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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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Title: 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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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 AD patients
- Baricitinib is a potential treatment option for AD.

Abstract

BACKGROUND: Baricitinib, an oral selective inhibitor of Janus kinase (JAK)1 and JAK2, modulates pro-inflammatory cytokine signaling.

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 (TCS) for 4 weeks before randomization to once daily placebo, baricitinib 2 mg, or baricitinib 4 mg for 16 weeks. Use of TCS was permitted during the study. Primary outcome was the proportion of patients achieving $\geq 50\%$ reduction in the Eczema Area and Severity Index (EASI-50) compared to placebo.

RESULTS: Significantly more baricitinib 4-mg patients achieved EASI-50 compared to placebo (61% vs 37%; $P=0.027$) at 16 weeks. The proportion of baricitinib 2- and 4-mg patients achieving EASI-50 compared to placebo was significant as early as week 4. Baricitinib also improved pruritus and sleep loss. Treatment-emergent adverse events were reported in 24 (49%) placebo, 17 (46%) baricitinib 2-mg, and 27 (71%) baricitinib 4-mg patients.

LIMITATIONS: A TCS standardization period prior to randomization reduced disease severity, limiting the ability to compare results to baricitinib monotherapy. Longer studies are required to confirm baricitinib efficacy and safety in AD patients.

CONCLUSIONS: Baricitinib used with TCS reduced inflammation and pruritus in patients with moderate-to-severe atopic dermatitis (AD).

Key Words: Atopic dermatitis, baricitinib, EASI, JAK-STAT signaling, phase 2, pruritus, SCORAD, topical corticosteroids.

INTRODUCTION

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease,¹ with a prevalence of 7–10% in United States adults,¹⁻⁴ and up to 13% worldwide.⁵ The cutaneous inflammatory reaction of AD is accompanied by intense pruritus and negatively impacts health-related quality of life (HRQoL).⁶ Lesional skin of AD contains elevated levels of inflammatory cytokines, including Th2 (IL-4, IL-13, IL-31), Th22 (IL-22), and Th1 (IFN γ), many of which depend on Janus kinase (JAK)/signal transducer and activator of transcription (STAT) intracellular signaling. Baricitinib is a selective JAK1 and JAK2 inhibitor⁷ currently approved for the treatment of moderately to severely active RA in adults in Europe, Japan, and other countries.

Available systemic immunosuppressants and phototherapy have safety concerns with 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 on dupilumab with background topical corticosteroids (TCS).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 using TCS to identify individuals 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 IRB (Columbia, MD; Pro00015579). Ethics approval was obtained for all sites.

Treatment

Patients were randomized using an interactive response technology (IRT) system in a 4:3:3 ratio to once daily (QD) placebo, 2, 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 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 triamcinolone (0.1%) cream for 4 weeks prior to randomization and were required to meet entry criteria at randomization to ensure they were 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 ≥ 18 years of age with moderate-to-severe AD¹² (Eczema Area and Severity Index [EASI]¹³ ≥ 12 and $>10\%$ body surface area involvement at screening and randomization, and diagnosis ≥ 2 years before first visit).

Patients were required to have inadequate response to emollients plus TCS (with or without topical calcineurin inhibitors and/or antibiotics); systemic corticosteroids (with or without phototherapy); or immunosuppressants.

Efficacy Measures

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

Safety assessments

Clinical laboratory tests, 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 only controlled for the primary efficacy analyses using stepwise hypothesis-testing strategy, first comparing 4 mg baricitinib versus placebo, then 2 mg versus placebo. A chi-square test with an alpha of 0.05 was used to detect differences between baricitinib and placebo. All patients who

discontinued the study or study treatment prior to week 16 were defined as non-responders.

Continuous secondary outcomes collected longitudinally were analyzed using mixed effects model repeated measures (MMRM). Covariates included treatment, visit, country, treatment-by-visit interaction, baseline, and baseline-by-visit. This model accounts for missing data using 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 using an analysis of covariance (ANCOVA) model with fixed effects for treatment and country plus the baseline value as a covariate. Categorical secondary outcomes were analyzed using chi-square or Fisher's exact tests, when needed. No multiplicity adjustment was used in the analysis of secondary outcomes.

RESULTS

Patients

Among 187 screened patients, 124 enrolled; 104 in the US and 20 in Japan. Patients were randomized to placebo QD plus TCS (n=49), baricitinib 2 mg QD plus TCS (n=37), or baricitinib 4 mg QD plus TCS (n=38), respectively (Fig 1). 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, disease severity of 7 patients improved such as they no longer met inclusion criteria to participate to the study. However in all the other patients, changes in skin severity score during the

standardization period were not significant, indicating stable disease using TCS prior to randomization.

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

A larger proportion of patients discontinued placebo plus TCS (41%) compared to baricitinib plus TCS (27% on 2 mg and 24% on 4mg), including discontinuations due to lack of efficacy (placebo 18%; baricitinib 2 mg 11%, baricitinib 4 mg 0%) that also tended to occur earlier (Supplemental Fig 1).

EFFICACY

Primary Objective – EASI-50

The proportion of baricitinib 4 mg plus TCS patients achieving EASI-50 at week 16 was significantly greater than in placebo plus TCS ($p=0.027$) (Fig 2). While the proportion of patients who achieved EASI-50 with the baricitinib 2 mg plus TCS dose was similar to that observed in baricitinib 4 mg plus TCS, the baricitinib 2 mg plus TCS response was not statistically significant compared to placebo ($p=0.065$). These changes occurred while baricitinib patients used approximately 30% less TCS monthly after randomization (based on mean TCS container weight) than placebo patients.

Secondary endpoints

EASI

The difference in the proportion of baricitinib 2- and 4-mg patients achieving EASI-50 to placebo was also statistically significant at weeks 4, 8, and 12. Percent change from baseline in EASI score using MMRM showed statistically significant improvement for all time points for baricitinib 4 mg compared to placebo. The baricitinib 2 mg dose response was statistically significant at weeks 4, 8, and 16. Week 16 LOCF analysis of the percent change from baseline in EASI score showed a significant difference for the baricitinib 2 and 4 mg doses compared to placebo (Fig 2).

An approximately 20% difference in placebo plus TCS response 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 (baricitinib 4 mg plus TCS MMRM, 65% vs. week 16 LOCF, 62%; baricitinib 2 mg plus TCS MMRM, 64% vs. week 16 LOCF, 60%).

SCORAD

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

Dermatology Life Quality Index

Total DLQI improved in both treatment groups relative to placebo, which was significant at week 4 (Supplemental Fig 7). The difference between baricitinib 4 mg plus TCS and

placebo plus TCS was also significant at weeks 8 and 12. The LOCF analysis showed that baricitinib 4 mg plus TCS was significantly better than placebo plus TCS at week 16.

SAFETY

Discontinuations because of adverse events from baseline through week 16 included 5 patients (10%) from the placebo plus TCS group (lymphopenia, 3 patients; eczema; AD), 1 patient (3%) from the baricitinib 2 mg plus TCS group (neutropenia), and 5 patients (13%) from the baricitinib 4 mg plus TCS group (white cell counts decreases, 2 patients; abnormal lymphocyte count ; headache; eczema) (Fig 1 and Table II). One patient (baricitinib 4 mg plus TCS group) experienced a serious adverse event during the treatment phase (benign polyp of the large intestine). No deaths occurred.

On-treatment adverse events occurring in more than 2 patients in any treatment group are listed in Table II. In the baricitinib 4-mg group, headache, blood creatine phosphokinase increased, and nasopharyngitis occurred in 3 to 5 patients. Infections were not increased in the medication groups compared to placebo. No patients in the baricitinib plus TCS groups had herpes zoster infections, while 1 patient in the placebo plus TCS group did during the washout period.

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

Among hematology parameters, there were decreases from baseline to weeks 4 and 8 in leucocytes and neutrophils for both baricitinib plus TCS groups that were not observed in placebo (Supplemental Fig 9). These changes were transient, with no discernable difference among the 3 treatment groups at the end of treatment (LOCF). Platelet increases (mean increase 13% (SD 24.4) in baricitinib 4-mg group [LOCF]) over time were observed in baricitinib plus TCS, not in placebo plus TCS.

DISCUSSION

In this phase 2 study evaluating JAK1/JAK2 inhibition in adult AD patients, baricitinib treatment conferred clinically meaningful improvement in multiple measures of disease severity. Specifically, a significantly greater proportion of moderate-to-severe AD patients treated with once-a-day oral baricitinib at the 4-mg dose plus TCS achieved EASI-50 at week 16 compared to placebo plus TCS. At week 16, patients on baricitinib 2 mg plus TCS and 4 mg plus TCS achieved an approximately 65% reduction in disease severity (EASI), compared to a 46% placebo plus TCS response, 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 providing mid-potency TCS for at least 4 weeks prior to randomization to select patients not entirely controlled by TCS and requiring additional therapy. Use of TCS was allowed during the study, perhaps also narrowing the ability to compare with other monotherapy studies. The EASI ≥ 12 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 to placebo, if reductions in TCS use occur more often in the active arms of the study. During this study, baricitinib patients used approximately 30% less TCS (by weight) monthly after randomization than placebo patients, which is similar to a clinical trial of dupilumab in AD patients.¹⁷

Several pre-clinical and clinical studies implicating Th2 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 (pan-JAK inhibitor) showed clinical improvement in patients with mild-moderate AD, highlighting the potential for JAK inhibition in AD patients.^{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 compared to 21% on placebo, accompanied by less clinical improvement, suggesting that reductions in both inflammation and pruritus are therapeutically important in AD patients.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 TCS, compared to 29% on placebo plus TCS.¹¹ Dupilumab plus TCS also resulted in a 77% reduction from baseline in EASI compared to 43% on placebo plus TCS. Notably, in our phase 2 baricitinib study, improvement in pruritus began as early as week 1, achieving a 45% change in Itch NRS and a 44% change in SCORAD pruritus for baricitinib 4 mg plus TCS at week 4, compared to 16–17% in placebo plus TCS.

Whether the rapid reduction in itch following baricitinib treatment in AD could be mediated by interrupting pruritogenic cytokines such as thymic stromal lymphopoietin (TSLP), IL-4, or IL-31 remains to be determined.^{21,22} Baricitinib 4 mg plus TCS also resulted in 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. These results suggest that baricitinib may provide an oral approach that modulates similar targets as biologics treating AD.

In this study, there were no deaths. More dose-dependent total adverse events occurred in the baricitinib 4-mg group compared to placebo. Headache, increased blood creatine phosphokinase, and nasopharyngitis were the most common on-treatment adverse events in baricitinib groups, and exacerbation of AD was most common in placebo (Table II). Increases in CPK 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 rheumatoid arthritis patients,¹⁹ were not observed in this baricitinib study. 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. Usage of TCS during the standardization period lowered the overall severity of patients subsequently treated with baricitinib, which also limited the ability to compare the efficacy of baricitinib to

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 QD oral regimen. Additional studies are warranted to further investigate the role of baricitinib in AD.

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Abbreviations

Abbreviations used:

AD:	atopic dermatitis
ANCOVA:	analysis of covariance
CPK:	creatine phosphokinase
DLQI:	Dermatology Life Quality Index
EASI:	Eczema Area and Severity Index
HRQoL:	health-related quality of life
IGA:	Investigator's Global Assessment
ITT:	intent-to-treat
JAK:	janus kinase
LOCF:	last observation carried forward
MMRM:	mixed effects model repeated measures
NRS:	Numeric Rating Scale
POEM:	Patient-Oriented Eczema Measure
QD:	daily
SCORAD:	Scoring Atopic Dermatitis
SD:	standard deviation
STAT:	signal transducer and activator of transcription
TCS:	topical corticosteroids
TEAE:	treatment-emergent adverse event

Figure Legends

Fig 1. Patient disposition.

Fig 2. Percentage of patients achieving EASI-50 (A) and percentage change from baseline in EASI score (B).

^aLast observation is week 16 LOCF.

* $p < 0.05$

** $p \leq 0.01$

*** $p \leq 0.001$

EASI, Eczema Area and Severity Index; MMRM, mixed effect model repeated measures; TCS, topical corticosteroids

Fig 3. SCORAD total percent change from baseline (A), pruritus change from baseline (B), and sleep loss change from baseline (C).

^aLast observation is week 16 LOCF.

MMRM, mixed effect model repeated measures; SCORAD, Scoring Atopic Dermatitis; TCS, topical corticosteroids.

* $p < 0.05$

** $p \leq 0.01$

*** $p \leq 0.001$

Fig 1. Patient disposition.

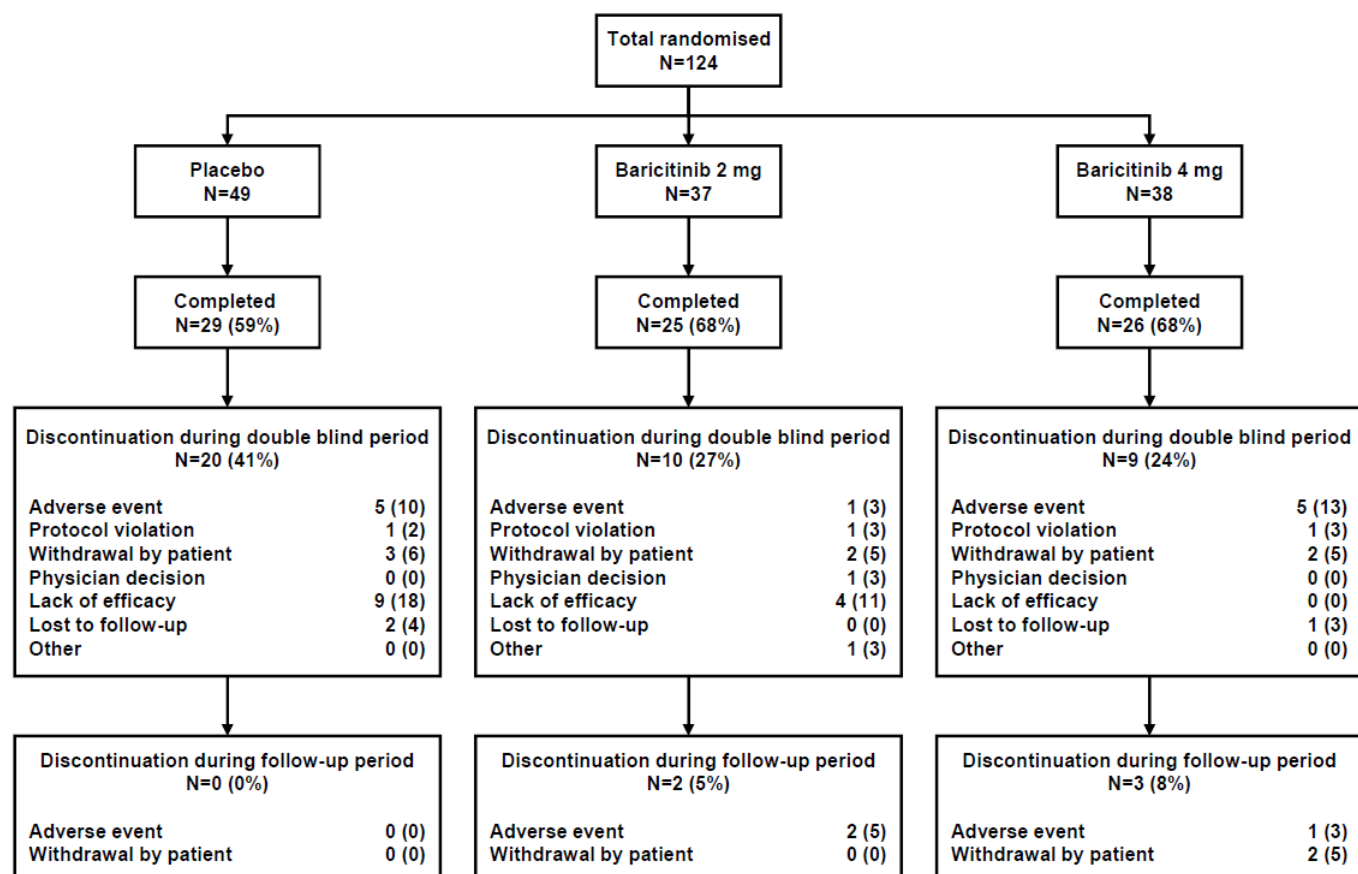
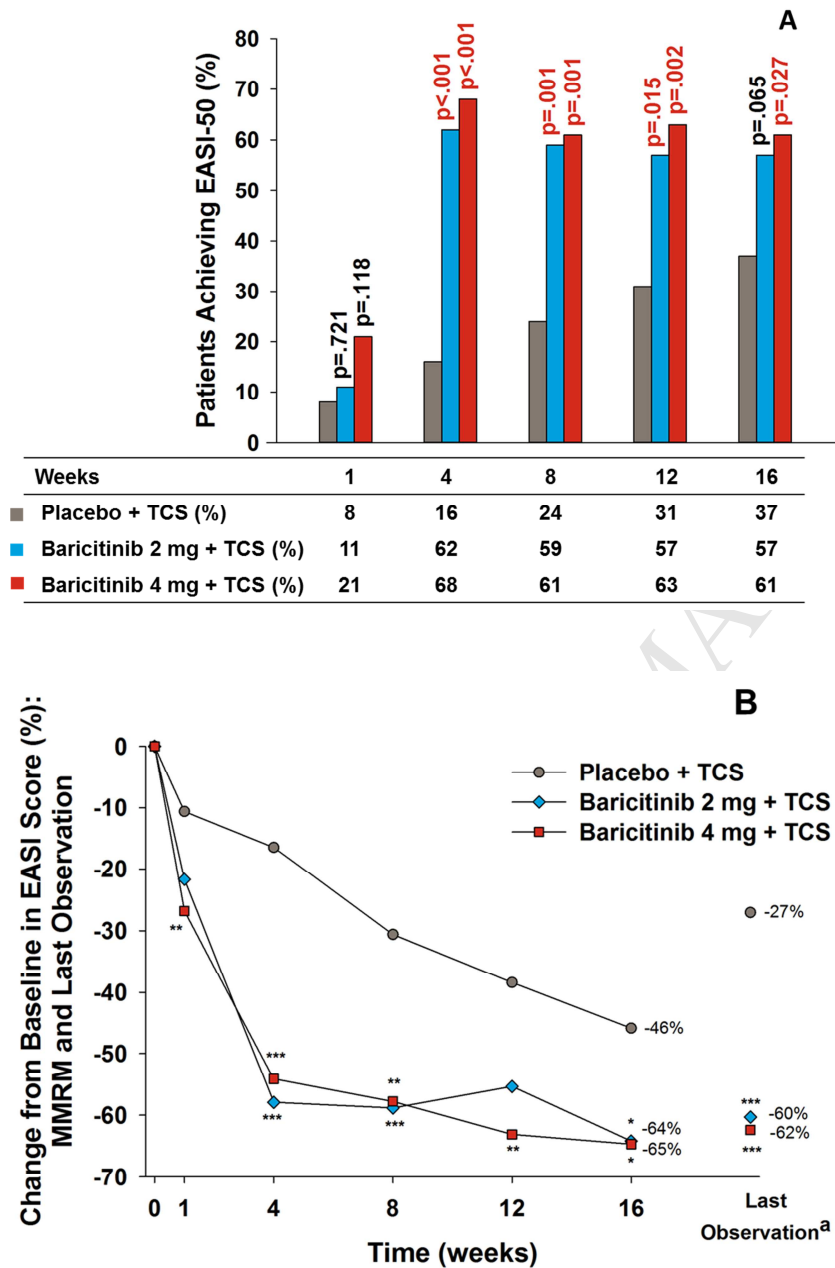


Fig 2. Percentage of patients achieving EASI-50 (A) and percentage change from baseline in EASI score (B).



^aLast observation is week 16 LOCF.

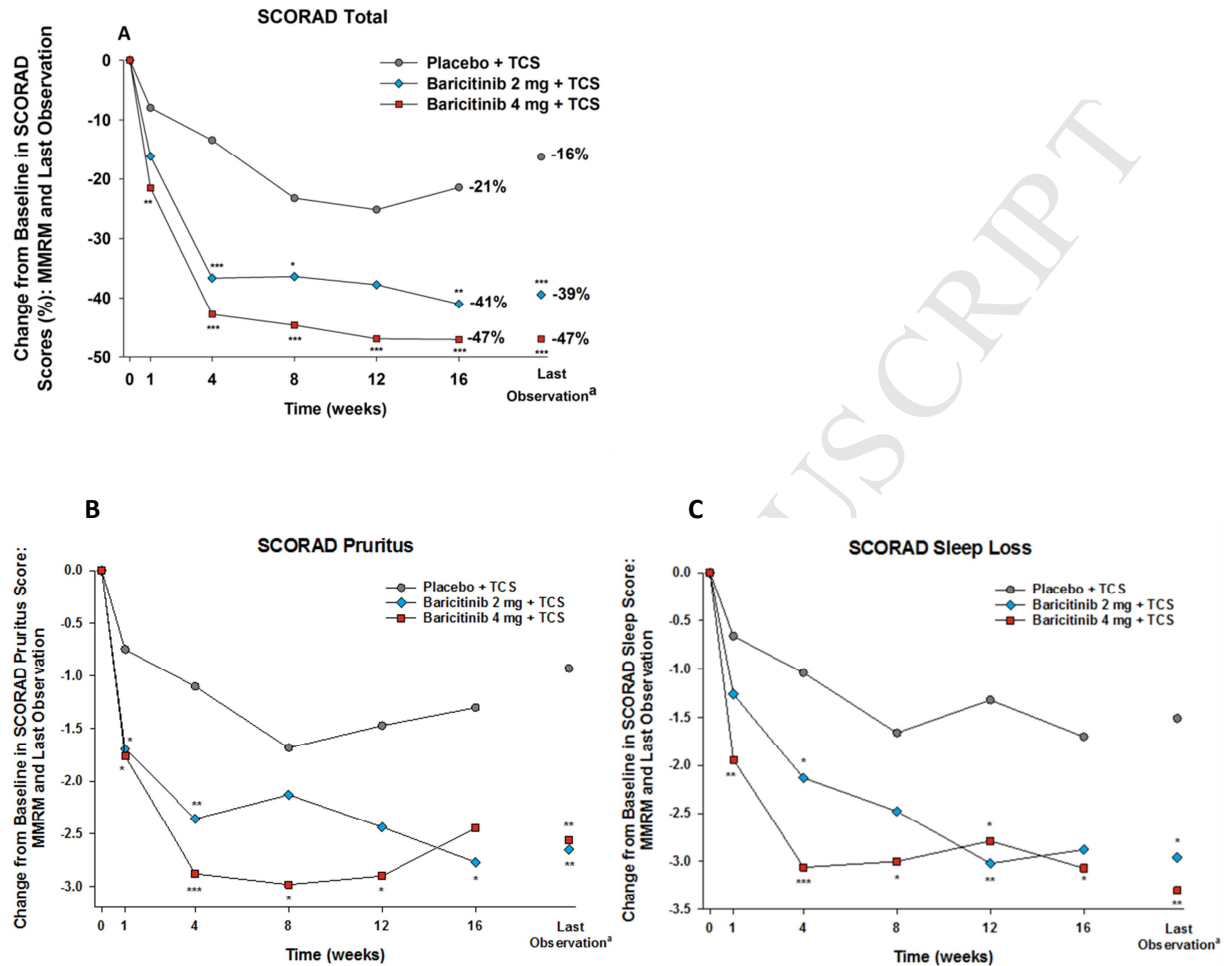
* $p < 0.05$

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* $p < 0.05$

** $p \leq 0.01$

*** $p \leq 0.001$

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)	35 (28.0-48.0)	42 (26.0-52.0)	32.5 (26.0-48.0)	p=0.508
Male sex – no. (%)	24 (49)	22 (59)	22 (58)	p=0.565
Race – no. (%)				p=0.553
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=0.035
Median EASI score (IQR)*†	22.1 (15.3-28.0)	22.1 (16.8-32.3)	19.5 (13.7-25.9)	p=0.405
Median IGA score (IQR)‡	3 (2-5)	3 (3-5)	3 (2-5)	p=0.457
Median Itch NRS (IQR)§	7 (5-7)	6 (5-3)	6.5 (5-3)	p=0.164
Median total SCORAD score (IQR)¶	55 (44.9-63.8)	53.3 (49.9-61.1)	57.6 (49.5-64.9)	p=0.845
Median POEM score (IQR)‖	20 (17.0-23.0)	17 (12.0-25.0)	20.5 (11.0-26.0)	p=0.641
Median DLQI score (IQR)#	15 (10.0-19.0)	10 (7.0-17.0)	11 (8.0-17.0)	p=0.254

IQR, interquartile range; TCS, topical corticosteroids.

* Eczema Area and Severity Index (EASI) scores range from 0 to 72, with higher scores indicating greater severity. Investigator's Global Assessment (IGA) uses a 6-point scale ranging from clear to very severe disease.

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

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

¶ Scoring Atopic Dermatitis (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.

‖ Patient-Oriented Eczema Measure (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.

Dermatology Life Quality Index (DLQI) evaluates health-related quality of life on a scale of 0 to 30.

Table II. Adverse events

Characteristics	Placebo plus TCS N = 49	Baricitinib 2 mg plus TCS N = 37	Baricitinib 4 mg plus TCS N = 38
Treatment-emergent adverse or serious adverse event during the treatment period			
At least 1 TEAE (%)	24 (49)	17 (46)	27 (71)
At least 1 treatment-emergent serious adverse event (%)	0	0	1 (3)*
TEAE resulting in death during treatment and follow up period	0	0	0
TEAEs leading to treatment discontinuation (%)	5 (10)	1 (3)	5 (13)
TEAEs occurring in 3 or more patients per treatment group (%)			
Headache	0	2 (5)	5 (13)
Blood 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)† (%)			
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

TEAE, treatment-emergent adverse event; TCS, topical corticosteroids

*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.

Supplemental Material

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to Guttman-Yassky E, Silverberg J, Nemoto O, et al. Baricitinib in patients with moderate-to-severe atopic dermatitis: a phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study

Supplemental Material

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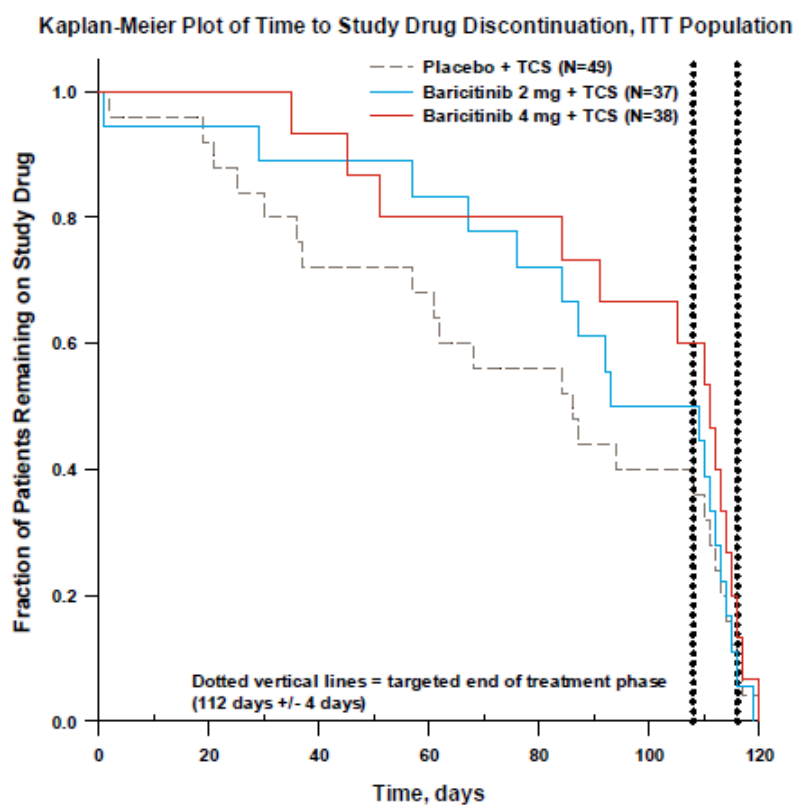
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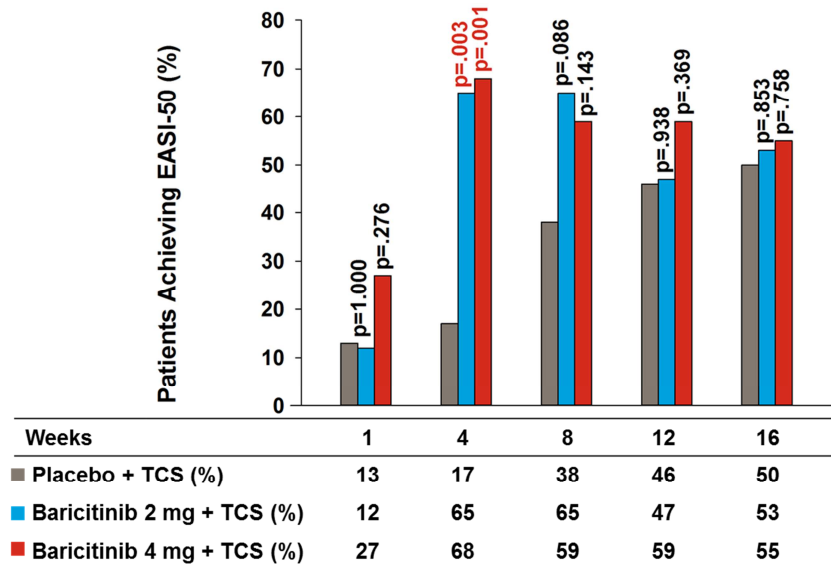
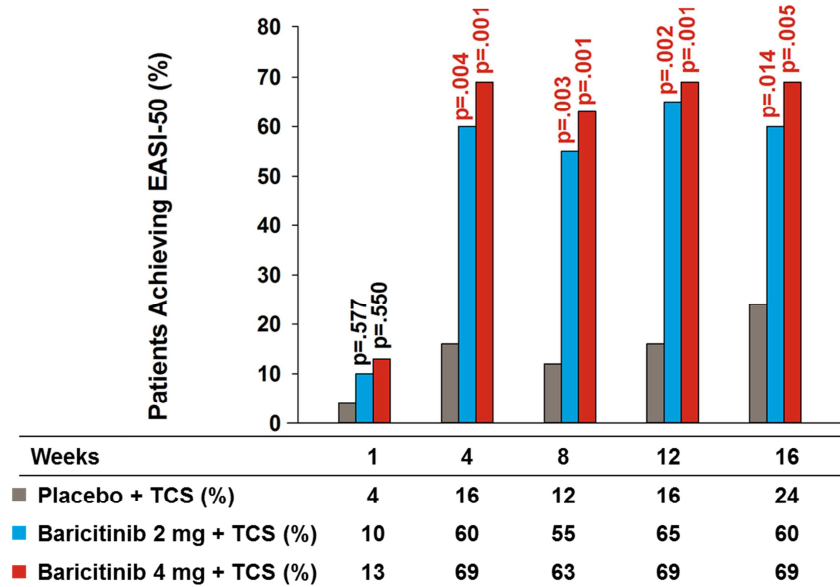
Jamie Weisman, Advanced Medical Research, PC, Atlanta, GA, USA.

Supplemental Material

Supplemental Fig 1. Kaplan Meier plot of time to study drug discontinuation.

Note: Patients without a treatment end date were not included.
Discontinuation of study drug could be due to any reason.
ITT, intent to treat; N, number of patients; TCS, topical corticosteroids

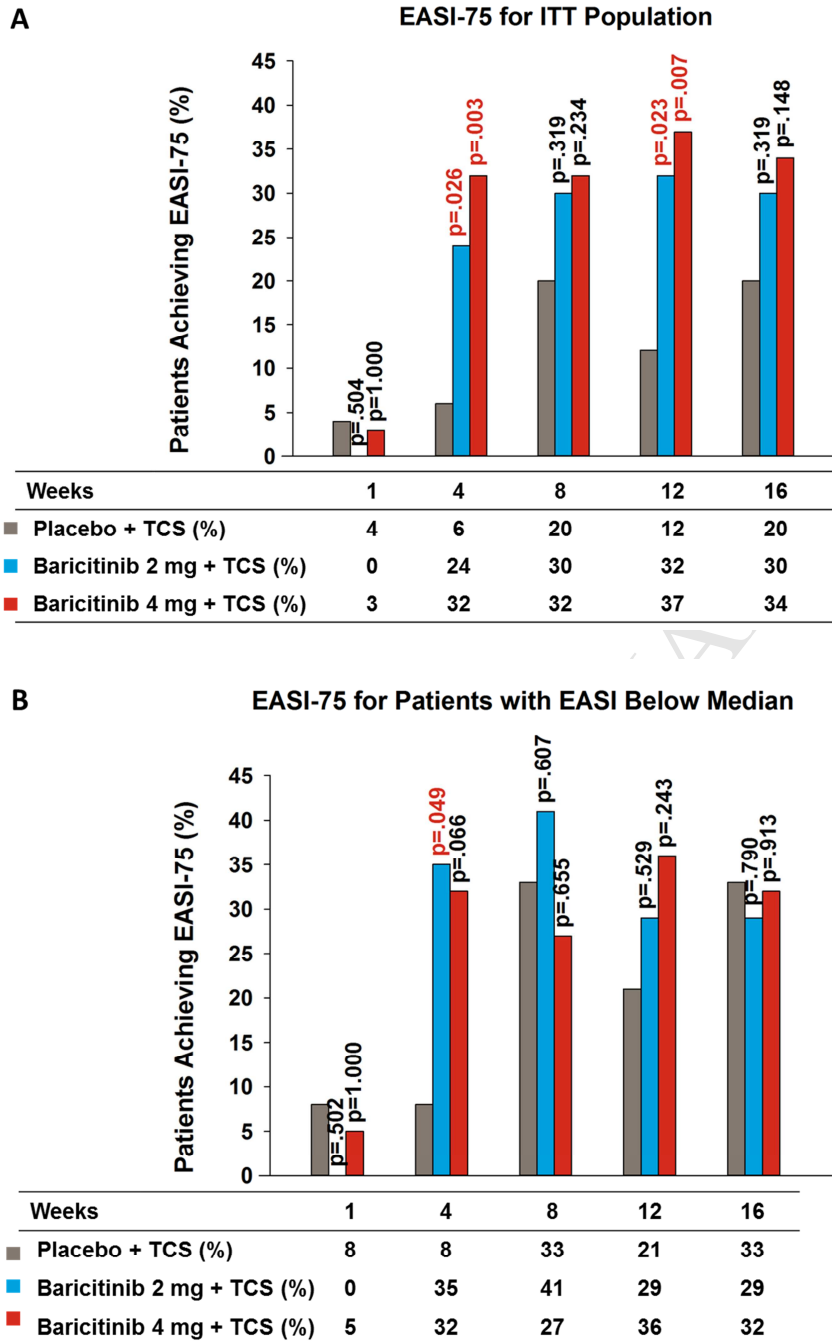
Supplemental Material

Supplemental Fig 2. EASI-50 for Patients with baseline EASI below (A) and above median (B).**A EASI-50 for Patients with Baseline EASI Below Median (≤ 21.2)****B EASI-50 for Patients with Baseline EASI Above Median (>21.2)**

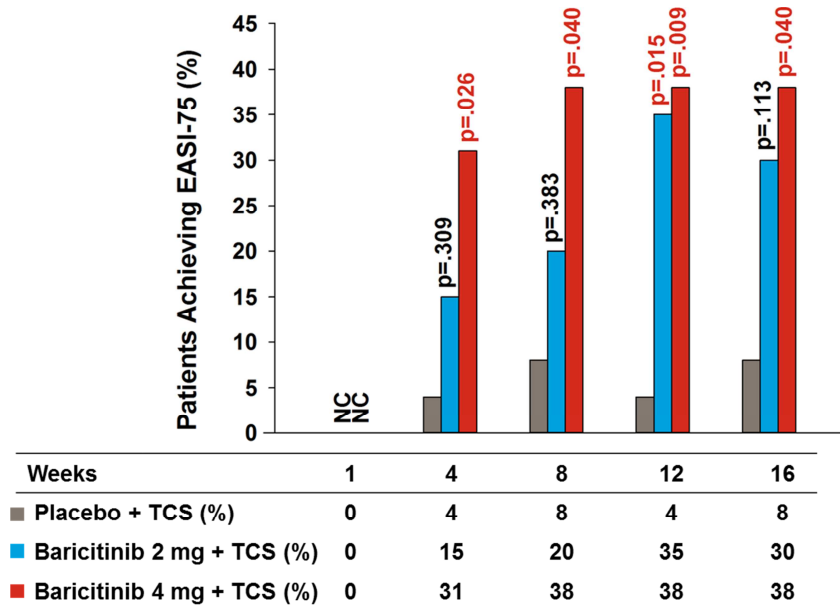
EASI, Eczema Area and Severity Index; N, number patients; TCS, topical corticosteroids

Supplemental Material

Supplemental Fig 3. Percentage of patients achieving EASI-75.



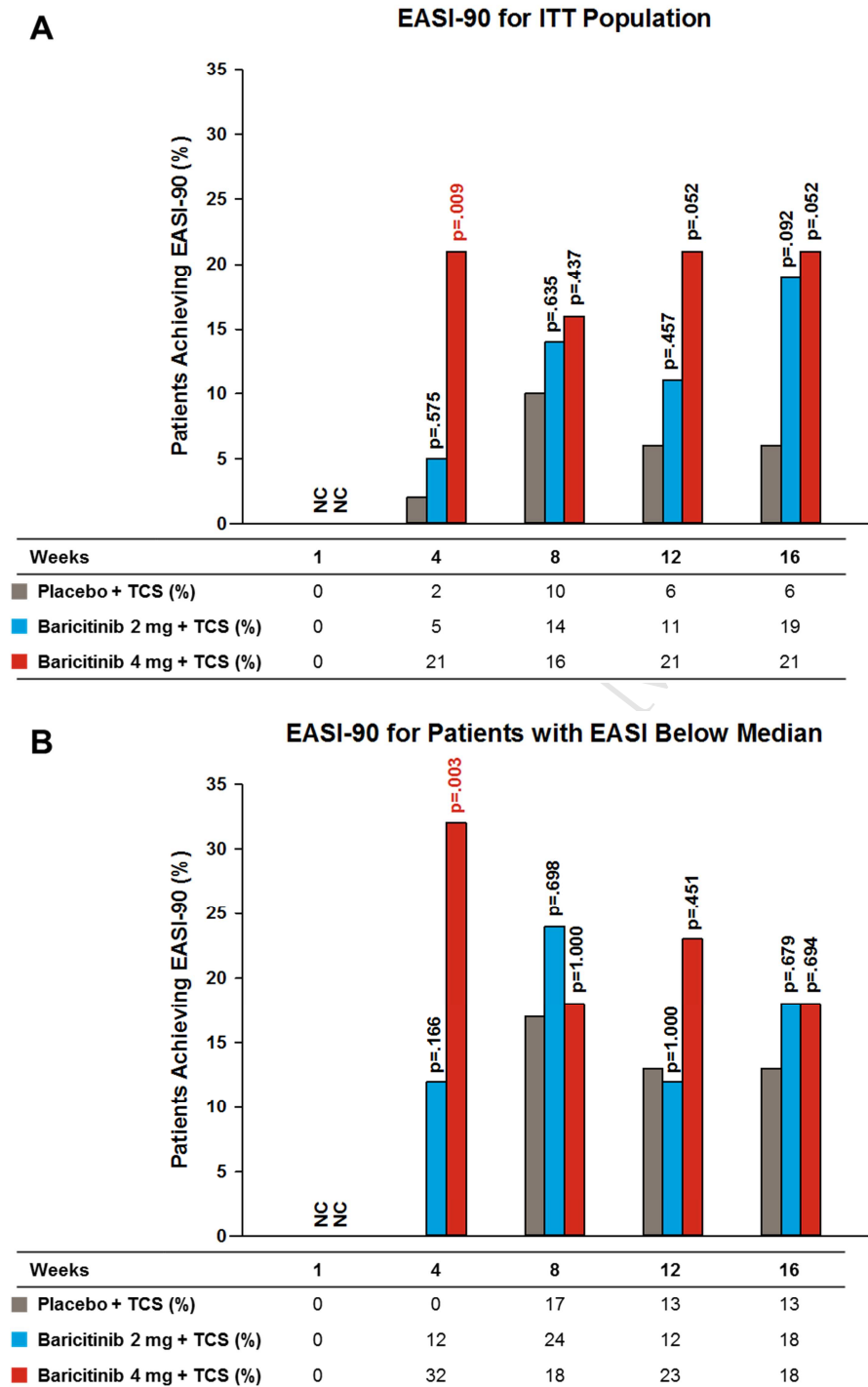
Supplemental Material

C EASI-75 for Patients with EASI Above Median

EASI, Eczema Area and Severity Index; N, number of patients; NC, No count; TCS, topical corticosteroids

Supplemental Material

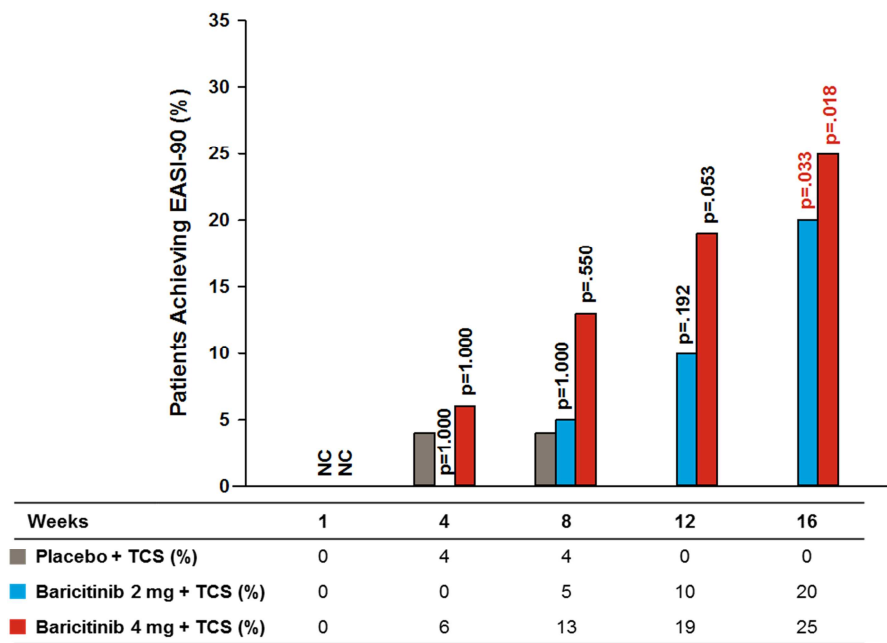
Supplemental Fig 4. Percentage of patients achieving EASI-90.



Supplemental Material

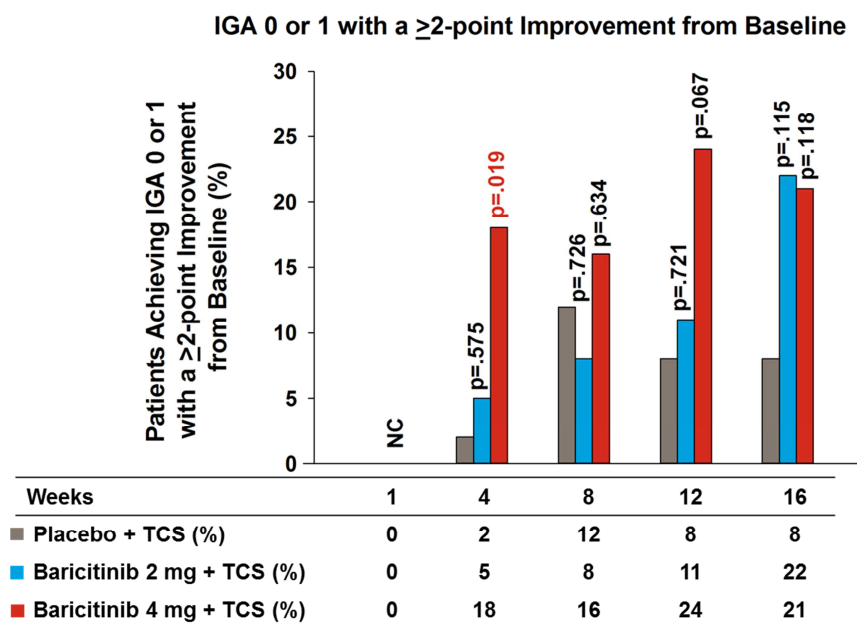
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EASI-90 for Patients with EASI Above Median



EASI, Eczema Area and Severity Index; N, number of patients; NC, No count; TCS, topical corticosteroids

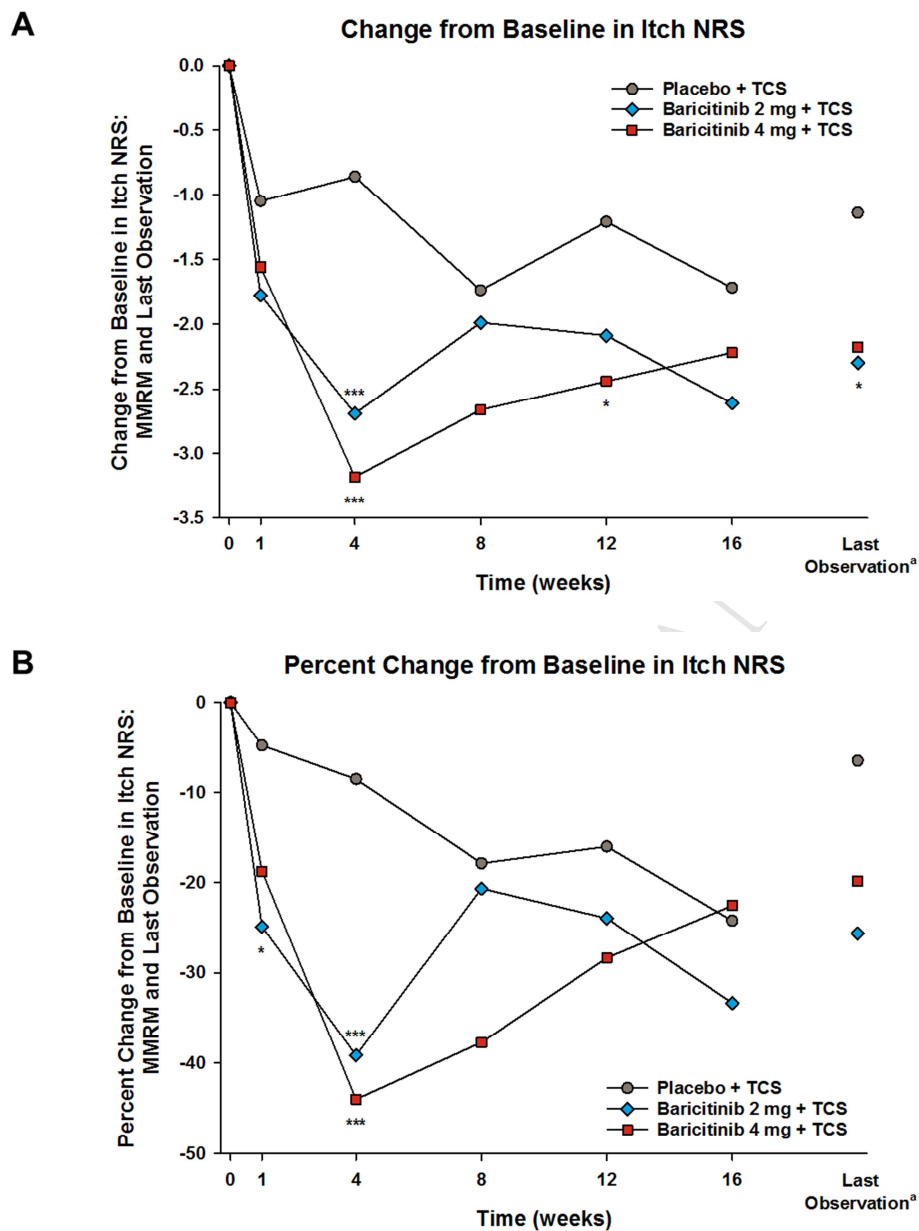
Supplemental Material

Supplemental Fig 5. Percentage of patients achieving IGA of 0 or 1 with ≥ 2 point improvement from baseline.

EASI, Eczema Area and Severity Index; N, number of patients; IGA, Investigator Global Assessment; NC, no count; p, chi-square p-value of respective treatment compared to placebo using nonresponder imputation; TCS, topical corticosteroids

Note: Data tables display percentages.

Supplemental Material

Supplemental Fig 6. Itch NRS mean change (A) and mean percent change (B) from baseline.

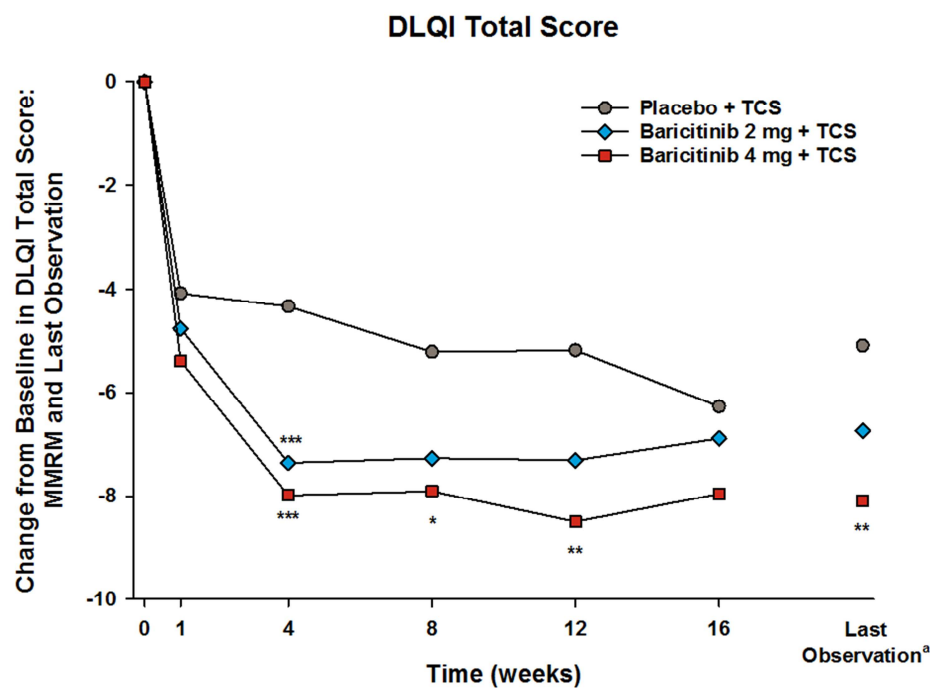
^aLast observation is week 16 LOCF.

MMRM, mixed effect model repeated measures; NRS, numeric rating scale; TCS, topical corticosteroids

Two-sided p values: *p<0.05; **p<0.01; ***p<0.001

Supplemental Material

Supplemental Fig 7. Change from baseline in DLQI total score: MMRM and Week 16 LOCF.

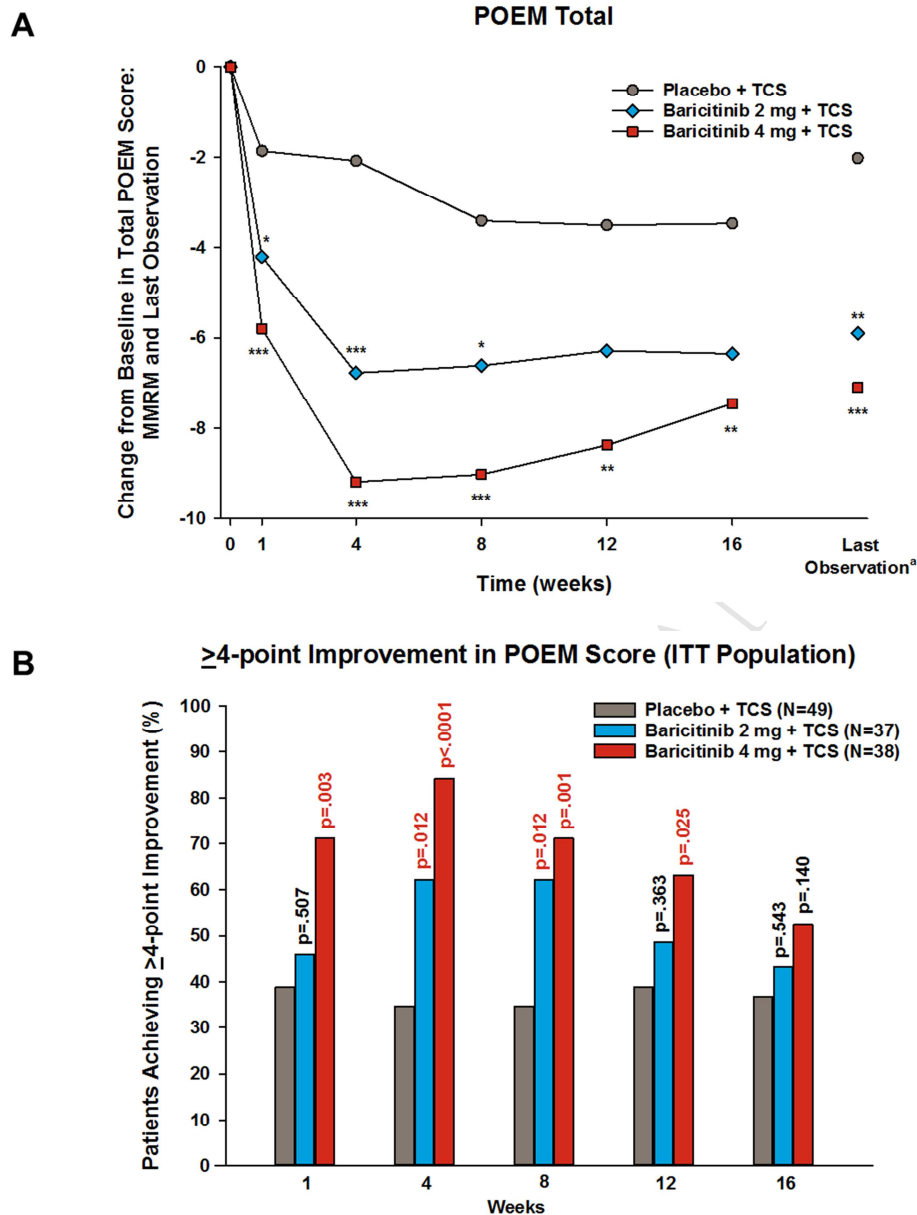


^aLast observation is week 16 LOCF.

DLQI, Dermatology Life Quality Index; MMRM, mixed effect model repeated measures; TCS, topical corticosteroids
Two-sided p values: * $p < 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$

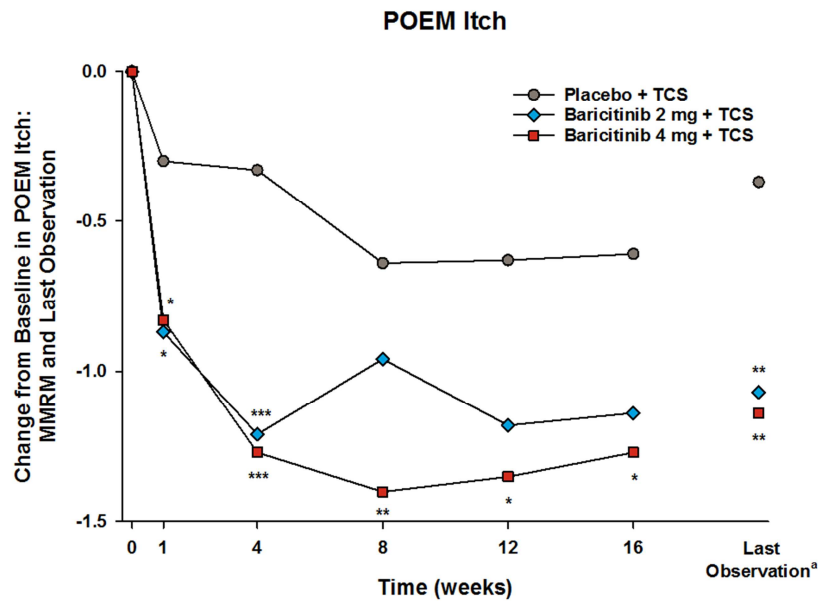
Supplemental Material

Supplemental Fig 8. POEM total, itch, and sleep score:

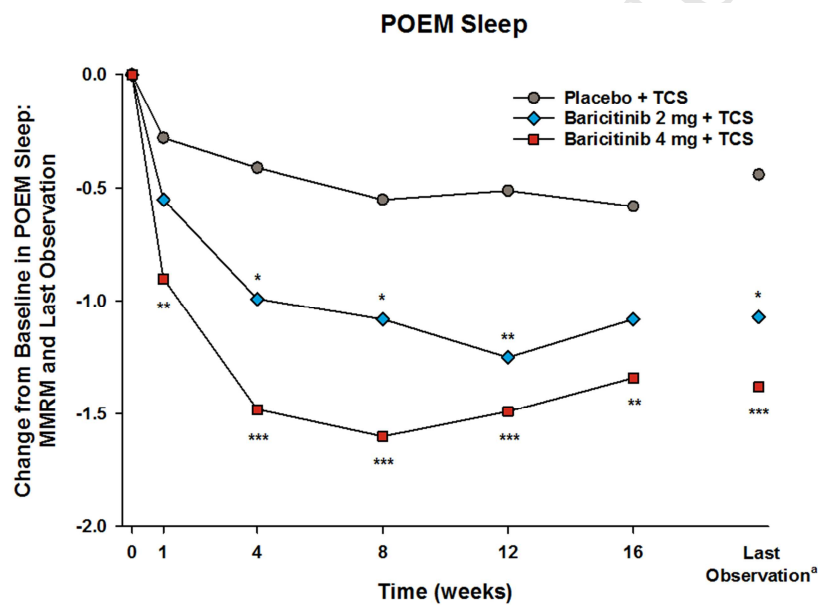
(A, C, D) change from baseline (B) POEM scores ≥ 4 point improvement

Supplemental Material

C



D



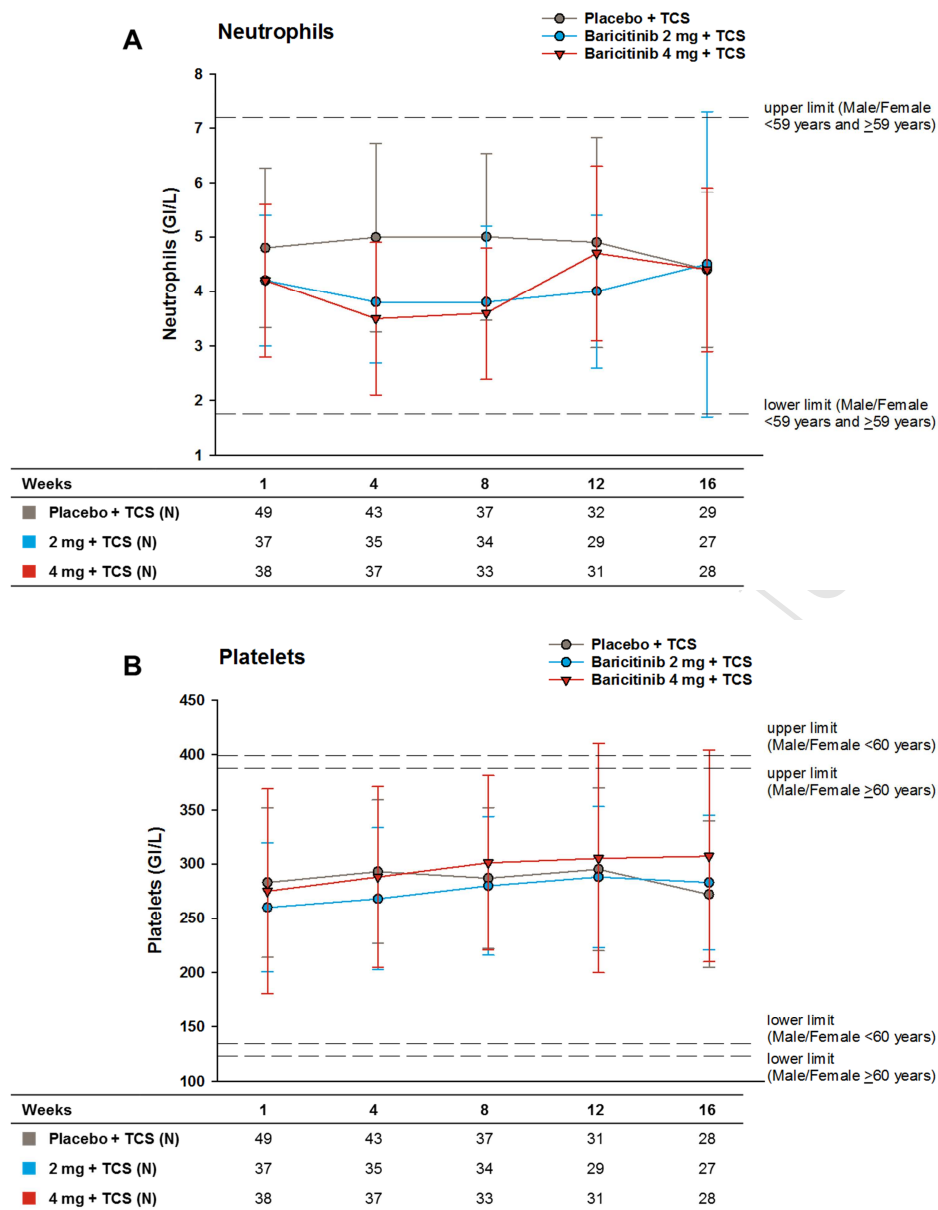
^aLast observation is week 16 LOCF.

MCID, minimal clinically important difference; MMRM, mixed effect model repeated measures; POEM, Patient Oriented Efficacy Measure; TCS, topical corticosteroids

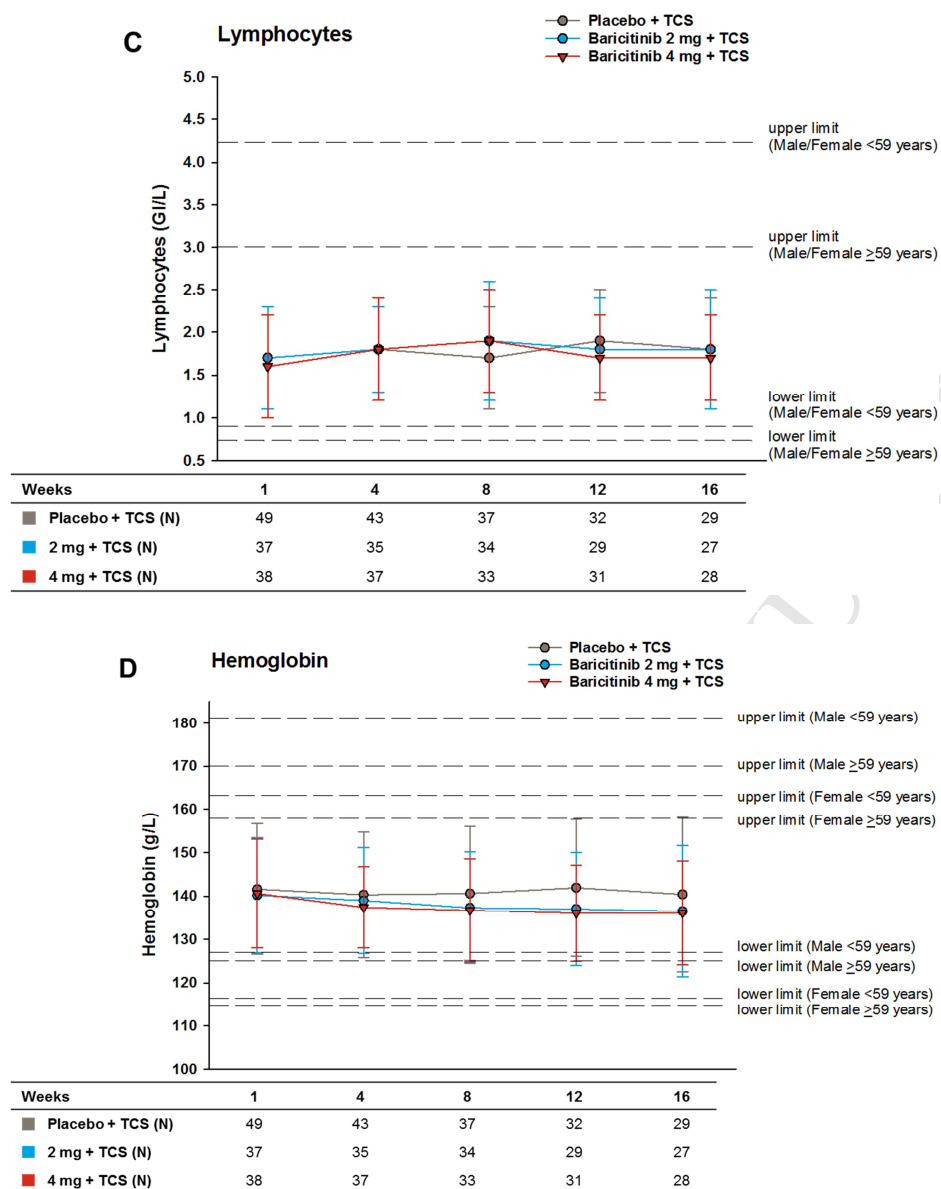
Two-sided p values: * p<0.05; ** p<0.01; *** p<0.001

Supplemental Material

Supplemental Fig 9. Mean laboratory values over time.



Supplemental Material



Error bars are 95% confidence interval about the mean.

N, number of patients; TCS, topical corticosteroids

Supplemental Efficacy Data - Exploratory Objectives**Patient-Oriented Eczema Measure**

The POEM was an exploratory endpoint. Baricitinib 4 mg plus TCS showed significant improvement over placebo plus TCS in reducing total POEM scores, as well as statistically significant reductions in POEM items of itch and sleep, starting at week 1 and throughout the study (Supplemental Fig 8). There was also a significant difference in proportion of patients achieving a clinically meaningful reduction in POEM scores (minimal clinically important difference [MCID] 4 points¹) in the baricitinib 4 mg plus TCS compared to placebo plus TCS.

Baseline Disease Severity Analysis

An exploratory analysis of baseline disease severity on treatment response showed that most placebo plus TCS patients achieving EASI-50 during the trial were in the population with lower EASI baseline scores (below median). In contrast, 69% of baricitinib 4 mg plus TCS patients with EASI above median at baseline achieved EASI-50, compared to 55% in patients with EASI below median (Supplemental Fig 2). The proportion of patients on baricitinib plus TCS achieving EASI-75 ($\geq 75\%$ improvement) and EASI-90 ($\geq 90\%$ improvement) compared to placebo plus TCS was also assessed (Supplemental Fig 3 and Supplemental Fig 4). Additionally, the proportion of patients achieving an IGA of 0 or 1 with a ≥ 2 -point improvement from baseline is provided in Supplemental Fig 5.

Itch Numeric Rating Scale

Supplemental Material

The Itch NRS improved from baseline for each baricitinib plus TCS treatment group compared to placebo plus TCS starting at week 1 and continued through week 16 (Supplemental Fig 6). The greatest difference between the treatment groups and the placebo treatment group was observed at week 4.

Investigators Global Assessment

This study used a 6-point IGA scale ranging from clear to very severe disease.¹ Twenty-one percent of baricitinib 4 mg plus TCS patients and 22% of patients receiving baricitinib 2 mg plus TCS achieved an IGA score of 0 or 1 (clear or almost clear skin) with a ≥ 2 -point improvement from baseline compared to 8% of placebo plus TCS patients. A statistically significant difference was only observed at week 4 for the baricitinib 4 mg plus TCS group compared to placebo plus TCS (Supplemental Fig 5).

Pharmacokinetics

Data from all patients who received at least 1 dose of baricitinib and provided at least 1 post-dose PK sample were included in the analyses. The geometric means of the maximum observed concentrations were 18.5 ng/mL (70.0% CV) and 37.7 ng/mL (38.9% CV) for the 2- and 4-mg treatment groups, respectively.

The maximum baricitinib concentrations ($C_{\max}$) values observed in this study were generally lower than those from previous studies in patients with rheumatoid arthritis (RA),² where, the average maximum concentration ($C_{\max}$) observed in this study after multiple 4-mg QD baricitinib dosing (37.7 ng/mL) was lower than that in patients with

Supplemental Material

rheumatoid arthritis of 53.4 ng/mL (21.8% CV). Baricitinib is primarily excreted unchanged in urine, so the lower steady state concentration in atopic dermatitis compared to rheumatoid arthritis likely reflects the better renal function in the atopic dermatitis population.

Supplemental Safety Data

Two additional serious adverse events were reported in baricitinib 2-mg plus TCS patients after treatment discontinuation. One patient reported severe cases of cellulitis, Staphylococcal infection, and an uncontrolled eczema flare 1 week after completion of treatment. The second patient had a severe case of acute bronchitis partly due to an underlying alpha-1 antitrypsin deficiency diagnosis, which was not disclosed at screening. This patient had discontinued study drug shortly before the event.

Supplemental References

1. Schram ME, Spuls PI, Leeflang MM, Lindeboom R, Bos JD, Schmitt J. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference. *Allergy*. 2012;67(1):99-106.