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ORIGINAL ARTICLE

Impact of baricitinib in combination with topical steroids on atopic dermatitis symptoms, quality of life and functioning in adult patients with moderate-to-severe atopic dermatitis from the BREEZE-AD7 Phase 3 randomized trial

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Abstract

Background Baricitinib is an oral, selective, reversible Janus kinase 1/2 inhibitor approved in the European Union and Japan and under investigation in the United States for treatment of atopic dermatitis (AD).

Objectives To evaluate the impact of baricitinib plus background topical corticosteroids (TCS) on health-related quality of life (HRQoL), how AD symptoms impact work productivity and life functioning, and treatment benefit using patient-reported outcome (PRO) assessments in patients with moderate-to-severe AD previously experiencing inadequate response to TCS.

Methods Adult patients with AD in BREEZE-AD7, a Phase 3, multicentre, double-blind trial, were randomised 1 : 1 : 1 to daily oral placebo (control) or baricitinib 4- or 2-mg plus TCS. PROs reported Week 1 through Week 16: Dermatology Life Quality Index (DLQI), Work Productivity and Activity Impairment-AD (WPAI-AD); Patient-Reported Outcomes Measurement Information System (PROMIS) Itch and Sleep measures, and Patient Benefit Index (PBI). Data were analysed using logistic regression (categorical) and mixed model repeated measures (continuous). PBI scores were analysed using analysis of variance.

Results A total of 329 patients were randomised. Treatment with baricitinib 4-mg (N = 111) or 2 mg (N = 109) plus TCS led to rapid, statistically significant improvements [vs. TCS plus placebo (N = 109)] in DLQI ≥4-point improvement starting at Week 2 (4-mg plus TCS, $P \leq 0.001$; 2-mg plus TCS $P \leq 0.05$), change from baseline in WPAI-AD presenteeism at Week 1 (4-mg plus TCS, $P \leq 0.01$; 2-mg plus TCS $P \leq 0.05$) and PROMIS itch interference at Week 2 (4-mg plus TCS $P \leq 0.01$). Improvements were sustained through Week 16 for baricitinib 4-mg. Statistically significant improvements were observed at Week 16 for PBI global score (4-mg plus TCS, $P \leq 0.001$; 2-mg plus TCS $P \leq 0.05$).

Conclusions Baricitinib plus TCS vs. placebo plus TCS showed significant improvements in treatment benefit at Week 16 and rapid significant improvements in HRQoL and impact of AD symptoms on work productivity and functioning through 16 weeks.

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Conflicts of interest

AW has received grants, personal fees or non-financial support from AbbVie, Almirall, Beiersdorf, Bioderma, Chugai, Eli Lilly and Company, Galapagos, Galderma, Hans Karrer, Leo Pharma, L'Oreal, Maruho, MedImmune, Novartis, Pfizer, Pierre Fabre, Regeneron, Santen and Sanofi-Aventis; TN has received speaker's fees from Maruho and Sanofi; CM is an Investigator, Consultant, Advisory Board Member, Speaker for and/or receives honoraria from Aquinox Pharma, Asana BioSciences, AbbVie, Brickell Biotech, Dermavant, Eli Lilly and Company, Galderma, Glenmark, GSK-Stiefel, Hoffman-LaRoche Ltd, Hoffman-LaRoche-Posay, Leo Pharma, Pfizer, Regeneron-Sanofi, Valeant and Vitae; KP reports personal

fees from Almirall, AbbVie, Biogen, Janssen, Eli Lilly and Company, Celgene, Galderma, Janssen, Leo Pharma, Novartis, Pierre Fabre, Sanofi, Sandoz and Sun Pharma outside the submitted work; PL has served as an investigator for AbbVie and Regeneron/Sanofi-Genzyme, has served as an advisor/consultant for AbbVie, Arbonne, Amyris, Bodewell, Burt's Bees, Dermavant, Dermira, Eli Lilly and Company, Galderma, Johnson and Johnson, Kiniksa, Leo Pharma, L'Oreal, Micreos, Pfizer, Pierre Fabre, Regeneron/Sanofi-Genzyme, Theraplex and Verrica; has served as a speaker for Galderma, L'Oreal and Pfizer, and has a patent with Theraplex AIM. MA has served as advisor and/or paid speaker for and/or participated in research projects sponsored by Abbott/AbbVie, ALK Scherax, Almirall, Amgen, Beiersdorf, Biogen Idec, BMS, Boehringer Ingelheim, Celgene, Centocor, Dermira, Eli Lilly and Company, Forward Pharma, Fresenius, Galderma, GSK, Hexal, Incyte, Janssen-Cilag, LEO Pharma, Medac, Menlo, Merck, MSD, Mylon, Novartis, Pfizer, Regeneron, Sandoz, Sanofi-Aventis, Stallergenes, Stiefel, Teva, TK, Trevi, UCB and Xenoport; JIS has received honoraria as a consultant and/or advisory board member for Abbvie, Afyx, Arena, Asana, BioMX, Bluefin, Bodewell, Boehringer Ingelheim, Celgene, Dermavant, Dermira, Eli Lilly, Galderma, GlaxoSmithKline, Incyte, Kiniksa, Leo, Luna, Menlo, Novartis, Pfizer, RAPT, Regeneron, Sanofi; speaker for Pfizer, Regeneron, Sanofi; institution received grants from Galderma; MT has been a co-investigator for AbbVie, Boehringer, Eli Lilly and Company, Galderma, Janssen-Cilag, Leo Pharma, Pierre Fabre, Sanofi-Regeneron, and UCB and a speaker for Sanofi-Regeneron and Janssen-Cilag; CP has been an investigator and consultant for AbbVie, Almirall, Amgen, Boehringer, Celgene, Eli Lilly and Company, Galderma, Janssen-Cilag, Leo Pharma, Merck, Novartis, Pfizer, Pierre Fabre, Regeneron, Sanofi (AD) and UCB pharma; MJR, AMD, EP, FEY, LS and SB are employees and shareholders of Eli Lilly and Company.

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Introduction

Atopic dermatitis (AD) is a common, chronic, relapsing, highly symptomatic inflammatory skin disease.[1–4] Pruritus is the primary source of morbidity in AD,[5,6] and scratching can lead to bleeding and secondary infections associated with AD skin lesions.[7] Worsening of pruritus at night can result in sleep disturbances.[8,9] In addition to pruritus, patients report skin pain as an important symptom.[10] The signs and symptoms of AD can have profound negative effects on patients' health-related quality of life (HRQoL), including impaired work productivity and non-work activities, mental health and other HRQoL.[11–14]

Current guidelines indicate emollients and topical corticosteroids (TCS) are the mainstay of AD treatment, where less severe AD can be controlled by appropriate skincare and TCS, but more severe AD usually requires additional treatments such as systemic medications or phototherapy. While systemic therapies can be effective, the risks for adverse events preclude their continuous long-term use, indicating the need for alternative treatments. Furthermore, despite the use of systemic therapies, most patients will still experience flares as part of their underlying disease. Thus, TCS are typically used intermittently as background therapy in combination with systemic medications to manage acute AD lesions. Dupilumab, a new injectable biologic, has been approved for the treatment of AD, showing short-term efficacy, long-term efficacy up to 76 weeks and a favourable benefit–risk profile in patients with AD.[15,16] Despite this new advanced treatment, additional options are needed to fulfil patients' unmet medical needs.

Baricitinib is an oral, selective and reversible Janus kinase 1 and 2 inhibitor [17] approved in the European Union and Japan and under investigation in the United States and other countries for the treatment of moderate-to-severe AD in adult patients who are candidates for systemic therapy.[18] Baricitinib is also approved in adults with moderately-to-severely active rheumatoid arthritis in 70 countries and is in late-stage development for adults with alopecia areata. In previous Phase 3 trials in adults with moderate-to-severe AD, once-daily oral baricitinib 4- and 2-mg were shown to be effective as monotherapy in treating patients with an inadequate response to TCS.[19] Patients receiving baricitinib showed significant improvements in achieving clear or almost clear skin at 16 weeks vs. placebo. In a recent Phase 3 trial (BREEZE-AD7), baricitinib 4- and 2-mg therapy plus TCS were reported as effective in significantly improving the signs and symptoms of AD vs. placebo plus TCS in adults with moderate-to-severe AD with a previous inadequate response to TCS.[20]

A patient's perspective on their treatment is important in medical decision-making. Patient-reported outcome measures

ClinicalTrials.gov-NCT03733301

provide insights into how benefits in controlling symptoms extend to improvements in both disease severity and how AD affects functioning in work and daily life. From the BREEZE-AD7 study, we present efficacy of baricitinib plus TCS using functional measures of HRQoL, work productivity and life activities, symptom impact and treatment benefit in adults with moderate-to-severe AD with previous inadequate response to TCS.

Materials and methods

Study patients

Patients aged ≥18 years with a diagnosis of AD, as defined by the American Academy of Dermatology, at least 12 months before screening, were included. Eligible patients had a documented history of inadequate response to topical medications and thus met criteria for systemic therapy. Additional details on BREEZE-AD7 study design and patients, including settings and location where data were collected, blinding, randomisation and inclusion/exclusion criteria, are presented elsewhere.[20]

Compliance with ethics guidelines

The ethics review boards at each study site provided study protocol approval and informed consent form. The sponsor and investigators conducted the studies in accordance with the Declaration of Helsinki, applicable ICH-GCP guidelines, and applicable laws and regulations. Informed consent was obtained from all individual participants included in the studies or their legally acceptable representatives before study procedures were performed.

Study design

BREEZE-AD7 (NCT03733301) was a multicentre, randomised, double-blinded, placebo-controlled Phase 3 clinical trial. Patients were randomised 1 : 1 : 1 to receive oral placebo, baricitinib 2- or 4-mg plus TCS once daily for 16 weeks (Fig. S1). At baseline, patients were instructed to apply moderate potency TCS until lesions were clear or almost clear and then to switch to mild potency TCS for 7 days and then stop. If lesions reappeared, patients could resume the regimen. Patients experiencing unacceptable or worsening symptoms after 2 weeks of treatment may have been rescued with high- or ultra-high potency TCS or oral systemic agents. Patients who required rescue using oral systemic agents discontinued study treatment.

Patient-reported outcome measures and endpoints

The study objective was to evaluate the impact of baricitinib plus background TCS on patient-reported measures of HRQoL, AD symptom impact, work and daily life functioning, and treatment benefit.

The Dermatology Life Quality Index (DLQI) is a validated questionnaire covering various aspects of a patient's HRQoL.[21] Higher scores indicate greater impairment of HRQoL. A ≥4-point change from baseline in DLQI total score is considered the minimal clinically important difference;[22] a total score from 2 to 5 indicates having a small effect on a patient's HRQoL; and a total score of 0 to 1 indicates having no effect on a patient's HRQoL.[23]

The Work Productivity and Activity Impairment-AD (WPAI-AD) questionnaire records impairment due to AD during the past 7 days.[24] The WPAI-AD consists of four domains: absenteeism, presenteeism, work productivity loss (absenteeism plus presenteeism) and activity outside of work. Only employed patients answered questions related to absenteeism, presenteeism and work productivity loss; all patients answered the question related to activity outside of work. Scores are calculated as impairment percentages, with higher scores indicating greater impairment and less productivity.

Patient-Reported Outcome Measurement Information System (PROMIS) item banks are a set of person-centred measures that evaluate physical, mental and social health in adults and children.[25,26] The PROMIS Itch Short Form instruments measure how much itch interferes with HRQoL in the past 7 days across several item banks.[27–29] Patients also completed the PROMIS Sleep-Related Impairment Short Form instrument, which measures self-reported perceptions of impairment related to general aspects of sleep 'in the past 7 days'.[30–32] PROMIS instrument scores are T scores, where a higher score indicates greater impairment.

The Patient Benefit Index (PBI) measures patient-defined treatment objectives and benefits.[33,34] A patient needs questionnaire is completed before treatment begins. Patients rate the importance of specific treatment goals from 0 'not important at all' to 4 'very important'. During or at the end of treatment, the patient completes the Patient Benefit Questionnaire, in which the items are rated from 0 'did not help at all' to 4 'helped a lot'. The PBI derives a global score for each patient from ratings on each questionnaire, with higher scores indicating greater benefit. Responses can also be scored based on 6 rating subscales scales: social impairment, psychological impairment, impairment due to therapy, physical impairment and confidence in therapy. Patients with PBI of 1 or greater are considered as having at least minimum patient-relevant treatment benefit.

Translations for the PROMIS instruments and PBI questionnaires were not available in all countries; thus, they were completed by a subset of the patients for whom translations were available according to language.

Statistical analysis

The analysis population comprised all randomised patients, regardless of whether they received the correct treatment. Treatment comparisons between baricitinib and placebo for DLQI categorical endpoints [≥4-point improvement in DLQI total

score, DLQI total score ≤5 and DLQI (0,1)] were performed using logistic regression analysis with region, baseline vIGA-AD, baseline value and treatment group as factors. Only patients with baseline DLQI total score ≥4 for the 4-point or more improvement endpoint and patients with baseline DLQI total score >5 for the DLQI total score ≤5 endpoint were included. Mean change from baseline for continuous measures (PROMIS and WPAI-AD) was evaluated using a restricted maximum likelihood-based mixed model repeated measures (MMRM), where the model includes treatment, region, baseline disease severity [validated Investigator Global Assessment for AD (vIGA-AD)], visit and treatment-by-visit-interactions as fixed categorical effects and baseline and baseline-by-visit-interaction as fixed continuous effects. Treatment comparisons for PBI scores were analysed using an analysis of variance model, where treatment, region and baseline vIGA-AD were included as factors. The *P*-values for treatment comparisons were not adjusted for multiplicity.

Data collected after first rescue therapy or permanent study drug discontinuation were considered missing. Non-responder imputation was used to impute missing values for categorical variables. No explicit imputations were conducted for continuous measures; MMRM analysis was performed to mitigate the impact of missing data because it yields valid inferences assuming that missing observations are missing-at-random. Observed data were used to analyse continuous PBI scores as the postbaseline data were collected only once during the treatment period. Per the study protocol, WPAI-AD outcomes were prespecified as secondary objectives, and DLQI, PROMIS and PBI outcomes were prespecified as exploratory objectives. Statistical analyses were performed using SAS® version 9.4 or higher (SAS Institute, Cary, NC, USA).

Results

Subject disposition and demographics

Patient demographic and baseline characteristics are presented in Table 1. As reported previously, 329 patients were randomised in the study (placebo + TCS, *N* = 109; baricitinib 4-mg + TCS, *N* = 111; baricitinib 2-mg + TCS, *N* = 109).[20] Baseline characteristics and illness severity measures were similar across treatment groups. High impairment of HRQoL at baseline was indicated by a mean DLQI total score of 15.[23] Study discontinuation included 6.4% in the placebo plus TCS group, 3.6% in the baricitinib 4-mg plus TCS group and 8.3% in the baricitinib 2-mg plus TCS group. The rate of rescue therapy was 9.2% in the placebo group, 4.6% in baricitinib 2-mg and 5.4% in the baricitinib 4-mg group.

Table 1 Demographics and baseline characteristics of patients

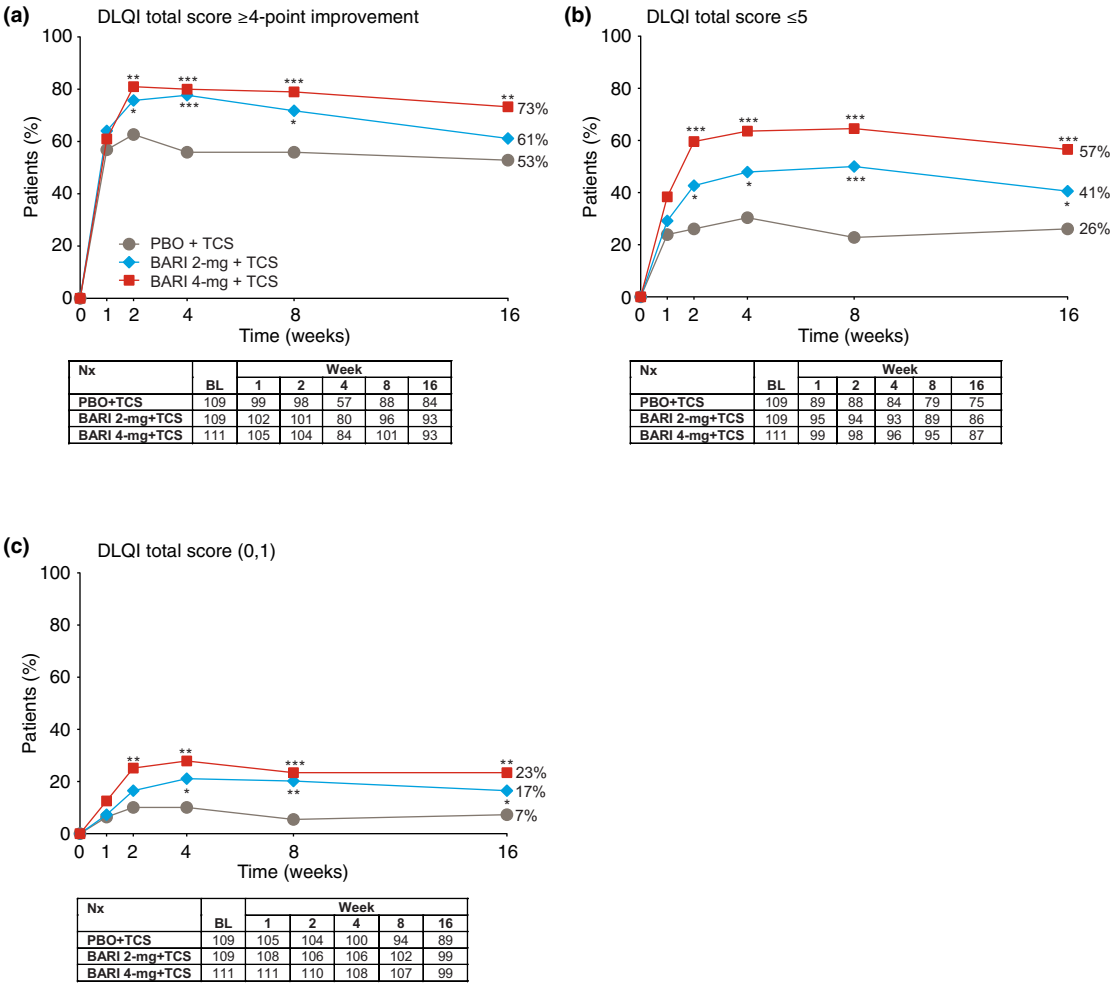
Parameter	PBO + TCS *N* = 109	BARI 2-mg + TCS *N* = 109	BARI 4-mg + TCS *N* = 111
Age, years	33.7 (13.2)	33.8 (12.8)	33.9 (11.4)
Female, %	34.9	35.8	32.4
Race, %			
Caucasian	42.2	45.9	48.6
Asian	52.3	52.3	48.6
Multiple	5.5	1.8	2.7
Prior systemic therapy use, %	68.8	63.3	61.8
Prior cyclosporine use, %	37.9	32.7	30.6
BSA affected by AD	48.1 (24.4)	50.6 (21.6)	52.1 (23.3)
vIGA-AD of 4 at baseline, %	44.4	45.9	45.0
Itch NRS	7.4 (1.7)	7.0 (2.1)	7.0 (2.0)
DLQI	15.0 (7.9)	15.0 (7.7)	14.7 (7.9)
WPAI-AD			
Activity	52.9 (28.0)	57.1 (25.3)	52.2 (26.0)
Presenteeism	43.0 (26.5)	49.4 (24.6)	45.1 (26.7)
Absenteeism	10.9 (25.5)	9.1 (20.3)	8.8 (21.6)
Work productivity loss	45.8 (28.5)	51.7 (25.5)	47.0 (27.6)
PROMIS Itch			
Scratching behaviour	59.8 (7.5)	58.3 (8.0)	59.3 (8.5)
Interference	53.7 (8.8)	51.9 (7.7)	51.8 (7.7)
Mood and sleep	58.9 (8.6)	56.3 (7.8)	56.7 (8.8)
Activity and clothing	56.4 (9.3)	55.0 (8.1)	54.4 (8.6)
Sleep-related impairment	60.6 (10.7)	60.7 (8.8)	58.1 (9.2)

DLQI

At Week 2, significantly greater proportions of patients in both baricitinib plus TCS treatment groups vs. placebo plus TCS reported scores that met or exceeded the minimal clinically important difference threshold for DLQI total score (≥4-point improvement; Fig. 1a). Similarly, significantly greater proportions of patients in baricitinib plus TCS treatment groups vs. placebo plus TCS reported scores indicating AD symptoms had no more than a small effect on patient HRQoL (DLQI total score ≤5) or had no effect [DLQI (0,1)] starting at Week 2 (baricitinib 4-mg plus TCS) or Week 4 (baricitinib 2-mg plus TCS; Fig. 1b, c). Overall, statistically significant improvements in HRQoL observed within the first 8 weeks were sustained through Week 16, except for DLQI total score ≥4-point improvement in the 2-mg baricitinib plus TCS group (Fig. 1a).

WPAI-AD

Patients treated with baricitinib 4- or 2-mg plus TCS demonstrated significantly less impairment in daily activities vs. patients treated with placebo (Fig. 2a). These differences



Nx		Week				
	BL	1	2	4	8	16
PBO+TCS	109	99	98	57	88	84
BARI 2-mg+TCS	109	102	101	80	96	93
BARI 4-mg+TCS	111	105	104	84	101	93

Nx		Week				
	BL	1	2	4	8	16
PBO+TCS	109	89	88	84	79	75
BARI 2-mg+TCS	109	95	94	93	89	86
BARI 4-mg+TCS	111	99	98	96	95	87

Nx		Week				
	BL	1	2	4	8	16
PBO+TCS	109	105	104	100	94	89
BARI 2-mg+TCS	109	108	106	106	102	99
BARI 4-mg+TCS	111	111	110	108	107	99

Figure 1 Dermatology Life Quality Index Outcomes (NRI). Proportion of patients achieving (a) 4 or more point improvement in DLQI total score; (b) a DLQI total score ≤5; and (c) a 0 or 1 on the DLQI, in patients receiving BARI 4-, 2-mg and placebo plus TCS through Week 16. *P*-values for BARI vs. PBO: *$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$, BARI, baricitinib; BL, baseline; DLQI, Dermatology Life Quality Index; NRI, non-responder imputation; Nx, number of patients with non-missing values; PBO, placebo; TCS, topical corticosteroids. Table beneath the graph includes number of patients with non-missing values at the indicated time points. Patient population includes all randomised patients. Patients from the analysis shown in panel (a) had a baseline DLQI total score ≥4 and panel (b) had a baseline DLQI total score >5. DLQI (0,1) categorical data were previously reported.[20]

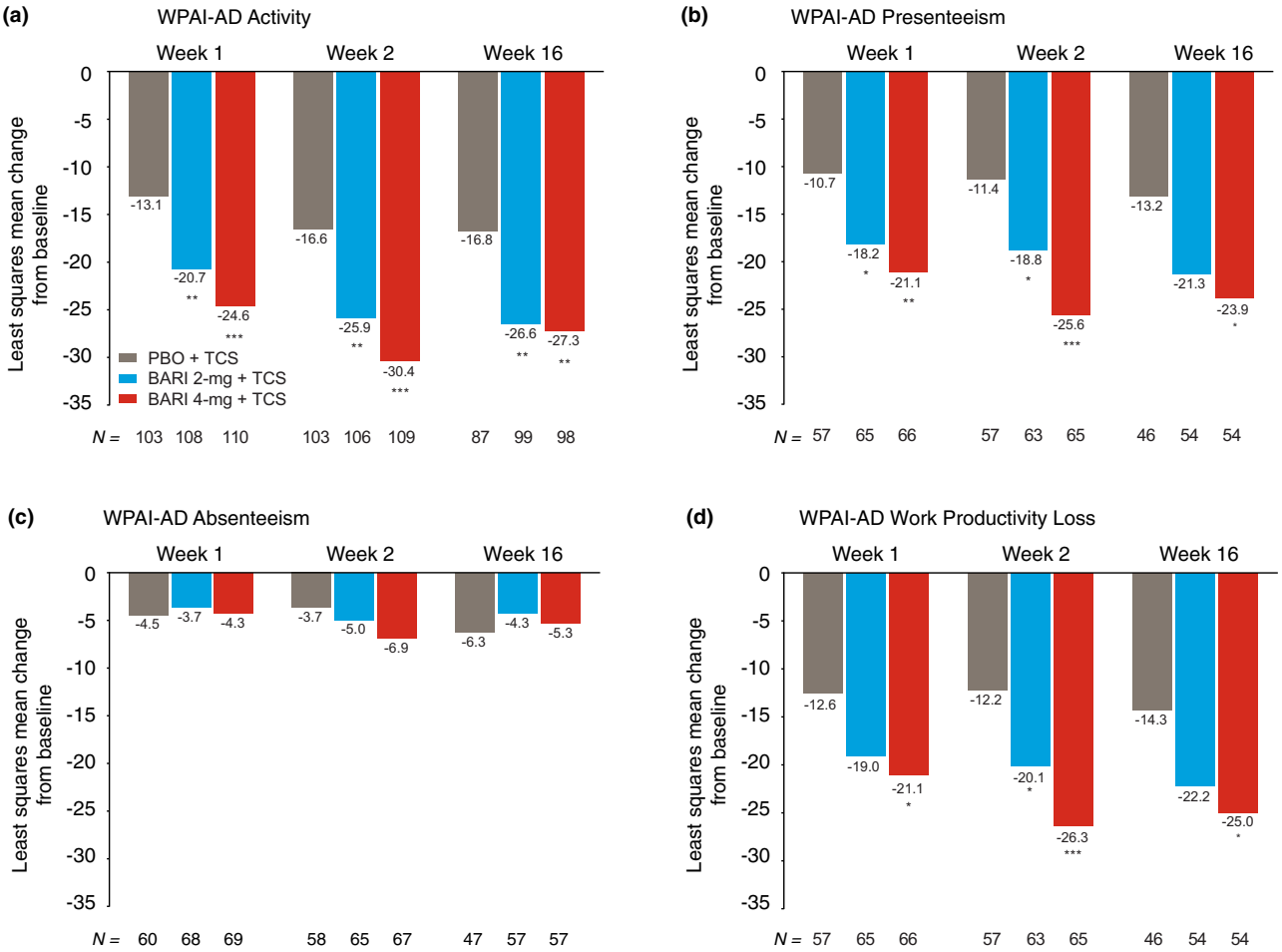


Figure 2 Work Productivity and Activity Impairment (MMRM). Change from baseline in WPAI-AD (a) activity, (b) presenteeism, (c) absenteeism and (d) work productivity loss domains for BARI 4-, 2-mg and PBO plus TCS at Weeks 1, 2, and 16. *P*-values for BARI vs. PBO: $*P \leq 0.05$, $**P \leq 0.01$, $***P \leq 0.001$. BARI, baricitinib; MMRM, mixed effect repeated measures; Nx, number of patients with non-missing values; PBO, placebo; TCS, topical corticosteroids; WPAI-AD, Work Productivity and Activity Impairment-Atopic Dermatitis. Numbers beneath the graph include number of patients with non-missing values at the indicated time points. Patient population includes all randomised patients. Only employed patients answered questions related to absenteeism, presenteeism and work productivity loss; all patients answered the question related to activity outside of work. Higher scores indicate greater impairment and less productivity.

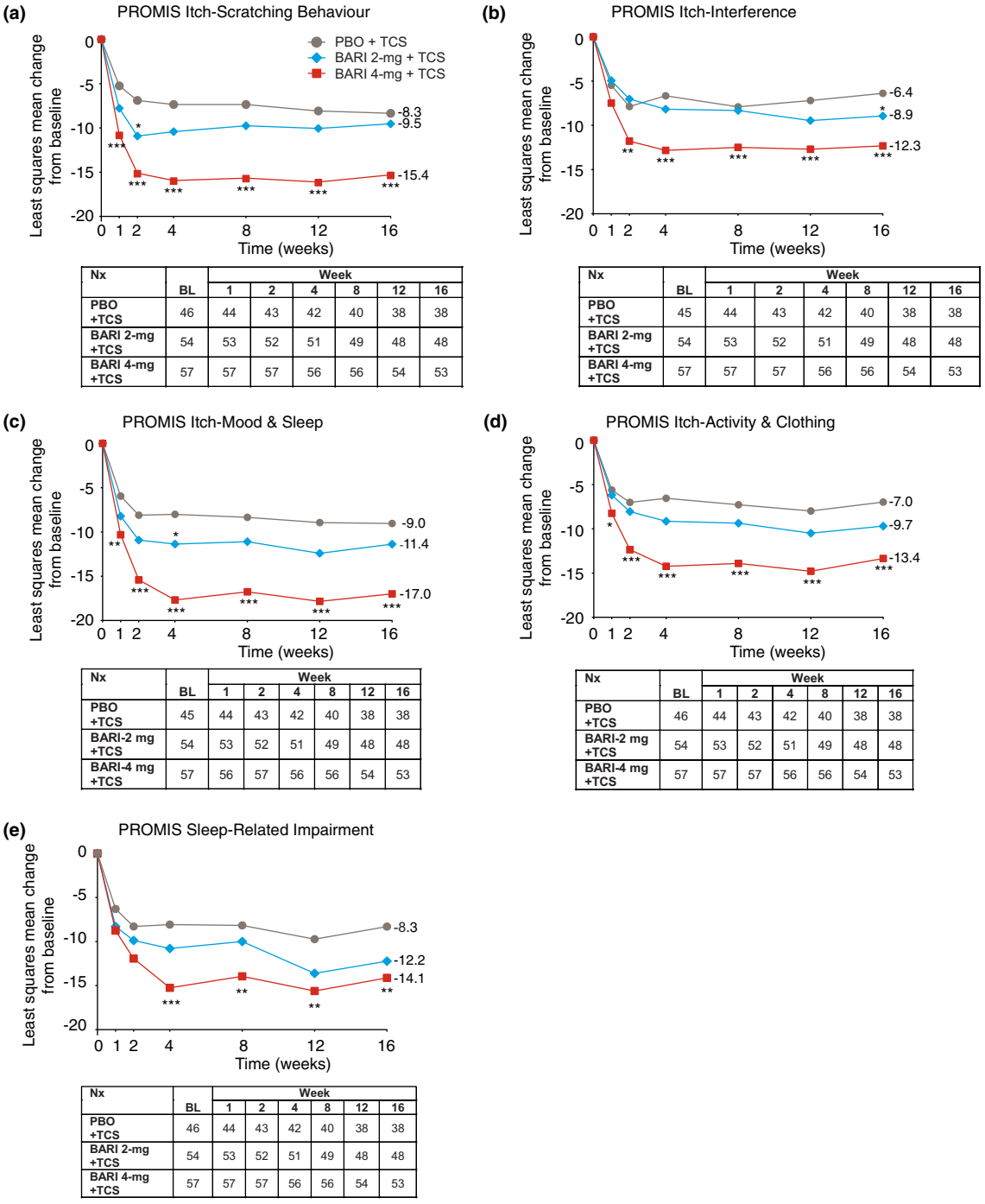
occurred at Week 1 and continued through Week 16. Similarly, patients treated with baricitinib 4-mg plus TCS vs. placebo plus TCS experienced significant reductions in presenteeism through Week 16 (Fig. 2b); there were no differences across treatments for absenteeism (Fig. 2c). Overall work productivity loss mirrored results for presenteeism (Fig. 2d).

PROMIS Itch

Scratching behaviour At Week 1, statistically significant improvements from baseline were observed in the baricitinib 4-mg plus TCS treatment group vs. placebo plus TCS for the scratching behaviour outcome, and improvements were sustained through Week 16 (Fig 3a). Statistically significant improvements from baseline were also observed in the baricitinib 2-mg plus TCS treatment group vs. placebo plus TCS at Week 2.

Itch interference At Week 2, statistically significant improvements from baseline were observed in the baricitinib 4-mg plus TCS treatment group vs. placebo plus TCS for the itch interference outcome, and improvements were sustained through Week 16 (Fig. 3b). A statistically significant improvement from baseline was also observed in the baricitinib 2-mg plus TCS treatment group vs. placebo plus TCS at Week 16.

Mood and sleep At Week 1, statistically significant improvements from baseline were observed in the baricitinib 4-mg plus



Nx	BL	Week 1	2	4	8	12	16
PBO +TCS	46	44	43	42	40	38	38
BARI 2-mg +TCS	54	53	52	51	49	48	48
BARI 4-mg +TCS	57	57	57	56	56	54	53

Nx	BL	Week 1	2	4	8	12	16
PBO +TCS	45	44	43	42	40	38	38
BARI 2-mg +TCS	54	53	52	51	49	48	48
BARI 4-mg +TCS	57	57	57	56	56	54	53

Nx	BL	Week 1	2	4	8	12	16
PBO +TCS	45	44	43	42	40	38	38
BARI-2 mg +TCS	54	53	52	51	49	48	48
BARI-4 mg +TCS	57	56	57	56	56	54	53

Nx	BL	Week 1	2	4	8	12	16
PBO +TCS	46	44	43	42	40	38	38
BARI-2 mg +TCS	54	53	52	51	49	48	48
BARI-4 mg +TCS	57	57	57	56	56	54	53

Nx	BL	Week 1	2	4	8	12	16
PBO +TCS	46	44	43	42	40	38	38
BARI 2-mg +TCS	54	53	52	51	49	48	48
BARI 4-mg +TCS	57	57	57	56	56	54	53

Figure 3 Patient-Reported Outcome Measurement Information System Item Banks (MMRM). Change from baseline in PROMIS Itch item banks (a) scratching behaviour, (b) interference, (c) mood and sleep, (d) activity and clothing items, and (e) sleep-related impairment in patients receiving BARI 4-, 2-mg and PBO plus TCS through Week 16. *P*-values for BARI vs. PBO: *$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$. BARI, baricitinib; BL, baseline; MMRM, mixed effect repeated measure; Nx, number of patients with non-missing values; PBO, placebo; PROMIS, Patient-Reported Outcome Measurement Information System; TCS, topical corticosteroids. Table beneath the graph includes number of patients with non-missing values at the indicated time points. Table beneath the graph includes number of patients with non-missing values at the indicated time points. A subset of patients for whom translations were available according to language completed the PROMIS instruments. Patient population includes all randomised patients. PROMIS instrument scores are T scores, where a higher score indicates greater impairment.

TCS treatment group vs. placebo plus TCS for the mood and sleep outcome, and improvements were sustained through Week 16 (Fig. 3c). A statistically significant improvement from baseline was also observed in the baricitinib 2-mg plus TCS treatment group vs. placebo plus TCS at Week 4.

Activity and clothing At Week 1, statistically significant improvements from baseline were observed in the baricitinib 4-mg plus TCS treatment group vs. placebo plus TCS for the activity and clothing outcome (Fig. 3d). Improvements were sustained through Week 16 (Fig. 3d).

PROMIS sleep-related impairment

Patients treated with baricitinib 4-mg plus TCS reported significantly greater improvement in daytime sleep functioning related to sleep loss at Week 4 vs. patients treated with placebo plus TCS, and this improvement was sustained through Week 16 (Fig. 3e).

PBI

At Week 16, patients treated with either baricitinib 4-mg plus TCS or 2-mg plus TCS had a significantly greater PBI total score vs. patients treated with placebo plus TCS (Fig. 4a). For the PBI subscales, patients who received baricitinib 4 mg plus TCS had significantly greater goal attainment related to social impairment, psychological impairment, impairment due to therapy, physical impairment and confidence in healing than patients treated with placebo plus TCS. Patients who received baricitinib 2-mg plus TCS had similar results for the goals related to psychological impairment, impairment due to therapy and confidence in healing. Significantly greater proportions of patients in both baricitinib plus TCS treatment groups vs. placebo plus TCS reported a PBI total score that met or exceeded the minimum patient-relevant treatment benefit (Fig. 4b).

Discussion

Moderate-to-severe AD can have a profound negative effect on HRQoL,[14] reflected by high mean DLQI values observed at baseline in this study. Results reported here demonstrated that baricitinib 2- and 4-mg plus TCS result in improved HRQoL, work productivity, daily life functioning and symptom impact.

A greater proportion of patients treated with baricitinib 2- or 4-mg plus TCS achieved statistically significant improvements vs. patients treated with placebo plus TCS in ≥4-point improvement in DLQI total score (baricitinib 4-mg plus TCS only), DLQI total score ≤5 endpoint and DLQI (0,1). Approximately 60% and 40% of patients with baricitinib 4- and 2-mg plus TCS, respectively, reported AD symptoms had a small impact on their life (DLQI total score ≤5) through Week 16.

Pruritus is the main morbidity affecting patients with AD and contributes to other conditions including sleeplessness and anxiety/depression.[8,9,35,36] Baricitinib 4-mg plus TCS improved HRQoL related to pruritus and sleeplessness, as shown by mean improvements in the PROMIS instruments. PROMIS results

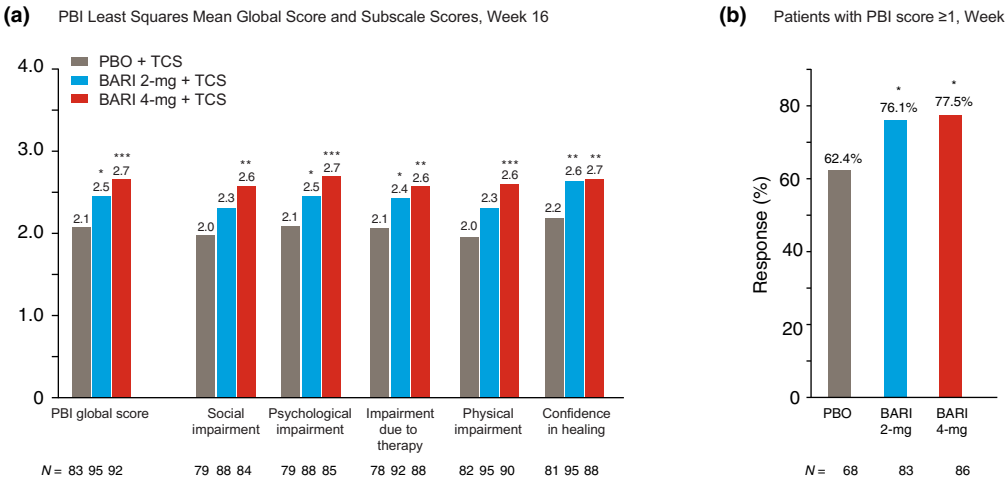


Figure 4 Patient Benefit Index. (a) Mean global and subscale scores on the PBI in patients receiving BARI 4-, 2-mg and PBO plus TCS at Week 16. (b) Mean PBI global score ≥1 in patients receiving BARI 4-, 2-mg and PBO plus TCS at Week 16. *P*-values for BARI vs. PBO: *$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$. BARI, baricitinib; Nx, number of patients with non-missing values; PBI, Patient Benefit Index; PBO, placebo; TCS, topical corticosteroids. Numbers beneath the graph include number of patients with non-missing values at the indicated time points. A subset of patients for whom translations were available according to language completed the PBI questionnaires. Patient population includes all randomised patients. Higher PBI scores indicate greater benefit, and patients with PBI of 1 or greater are considered as having at least minimum patient-relevant treatment benefit.

also revealed decreased scratching behaviour due to pruritus and decreased interference in life choices, including selection of activities and clothing. Thus, while baricitinib was previously shown to relieve the severity of itch, often within 1 or 2 days of beginning therapy,[20,37] these findings reinforce that symptom relief translates to improved functioning in work and daily life beginning soon after the start of therapy.

In addition to improvements in HRQoL and symptom impact, this study also demonstrates that treatment with baricitinib plus TCS increases work productivity. Presenteeism refers to the outcome in which patients may be physically present at work, but their ability to work efficiently and remain focussed is compromised. Given the nature of pruritus, impact on work functioning is typically observed by greater presenteeism than absenteeism because the continual presence of pruritus impairs concentration.[12,38] Findings reported here are consistent with these observations in that, while absenteeism was not problematic, patients had a significant percentage of time at work captured as presenteeism, which then showed early and sustained improvement with baricitinib plus TCS therapy. Consistent with the DLQI outcomes, patients, including non-employed patients, also found that baricitinib therapy plus TCS improved their engagement in non-work activities.

Baricitinib previously demonstrated efficacy in treating AD as a monotherapy and plus TCS.[20,37] The use of TCS in this study mirrors clinical practice where TCS is a supplement for treatment of active lesions. Patients' goals are a necessary component of treatment decision-making. In this study, patients' goals were assessed using the PBI, and the majority of patients treated with baricitinib indicated benefits in achieving relevant personal goals previously defined by the individual patient. The benefits included both satisfaction with improvements in emotional and physical goals as well as confidence in treatment and satisfaction with overall treatment burden, showing a significant added value with use of baricitinib plus TCS therapy.

A limitation of these studies is that generalizability of these findings might be limited by the demographics of the study populations, over-representing relatively young adult white men. Another limitation is that the PROMIS and PBI measures were only available for a subset of the patients. However, given that the baseline demographics and characteristics were similar across treatment groups, this limitation does not appear to have introduced bias for these measures. The WPAI-AD, PROMIS and PBI measures are not yet employed to assess patient outcomes in a routine clinical setting, and the PROMIS measures in their current form may be too lengthy for routine clinical use; however, each measure was validated for feasibility and reliability in clinical studies [28,32,33] and should provide information about if and to what extent patient-defined objectives and benefits were met. Another consideration is that AD is a chronic disease that often follows a relapsing–remitting cycle over a patients' lifetime; thus, the 16-week timeframe should be expanded to completely understand the effects of baricitinib treatment on patient-reported outcomes and the durability of these results. Additional studies of bariticinib as a long-term therapy in AD are underway and will provide evidence of the longer persistence of these treatment benefits.

In summary, daily treatment with baricitinib 2- and 4-mg plus TCS, vs. placebo plus TCS, achieved clinically meaningful results in patient-reported outcomes. While improving severity of skin disease remains the primary focus to evaluate treatment efficacy, incorporating the patient perspective and assessing functional impacts of treatment remain integral to evaluating the overall treatment benefit. Here, baricitinib 2- and 4-mg plus TCS therapy resulted in early benefits in HRQoL, symptom impact and patient function across life domains that were sustained to Week 16 and resulted in overall treatment benefit.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Study design.

