Baricitinib in adult patients with moderate-to-severe atopic dermatitis: A phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study

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Background: Baricitinib, an oral selective inhibitor of Janus kinase 1 and Janus kinase 2, modulates proinflammatory cytokine signaling.

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This study was designed jointly by consultant experts and representatives of the funder, Eli Lilly and Company. Data were collected by investigators and analyzed by the funder. Safety data were reviewed at regular intervals by an independent data monitoring committee. All authors participated in data analysis and interpretation and review of the draft and final manuscript, and they provided critical comment, including regarding the decision to submit the manuscript for publication with medical writing support paid by the funder. The authors had full access to the data and verified the veracity, accuracy, and completeness of the data and analyses, as well as the fidelity of this report to the protocol. All authors made the decision to submit the manuscript for publication.

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Objectives: The efficacy and safety of baricitinib were evaluated in patients with moderate-to-severe atopic dermatitis (AD).

Methods: In this phase 2, randomized, double-blind, placebo-controlled study, 124 patients with moderate-to-severe AD applied topical corticosteroids (TCSs) for 4 weeks before randomization to once-daily placebo, 2 mg of baricitinib, or 4 mg of baricitinib for 16 weeks. Use of TCSs was permitted during the study. The primary outcome was the proportion of patients achieving at least a 50% reduction in the Eczema Area and Severity Index (EASI-50) compared with placebo.

Results: Significantly more patients who received baricitinib, 4 mg, achieved EASI-50 than did patients receiving placebo (61% vs 37% [P = .027]) at 16 weeks. The difference between the proportion of patients receiving baricitinib, 2 or 4 mg, who achieved EASI-50 and the proportion of patients receiving placebo and achieving EASI-50 was significant as early as week 4. Baricitinib also improved pruritus and sleep loss. Treatment-emergent adverse events were reported in 24 of the patients receiving placebo (49%), 17 of those receiving 2 mg of baricitinib (46%), and 27 of those receiving 4 mg of baricitinib (71%).

Limitations: A TCS standardization period before randomization reduced disease severity, limiting the ability to compare results with those of baricitinib monotherapy. Longer studies are required to confirm baricitinib's efficacy and safety in patients with AD.

Conclusions: Baricitinib used with TCSs reduced inflammation and pruritus in patients with moderate-to-severe AD. (J Am Acad Dermatol 2019;80:913-21.)

Key words: atopic dermatitis; baricitinib; EASI; JAK-STAT signaling; phase 2; pruritus; SCORAD; topical corticosteroids.

CAPSULE SUMMARY

- New systemic treatments are needed for atopic dermatitis (AD).
- Baricitinib, an oral inhibitor of Janus kinases 1 and 2, in combination with topical corticosteroids was superior to placebo in a 16-week phase 2 trial of adult patients with AD.
- Baricitinib is a potential treatment option for AD.

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease,[1] with a prevalence of 7% to 10% in US adults[1-4] and up to 13% worldwide.[5] The cutaneous inflammatory reaction of AD is accompanied by intense pruritus and negatively affects health-related quality of life (HRQoL).[6] Lesional skin of AD contains elevated levels of inflammatory cytokines, including T-helper 2 cells (interleukin 4 [IL-4], IL-13, and IL-31), T-helper 22 cells (IL-22), and T-helper 1 cells (interferon gamma), many of which depend on Janus kinase (JAK)/signal transducer and activator of transcription intracellular signaling. Baricitinib is a selective JAK1 and JAK2 inhibitor[7] that is currently approved for the treatment of moderately to severely active rheumatoid arthritis in adults in Europe, Japan, and other countries.

Available systemic immunosuppressants and phototherapy have safety concerns with regard to long-term therapy and limited efficacy.[8,9] Dupilumab, a biologic, blocks receptor binding of IL-4 and IL-13.[10] Less than 40% of patients achieved clear or almost clear skin when taking dupilumab with background topical corticosteroids (TCSs).[11] Therefore, oral therapies for long-term management of AD are needed for patients who prefer oral therapy or are inadequately controlled by current therapies. This phase 2 trial included a standardization period with use of TCS to identify individuals whose AD was inadequately controlled by TCS. Use of TCS was permitted during the study to mirror real-life clinical practice.

METHODS

Study design and oversight

A randomized, 16-week, double-blind, placebo-controlled study (NCT02576938) was conducted at 13 centers in the United States and Japan between February 2016 and March 2017. The study was conducted in accordance with ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The majority of sites were approved by the Chesapeake Institutional Review

Abbreviations used:

AD:	atopic dermatitis
CPK:	creatine phosphokinase
DLQI:	Dermatology Life Quality Index
EASI:	Eczema Area and Severity Index
EASI-50:	50% improvement in EASI score
HRQoL:	health-related quality of life
IL:	interleukin
IRT:	interactive response technology
JAK:	Janus kinase
LOCF:	last observation carried forward
MMRM:	mixed effects model repeated measures
NRS:	Numeric Rating Scale
SCORAD:	Scoring Atopic Dermatitis
TCS:	topical corticosteroid

Board (Columbia, MD) (Pro00015579). Ethics approval was obtained for all sites.

Treatment

Patients were randomized by using an interactive response technology (IRT) system in a 4:3:3 ratio to once-daily placebo or 2-mg or 4-mg baricitinib tablets. Blocked randomization with stratification was used with 2 strata and 150 randomization numbers per stratum in blocks of 10. PAREXEL (Waltham, MA) generated the randomization schedule and maintained the IRT. Investigators enrolled patients and dispensed interventions per assignments provided by the IRT. Patients, investigators, and study site personnel were blinded to treatment allocation. Randomization was stratified by country.

Four weeks before randomization and throughout the study, patients discontinued systemic treatment for AD and other prohibited medications. Patients were provided with triamcinolone (0.1%) cream for 4 weeks before randomization and were required to meet entry criteria at randomization to ensure that their AD was inadequately controlled with triamcinolone. Triamcinolone was used throughout the study according to the labeling or as recommended by the investigator.

Patients

Patients could participate if they were at least 18 years of age and had moderate-to-severe AD[12] (Eczema Area and Severity Index [EASI][13] $\geq$12 and >10% body surface area involvement at screening and randomization, as well as diagnosis $\geq$2 years before first visit). Patients were required to have inadequate response to emollients plus TCSs (with or without topical calcineurin inhibitors and/or antibiotics), systemic corticosteroids (with or without phototherapy), or immunosuppressants.

Efficacy measures

The primary outcome was the proportion of patients achieving a 50% improvement from baseline in their EASI score (EASI-50) at week 16. Additional disease severity assessments included changes from baseline in EASI and Scoring Atopic Dermatitis (SCORAD) scores[14] and proportion of patients achieving an Investigator's Global Assessment score of 0 or 1 with a 2-point or greater improvement from baseline in the Itch Numeric Rating Scale (NRS). HRQoL was assessed by using the Dermatology Life Quality Index (DLQI).[15] Changes from baseline in patient-reported disease severity as assessed by the Patient-Oriented Eczema Measure[16] were an exploratory end point.

Safety assessments

Clinical laboratory tests, evaluation of vital signs, and other safety assessments were performed by blinded investigators. Incidence and severity of all adverse events were recorded.

Statistical analysis

This study had 90% power to detect a 35% difference in EASI-50 response rate at week 16 between placebo and baricitinib. Type I error was controlled only for the primary efficacy analyses by using a stepwise hypothesis-testing strategy, first comparing 4 mg of baricitinib with placebo and then 2 mg with placebo. A chi-square test with an α value of 0.05 was used to detect differences between baricitinib and placebo. All patients who discontinued the study or study treatment before week 16 were considered nonresponders.

Continuous secondary outcomes collected longitudinally were analyzed by using mixed effects model repeated measures (MMRMs). Covariates included treatment, visit, country, treatment-by-visit interaction, baseline, and baseline by visit. This model accounts for missing data by using a missing-at-random assumption. Treatment estimates for pairwise treatment comparisons and standard errors from MMRM analyses were used to produce *P* values. A week 16 last observation carried forward (LOCF) analysis was performed for change and percent change from baseline by using an analysis of covariance (ANCOVA) model with fixed effects for treatment and country plus the baseline value as a covariate. Categoric secondary outcomes were analyzed by using chi-square or Fisher's exact tests when needed. No multiplicity adjustment was used in the analysis of secondary outcomes.

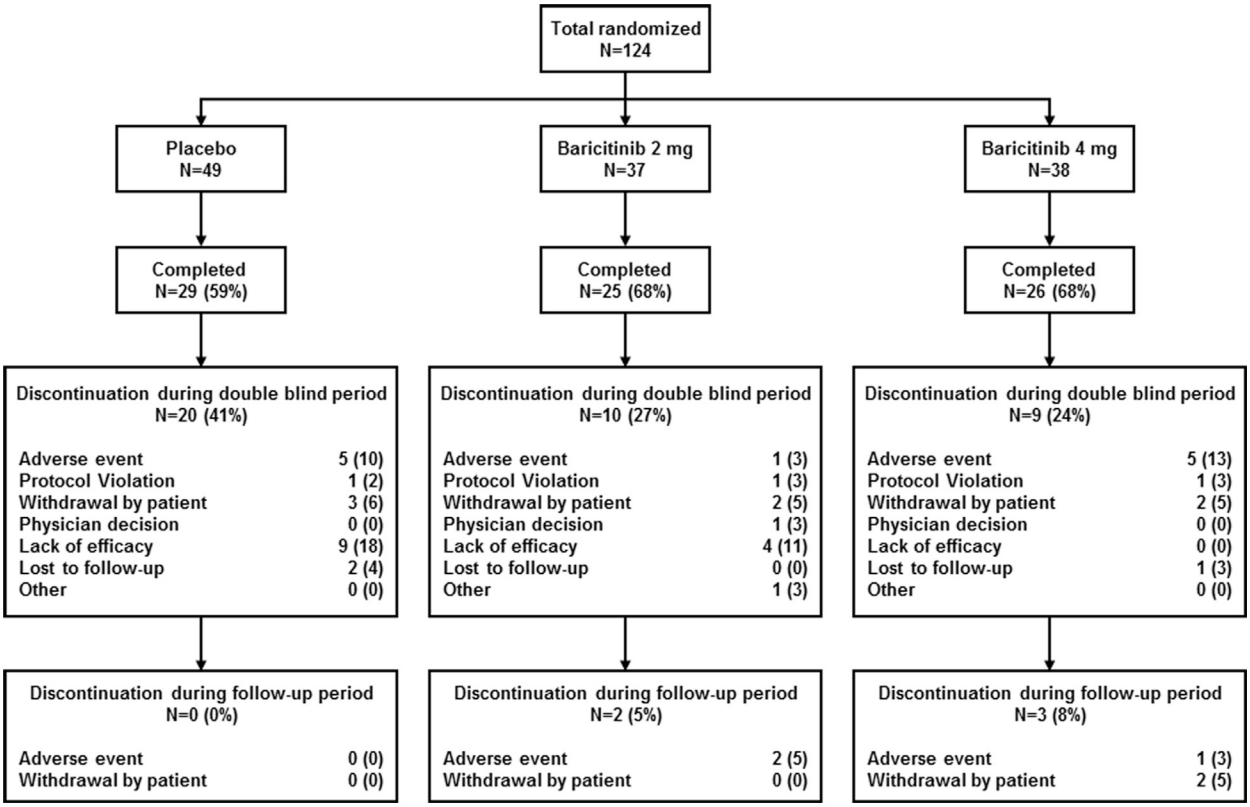

Fig 1. Patient disposition.

RESULTS

Please see Supplemental Figures 1 to 9 at http://www.jaad.org. Note that corresponding text for Supplemental Figs 2, 3, 4, 5, and 8 is available at https://data.mendeley.com/datasets/szb4ggs9rk/1.

Patients

Among 187 screened patients, 124 enrolled (104 in the United States and 20 in Japan). Patients were randomized to placebo once daily plus a TCS (n = 49), 2 mg of baricitinib once daily plus a TCS (n = 37), or 4 mg of baricitinib once daily plus a TCS (n = 38) (Fig 1). The median EASI score for all randomized patients (N = 124) was similar at screening and baseline (21.0 vs 21.2, respectively). During the TCS standardization period, the disease severity of 7 patients improved such that they no longer met the inclusion criteria to participate in the study. In all the other patients, however, changes in skin severity score during the standardization period were not significant, indicating stable disease with use of a TCS before randomization.

All randomized patients were included in the intent-to-treat population. Baseline demographic and clinical characteristics are presented in Table I, and patient disposition is depicted in Fig 1. The treatment groups were similar in baseline characteristics except for median disease duration (Table I).

A larger proportion of patients discontinued placebo plus a TCS (41%) than discontinued baricitinib plus a TCS (27% receiving 2 mg and 24% receiving 4 mg), including discontinuations owing to lack of efficacy (placebo, 18%; 2 mg of baricitinib, 11%; and 4 mg of baricitinib, 0%), which also tended to occur earlier (Supplemental Fig 1; available at http://www.jaad.org).

Efficacy

Primary objective: EASI-50. The proportion of patients receiving baricitinib, 4 mg, plus a TCS who achieved EASI-50 at week 16 was significantly higher than the proportion in the placebo-plus-TCS group who achieved EASI-50 ($P = .027$) (Fig 2). Whereas the proportion of patients who achieved EASI-50 with the dose of 2 mg of baricitinib plus a TCS was similar to that observed in the group that received 4 mg of baricitinib plus a TCS, the response with 2 mg of baricitinib plus a TCS was not statistically significant compared with the response with placebo ($P = .065$). These changes occurred while patients receiving baricitinib used approximately 30% less TCS monthly after randomization (based on mean TCS container weight) than did patients who received placebo.

Table I. Demographic and clinical characteristics of the patients at baseline

Characteristics	Placebo plus TCS (n = 49)	Baricitinib, 2 mg, plus TCS (n = 37)	Baricitinib, 4 mg, plus TCS (n = 38)	Treatment group comparison *P* value
Median age (IQR), y	35 (28.0-48.0)	42 (26.0-52.0)	32.5 (26.0-48.0)	*P* = .508
Male sex, n (%)	24 (49)	22 (59)	22 (58)	*P* = .565
Race, n (%)				*P* = .553
White	23 (47)	20 (54)	18 (47)	
Black	7 (14)	9 (24)	9 (24)	
Asian	16 (33)	8 (22)	9 (24)	
Native Hawaiian, other Pacific islander	1 (2)	0	2 (5)	
Multiple	2 (4)	0	0	
Median disease duration (IQR)	17.7 (7.3-29.5)	26.4 (18.3-40.5)	22.0 (6.4-30.7)	*P* = .035
Median EASI score (IQR)*†	22.1 (15.3-28.0)	22.1 (16.8-32.3)	19.5 (13.7-25.9)	*P* = .405
Median IGA score (IQR)‡	3 (3, 4)	3 (3, 4)	3 (3, 4)	*P* = .457
Median Itch NRS (IQR)§	7 (6, 8)	6 (5, 8)	6.5 (4, 8)	*P* = .164
Median total SCORAD score (IQR)¶	55 (44.9-63.8)	53.3 (49.9-61.1)	57.6 (49.5-64.9)	*P* = .845
Median POEM score (IQR)‖	20 (17.0-23.0)	17 (12.0-25.0)	20.5 (11.0-26.0)	*P* = .641
Median DLQI score (IQR)#	15 (10.0-19.0)	10 (7.0-17.0)	11 (8.0-17.0)	*P* = .254

DLQI, Dermatology Life Quality Index; *EASI*, Eczema Area and Severity Index; *IGA*, Investigator's Global Assessment; *IQR*, interquartile range; *NRS*, Numeric Rating Scale; *POEM*, Patient-Oriented Eczema Measure; *SCORAD*, Scoring Atopic Dermatitis; *TCS*, topical corticosteroid.

*EASI scores range from 0 to 72, with higher scores indicating greater severity.

†Median EASI score for all randomized patients (n = 124) was similar at screening and baseline (21.0 vs 21.2, respectively). However, 7 patients failed screening based on improvement in disease severity, resulting in an EASI score less than 12 at baseline. The mean EASI percent improvement during TCS standardization for the patients who failed screening was approximately 75% (mean EASI at screening of 19.6; mean EASI at baseline of 4.9).

‡IGA uses a 6-point scale ranging from clear to very severe disease.

§Itch NRS, ranging 0 (no itch) to 10 (worst itch imaginable).

¶SCORAD is a combined score of investigator-reported disease severity and affected body surface area and patient-reported symptoms of itch and sleep dysfunction; scores range from 0 to 103.

‖POEM, a composite measure of patient-reported symptoms, including the effect of symptoms on sleep, evaluates the frequency of symptoms (including itching) and the effect of atopic dermatitis on sleep on a scale of 0 to 28.

#DLQI evaluates health-related quality of life on a scale of 0 to 30.

Secondary end points

EASI. The difference between the proportion of patients receiving 2 or 4 mg of baricitinib and achieving EASI-50 and the proportion of patients receiving placebo and reaching EASI-50 was also statistically significant at weeks 4, 8, and 12. Percent change from baseline in EASI score determined by using MMRMs showed statistically significant improvement for all time points for baricitinib, 4 mg, compared with for placebo. The response to baricitinib, 2 mg, was statistically significant at weeks 4, 8, and 16. A week 16 LOCF analysis of the percent change from baseline in EASI score showed a significant difference for the 2- and 4-mg doses of baricitinib compared with placebo (Fig 2). An approximately 20% difference in response to placebo plus a TCS was observed in the percent change from baseline in EASI score depending on the imputation procedure used (MMRM, 46% vs week 16 LOCF, 27%). There was no meaningful change in response for the baricitinib-plus-TCS groups based on imputation procedure (4 mg of baricitinib-plus-TCS MMRM, 65% vs week 16 LOCF, 62%; 2 mg of baricitinib-plus-TCS MMRM, 64% vs week 16 LOCF, 60%).

SCORAD score. Baricitinib, 4 mg, plus a TCS was significantly better than placebo plus a TCS at decreasing disease severity based on percent change from baseline in SCORAD score throughout the study (Fig 3). The patient-reported SCORAD scores on the items pruritus and sleep loss also revealed significant improvement with both baricitinib doses compared with placebo at various time points. Itch NRS response is presented in Supplemental Fig 6 (available at http://www.jaad.org).

DLQI. Total DLQI improved in both treatment groups relative to placebo, with significant improvement at week 4 (Supplemental Fig 7; available at http://www.jaad.org). The difference between baricitinib, 4 mg, plus a TCS and placebo plus a TCS was also significant at weeks 8 and 12. The LOCF analysis showed that baricitinib, 4 mg, plus a TCS was significantly better than placebo plus a TCS at week 16.

Safety

The patients discontinuing treatment because of adverse events from baseline through week 16 included 5 patients (10%) from the placebo-plus-TCS group (lymphopenia in 3 patients, eczema in 1,

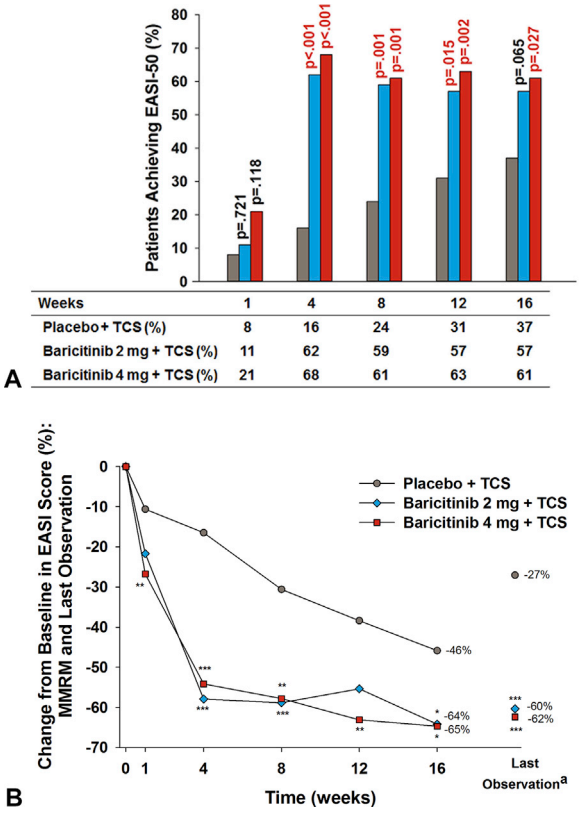

Fig 2. Percentage of patients achieving a 50% reduction in Eczema Area and Severity Index (EASI) (EASI-50) (**A**) and percentage change from baseline in EASI score (**B**). [a]Last observation is week 16 last observation carried forward (LOCF). *$P < .05$, **$P \leq .01$, ***$P \leq .001$. *MMRM*, Mixed effect model repeated measure; *TCS*, topical corticosteroid.

and AD in 1); 1 patient (3%) from the group receiving baricitinib, 2 mg, plus a TCS (neutropenia); and 5 patients (13%) from the group receiving baricitinib, 4 mg, plus a TCS (2 patients with white cell count decreases, 1 with an abnormal lymphocyte count, 1 with headache, and 1 with eczema) (Fig 1 and Table II). One patient (in the group treated with baricitinib, 4 mg, plus a TCS) experienced a serious adverse event during the treatment phase (benign polyp of the large intestine). No deaths occurred.

During-treatment adverse events occurring in more than 2 patients in any treatment group are listed in Table II. In the group that received 4 mg of baricitinib, headache, increased blood level of creatine phosphokinase (CPK), and nasopharyngitis occurred in 3 to 5 patients. Infections were not increased in the groups treated with medication compared with in those who received placebo. No patients in the baricitinib-plus-TCS groups had herpes zoster infections, whereas 1 patient in the placebo-plus-TCS group did have a herpes zoster infection during the washout period.

There were few notable trends over time in clinical chemistry between treatment groups. One exception was CPK level in both baricitinib-plus-TCS groups, with a median increase of 30 U/L or more at week 16. Patients with changes in CPK level were asymptomatic.

Among hematology parameters, there were decreases from baseline to weeks 4 and 8 in leukocyte and neutrophil counts for both baricitinib-plus-TCS groups that were not observed with placebo (Supplemental Fig 9; available at http://www.jaad.org). These changes were transient, with no discernable difference among the 3 treatment groups at the end of treatment (according to LOCF). Platelet increases (mean increase 13% [standard deviation 24.4]) in the group treated with 4 mg of baricitinib (based on LOCF) over time were observed in the baricitinib-plus-TCS group but not in the placebo-plus-TCS group.

DISCUSSION

In this phase 2 study evaluating JAK1/JAK2 inhibition in adult patients with AD, baricitinib treatment conferred clinically meaningful improvement in multiple measures of disease severity. Specifically, a significantly greater proportion of patients with moderate-to-severe AD treated with once-a-day oral baricitinib at the 4-mg dose plus a TCS achieved EASI-50 at week 16 than those treated with placebo plus a TCS. At week 16, patients receiving 2 mg of baricitinib plus a TCS and those receiving 4 mg of baricitinib plus a TCS achieved an approximately 65% reduction in disease severity (based on EASI score) compared with a 46% response to placebo plus a TCS, with significant improvements seen as early as week 1. Significant improvements in other dimensions of AD, including symptoms and HRQoL measures, showed significant improvement in both dosing groups, reflecting improvements in clinical signs.

This study mimicked clinical practice by administering a mid-potency TCS for at least 4 weeks before randomization to select patients whose AD was not entirely controlled by TCS and who required additional therapy. Use of TCSs was allowed during the study, perhaps also narrowing the ability to compare results with those of other monotherapy studies. The EASI score of 12 or higher criterion was chosen to improve enrollment after the 4-week standardization period with TCS. Lower baseline disease severity required greater improvement from baseline to achieve significance. Additionally, patients' ability to discontinue or decrease TCS use during the study can further reduce the magnitude of treatment effect compared with placebo if reductions in TCS use

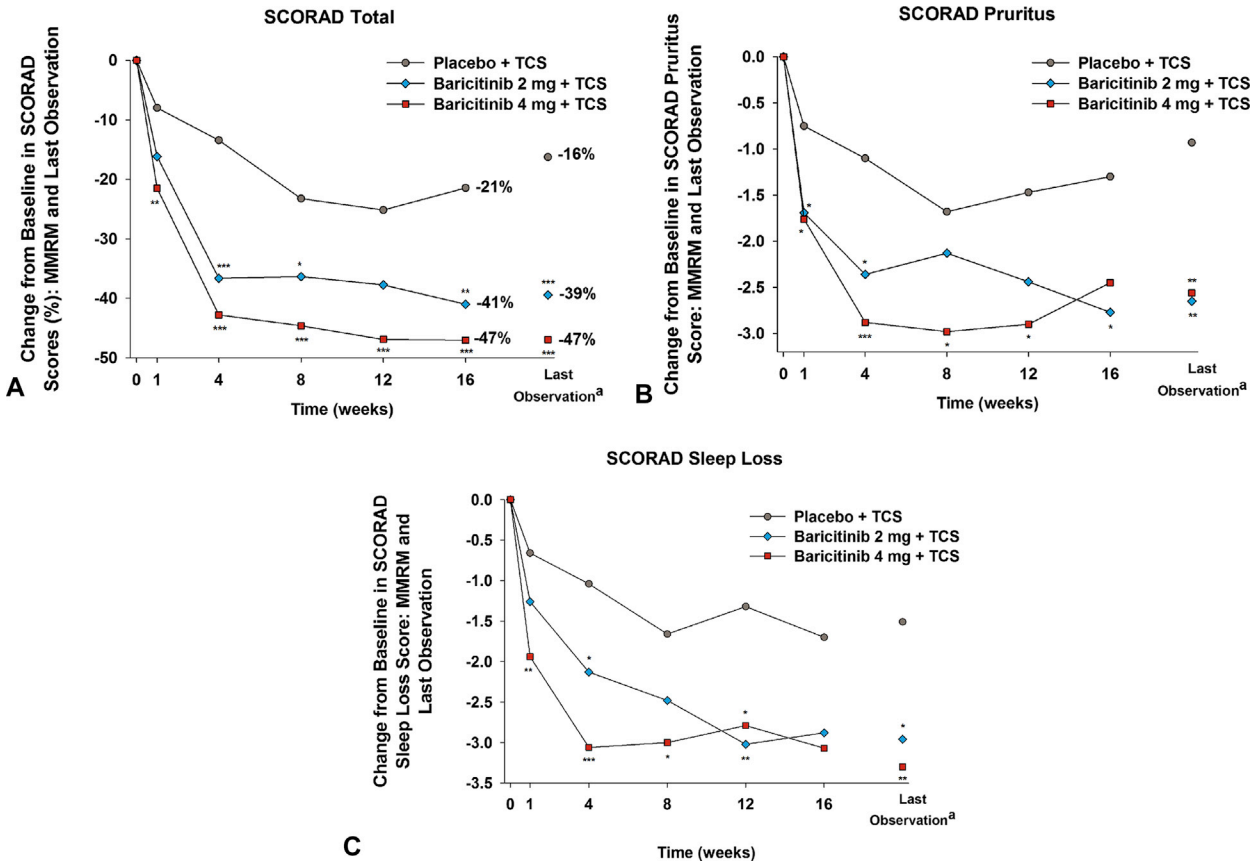

Fig 3. Scoring Atopic Dermatitis (SCORAD) total percent change from baseline (**A**), pruritus change from baseline (**B**), and sleep loss change from baseline (**C**). [a]Last observation is week 16 last observation carried forward (LOCF). *$P < .05$, **$P \leq .01$, ***$P \leq .001$. *MMRM*, Mixed effect model repeated measure; *TCS*, topical corticosteroid.

occurred more often in the active arms of the study. During this study, patients receiving baricitinib used approximately 30% less TCS (by weight) monthly after randomization than did patients receiving placebo, which is similar to what occurred in a clinical trial of dupilumab in patients with AD.[17]

Several preclinical and clinical studies implicating T-helper 2 cytokines, such as IL-31 and IL-13, support a role for JAK1- and JAK2-mediated signaling in the immunopathology of AD. Results from a phase 2 study with topical tofacitinib (a pan-JAK inhibitor) showed clinical improvement in patients with mild-to-moderate AD, highlighting the potential for JAK inhibition in patients with AD.[18,19]

A phase 2 study of nemolizumab, an IL-31 antibody, showed a 63% improvement in itch at week 12 for the 2 mg/kg-subcutaneous dose every 4 weeks versus 21% with placebo, accompanied by less clinical improvement, suggesting that reductions in both inflammation and pruritus are therapeutically important in patients with AD.[20] Similarly, studies of dupilumab, which blocks the receptor shared by IL-4 and IL-13, reported a 56% reduction in itch at week 16 for the 300-mg subcutaneous dose every other week plus a TCS versus 29% with placebo plus a TCS.[11] Dupilumab plus a TCS also resulted in a 77% reduction from baseline in EASI score compared with 43% with placebo plus a TCS. Notably, in our phase 2 baricitinib study, improvement in pruritus began as early as week 1, with achievement of a 45% change in itch NRS and a 44% change in SCORAD pruritus score for baricitinib, 4 mg, plus a TCS at week 4, compared with 16% to 17% with placebo plus a TCS. Whether the rapid reduction in itch following baricitinib treatment in AD could be mediated by interrupting pruritogenic cytokines such as thymic stromal lymphopoietin, IL-4, or IL-31 remains to be determined.[21,22] Baricitinib, 4 mg, plus a TCS also resulted in a 54% improvement from baseline in EASI by week 4, which was near the maximum efficacy (65%) observed at week 16. Improvement in itch was accompanied by improvements in disease severity and HRQoL.

Table II. Adverse events

Characteristic	Placebo plus TCS (n = 49)	Baricitinib, 2 mg, plus TCS (n = 37)	Baricitinib, 4 mg, plus TCS (n = 38)
TEAE or serious adverse event during the treatment period, n (%)			
≥1 TEAE	24 (49)	17 (46)	27 (71)
≥1 serious TEAE	0	0	1 (3)*
TEAE resulting in death during treatment and follow-up period	0	0	0
TEAEs leading to discontinuation of treatment	5 (10)	1 (3)	5 (13)
TEAEs occurring in ≥3 patients per treatment group, n (%)			
Headache	0	2 (5)	5 (13)
Blood level of creatine phosphokinase increased	0	1 (3)	5 (13)
Dermatitis, atopic	4 (8)	1 (3)	0
Nasopharyngitis	1 (2)	1 (3)	3 (8)
Cellulitis	3 (6)	1 (3)	0
Lymphopenia	3 (6)	0	0
TEAEs (Infections and Infestations), n (%)†			
Staphylococcal infection	0	2 (5)	0
Upper respiratory tract infection	1 (2)	0	2 (5)
Acute sinusitis	1 (2)	0	0
Pharyngitis	0	1 (3)	0
Subcutaneous abscess	1 (2)	0	1 (3)
Incision site infection	0	1 (3)	1 (3)
Skin infection	0	0	1 (3)
Wound infection	0	0	1 (3)
Post procedural cellulitis	0	1 (3)	0
Urinary tract infection	1 (2)	1 (3)	1 (3)
Cystitis	0	0	1 (3)
Body tinea	0	0	1 (3)
Conjunctivitis viral	1 (2)	0	0
Herpes simplex	0	0	1 (3)
Paronychia	1 (2)	0	0

TCS, Topical corticosteroid; *TEAE*, treatment-emergent adverse event.
*Serious adverse event of benign polyp of the large intestine during the treatment phase.
†Excluding nasopharyngitis and cellulitis, which are listed with TEAEs occurring in 3 or more patients per treatment group.

These results suggest that baricitinib may provide an oral alternative to biologics when treating AD.

In this study, there were no deaths. More dose-dependent total adverse events occurred in the group receiving baricitinib, 4 mg, than in the group receiving placebo. Headache, increased blood CPK level, and nasopharyngitis were the most common during-treatment adverse events in both baricitinib groups, and exacerbation of AD was the most common adverse event in the placebo group (Table II). The increases in CPK level observed with baricitinib treatment likely relate to an as-yet-unknown pharmacologic effect of JAK inhibition and were not associated with muscle-related adverse events, as previously reported with other JAK inhibitors and in different populations.[23-27] Potential adverse events observed with pan-JAK inhibition in other indications, including lymphopenia or herpes zoster reactivation, as reported in patients with rheumatoid arthritis,[19] were not observed in this study of baricitinib. Phase 3 trials are necessary before it can be concluded that these side effects are not significant concerns when using baricitinib for AD.

Limitations of this study include a relatively small sample size across several treatment arms, a short treatment period, and inability to include children. Use of TCSs during the standardization period lowered the overall severity of the disease of patients subsequently treated with baricitinib, which also limited the ability to compare the efficacy of baricitinib with that in monotherapy studies. Infrequent data collection (ie, at clinic visits) and instrument recall period may have contributed to larger variability in the patient-reported outcome results in this highly symptomatic disease. Future AD studies will include larger sample sizes and longer treatment periods in adults and may be extended to include pediatric patients.

CONCLUSION

In this phase 2 study, baricitinib was superior to placebo in improving signs and symptoms in adults

with moderate-to severe AD. Baricitinib plus TCS showed early and significant reduction in cutaneous inflammation and pruritus. Both baricitinib doses were well tolerated, with no new safety findings. Orally administered and balanced JAK1 and JAK2 inhibition provides an opportunity for therapy with a once-daily oral regimen. Additional studies are warranted to further investigate the role of baricitinib in AD.

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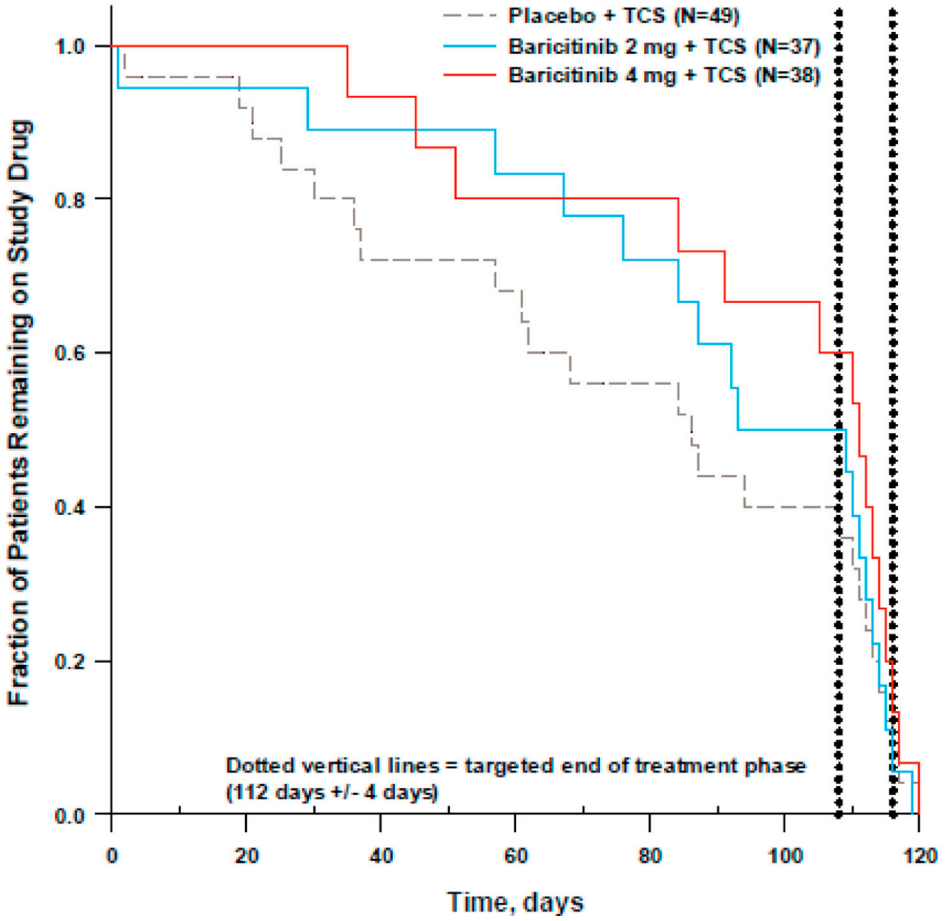
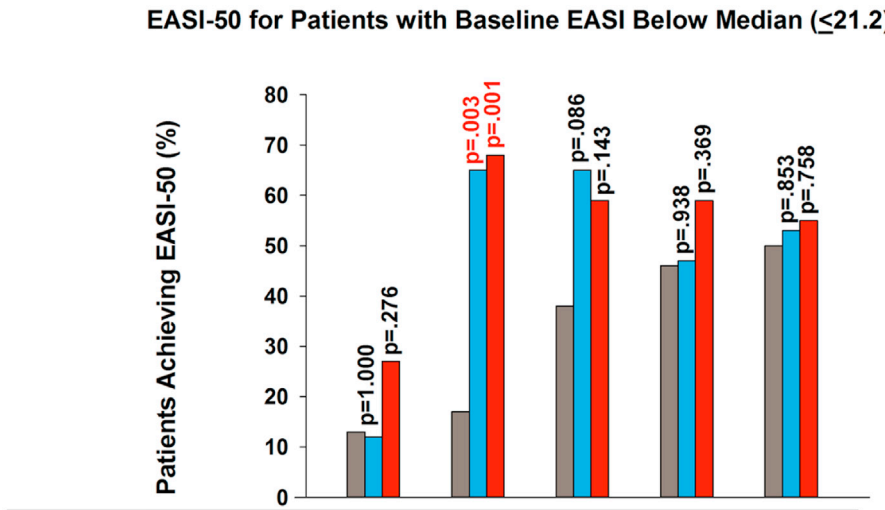
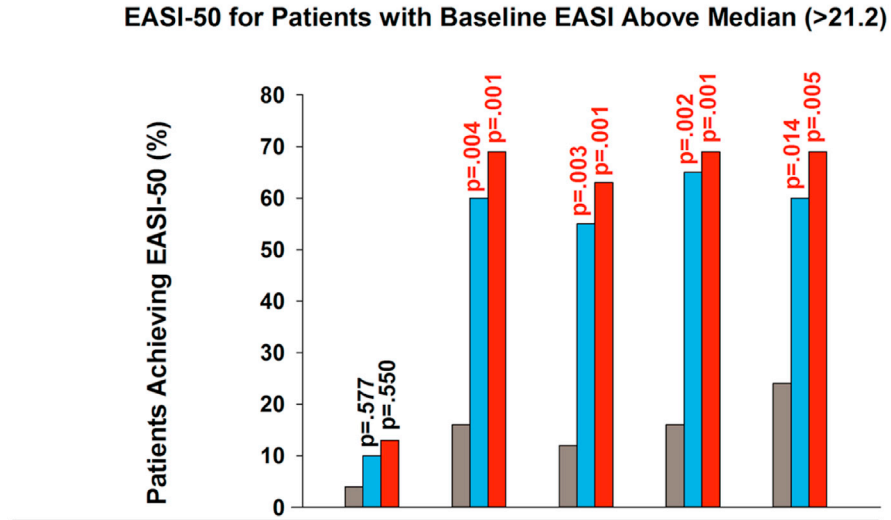


Supplemental Fig 1. Kaplan-Meier plot of time to study drug discontinuation. Patients without a treatment end date were not included. Discontinuation of study drug could be due to any reason. *ITT*, Intent-to-treat; *TCS*, topical corticosteroid.



Weeks	1	4	8	12	16
Placebo + TCS (%)	13	17	38	46	50
Baricitinib 2 mg + TCS (%)	12	65	65	47	53
Baricitinib 4 mg + TCS (%)	27	68	59	59	55

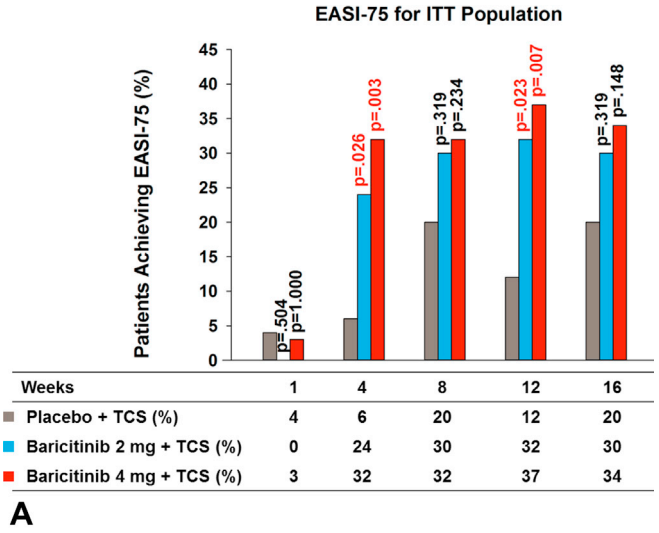
A



Weeks	1	4	8	12	16
Placebo + TCS (%)	4	16	12	16	24
Baricitinib 2 mg + TCS (%)	10	60	55	65	60
Baricitinib 4 mg + TCS (%)	13	69	63	69	69

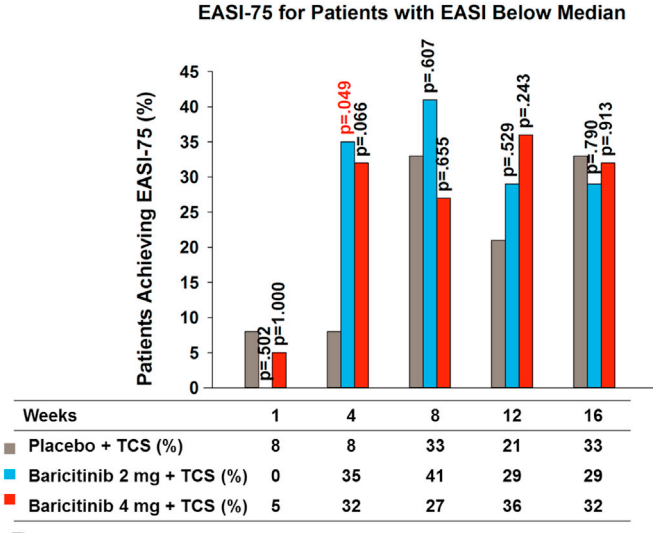
B

Supplemental Fig 2. Percentage of patients achieving a 50% reduction in Eczema Area and Severity Index (EASI-50) for patients with baseline EASI below (**A**) and above the median (**B**). *TCS*, topical corticosteroid.



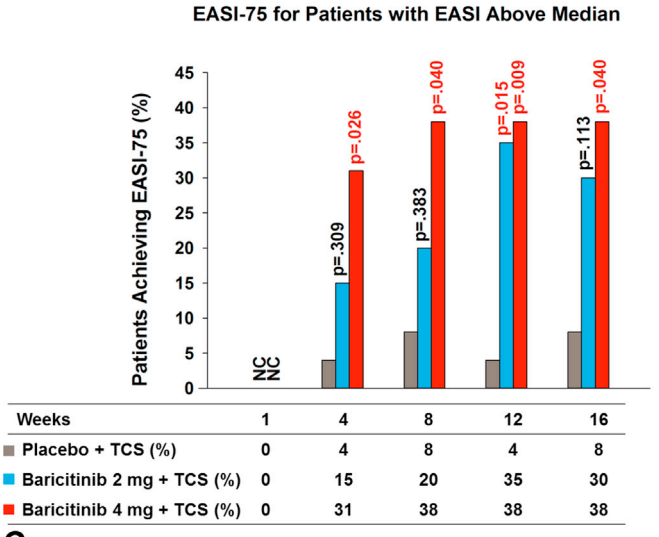
Weeks	1	4	8	12	16
Placebo + TCS (%)	4	6	20	12	20
Baricitinib 2 mg + TCS (%)	0	24	30	32	30
Baricitinib 4 mg + TCS (%)	3	32	32	37	34

A



Weeks	1	4	8	12	16
Placebo + TCS (%)	8	8	33	21	33
Baricitinib 2 mg + TCS (%)	0	35	41	29	29
Baricitinib 4 mg + TCS (%)	5	32	27	36	32

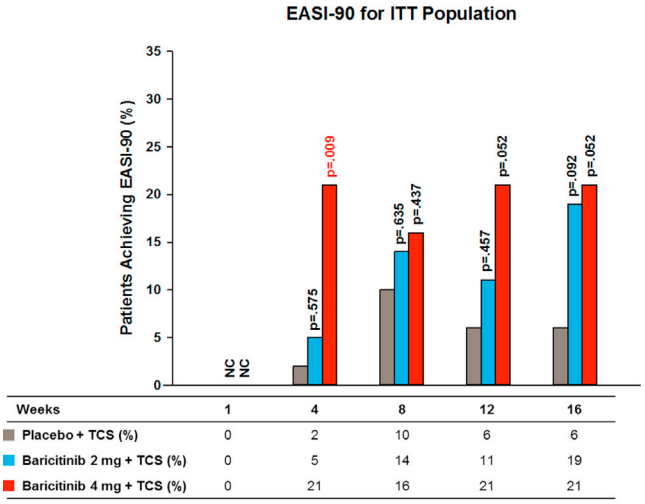
B



Weeks	1	4	8	12	16
Placebo + TCS (%)	0	4	8	4	8
Baricitinib 2 mg + TCS (%)	0	15	20	35	30
Baricitinib 4 mg + TCS (%)	0	31	38	38	38

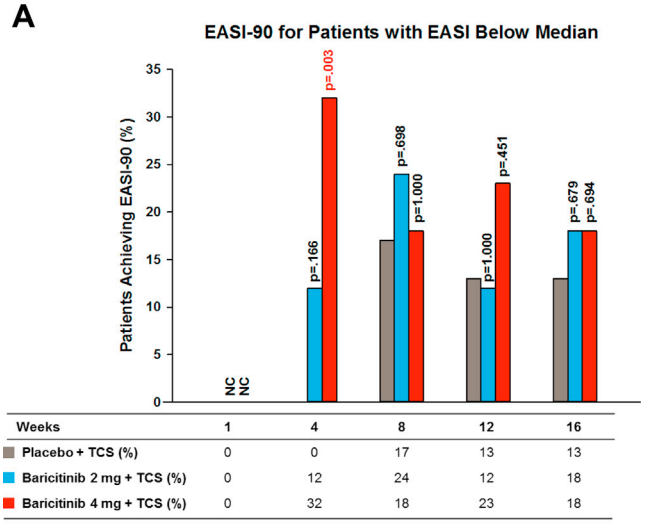
C

Supplemental Fig 3. Percentage of patients achieving EASI-75 for ITT population (**A**), patients with EASI below the median (**B**), and patients with EASI above the median (**C**). *EASI-75*, 75% improvement in EASI score; *ITT*, Intent-to-treat; *NC*, no count; *TCS*, topical corticosteroid.



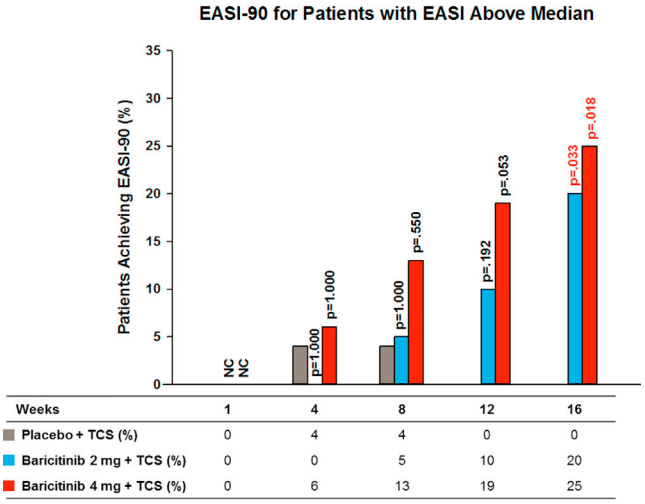
Weeks	1	4	8	12	16
Placebo + TCS (%)	0	2	10	6	6
Baricitinib 2 mg + TCS (%)	0	5	14	11	19
Baricitinib 4 mg + TCS (%)	0	21	16	21	21

A



Weeks	1	4	8	12	16
Placebo + TCS (%)	0	0	17	13	13
Baricitinib 2 mg + TCS (%)	0	12	24	12	18
Baricitinib 4 mg + TCS (%)	0	32	18	23	18

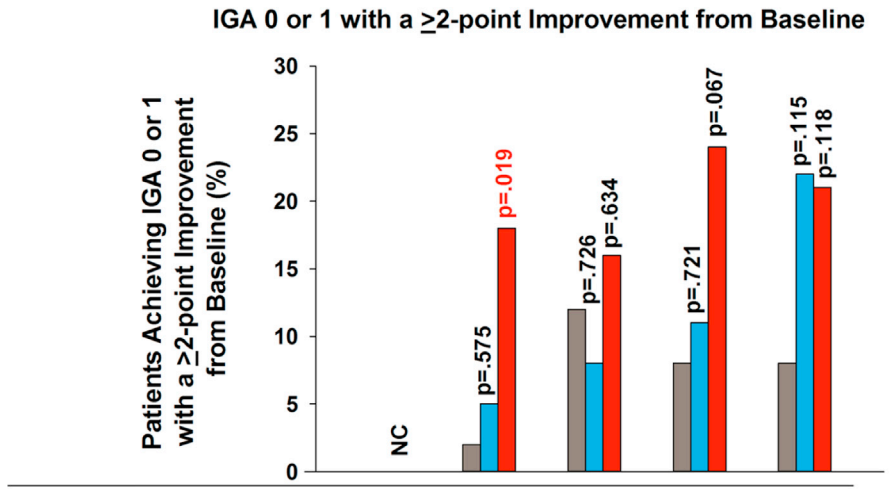
B



Weeks	1	4	8	12	16
Placebo + TCS (%)	0	4	4	0	0
Baricitinib 2 mg + TCS (%)	0	0	5	10	20
Baricitinib 4 mg + TCS (%)	0	6	13	19	25

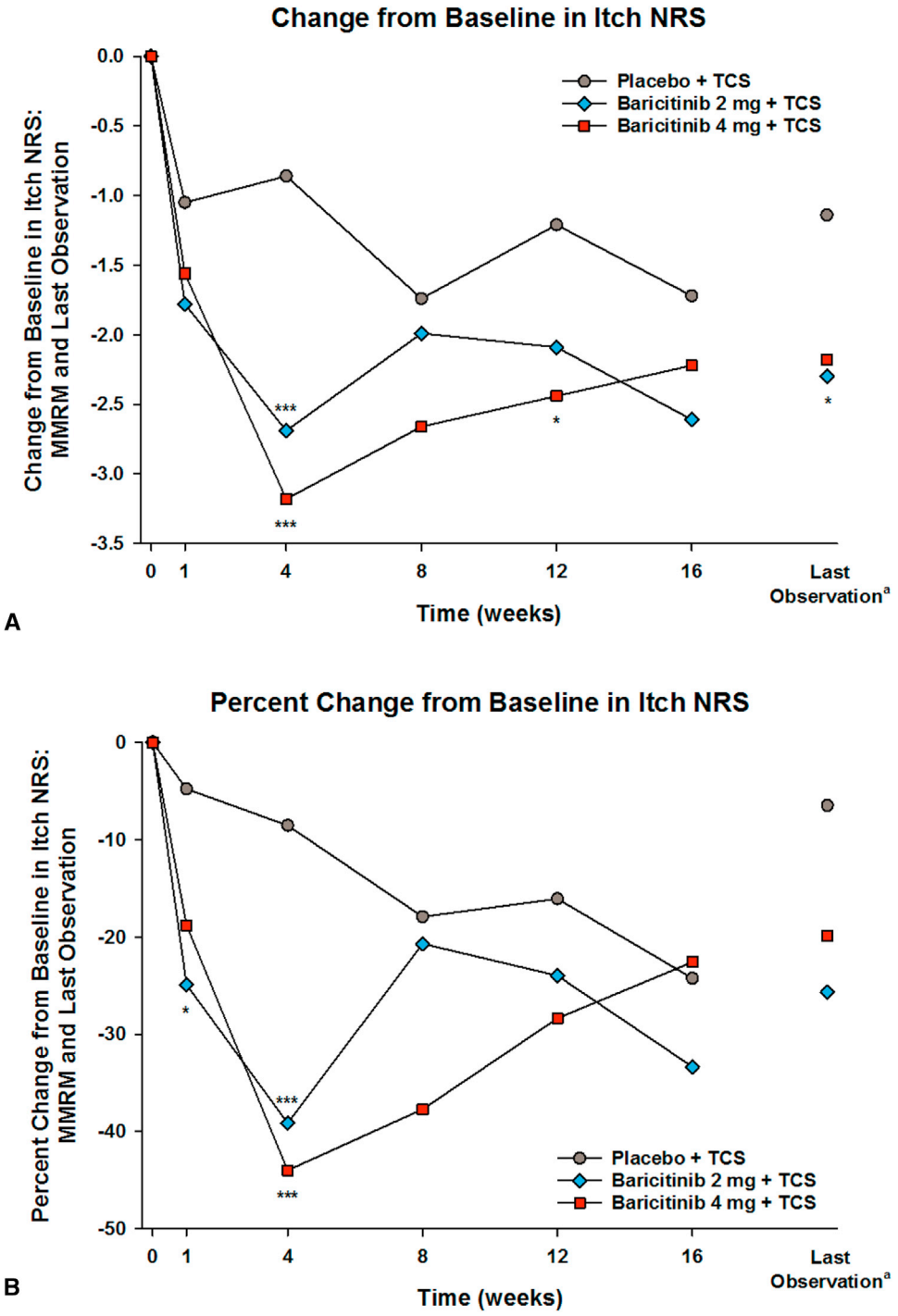
C

Supplemental Fig 4. Percentage of patients achieving EASI-90 for ITT population (**A**), patients with EASI below the median (**B**), and patients with EASI above the median (**C**). *EASI-90*, 90% improvement in EASI score; *ITT*, Intent-to-treat; *NC*, no count; *TCS*, topical corticosteroid.

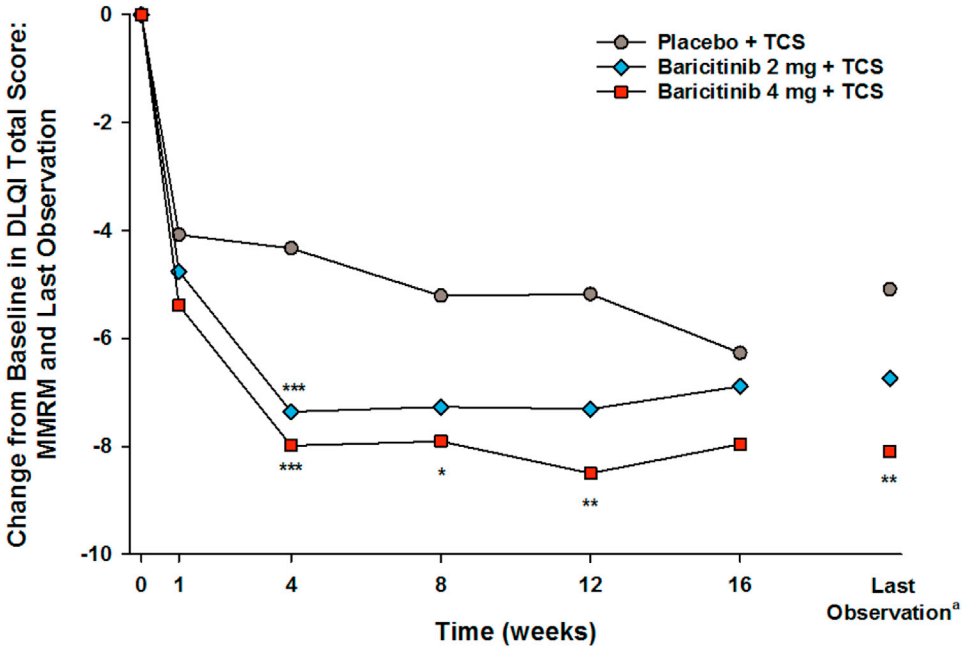


Weeks	1	4	8	12	16
Placebo + TCS (%)	0	2	12	8	8
Baricitinib 2 mg + TCS (%)	0	5	8	11	22
Baricitinib 4 mg + TCS (%)	0	18	16	24	21

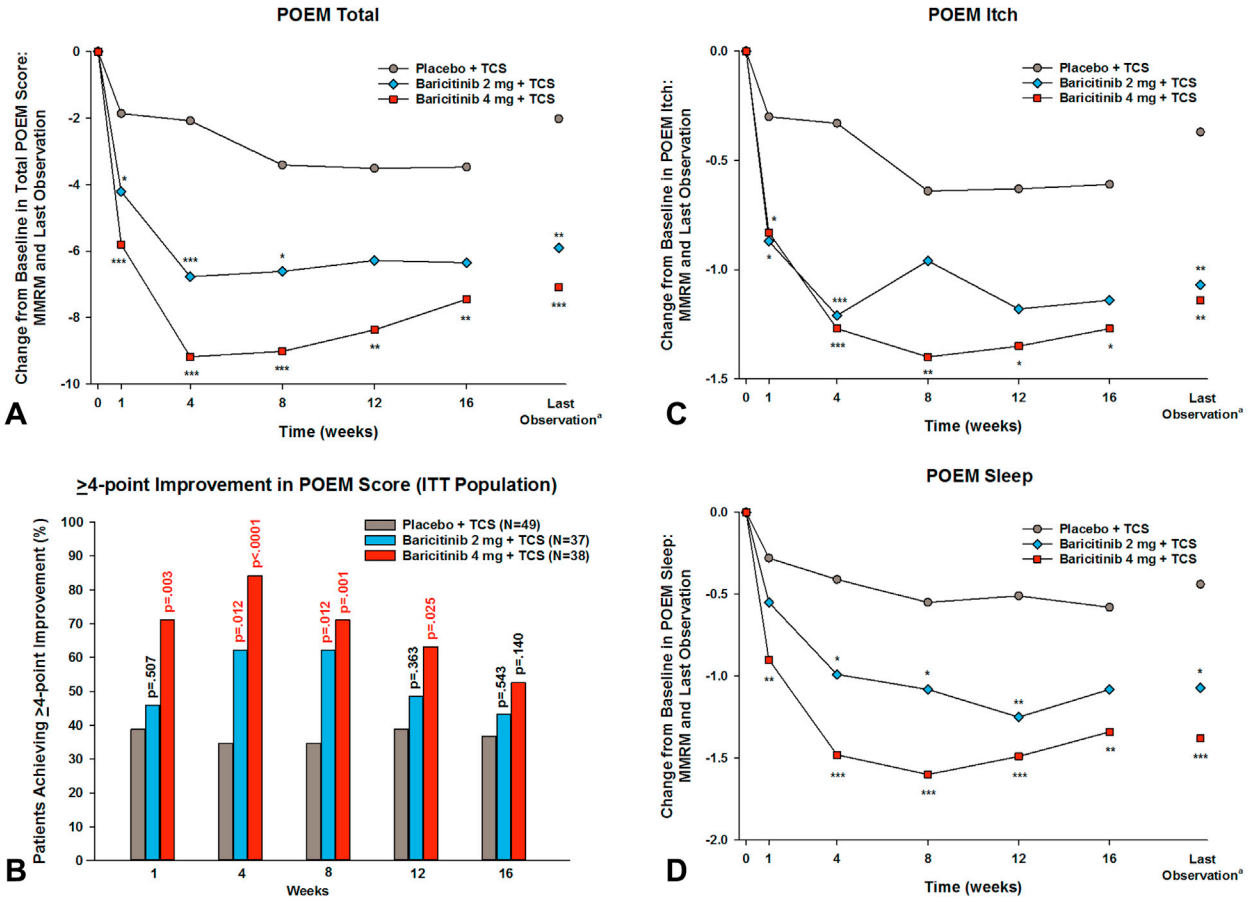
Supplemental Fig 5. Percentage of patients achieving Investigator's Global Assessment (IGA) score of 0 or 1 with a 2-point or greater improvement from baseline. Data tables display percentages. *EASI*, Eczema Area and Severity Index; *NC*, no count; *TCS*, topical corticosteroid.



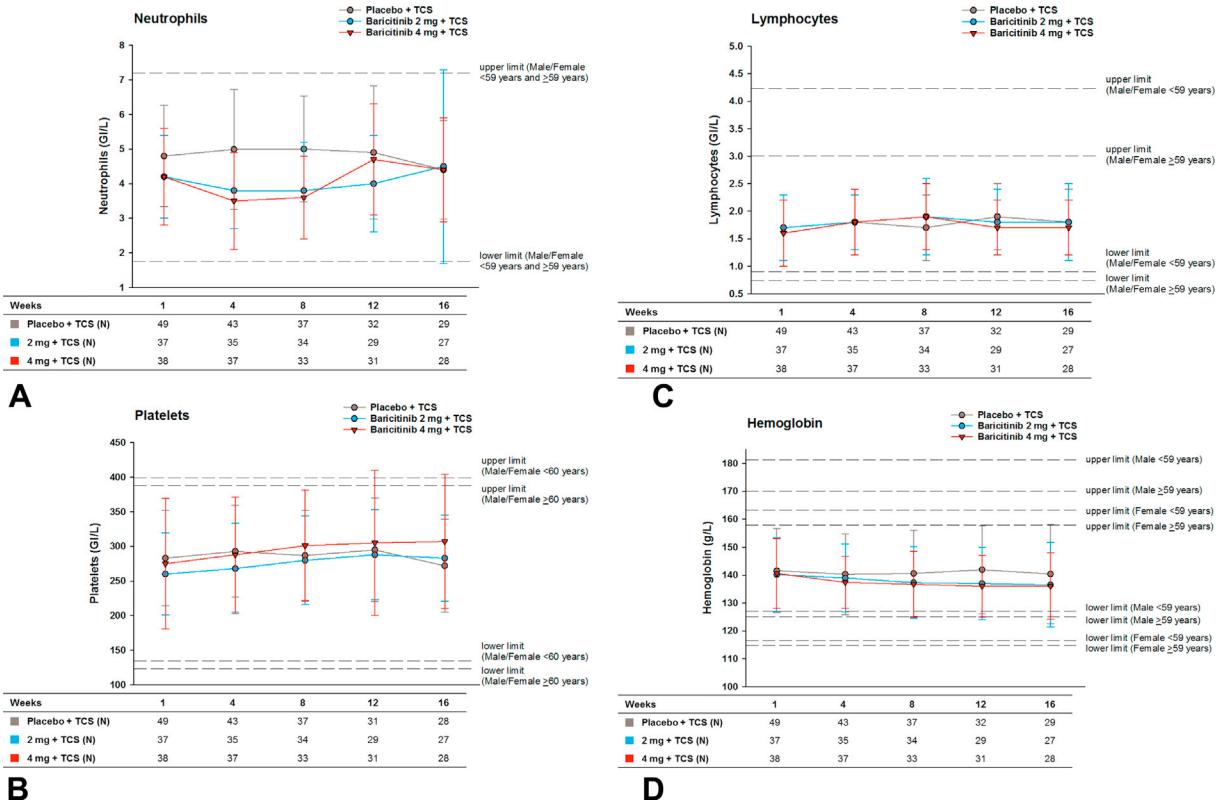
Supplemental Fig 6. Itch Numeric Rating Scale (NRS) mean change (**A**) and mean percent change (**B**) from baseline. [a]Last observation is week 16 last observation carried forward. Two-sided *P* values: **P* < .05, ***P* ≤ .01, ****P* ≤ .001. *MMRM*, Mixed effect model repeated measure; *TCS*, topical corticosteroid.



Supplemental Fig 7. Change from baseline in Dermatology Life Quality Index (DLQI) total score: mixed effect model repeated measures (MMRMs) and week 16 last observation carried forward. [a]Last observation is week 16 last observation carried forward. Two-sided *P* values: $^{*}P < .05$, $^{**}P \leq .01$, $^{***}P \leq .001$. *TCS*, Topical corticosteroid.



Supplemental Fig 8. Patient-Oriented Eczema Measure (POEM) total, itch, and sleep score. **A**, **C**, and **D**, change from baseline. **B**, POEM scores reflecting 4-point or greater improvement. Two-sided *P* values: $^{*}P < .05$, $^{**}P \leq .01$, $^{***}P \leq .001$. *MMRM*, Mixed effect model repeated measure; *TCS*, topical corticosteroid.



Supplemental Fig 9. Mean laboratory values over time. *TCS*, Topical corticosteroid.