendix to Bieber T, Simpson EL, Silverberg JI, et al. Abrocitinib versus placebo or dupilumab for atopic dermatitis. *N Engl J Med*. 2021;384:1101-12.

Events of Special Interest

- Three serious infections were reported in two patients with abrocitinib 100 mg (pneumonia and oral herpes in one patient and infectious diarrhea in another) – each resolved
- All cases of herpes zoster were uncomplicated and none were multidermatomal
- Two malignant neoplasms were reported — one in the 200-mg abrocitinib group (cutaneous squamous-cell carcinoma) and one in the dupilumab group (invasive intraductal breast neoplasia)
- No major cardiovascular AEs or thromboembolic events occurred during the trial
- Thrombocytopenia was reported in 2 patients in the 200-mg abrocitinib group, with a nadir of platelet counts of 110 $\times 10^3/\mu L$ in one patient and 118 $\times 10^3/\mu L$ in the other. No patient had a platelet count of less than 75 $\times 10^3/\mu L$, as confirmed by means of repeated blood measurements.

	Placebo + Topicals (N=131)	Abrocitinib 100 mg QD + Topicals (N=238)	Abrocitinib 200 mg QD + Topicals (N=226)	Dupilumab 300 mg Q2W + Topicals (N=242)
Serious infection – no. (%)	0	2 (0.8)	0	0
Herpes zoster[a] – no. (%)	0	2 (0.8)	4 (1.8)	0
Eczema herpeticum – no. (%)	1 (0.8)	1 (0.8)	0	0
Malignancy[b] – no. (%)	0	0	1 (0.4)	1 (0.4)
Thrombocytopenia	0	0	2 (0.9)	0

[a]Four patients (1.8%) who received abrocitinib 200 mg and two (0.8%) who received 100 mg had herpes zoster infection; in the 200 mg group, severity was mild in three patients and moderate in one patient; in the 100 mg group, severity was moderate in one patient and severe in one patient; all cases were uncomplicated, none were multidermatomal, and all resolved except for one that was resolving at the time of this report.
[b]Two malignancies confirmed by the external data monitoring committee

QD, once daily; Q2W, every 2 weeks.

Bieber T, Simpson EL, Silverberg JI, et al. Abrocitinib versus placebo or dupilumab for atopic dermatitis. *N Engl J Med*. 2021;384:1101–12.

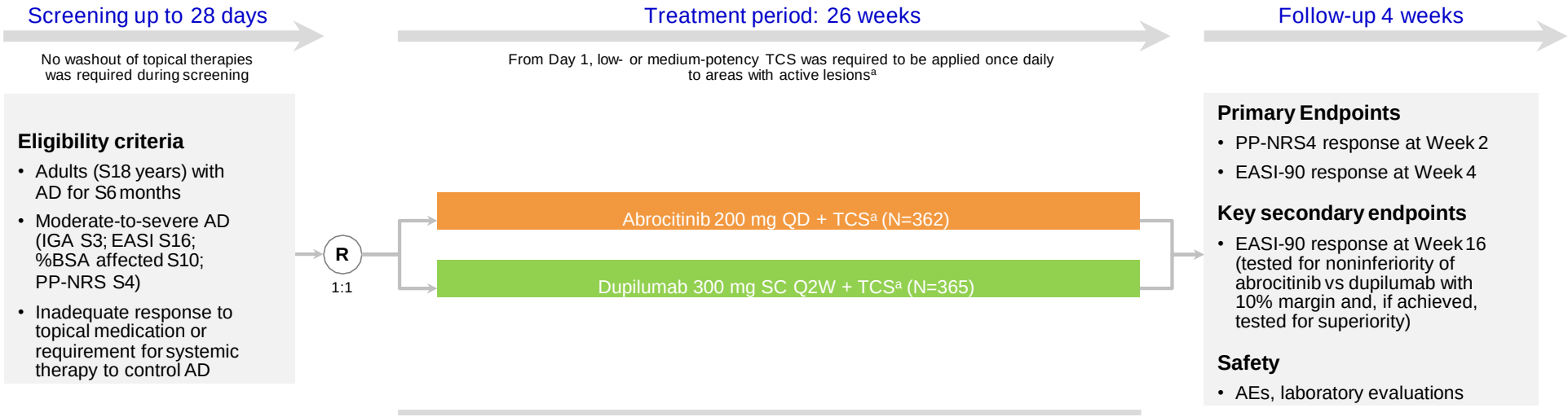
JADE DARE: Efficacy and Safety of Abrocitinib Versus Dupilumab in Adults With Moderate-to-Severe Atopic Dermatitis Receiving Background Topical Therapy:

A 26-Week Randomized Head-to-Head Trial

Kristian Reich,[1] Jacob P. Thyssen,[2] Andrew Blauvelt,[3] Killian Eyerich,[4] Weily Soong,[5] Zakiya P. Rice,[6] H. Chih-ho Hong,[7] Norito Katoh,[8] Fernando Valenzuela,[9] Marco DiBonaventura,[10] Tamara A. Bratt,[11] Fan Zhang,[11] Claire Clibborn,[12] Ricardo Rojo,[11] Hernan Valdez,[10]
Urs Kerkmann[13]

Presented at the 30th EADV Congress; September 29–October 2, 2021; Virtual.

- JADE DARE was a 26-week, Phase IIIb, randomized, double-blind, double-dummy, active-controlled trial (NCT04345367)



- Overall family-wise type 1 error rate for the primary and key secondary endpoints was controlled at the 2-sided 5% level using a sequential multiple-testing procedure
- P values were obtained from analyses that were adjusted for baseline AD severity (moderate or severe)

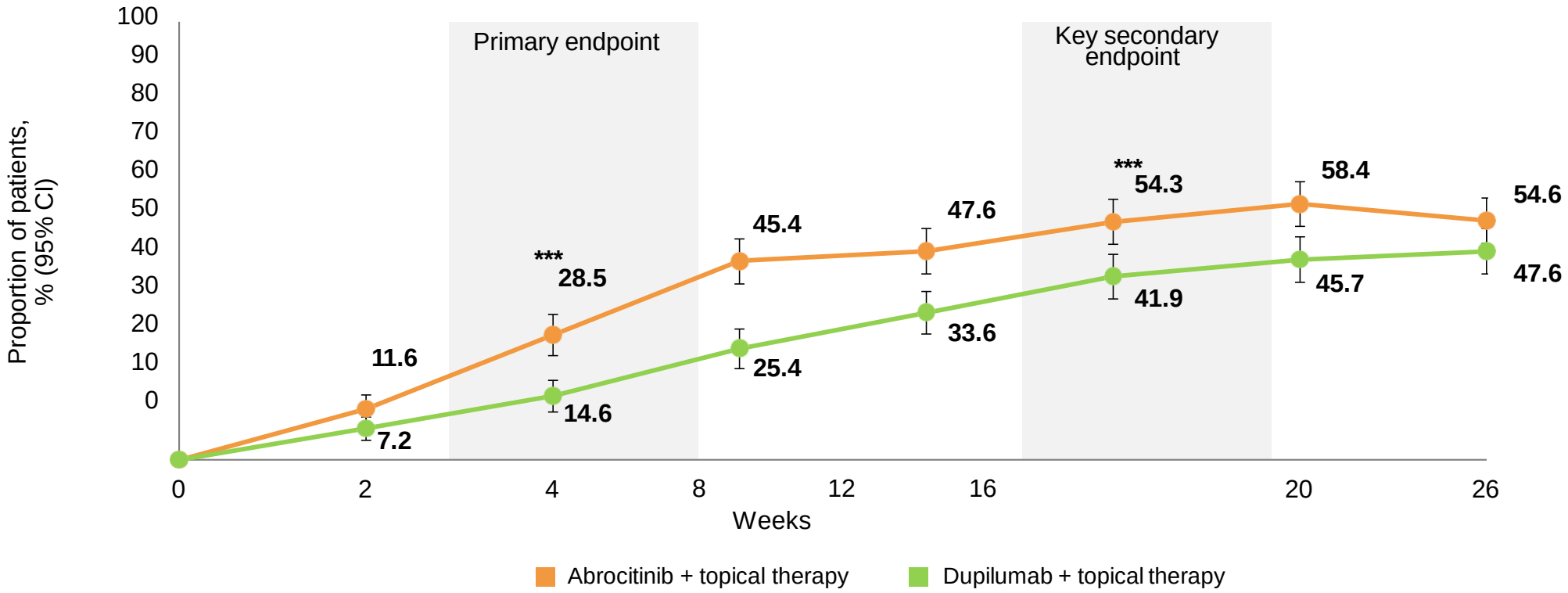
[a]TCS encompasses topical medicated therapy, Topical calcineurin inhibitors or a phosphodiesterase-4 inhibitor were permitted to be used instead of TCS in body areas of thin skin or if continued treatment with TCS was considered unsafe. Non-medicated topical emollients were requited to be applied at least twice daily to all body areas affected with AD.

AD, atopic dermatitis; AE, Adverse Event; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; PP-NRS4, Peak Pruritus Numerical Rating Scale; Q2W, once every two weeks; QD, once daily, SC, subcutaneous; TCS, topical corticosteroids; R, randomization

Results

EASI-90 Response

- The EASI-90 response rates at Week 4 (primary endpoint) and Week 16 (key secondary endpoint) were significantly higher in the abrocitinib group compared with the dupilumab group

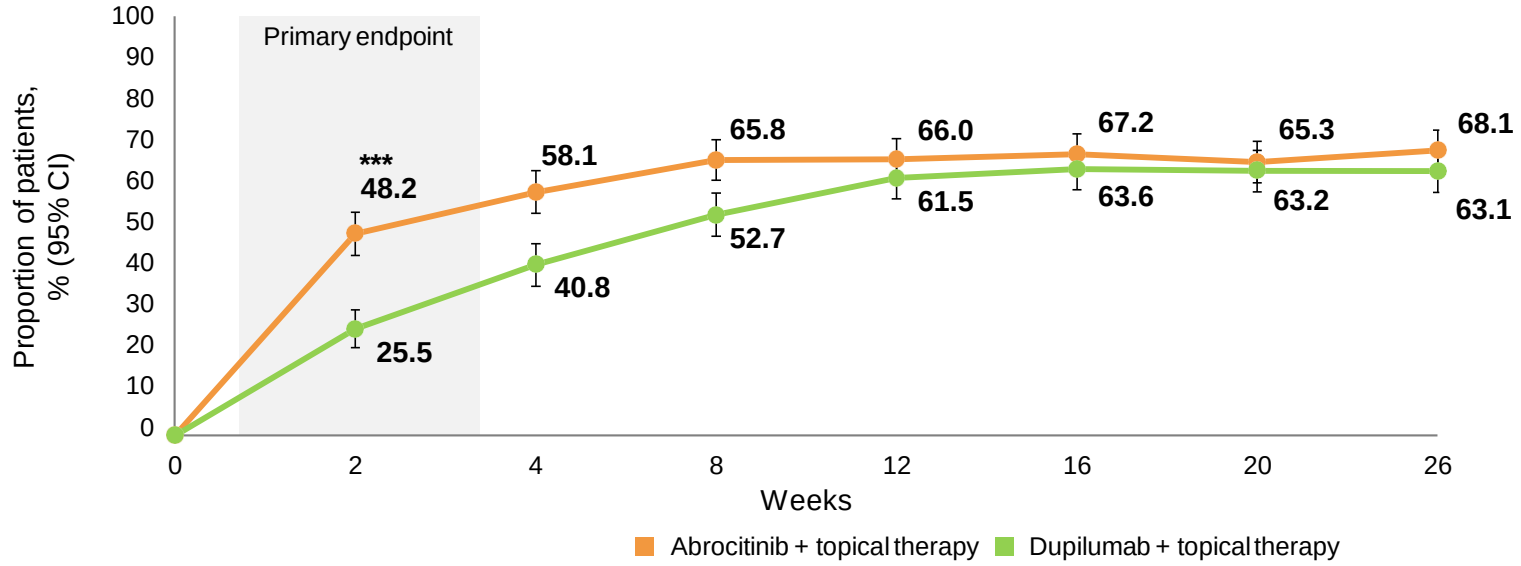


Two-sided ***p<0.001 vs dupilumab + topical therapy calculated using the Cochran-Mantel-Haenszel method adjusted by baseline disease severity.
CI, confidence interval; EASI-90, S90% improvement from baseline in Eczema Area and Severity Index.
Reich K, et al. Poster presented at: 30th EADV Congress - Virtual; September 29–October 2, 2021.

Results

PP-NRS4 Response

- The PP-NRS4 response rate at Week 2 (primary endpoint) was significantly higher in the abrocitinib group compared with the dupilumab group



Two-sided ***p<0.001 vs dupilumab + topical therapy calculated using the Cochran-Mantel-Haenszel method adjusted by baseline disease severity.
CI, confidence interval; PP-NRS4, S4-point improvement from baseline in the Peak Pruritus Numerical Rating Scale.
PP-NRS: © Regeneron Pharmaceuticals, Inc., and Sanofi,2017.
Reich K, et al. Poster presented at: 30th EADV Congress - Virtual; September 29–October 2, 2021.

Results

Summary of AEs

- Few patients had TEAEs that were serious, severe, or led to study discontinuation
- Nausea, headache, and acne were the most common TEAEs reported by patients taking abrocitinib
- Conjunctivitis was more frequent in the dupilumab group
- 2 deaths, both in the abrocitinib 200 mg group, were not related to treatment
  - 1 patient died from COVID-19
  - 1 patient died from cardiopulmonary arrest and intracranial hemorrhage
- Only 1 serious adverse event was related to treatment
  - 1 patient developed rhabdomyolysis in the dupilumab group

Patients, n (%)	Abrocitinib 200 mg (N=362)	Dupilumab 300 mg (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 (3)
TEAEs leading to drug discontinuation (continued study)[b]	0	1 (0.3)
Most frequently reported TEAEs (≥5% of patients in any group)		
Nausea[c]	70 (19)	8 (2)
Headache	47 (13)	24 (7)
Acne[d]	46 (13)	10 (3)
Conjunctivitis[d]	8 (2)	35 (10)

[a]An adverse event that prevents normal everyday activities. Severe is a category utilized for rating the intensity of an event, and both TEAEs and serious TEAEs can be assessed as severe. [b]The adverse event leading to dupilumab discontinuation was mild dryness of the eyes from study day 19. [c]Oral study medication was to be swallowed whole, with or without food, except on study visit days, which required fasting. In participants who experienced nausea, administration of oral medication with food was considered. [d]Per the study protocol, in all cases of acne, conjunctivitis, herpes zoster, and folliculitis, the collection of additional details was required.

COVID-19, coronavirus disease 2019; TEAE, treatment-emergent adverse event.

Reich K, et al. Poster presented at: 30th EADV Congress - Virtual; September 29–October 2, 2021.

Janus kinase inhibitors (JAKi)

Share

CURRENT STATUS
European Commission final decision

Procedure started → Under evaluation → PRAC recommendation → CHMP opinion → European Commission final decision

EMA confirms measures to minimise risk of serious side effects with Janus kinase inhibitors for chronic inflammatory disorders

On 23 January 2023, EMA's human medicines committee (CHMP) endorsed the measures recommended by the Pharmacovigilance Risk Assessment Committee (PRAC) to minimise the risk of serious side effects with Janus kinase (JAK) inhibitors used to treat several chronic inflammatory disorders. These side effects include cardiovascular conditions, blood clots, cancer and serious infections..

These medicines should be used in the following patients only if no suitable treatment alternatives are available: those aged 65 years or above, those at increased risk of major cardiovascular problems (such as heart attack or stroke), those who smoke or have done so for a long time in the past and those at increased risk of cancer.

JAK inhibitors should be used with caution in patients with risk factors for blood clots in the lungs and in deep veins (venous thromboembolism, VTE) other than those listed above. Further, the doses should be reduced in patient groups who are at risk of VTE, cancer or major cardiovascular problems, where possible.

The recommendations follow a review of available data, including the final results from a clinical trial[1] of the JAK inhibitor Xeljanz (tofacitinib) and preliminary findings from an observational study involving Olumiant. The review also included advice from an expert group of rheumatologists, dermatologists, gastroenterologists and patient representatives.

Label update across JAK inhibitors (JAKi) – What`s new?

No change to therapeutic indications

New warnings and precautions for population at risk, no new contraindications

Extrapolation from RA data to all JAKi across indications

Harmonization of reduced dosing for at risk population across JAK inhibitors*

Updated warnings and precautions for population at risk

For the following patients, these medicines should only be used if no suitable treatment alternatives are available:

Those aged 65 years and older

Those with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors (such as current or past long-time smokers)

Those with malignancy risk factors (e.g. current malignancy or history of malignancy)

JAK inhibitors should be used with caution in patients with risk factors for blood clots in the lungs and in deep veins (venous thromboembolism, VTE) other than those listed above

*The doses should be reduced in patient groups who are at risk of VTE, cancer or major cardiovascular problems, where possible.

JAK=Janus kinase; VTE=venous thromboembolism.

1. European Medicines Agency. JAK inhibitors: art 20 - public health communication - 27 Jan 2023_rev.1_EMA opinion 2 abrocitinib Summary of product characteristics. Pfizer. 2023. 2. bari Eumb| Summary of product characteristics. Rinvoq. 2023. 3. Upadacitinib. Summary of product characteristics. Abbvie. 2023

Venous Thromboembolism Rates within the Context of the Atopic Dermatitis Disease Population

Incidence rates of VTE events in patients with AD

AD RWE[a,1,2]

VTE	DVT	PE
0.18-0.24	0.19	0.07

per 100 PYE

JAKi in AD RCTs[b,3-5]

VTE	DVT	PE
0.06-0.30	0.00-0.12	0.06-0.18

per 100 PYE

Meta-analysis[c,6]

AD RWE
0.23

JAKi in AD RCTs
0.15

per 100 PYE

[a]AD cohorts inclusive of patients with mild to severe AD. [b]Clinical trial populations with moderate to severe AD treated with abrocitinib, upadacitinib, or baricitinib. [c]Two cohort studies and 15 RCTs with a total of 466 993 participants were included. AD=atopic dermatitis; DVT=deep vein thrombosis; JAKi=janus kinase inhibitor; PE=pulmonary embolism; PYE=patient-years of exposure, RCT=randomized clinical trial; RWE=real world evidence; VTE=venous thromboembolic event. 1. Meyers KJ, et al. Dermatol Ther (Heidelb). 2021;11(3):1041-1052. 2. Schneeweiss MC, et al. JAMA Dermatol. 2021;157(7):805-816. 3. Simpson EL, et al. Am J Clin Dermatol. 2021;22(5):681-703. 4. EMA. EPAR - Assessment report. https://www.ema.europa.eu/en/documents/variation-report/rinvoq-h-c-004760-ii-0006-g-epar-assessment-report-variation_en.pdf 5. Bieber T, et al. Presented at EADV 2022. 6. Chen T, et al. JAMA Dermatol. 2022;158(10):1254-1261.

Major Adverse Cardiovascular Event Rates within the Context of the Atopic Dermatitis Disease Population

Incidence rates of MACE events in AD

RWE[1]

0.15[a]-0.63[b]
per 100 PYE

RWE Population[1]		
	Mild AD (n=26,898)	**Severe AD** (n=2,527)
Female, %	54.0%	52.9%
Age (years), mean (SD)	23.8 (12.9)	34.8 (16.5)
BMI (kg/m^2), mean (SD)	NA	NA
Prior systemic therapy	AD without systemic therapy was classified as mild	Patients were classified as having severe AD when they received systemic therapy for AD

JAKi RCTs[c,2-4]

0.1-0.18
per 100 PYE

Baricitinib RCT Population[4]	
	Moderate to severe AD (n=2,636)
Female, %	39%
Age (years), mean (SD)	36.5 (13.7)
BMI (kg/m^2), mean (SD)	25.9 (5.4)
Prior systemic therapy, %	61.3%

aIR estimate for patients with mild AD. bIR estimate for patients with severe AD. cClinical trial populations with moderate to severe AD treated with abrocitinib, upadacitinib, or baricitinib. AD=atopic dermatitis; JAK=Janus kinase inhibitor; MACE=major adverse cardiac event; PYE=patient-years of exposure; RCT=randomized clinical trial; RWE=real world evidence. 1. Andersen et al. J Allergy Clin Immunol Pract. 2021;9:3132-3142. 2. Bunyavanich S, et al. Am J Clin Dermatol. 2021;22(5):699-707. 3. EMA-Rinvoq Assessment report: https://www.ema.europa.eu/en/documents/variation-report/rinvoq-h-c-004760-x-0006-g-epar-assessment-report-variation_en.pdf. 4. Bieber T, et al. Presented at EADV 2022.

The infection risks of JAK inhibition, **to practice….**

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DOI: 10.1111/jdv.19426

SYSTEMATIC REVIEW

JEADV JOURNAL OF THE EUROPEAN ACADEMY OF DERMATOLOGY & VENEREOLOGY

The safety of systemic Janus kinase inhibitors in atopic dermatitis: A systematic review and meta-analysis of randomized controlled trials

Sanghyuk Yoon[1] | Kihun Kim[1,2] | Kihyuk Shin[3,4,5] | Hoon-Soo Kim[3] | Byungsoo Kim[3] | Moon-Bum Kim[3] | Hyun-Chang Ko[3,4,5] | Yun Hak Kim[1,2]

Eligibility criteria

The research question was defined as follows: '**Does the use of JAK inhibitors increase adverse events in patients with atopic dermatitis?**'.

Accordingly, randomized controlled trials containing information on adverse events associated with the use of JAK inhibitors for the treatment of AD were considered. Through the collective deliberation of all authors, a total of 11 adverse events were selected for incorporation in this study. These included six side effects, which have been highlighted with noteworthy significance in most previous investigations, as well as five adverse events which have been frequently documented and observed across several studies. The control group was clearly defined as either the placebo group or the untreated standard group.

Yoon et al., J Eur Acad Dermatol Venereol. 2023;00:1–10.

Integrated analysis of adverse events when using JAK inhibitors

Outcome	Number of results(n)	JAK inhibitor Events (n)	JAK inhibitor Total (n)	Placebo Events (n)	Placebo Total (n)	Heterogeneity (%)	Relative risk (95% confidence interval)
Serious infection	11	31	3,877	11	1,644	0	0.88 (0.44-1.77)
Herpes zoster	15	63	5,218	7	2,319	0	1.97 (1.03-3.77)
NMSC	14	6	4,932	1	2,214	0	0.97 (0.25-3.81)
Malignancies other than NMSC	14	4	4,932	3	2,214	0	0.58 (0.14-2.33)
MACE	14	2	4,932	0	2,214	0	1.07 (0.11-10.17)
VTE	15	1	5,143	1	2,270	0	0.50 (0.05-4.76)
Headache	14	316	4,816	89	2,121	0	1.43 (1.13-1.81)
Nasopharyngitis	15	543	5,007	204	2,263	0	1.15 (0.98-1.35)
Acne	10	308	3,525	26	1,482	0	4.97 (3.38-7.31)
Blood creatinine phosphokinase elevation	14	298	4,534	60	2,128	0	1.82 (1.40-2.36)
Nausea	7	168	1,905	12	624	0	3.74 (2.07-6.78)

The present systematic review and meta-analysis showed a varied risk of adverse events among patients with AD exposed to JAK inhibitors. Herpes zoster, headache, acne, blood creatinine phosphokinase elevation and nausea seem to be rather common among these patients, whereas the risk of all other adverse events, including other serious infections, malignancy, VTE and MACE, did not increase.

Yoon et al., J Eur Acad Dermatol Venereol. 2023;00:1–10.
NMSC, non-melanoma skin cancer; MACE, major adverse cardiovascular event; VTE: venous thromboembolism

RCP Tabella 1. Valori di laboratorio e linee guida di monitoraggio

Inizio del trattamento

Il trattamento non deve essere iniziato nei pazienti con una conta assoluta dei linfociti (ALC, *Absolute Lymphocyte Count*) < 0,5 x 10^9 cellule/L, con una conta assoluta dei neutrofili (ANC, *Absolute Neutrophil Count*) < 1 x 10^9 cellule/L o con livelli di emoglobina (Hb) < 8 g/dL (vedere paragrafi 4.4 e 4.8).

Valore di laboratorio	Azione	Linee guida per il monitoraggio
Conta assoluta dei neutrofili (ANC)	Il trattamento deve essere interrotto se la ANC è < 1 x 10^9 cellule/L e può essere ripreso quando la ANC ritorna al di sopra di tale valore	Valutare al basale e in seguito non più tardi di 12 settimane dopo l'inizio del trattamento. Successivamente, valutare in base alla gestione del singolo paziente.
Conta assoluta dei linfociti (ALC)	Il trattamento deve essere interrotto se la ALC è < 0,5 x 10^9 cellule/L e può essere ripreso quando la ALC ritorna al di sopra di tale valore	
Emoglobina (Hb)	Il trattamento deve essere interrotto se l'Hb è < 8 g/dL e può essere ripreso quando l'Hb ritorna al di sopra di tale valore	
Transaminasi epatiche	Il trattamento deve essere temporaneamente interrotto se si sospetta un danno epatico indotto dal farmaco	Valutare al basale e successivamente in base alla gestione ordinaria del paziente.
Lipidi	I pazienti devono essere gestiti secondo le linee guida cliniche internazionali per la iperlipidemia	12 settimane dopo l'inizio del trattamento e, successivamente, in base alle linee guida cliniche internazionali per la iperlipidemia

Screening & monitoring

Inclucing CK !

Monitoring in routine patient management

		Laboratory parameters					Screening tests/evaluations				Serious infections[h]
		ALC	ANC	Hb	Lipids	AST/ALT	TB[f]	Viral hepatitis	Skin[g]	Vaccines	
Evaluate	At baseline	✓	✓	✓		✓	✓	✓			✓
	≤12 weeks after initiation	✓	✓	✓	✓						
	According to guidelines or routine management	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Treatment should not be initiated, or should be interrupted, in patients with:		<0.5 x 10^9 cells/L[e]	<1 x 10^9 cells/L[e]	<8 g/dL[e]		Increased AST/ALT and suspected drug-induced liver injury	Active TB				Active, serious[i], or opportunistic infection

“My” place in therapy

Moderate-to-severe AD

- Moderate-severe AD in patients
- Prurigo nodularis
- Non-cutaneous atopic diseases

- Low burden of disease
- Low itching
- Elderly >65 yo

- High-need patient (high EASI, high itch-NRS, high sleep-NRS, high DLQI, high POEMS)
- Limited use in elderly >65 yo
- Sensitive areas Hand involvement, Severe head/neck localization
- Current conjunctivitis or history of severe conjunctivitis
- Specific comorbid conditions: rheumatoid arthritis, Crohn’s Disease, psoriatic arthritis, alopecia areata
- Trypanophobia

Dupilumab

Tralokinumab

Upadacitinib
Baricitinib (AD+AA)
Abrocitinib

Preferring higher dose to start, when no safety concern arisen

Brief Remarks

Punti di forza del trattmento con JAK inibitori:

- Rapidità di risposta al trattamento

- Grande capacità di migliorare il prurito

- Tassi elevati di clearence completa o quasi completa (raggiungimento EASI 90 e 100)

Punti di debolezza del trattmento con JAK inibitori:

- Esami screening e monitoring (spesa per il paziente e time consuming per inizio del trattamento)

- Gestione degli eventi avversi

- Limiti su popolazioni speciali (vedi over 65)

- Necessità di vaccinazione anti-herpes zoster prima di iniziare terapia (altrimenti selezione del paziente)