



**HAL**  
open science

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

Marjolein de Bruin-Weller, Esther Serra-Baldrich, Sebastien Barbarot, Susanne Grond, Christopher Schuster, Helmut Petto, Jean-Philippe Capron, Afaf Raibouaa, Thomas Werfel

► **To cite this version:**

Marjolein de Bruin-Weller, Esther Serra-Baldrich, Sebastien Barbarot, Susanne Grond, Christopher Schuster, et al.. Indirect Treatment Comparison of Baricitinib versus Dupilumab in Adults with Moderate-to-Severe Atopic Dermatitis. *Dermatology and Therapy*, 2022, 12 (6), pp.1481-1491. 10.1007/s13555-022-00734-w . hal-04076853

**HAL Id: hal-04076853**

**<https://hal.inrae.fr/hal-04076853v1>**

Submitted on 21 Apr 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License



BRIEF REPORT

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

Marjolein S. de Bruin-Weller · Esther Serra-Baldrich · Sebastien Barbarot ·  
Susanne Grond · Christopher Schuster · Helmut Petto ·  
Jean-Philippe Capron · Afaf Raibouaa · Thomas Werfel

Received: March 1, 2022 / Published online: May 11, 2022  
© The Author(s) 2022

## ABSTRACT

**Introduction:** Indirect treatment comparison was used to compare approved doses of baricitinib and dupilumab for treating adult patients with moderate-to-severe atopic dermatitis (AD) who are candidates for systemic therapy.

**Methods:** Baricitinib and dupilumab were compared (Bucher method) at weeks 4 and 16. Performance in combination with topical corticosteroids (TCS) was analyzed in patients with inadequate response or inadvisable to topical

therapies (population A) and cyclosporine (population B). Population A was additionally examined as monotherapy.

**Results:** For the Eczema Area and Severity Index (EASI) 75, baricitinib and dupilumab were similar. A  $\geq 4$ -point improvement in itch numerical rating scale (NRS) was significantly more likely with baricitinib 4 mg than dupilumab in population A as monotherapy (RR = 2.62, 95% CI 1.22, 5.61,  $p = 0.013$ ) and in TCS combination at week 4. These differences were not significant by week 16. For the Dermatology Life Quality Index (DLQI), baricitinib 4 mg and dupilumab were similar on mean difference in change from baseline (MD<sub>cfb</sub>), though some differences were seen between baricitinib 2 mg and dupilumab at week 16 for the population A monotherapy (MD<sub>cfb</sub> = 2.05, 95% CI 0.53, 3.56,  $p = 0.016$ ) and TCS combination therapy (MD<sub>cfb</sub> = 2.48, 95% CI 0.46, 4.50,  $p = 0.016$ ) groups, and in population B (MD<sub>cfb</sub> = 3.38 95% CI 1.18, 5.58,  $p = 0.003$ ).

**Conclusions:** Baricitinib potentially offers more rapid improvement in itch while providing similar efficacy on EASI75 and DLQI outcomes compared with dupilumab.

---

M. S. de Bruin-Weller (✉)  
Department of Dermatology and Allergology,  
University Medical Center, Utrecht, The  
Netherlands  
e-mail: m.s.debruin-weller@umcutrecht.nl

E. Serra-Baldrich  
Department of Dermatology, Cutaneous Allergy  
Unit, Hospital Sant Pau, Universitat Autònoma  
Barcelona, Barcelona, Spain

S. Barbarot  
Department of Dermatology, Nantes Université,  
CHU Nantes, INRAE, UMR 1280 PhAN, 44000  
Nantes, France

S. Grond · C. Schuster · H. Petto · J.-P. Capron ·  
A. Raibouaa  
Eli Lilly and Company, Indianapolis, IN, USA

T. Werfel  
Division of Immunodermatology and Allergy  
Research, Department of Dermatology and Allergy,  
Hannover Medical School, Hannover, Germany

**Keywords:** Atopic dermatitis; Indirect treatment comparison; Systemic therapies

### Key Summary Points

Head-to-head (H2H) trial evidence regarding the performance of novel therapies versus their competitors is often lacking.

Indirect treatment comparisons (ITC) allow the results of existing trials to be compared in a rigorous way and can help to bridge knowledge gaps when H2H comparisons are not available.

Baricitinib represents an approved oral treatment option for adult patients with moderate-to-severe AD that offers similar efficacy on the Eczema Area and Severity Index (EASI)75 and Dermatology Life Quality Index (DLQI) to dupilumab when indirectly compared.

Baricitinib potentially offers more rapid improvement in itch, a key symptom for patients, than dupilumab when indirectly compared.

## INTRODUCTION

Baricitinib, a selective Janus kinase (JAK)1/JAK2 inhibitor, is approved in several countries for the treatment of moderate-to-severe atopic dermatitis (AD) in adults who are candidates for systemic therapy [1]. It has proven effective both as monotherapy and in combination with topical corticosteroids (TCS) [2, 3].

At present, there are no existing head-to-head (H2H) trials comparing the efficacy of baricitinib with other approved systemic therapies available for the management of AD in this patient population. In such circumstances, methodological tools such as indirect treatment comparisons (ITC) are often employed by researchers [4, 5]. ITC methodologies use the results of direct comparisons with a common comparator, such as placebo (PBO), to evaluate the relative efficacy of different interventions.

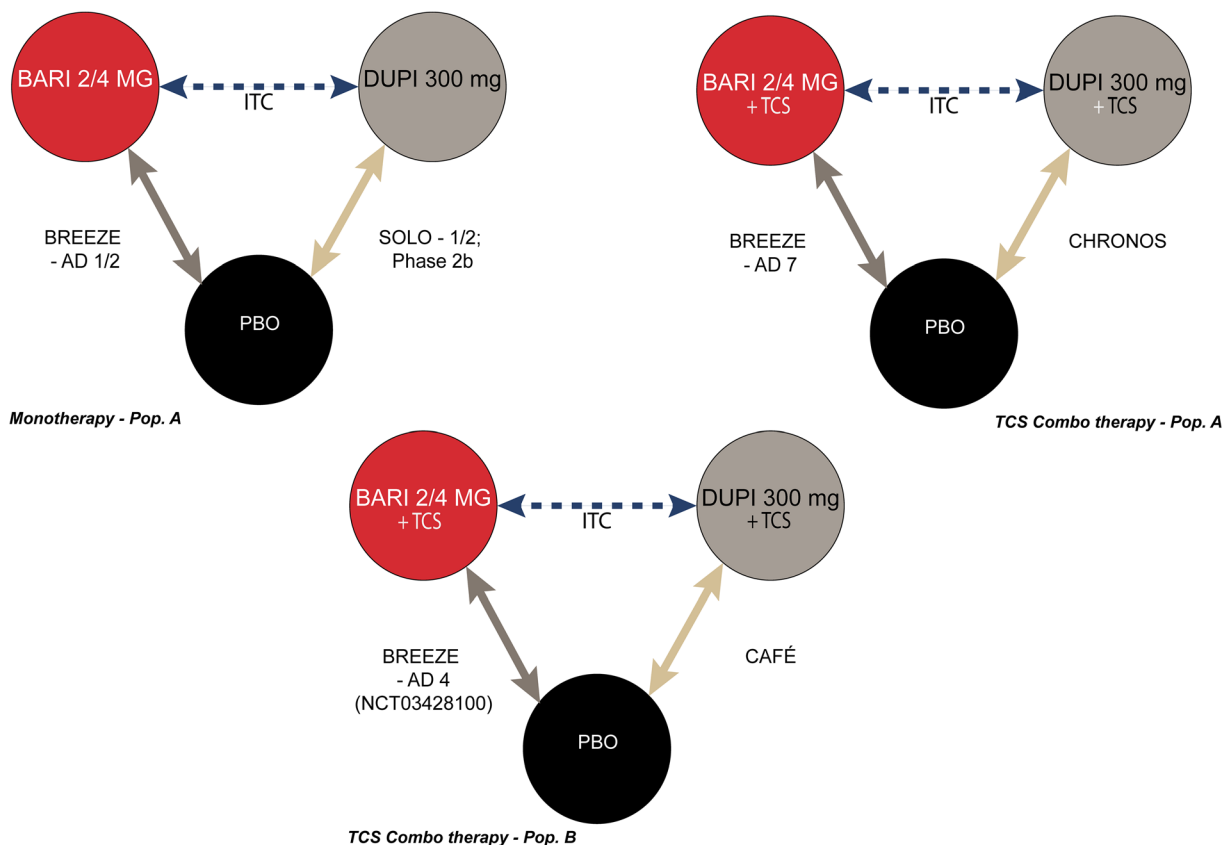
To support physicians when choosing appropriate treatments for AD, we conducted an ITC across all approved systemic therapies for the treatment of moderate-to-severe AD in adults with PBO-controlled randomized controlled trial evidence.

## METHODS

To identify relevant studies for our ITC, we systematically reviewed the literature for placebo-controlled trials evaluating systemic therapies in adults with moderate-to-severe AD over four waves starting in 2018 with updates in 2019, and May and December 2020. Eligibility criteria for the review were: studies in adults with confirmed moderate-to-severe AD; randomized controlled trials of a comparative investigation (one of which could be PBO); and studies published in English or German. We interrogated MEDLINE and Embase, both via Ovid Search Platform, and The Cochrane Central Register of Controlled Trials (CENTRAL) for published studies as well as ClinicalTrials.gov (<http://clinicaltrials.gov/>), the International Clinical Trials Registry Platform Search Portal, and the search portal of the World Health Organization to identify potentially relevant studies based on ongoing trials.

The only approved treatments with PBO-controlled trial data identified by the review at this time were dupilumab [6] and baricitinib. The approved dose of dupilumab (300 mg subcutaneously every 2 weeks following a loading dose of 600 mg) [7, 8] was then indirectly compared with baricitinib 2/4 mg once daily [1] using PBO as the common comparator (Fig. 1). When treatment data were available from more than one study versus PBO, standard meta-analysis methods were applied before conducting ITC by means of the Bucher methodology ITC [5].

Patient-level data were available for all baricitinib studies, whereas for dupilumab outcomes, data were extracted from the published literature. The ITC was conducted in two patient populations with subcohorts: population A and population B. Population A consisted



**Fig. 1** Structure of ITC analysis of BARI 2/4 mg versus DUPI 300 mg Q2W. *BARI* baricitinib, *DUPI* dupilumab, *ITC* indirect treatment comparison, *QxW* every *x* weeks, *TCS* topical corticosteroids. Population A: patients who

were intolerant of, had contraindications to, or did not respond to topical treatments. Population B: patients who were also intolerant of, had contraindications to, or did not respond to, cyclosporine

of two cohorts, while population B included only one cohort:

Population A: patients who were intolerant of, had contraindications to, or did not respond to topical treatments

- Cohort 1: patients receiving baricitinib or dupilumab as monotherapy
- Cohort 2: patients receiving baricitinib or dupilumab in combination with TCS

Population B: patients who were also intolerant of, had contraindications to, or did not respond to cyclosporine:

- Cohort 1: patients receiving baricitinib or dupilumab in combination with TCS

The ITC was based on the relative efficacy (relative risk [RR]) of the two agents assessed

versus PBO for each of the binary outcomes. Where RRs were > 1, results favored baricitinib, while RRs < 1 favored dupilumab. For Dermatology Life Quality Index (DLQI) assessments, the ITC was based on mean difference in change from baseline (MDc<sub>fb</sub>). MDc<sub>fb</sub> > 0 favored dupilumab while MDc<sub>fb</sub> < 0 favored baricitinib. An overview of the population groups is provided in Table 1.

Informed by the primary and key secondary endpoints common across the trials identified in the systematic literature review, we assessed the following efficacy outcomes in our study at week 4 and again at week 16: the proportion of patients with ≥ 75% improvement in Eczema Area and Severity Index (EASI75), the proportion of patients with ≥ 4-point improvement in itch Numeric Rating Scale (NRS) from baseline

**Table 1** Relevant trials identified by systematic literature review

Patient population of adults with moderate-to-severe AD	BARI randomized clinical trials	DUPI randomized clinical trials
Population A: patients who had failed topical treatment, or had contraindication to or were intolerant of topical treatments	Monotherapy: BREEZE-AD1 [3] BREEZE-AD2 [3]  TCS combination therapy: BREEZE-AD7 [4]	Monotherapy: SOLO-1 [21] SOLO-2 [10] Phase 2b [22]  TCS combination therapy: CHRONOS [23]
Population B: patients who had inadequate response to existing topical medications and failed cyclosporine, or had contraindications to or were intolerant to cyclosporine	TCS combination therapy: BREEZE-AD4 (NCT03428100) [24]	TCS combination therapy: CAFÉ [25]

While we deemed a phase II trial of dupilumab to meet the inclusion criteria, a phase II trial of baricitinib had too small a sample size for inclusion

*AD* atopic dermatitis, *BARI* baricitinib, *DLQI* Dermatology Life Quality Index, *DUPI* dupilumab, *TCS* topical corticosteroid

(peak daily pruritus NRS score used as equivalent; both instruments measure worst level of itch within the past 24 h [9–11]), and change from baseline (CFB) in Dermatology Life Quality Index (DLQI).

Missing data were accounted for by non-responder imputation (NRI) for binary outcomes, while for the DLQI, least-squared means were selected from the relevant included studies. Patients in receipt of rescue treatment or who discontinued treatment were considered non-responders. Statistical analyses were conducted using the CHEETAH tool (Indirect Comparison on results from 2 Meta-Analyses version 1.1), a program developed by Eli Lilly based on the R package “meta” [12].

### Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

## RESULTS

At the time of the systematic literature review (SLR), nine parallel PBO trials (four baricitinib and five dupilumab) covering 3364 patients were identified to inform the ITC (Table 1). Baseline characteristics for each of the trials are given in Table 2 and are consistent with comparable disease severity based on EASI, itch, and DLQI scores across all included studies. The results of the ITC analysis are summarized in Table 3. In population A at week 4, there was no significant difference between EASI75 response rates for either treatment group, though RR values numerically favored both baricitinib 2 and 4 mg. Similarly, at week 16 there was no statistically significant difference, though in this instance, RR values numerically favored dupilumab. This pattern was replicated in population B.

With respect to  $\geq 4$ -point improvement in itch NRS from baseline between baricitinib 2 or 4 mg and dupilumab in either monotherapy or TCS combination therapy studies at week 16, no

**Table 2** Baseline characteristics of patients in monotherapy studies included in the ITC

Study	Molecule (therapy)	Baseline population pooled data <sup>a,b</sup> (n)	Age (years; mean) [SD]	Mean baseline scores (SD)		
				EASI	DLQI	Itch/ pruritis <sup>d</sup> NRS
BREEZE-AD1	BARI (Mono)	497	35.5 (13.3)	31.8 (12.8)	13.8 (7.3)	6.6 (2.1)
BREEZE-AD2	BARI (Mono)	490	35.0 (13.3)	33.5 (13.8)	14.5 (8.0)	6.7 (2.2)
BREEZE-AD7	BARI (Combi)	329	33.8 (12.5)	29.7 (12.3)	15.0 (7.8)	7.1 (1.9)
BREEZE-AD4	BARI (Combi)	370	38.0 (13.8)	31.5 (12.5)	13.9 (7.5)	6.8 (2.0)
SOLO 1	DUPI (Mono)	448	38.5 <sup>c</sup>	31.1 <sup>c</sup>	13.5 <sup>c</sup>	7.7 <sup>c</sup>
SOLO 2	DUPI (Mono)	469	34.5 <sup>c</sup>	29.6 (N/A)	15.0 (N/A)	7.8
Phase 2b trial	DUPI (Mono)	125	38.3 (12.6)	33.4 (14.2)	13.7 (6.7)	6.3 (1.8) <sup>c</sup> /6.5 (2.0)
CHRONOS	DUPI (Combi)	421	35.6 (N/A)	29.9 (N/A)	13.9 <sup>c</sup>	7.6 <sup>c</sup>
CAFÉ	DUPI (Combi)	215	38.2 (13.1)	33.1 (10.1)	13.5 <sup>c</sup>	6.5 (2.3)

N/A not applicable

<sup>a</sup>Pooled data for approved dosage regimens and placebo

<sup>b</sup>In BREEZE-AD1, patients were randomized to receive baricitinib 2 mg ( $n = 123$ ), baricitinib 4 mg ( $n = 125$ ), baricitinib 1 mg ( $n = 127$ ; not included in pooled data), or placebo ( $n = 249$ ); in BREEZE-AD2, patients were randomized to receive baricitinib 2 mg ( $n = 123$ ), baricitinib 4 mg ( $n = 123$ ), baricitinib 1 mg ( $n = 125$ ; not included in pooled data), or placebo ( $n = 244$ ). In BREEZE-AD4, all patients received TCS and were randomized to baricitinib 2 mg ( $n = 185$ ), baricitinib 4 mg ( $n = 92$ ), baricitinib 1 mg ( $n = 93$ ; not included in pooled data), or placebo ( $n = 93$ ); in BREEZE-AD7, all patients received TCS and were randomized to baricitinib 2 mg ( $n = 109$ ), baricitinib 4 mg ( $n = 111$ ), or placebo ( $n = 109$ ). In SOLO 1, patients were randomized to receive dupilumab 300 mg Q2W ( $n = 224$ ), dupilumab 300 mg Q1W ( $n = 223$ ; not included in pooled data), or placebo ( $n = 224$ ); in SOLO 2, patients were randomized to receive dupilumab 300 mg Q2W ( $n = 233$ ), dupilumab 300 mg Q1W ( $n = 239$ ; not included in pooled data), or placebo ( $n = 236$ ); in the phase 2b trial, patients were randomized to receive dupilumab 300 mg Q2W ( $n = 64$ ), placebo ( $n = 61$ ), or other regimens not included in pooled data: dupilumab 100 mg Q4W ( $n = 65$ ), dupilumab 300 mg Q4W ( $n = 65$ ), dupilumab 300 mg Q1W ( $n = 63$ ), or dupilumab 200 mg Q2W ( $n = 61$ ). In CHRONOS, all patients received TCS and were randomized to dupilumab 300 mg Q2W ( $n = 106$ ), dupilumab 300 mg Q1W ( $n = 319$ ; not included in pooled data), or placebo ( $n = 315$ ); in CAFÉ, all patients received TCS and were randomized to dupilumab 300 mg Q2W ( $n = 107$ ), dupilumab 300 mg Q1W ( $n = 110$ ; not included in pooled data), or placebo ( $n = 108$ )

<sup>c</sup>Weighted median values

<sup>d</sup>For the baricitinib trials, Itch NRS is reported, and for the dupilumab studies, peak pruritus is reported. The phase 2b trial reported both itch and pruritus NRS

<sup>e</sup>Placebo only

**Table 3** Results of the indirect treatment comparison of baricitinib and dupilumab in adult patients with moderate-to-severe atopic dermatitis (AD)

Outcome	Therapy (population)	BARI 2 mg versus DUPI 300 mg Q2W	BARI 4 mg versus DUPI 300 mg Q2W
Relative risk (95% CI)			
EASI75 at Week 4	Monotherapy (pop. A)	1.32 (0.66, 2.63), $p = 0.427$	1.84 (0.96, 3.52), $p = 0.064$
	TCS combo therapy (pop. A)	1.00 (0.49, 2.02), $p = 0.990$	1.45 (0.74, 2.85), $p = 0.281$
	TCS combo therapy (pop. B)	1.35 (0.49, 3.69), $p = 0.559$	2.19 (0.80, 5.99), $p = 0.128$
EASI75 at week 16	Monotherapy (pop. A)	0.66 (0.41, 1.05), $p = 0.081$	0.82 (0.52, 1.30), $p = 0.404$
	TCS combo therapy (pop. A)	0.62 (0.38, 1.02), $p = 0.058$	0.69 (0.43, 1.11), $p = 0.129$
	TCS combo therapy (pop. B)	0.76 (0.42, 1.38), $p = 0.365$	0.87 (0.46, 1.63), $p = 0.656$
Itch NRS $\geq$ 4 point improvement at week 4	Monotherapy (pop. A)	1.49 (0.66, 3.33), $p = 0.337$	<b>2.62 (1.22, 5.61), <math>p = 0.013</math></b>
	TCS combo therapy (pop. A)	1.14 (0.69, 2.91), $p = 0.345$	<b>2.16 (1.08, 4.31), <math>p = 0.029</math></b>
	TCS combo therapy (pop. B)	1.76 (0.55, 5.66), $p = 0.341$	2.98 (0.93, 9.59), $p = 0.066$
Itch NRS $\geq$ 4 point improvement at week 16	Monotherapy (pop. A)	0.65 (0.36, 1.17), $p = 0.147$	0.95 (0.55, 1.65), $p = 0.866$
	TCS combo therapy (pop. A)	0.63 (0.37, 1.08), $p = 0.096$	0.73 (0.43, 1.23), $p = 0.240$
	TCS combo therapy (pop. B)	0.87 (0.34, 2.22), $p = 0.768$	1.45 (0.56, 3.71), $p = 0.442$
Mean difference in change from baseline (95% CI)			
CFB DLQI at week 4	Monotherapy (pop. A)	<b>1.79 (0.33, 3.25), <math>p = 0.016</math></b>	-0.11 (-1.34, 1.12), $p = 0.86$
	TCS combo therapy (pop. A)	1.07 (-0.78, 2.92), $p = 0.256$	-0.62 (-2.46, 1.22), $p = 0.509$
	TCS combo therapy (pop. B)	0.56 (-1.45, 2.57), $p = 0.585$	-0.95 (-3.11, 1.21), $p = 0.388$

**Table 3** continued

Outcome	Therapy (population)	BARI 2 mg versus DUPI 300 mg Q2W	BARI 4 mg versus DUPI 300 mg Q2W
CFB DLQI at week 16	Monotherapy (pop. A)	<b>2.05 (0.53, 3.56), <math>p = 0.008</math></b>	0.68 (−0.77, 2.14), $p = 0.358$
	TCS combo therapy (pop. A)	<b>2.48 (0.46, 4.50), <math>p = 0.016</math></b>	1.09 (−0.93, 3.11), $p = 0.291$
	TCS combo therapy (pop. B)	<b>3.38 (1.18, 5.58), <math>p = 0.003</math></b>	2.00 (−0.41, 4.41), $p = 0.104$

For EASI75 and Itch NRS  $\geq 4$ , relative risk  $< 1$  indicates a result favoring dupilumab. Relative risk  $> 1$  indicates a result favoring baricitinib. For DLQI, MDcfc  $> 0$  indicates a result favoring dupilumab and MDcfc  $< 0$  favors baricitinib. Results that attained statistical significance are given in bold text

*BARI* baricitinib, *DLQI* Dermatology Life Quality Index, *DUPI* dupilumab, *EASI* Eczema Area and Severity Index, *NRS* Numeric Rating Scale, *Q<sub>x</sub>W* every  $x$  weeks

statistically significant differences were evident, although RR values numerically favored dupilumab except for baricitinib 4 mg in population B. At week 4, however,  $\geq 4$ -point itch NRS improvement was significantly more likely to be seen with baricitinib 4 mg than dupilumab in population A for both monotherapy and TCS combination trials. In population B, there were no statistically significant differences between baricitinib 2 or 4 mg compared with dupilumab in achieving  $\geq 4$ -point itch improvement at week 16; RR values numerically favored dupilumab for these comparisons apart from the  $\geq 4$ -point itch improvement seen in baricitinib 4 mg.

For DLQI, no significant differences were observed in MDcfc between baricitinib 4 mg and dupilumab as monotherapy or TCS combination therapy in either population at week 4 or week 16. However, DLQI at week 4 significantly favored dupilumab over baricitinib 2 mg in the population A monotherapy group. At week 16, DLQI MDcfc significantly favored dupilumab versus baricitinib 2 mg as both monotherapy in population A and TCS combination therapy in population A. This difference was also seen in population B at week 16 in our analysis. While these differences were statistically significant, they did not meet the criteria for being

clinically meaningful, where a meaningful clinical difference has been determined to be 4 [13].

## DISCUSSION

This indirect comparison analysis found that baricitinib and dupilumab might have similar efficacy across EASI75,  $\geq 4$ -point improvement in itch NRS, and DLQI improvement (baricitinib 4 mg) after 16 weeks of treatment, confirming the findings of a recently published network meta-analysis (NMA) and extending them to an earlier time point (week 4) [14].

For earlier time points, baricitinib 4 mg was associated with a higher likelihood of an improvement in itch relative to dupilumab. This finding is largely in keeping with the existing evidence on baricitinib and other JAK 1/2 inhibitors, where improvements in itch have been observed as early as one day after treatment initiation [15, 16]. When asked, patients often rate itch as the symptom they find most bothersome and rate as their most important treatment goal [17, 18]. The increased expression of pruritogens, including TSLP, IL-4, IL-13, and IL-31, is thought to be most important for itch induction in AD [19, 20]. These pruritogens may signal via JAKs



[21] and consequently be directly inhibited by baricitinib. Such inhibition may explain baricitinib's ability to rapidly reduce itch. By week 16, itch improvement was comparable to that achieved by dupilumab. Our findings will serve to support clinical decision-making with regards to treatment options, not only several months into patients' therapy but also in the early weeks after treatment initiation.

H2H trial data, considered to be the highest form of evidence, can take time to emerge, perhaps delaying access to potentially beneficial therapies for health systems and patients. In such circumstances, NMA and ITCs like our study can help to provide valuable evidence before H2H data are available. In this case, we chose an ITC framework as only one other drug was identified by the SLR. Several factors should be considered when interpreting our results. Evidence identified by the systematic review was more limited for the TCS combination groups than for monotherapy. Also, it is possible that differences in trial design, such as TCS use not being standardized across trials and different washout periods, limit cross-trial comparability in the AD research landscape. Heterogeneity across trials designs and statistical analysis that impact study outcomes in AD clinical research has been identified as a challenge for healthcare providers [22], though in this instance, there is evidence that these may favor dupilumab [23]. The lack of longer-term follow-up in our analysis also represents a limitation. This was a function of the period of PBO-controlled observation within the trials themselves; comparisons can only be made where there are PBO data available to populate the models. This could be resolved by the conduct of full H2H trials with a longer follow-up period, but such analysis lies outside the scope of this work. We did not assess differences in safety outcomes between the competing treatments.

## CONCLUSIONS

Baricitinib represents an approved oral treatment option for adult patients with moderate-to-severe AD that potentially offers more rapid

improvement in itch, a key symptom for patients, while it might also provide similar efficacy in terms of EASI75 and DLQI outcomes compared with dupilumab based on indirect evidence [24–28].

## ACKNOWLEDGEMENTS

**Funding.** The study and this analysis were funded by Eli Lilly and Company, as was the Rapid Service Fee associated with the publication of this manuscript.

**Medical Writing and/or Editorial Assistance.** Mr. Alan Ó Céilleachair, an employee of Eli Lilly and Company, provided scientific writing and editorial support on the manuscript. Support for this assistance was funded by Eli Lilly and Company.

**Authorship.** All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work, and have given their approval for this version to be published.

**Author Contributions.** Marjolein de Bruin-Weller contributed to the conception of the work, the design of the work and the interpretation of the data. Esther Serra-Baldrich, Sebastian Barbarot, Susanne Grond, and Christopher Schuster contributed to the interpretation of the data for the work. Afaf Raibouaa contributed to the conception of the work, the design of the work, and the acquisition of data for the work. Helmut Petto contributed to the conception of the work, design of the work, and the analysis and interpretation of data. Jean Phillippe Capron contributed to the analysis and interpretation of data. All authors contributed to critical revision of the work for important intellectual content.

**Disclosures.** Marjolein de Bruin-Weller has served as a consultant, advisory board member, and/or speaker for AbbVie, Almirall, Arena, Aslan, Galderma, Janssen, Leo Pharma, Pfizer,

Regeneron, and Sanofi-Genzyme, and Eli Lilly and Company. Esther Serra-Baldrich has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Abbvie, Novartis, Ammirall, Leo, Sanofi, Pfizer, and Eli Lilly and Company. Sebastien Barbarot has: received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Ammirall, Sanofi-Genzyme, Abbvie, Novartis, Janssen, Leo-Pharma, Pfizer, UCB Pharma, and Eli Lilly and Company; received support for attending meetings and/or travel from Ammirall, Sanofi-Genzyme, Abbvie, Novartis, Janssen, Leo-Pharma, Pfizer, UCB Pharma, and Eli Lilly and Company; and participated on a Data Safety Monitoring Board or Advisory Board for Ammirall, Sanofi-Genzyme, Abbvie, Novartis, Janssen, Leo-Pharma, Pfizer, UCB Pharma, and Eli Lilly and Company. Susanne Grond, Helmut Petto, and Jean Phillippe Capron are employees and shareholders of Eli Lilly and Company. Christopher Schuster and Afaf Raibouaa are employees of Eli Lilly and Company. Thomas Werfel has: received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Sanofi-Regeneron, Abbvie, Pfizer, Galderma, Leo, and Eli Lilly and Company; participated on a Data Safety Monitoring Board or Advisory Board for Sanofi-Regeneron, Abbvie, Pfizer, Galderma, Leo, and Eli Lilly and Company; and filled a leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid for German Societies for Dermatology (DDG) and Allergy (DGAKI).

**Compliance with Ethics Guidelines.** This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

**Data Availability.** Data sharing is not applicable to this article as no new datasets were generated or analyzed during the current study.

**Open Access.** This article is licensed under a Creative Commons Attribution-

NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc/4.0/>.

## REFERENCES

1. European Medicines Agency. EMA/505843/2020: An overview of Olumiant and why it is authorised in the EU. Amsterdam: European Medicines Agency; 2017, 23 November 2017.
2. Simpson EL, Lacour JP, Spelman L, Galimberti R, Eichenfield LF, Bissonnette R, et al. Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. *Br J Dermatol.* 2020;183(2):242–55.
3. Reich K, Kabashima K, Peris K, Silverberg JJ, Eichenfield LF, Bieber T, et al. Efficacy and safety of baricitinib combined with topical corticosteroids for treatment of moderate to severe atopic dermatitis: a randomized clinical trial. *JAMA Dermatol.* 2020;156(12):1333–43.
4. Strand V, McInnes I, Mease P, Nash P, Thom H, Kalyvas C, et al. Matching-adjusted indirect comparison: secukinumab versus infliximab in biologic-naïve patients with psoriatic arthritis. *J Comp Eff Res.* 2019;8(7):497–510.
5. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol.* 1997;50(6):683–91.
6. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, et al. Two phase 3 trials of

- dupilumab versus placebo in atopic dermatitis. *N Engl J Med*. 2016;375(24):2335–48.
7. US Food and Drug Administration. DUPIXENT® (dupilumab) injection, for subcutaneous use. Maryland; 2017. Contract No.: 16 November 2021.
  8. European Medicines Agency. EMA/414096/2019: Dupixent is authorised for use in the European Union. Amsterdam; 2017. Contract No.: 22 November 2021.
  9. Newton L, DeLozier AM, Griffiths PC, Hill JN, Hudgens S, Symonds T, et al. Exploring content and psychometric validity of newly developed assessment tools for itch and skin pain in atopic dermatitis. *J Patient Rep Outcomes*. 2019;3(1):42.
  10. Silverberg JI, DeLozier A, Sun L, Thyssen JP, Kim B, Yosipovitch G, et al. Psychometric properties of the itch numeric rating scale, skin pain numeric rating scale, and atopic dermatitis sleep scale in adult patients with moderate-to-severe atopic dermatitis. *Health Qual Life Outcomes*. 2021;19(1):247.
  11. Yosipovitch G, Reaney M, Mastey V, Eckert L, Abbe A, Nelson L, et al. Peak Pruritus Numerical Rating Scale: psychometric validation and responder definition for assessing itch in moderate-to-severe atopic dermatitis. *Br J Dermatol*. 2019;181(4):761–9.
  12. Balduzzi S, Rucker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health*. 2019;22(4):153–60.
  13. Basra MK, Salek MS, Camilleri L, Sturkey R, Finlay AY. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. *Dermatology*. 2015;230(1):27–33.
  14. Silverberg JI, Thyssen JP, Fahrback K, Mickle K, Cappelleri JC, Romero W, et al. Comparative efficacy and safety of systemic therapies used in moderate-to-severe atopic dermatitis: a systematic literature review and network meta-analysis. *J Eur Acad Dermatol Venereol*. 2021;35(9):1797–810.
  15. Buhl T, Rosmarin D, Serra-Baldrich E, Fernandez-Penas P, Igarashi A, Konstantinou MP, et al. Itch and sleep improvements with baricitinib in patients with atopic dermatitis: a post hoc analysis of 3 phase 3 studies. *Dermatol Ther (Heidelb)*. 2021;11(3):971–82.
  16. Blauvelt A, Teixeira HD, Simpson EL, Costanzo A, De Bruin-Weller M, Barbarot S, et al. Efficacy and safety of upadacitinib vs dupilumab in adults with moderate-to-severe atopic dermatitis: a randomized clinical trial. *JAMA Dermatol*. 2021;157(9):1047–55.
  17. Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, et al. Patient burden and quality of life in atopic dermatitis in US adults: a population-based cross-sectional study. *Ann Allergy Asthma Immunol*. 2018;121(3):340–7.
  18. Augustin M, Langenbruch A, Blome C, Gutknecht M, Werfel T, Stander S, et al. Characterizing treatment-related patient needs in atopic eczema: insights for personalized goal orientation. *J Eur Acad Dermatol Venereol*. 2020;34(1):142–52.
  19. Yang TB, Kim BS. Pruritus in allergy and immunology. *J Allergy Clin Immunol*. 2019;144(2):353–60.
  20. Weidinger S, Beck LA, Bieber T, Kabashima K, Irvine AD. Atopic dermatitis. *Nat Rev Dis Primers*. 2018;4(1):1.
  21. Gadina M, Le MT, Schwartz DM, Silvennoinen O, Nakayamada S, Yamaoka K, et al. Janus kinases to jakinibs: from basic insights to clinical practice. *Rheumatology (Oxford)*. 2019;58(Suppl 1):i4–16.
  22. Silverberg JI, Simpson EL, Armstrong AW, de Bruin-Weller MS, Irvine AD, Reich K. Expert perspectives on key parameters that impact interpretation of randomized clinical trials in moderate-to-severe atopic dermatitis. *Am J Clin Dermatol*. 2021;23:1–11.
  23. National Institute for Health and Care Excellence. Evidence-based recommendations on baricitinib for treating moderate to severe atopic dermatitis in adults. London: National Institute for Health and Care Excellence; 2021. Contract No.: TA681.
  24. Barbarot S, Auziere S, Gadkari A, Girolomoni G, Puig L, Simpson EL, et al. Epidemiology of atopic dermatitis in adults: results from an international survey. *Allergy*. 2018;73(6):1284–93.
  25. Thaçi D, Simpson EL, Beck LA, Bieber T, Blauvelt A, Papp K, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. *Lancet*. 2016;387(10013):40–52.
  26. Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet*. 2017;389(10086):2287–303.
  27. ClinicalTrials.gov. A long-term study of baricitinib (LY3009104) with topical corticosteroids in adults with moderate to severe atopic dermatitis that are not controlled with cyclosporine or for those who

cannot take oral cyclosporine because it is not medically advisable (BREEZE-AD4) 2018 [updated May 11th 2021]. Available from <https://clinicaltrials.gov/ct2/show/study/NCT03428100>.

28. de Bruin-Weller M, Thaci D, Smith CH, Reich K, Cork MJ, Radin A, et al. Dupilumab with

concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFE). *Br J Dermatol.* 2018;178(5):1083–101.