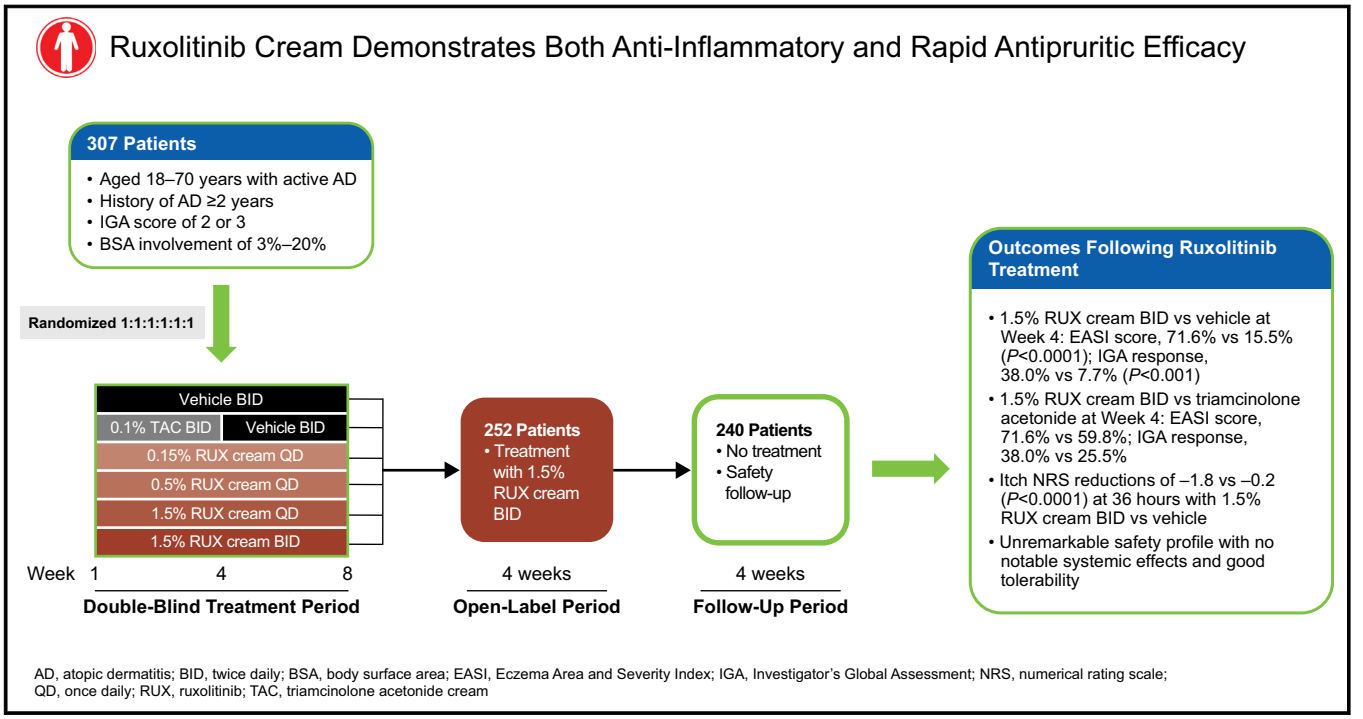
Treatment of atopic dermatitis with ruxolitinib cream (JAK1/JAK2 inhibitor) or triamcinolone cream

Brian S. Kim, MD, MTR,[a] Michael D. Howell, PhD,[b] Kang Sun, PhD,[b] Kim Papp, MD, PhD,[c] Adnan Nasir, MD, PhD,[d] and Michael E. Kuligowski, MD, PhD, MBA,[b] for the INCB 18424-206 Study Investigators

St Louis, Mo; Wilmington, Del; Waterloo, Ontario, Canada; and Raleigh, NC

GRAPHICAL ABSTRACT



AD, atopic dermatitis; BID, twice daily; BSA, body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; NRS, numerical rating scale; QD, once daily; RUX, ruxolitinib; TAC, triamcinolone acetonide cream

Background: Atopic dermatitis (AD) is a highly pruritic chronic inflammatory skin disorder. Ruxolitinib, a selective inhibitor of Janus kinase 1 and Janus kinase 2, potently suppresses cytokine signaling involved in AD pathogenesis.

Objective: We sought to evaluate the efficacy and safety of ruxolitinib (RUX) cream in adults with AD.

Methods: In this phase 2 study (NCT03011892), 307 adult patients with AD, an Investigator's Global Assessment score of 2

From [a]the Washington University School of Medicine, St Louis; [b]Incyte Corporation, Wilmington; [c]K. Papp Clinical Research and Probity Medical Research, Waterloo; and [d]Wake Research Associates LLC, Raleigh.

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Disclosure of potential conflict of interest: B. S. Kim has served as a consultant to AbbVie, Concert Pharmaceuticals, Incyte Corporation, Menlo Therapeutics, and Pfizer; has served on advisory boards for Cara Therapeutics, Celgene Corporation, Kiniksa Pharmaceuticals, Menlo Therapeutics, Regeneron Pharmaceuticals, Sanofi, and Theravance Biopharma; is a shareholder in Locus Biosciences and Nuogen Pharma; has a pending patent with Nuogen Pharma for Janus kinase inhibitors in chronic itch; and is founder and chief scientific officer of Nuogen Pharma. M. D. Howell, K. Sun, and M. E. Kuligowski are employees and shareholders of Incyte Corporation. K. Papp has received honoraria or clinical research grants as a consultant, speaker, scientific officer, advisory board member, and/or Steering Committee member for AbbVie, Akros, Amgen, Anacor, Arcutis, Astellas, Bausch Health/Valeant, Baxalta, Boehringer Ingelheim, Bristol-Myers Squibb, Can-Fite, Celgene, Coherus, Dermira, Dow Pharmaceuticals, Eli Lilly, Galderma, Genentech, Gilead, GlaxoSmithKline, InflaRx, Janssen, Kyowa Hakko Kirin, Leo, Medimmune, Meiji Seika Pharma, Merck (MSD), Merck Serono, Mitsubishi Pharma, Moberg Pharma, Novartis, Pfizer, PRCL Research, Regeneron, Roche, Sanofi-Aventis/Genzyme, Sun Pharmaceuticals, Takeda, and UCB. A. Nasir has served as an investigator for Kiniksa, Escalier Biosciences, Ironwood, Galderma, Affibody, Pfizer, Allergan, Lilly, AbbVie, Dermira, Leo Pharma, Asana, Incyte, Foamix, Cutanea, Biorasi, Sienna, Valeant, Menlo, BMS, Trevi, Aclaris, Gage, Brickell, and INCB.

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Corresponding author: Brian S. Kim, MD, MTR, Department of Medicine, Washington University School of Medicine, 660 South Euclid Ave, Box 8123, St Louis, MO 63110. E-mail: briankim@wustl.edu.

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or 3 (mild or moderate), and 3% to 20% affected body surface area were equally randomized for 8 weeks of double-blind treatment to RUX (1.5% twice daily [BID], 1.5% once daily [QD], 0.5% QD, 0.15% QD), vehicle, or triamcinolone cream (0.1% BID for 4 weeks, then vehicle for 4 weeks). Subsequently, patients could apply 1.5% RUX BID for 4 additional weeks of open-label treatment. The primary end point was the comparison between 1.5% RUX cream BID and vehicle in mean percentage change from baseline in Eczema Area and Severity Index at week 4.

Results: All RUX regimens demonstrated therapeutic benefit at week 4; 1.5% BID provided the greatest improvement in Eczema Area and Severity Index (71.6% vs 15.5%; $P < .0001$) and Investigator's Global Assessment responses (38.0% vs 7.7%; $P < .001$) versus vehicle. Rapid reductions in the itch numerical rating scale score occurred within 36 hours (1.5% BID vs vehicle, −1.8 vs −0.2; $P < .0001$) and were sustained through 12 weeks. Patients who transitioned to 1.5% RUX BID improved in all measures. RUX was not associated with clinically significant application-site reactions.

Conclusions: RUX cream provided rapid and sustained improvements in AD symptoms and was well tolerated. (J Allergy Clin Immunol 2020;145:572-82.)

Key words: *Atopic dermatitis, CCL17, IgE, itch, JAK inhibitor, Janus kinase, ruxolitinib, topical*

Abbreviations used

AD: Atopic dermatitis
AE: Adverse event
BID: Twice daily
EASI: Eczema Area and Severity Index
IGA: Investigator's Global Assessment
JAK: Janus kinase
NRS: Numerical rating scale
QD: Once daily
RUX: Ruxolitinib
TARC/CCL17: Thymus and activation-regulated chemokine/C-C motif chemokine ligand 17
TEAE: Treatment-emergent adverse event

Atopic dermatitis (AD) is a common inflammatory skin disorder with an estimated cost of $5.3 billion annually in the United States.[1] In addition to the dry and exudative skin lesions, pruritus is a key symptom of AD that results in sleep disturbances and profoundly reduced quality of life.[2-5] The Global Burden of Disease project identified AD as one of the most common diseases worldwide, increasing in prevalence, and having the second highest disability rank of all nonmalignant skin diseases.[6] Despite the significant impact of medical, quality of life, and cost of AD on society,[1] treatments remain limited in scope and efficacy.

AD is predominantly associated with a type 2 immune response characterized by the elevated production of the cytokines IL-4, IL-5, IL-13, and IL-31.[7-9] In addition, epithelial cell–derived cytokines, such as IL-25, IL-33, and thymic stromal lymphopoietin, have been shown to directly promote these type 2 cytokine responses by acting on various effector immune cells.[10-14] Moreover, there is increasing support for the contribution of type 3 immune responses associated with the production of IL-17, IL-22, and IL-23 to AD pathogenesis.[15,16] Indeed, AD is a complex condition, and there is emerging evidence that immune profiles vary on the basis of a patient's genetic background.[17] Given the potential heterogeneity of immune pathways that underlie AD, disrupting multiple cytokine networks at once presents a promising strategy for the treatment of AD.

Immune dysregulation in AD is further exacerbated by underlying skin barrier dysfunction.[8,18,19] Thus, the current standard of care includes topical emollients to restore barrier integrity as well as anti-inflammatory agents such as corticosteroids, calcineurin inhibitors, and a recently approved phosphodiesterase 4 inhibitor (crisaborole [currently approved in the United States and Canada]).[20-22] However, depending on the agent, clinical benefit can be limited because of insufficient efficacy, restrictions for use on sensitive skin areas, or side effects, including burning and stinging, thinning of the skin, telangiectasia, and even permanent striae distensae.[20,21] Moreover, topical corticosteroids and calcineurin inhibitors are generally not recommended for long-term use.[20,21] Thus, despite the current availability of topical treatments for AD, there is a clear need for a novel topical agent that is both highly effective and not burdened with the limitations described above.

The Janus kinase (JAK) family and signal transducer and activator of transcription family of transcription factors mediate intracellular signaling for more than 50 cytokines and growth factors.[23] Indeed, receptors for the cytokines associated with AD, including IL-4, IL-5, IL-13, IL-22, IL-23, IL-31, and thymic stromal lymphopoietin, have been implicated in triggering downstream JAK-signal transducer and activator of transcription signaling events.[7,24-26] However, various cytokines demonstrate differential dependence on specific JAKs, namely, JAK1, JAK2, JAK3, and tyrosine kinase-2, for their effect on target cell transcription.[27] Thus, JAK inhibitors provide the opportunity to impair multiple cytokine pathways simultaneously (Fig 1) and are approved for the treatment of several diseases, including rheumatoid arthritis, myelofibrosis, and polycythemia vera.[28] In addition, several JAK inhibitors are currently being evaluated in patients with AD.[27] Beyond disrupting cytokine signaling in immune cells, JAK inhibition was shown recently to alleviate chronic itch driven by type 2 cytokine engagements with their receptors on sensory neurons.[29] In addition, JAK inhibition may improve skin barrier function through the regulation of the skin barrier protein filaggrin.[30] Collectively, these studies support the concept that topical JAK inhibition represents a novel and multifaceted approach to treat AD via epithelial, immune, and neuronal mechanisms of action.

Ruxolitinib (RUX) is a potent, selective inhibitor of JAK1 and JAK2 that, when applied topically, provides the opportunity to directly target diverse pathogenic pathways that underlie AD.[31,32] This phase 2 study (NCT03011892) investigated the efficacy, safety, and tolerability of RUX cream in adults with AD.

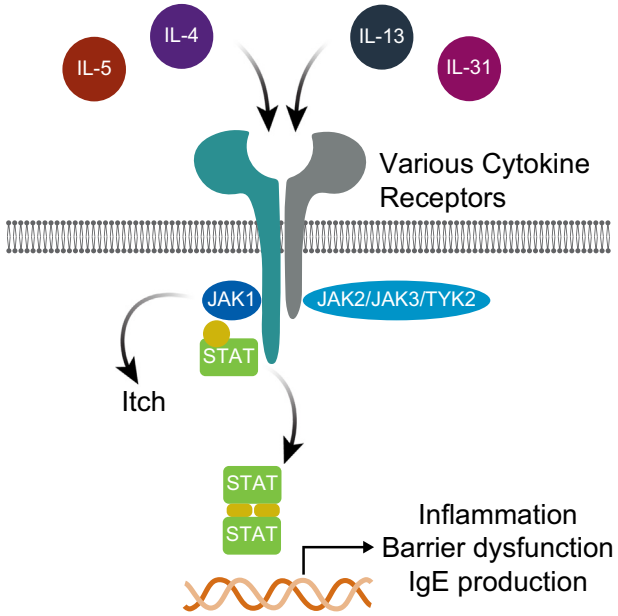

FIG 1. JAK-mediated signaling in AD. *STAT,* Signal transducer and activator of transcription; *TYK2,* Tyrosine kinase 2. Created with BioRender.

METHODS

Study design and treatment

This phase 2, randomized, double-blind, dose-ranging, vehicle- and active-controlled study in adult patients with AD was conducted in the United States and Canada at 52 study sites (ClinicalTrials.gov identifier: NCT03011892). Key inclusion criteria included age 18 to 70 years, active AD with a history of 2 or more years of duration, Investigator's Global Assessment (IGA) score of 2 or 3, and body surface area involvement of 3% to 20%. Key exclusion criteria included presence of active infections, use of topical AD treatments (besides bland emollients) within 2 weeks of baseline, and use of systemic immunosuppressive or immunomodulating agents within 4 weeks or 5 half-lives of baseline (whichever was longer).

Patients were stratified by Eczema Area and Severity Index (EASI) score (≤7 or >7) and equally randomized to vehicle control (cream) twice daily (BID), active control (0.1% triamcinolone cream BID for 4 weeks followed by vehicle for 4 weeks), or RUX cream (0.15% once daily [QD], 0.5% QD, 1.5% QD, or 1.5% BID) for 8 weeks of double-blinded treatment; patients who were randomized to RUX cream QD applied vehicle in the evenings to maintain the blind. All components of RUX cream vehicle are compendial and within the approved (safe) range of concentrations. After the blinded period, patients who were protocol-compliant with no safety concerns could receive an additional 4 weeks of treatment (open-label) with 1.5% RUX cream BID. The use of bland emollients (lacking urea or ceramides) and treatment of facial lesions with 2.5% hydrocortisone cream BID was permitted during the study.

An interactive response technology was used to manage study enrollment, including the randomization and tracking of patients. Patients and personnel at study sites and sponsor were blinded to treatment groups. This study was conducted in accordance with the Declaration of Helsinki, and informed consent was obtained for all patients. The study protocol was approved by each site's institutional review board.

Assessments

The primary end point analysis of this study was mean percentage change from baseline in EASI score at week 4 in patients treated with 1.5% RUX cream BID versus patients treated with vehicle BID.

Key secondary end points included mean percentage change from baseline in EASI score at week 4 in patients treated with various concentrations of RUX cream QD or BID versus patients treated with vehicle BID or 0.1% triamcinolone BID. Additional secondary end points included the proportion of patients achieving an IGA score of 0 to 1 who have an improvement of 2 or more points from baseline (IGA response), mean change from baseline in the itch numerical rating scale (NRS) score, and proportion of patients who achieved EASI-50, -75, and -90. For itch NRS, patients were provided an electronic diary; patients reported their worst level of itch during each 24-hour period from 0 (no itch) to 10 (worst imaginable itch). At week 4, blood samples were collected to assess the bioavailability of RUX. Safety and tolerability were assessed by monitoring the frequency, duration, and severity of adverse events (AEs) throughout the duration of the study. In exploratory analyses, serum levels of IgE and thymus and activation-regulated chemokine (TARC/CCL17) were measured at baseline and week 8. A cutoff of 200 kU/L was selected for IgE on the basis of total serum levels separating allergic and nonallergic forms of AD reported in the literature.[33,34] The median value of TARC/CCL17 (522 pg/mL) was used to separate patients by disease severity.[35]

Statistics

A total of 300 patients were needed for this study to provide a large safety database and adequate power for statistical comparisons in efficacy end points. For the primary and key secondary analyses, comparisons between each RUX cream treatment group and vehicle or active control based on mean percentage change from baseline in EASI were performed for the intent-to-treat population (all randomized patients) with a mixed model with repeated measures. All other secondary and exploratory efficacy measures were evaluated using descriptive statistics. The exploratory analyses of IgE and TARC/CCL17 were described using summary statistics, and differences between vehicle control and each treatment arm were conferred at $P < .05$. Efficacy analyses by baseline total IgE (<200 vs ≥200 kU/L) and TARC/CCL17 (≤522 vs >522 pg/mL) subgroups were performed for percentage changes from baseline in EASI score and determined using mixed-model repeated measures; significance was conferred at $P < .05$.

RESULTS

Patients

Between January 24, 2017, and November 7, 2017, 307 patients were randomized (vehicle, n = 52; triamcinolone, n = 51; 0.15% RUX QD, n = 51; 0.5% RUX QD, n = 51; 1.5% RUX QD, n = 52; 1.5% RUX BID, n = 50) and 260 (84.7%) completed treatment in the double-blind period. Of these 260 patients, 252 applied 1.5% RUX cream BID in the open-label period and 240 completed the open-label treatment (Fig 2). The median age of the intent-to-treat population was 35 years (interquartile range, 25-51 years), and a greater number of participants were women (54.7%; Table I). The mean baseline EASI score was 8.4 ± 4.7, with 31% and 69% of patients presenting with IGA grade 2 and 3, respectively. The mean itch NRS score was 6.0 ± 2.1, and patients experienced a mean of 7 ± 23 flares (median [interquartile range], 3 [1-7]) in the last 12 months. Patients' demographic and baseline clinical characteristics were evenly distributed across all groups (Table I).

Efficacy

Application of all concentrations of RUX cream resulted in statistically significant improvement from baseline in EASI score versus vehicle at each time point (weeks 2, 4, and 8) of the

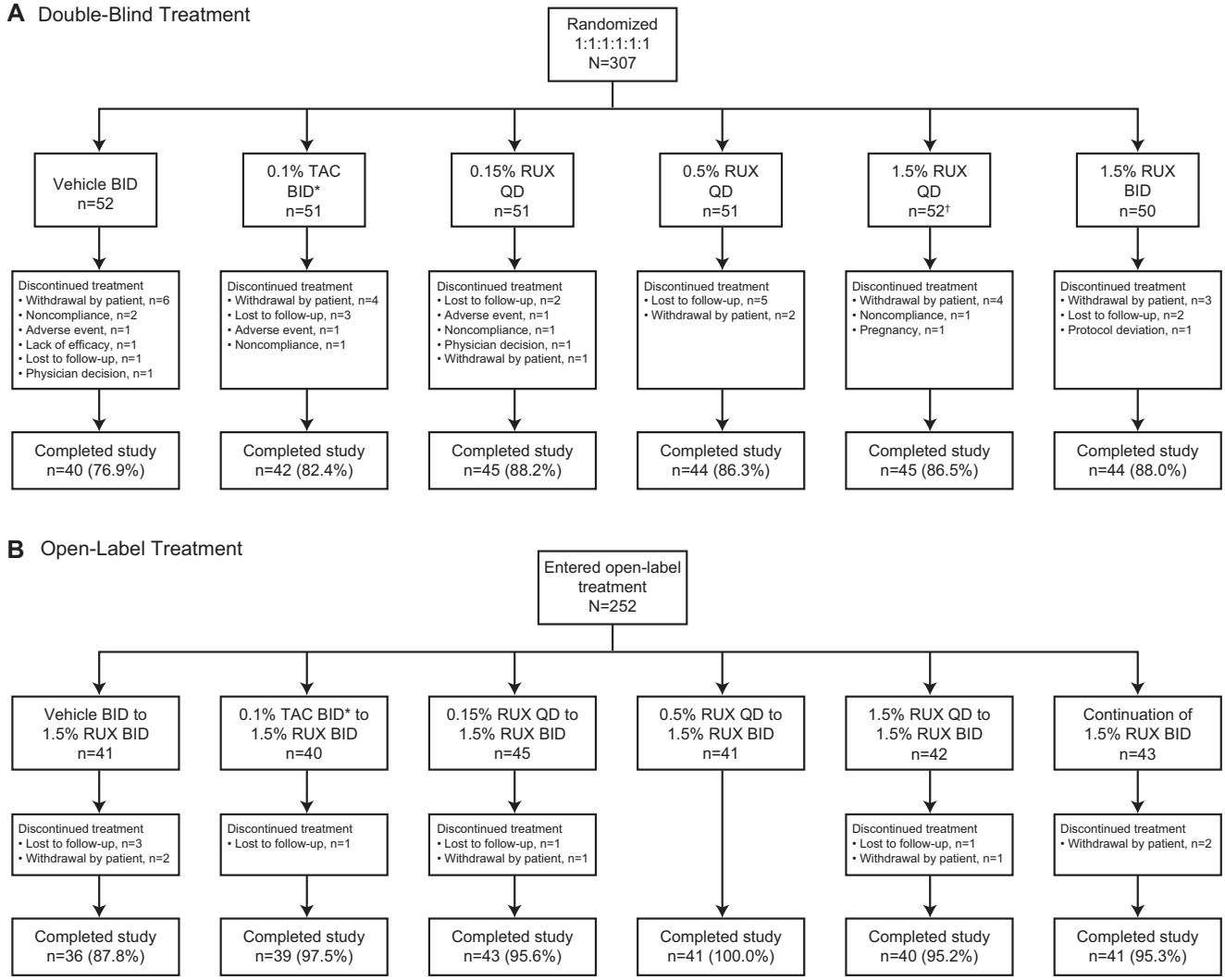

FIG 2. Patient disposition. **A,** Double-blind treatment. **B,** Open-label treatment. *TAC,* Triamcinolone acetonide cream. *The TAC arm received TAC 0.1% cream through week 4 and vehicle thereafter. †One patient did not receive treatment.

double-blind period. RUX cream demonstrated increasing improvement over time and with higher concentrations (Fig 3, *A*); representative clinical images are shown in Fig 3, *B*. For the primary efficacy end point, 1.5% RUX cream BID demonstrated a significantly greater mean percentage change from baseline in EASI scores versus vehicle at week 4 (71.6% vs 15.5%; $P < .0001$; Fig 3, *A*). Although statistical significance was not achieved, both 1.5% RUX groups (QD or BID) reported greater improvement compared with triamcinolone at this time point. In terms of key secondary efficacy end points, significantly more patients who applied 1.5% RUX cream BID achieved EASI-50, -75, and -90 (78.0%, 56.0%, 26.0%) versus vehicle (23.1%, 17.3%, 5.8%) at week 4. Of patients who applied triamcinolone, 66.7%, 47.1%, and 13.7% achieved EASI-50, -75, and -90, respectively, at week 4. Significantly more patients achieved IGA responses with 1.5% RUX cream BID versus vehicle at week 4 (38.0% vs 7.7%; $P < .001$) and week 8 (48.0% vs 9.6%; $P < .001$; Fig 4). A greater proportion of patients reached IGA responses in the 1.5% RUX cream BID group compared with triamcinolone (38.0% vs 25.5%) at week 4, although this was not statistically significant. At week 8, there were significantly more IGA responses with 0.5% RUX cream QD (31.4%; $P < .01$) and 1.5% RUX cream QD (30.8%, $P < .05$) versus vehicle (9.6%). Of note, no comparisons between RUX cream and triamcinolone at week 8 could be made because triamcinolone treatment was stopped at week 4. In terms of itch, significant reductions in itch NRS scores were observed as early as within 36 hours of initiation of treatment (1.5% RUX cream BID vs vehicle, –1.8 vs –0.2; $P < .0001$; Fig 5), and were sustained over the remainder of the 12 weeks of treatment.

Of patients who were initially treated with 1.5% RUX cream BID, 43 continued to open-label treatment for an additional 4 weeks (12 weeks of total treatment). The mean percentage

TABLE I. Patients' demographic and baseline clinical characteristics

Characteristic	Vehicle BID (n = 52)	TAC 0.1% BID (n = 51)	RUX cream 0.15% QD (n = 51)	RUX cream 0.5% QD (n = 51)	RUX cream 1.5% QD (n = 52)	RUX cream 1.5% BID (n = 50)	Total (N = 307)
Age (y), median (range)	31.5 (18.0-69.0)	35.0 (18.0-69.0)	38.0 (18.0-69.0)	37.0 (18.0-70.0)	37.0 (18.0-65.0)	35.5 (18.0-70.0)	35.0 (18.0-70.0)
Female, n (%)	32 (61.5)	28 (54.9)	26 (51.0)	27 (52.9)	31 (59.6)	24 (48.0)	168 (54.7)
Race, n (%)							
White	27 (51.9)	28 (54.9)	27 (52.9)	33 (64.7)	24 (46.2)	33 (66.0)	172 (56.0)
Black	15 (28.8)	13 (25.5)	17 (33.3)	10 (19.6)	17 (32.7)	13 (26.0)	85 (27.7)
Asian	8 (15.4)	8 (15.7)	5 (9.8)	8 (15.7)	10 (19.2)	2 (4.0)	41 (13.4)
Other	2 (3.8)	2 (3.9)	2 (3.9)	0	1 (1.9)	2 (4.0)	9 (2.9)
BSA (%), mean ± SD	9.5 ± 5.0	9.9 ± 5.5	9.2 ± 5.6	8.9 ± 5.1	9.7 ± 6.2	10.5 ± 5.2	9.6 ± 5.4
Facial lesions, n (%)	21 (40.4)	21 (41.2)	19 (37.3)	17 (33.3)	20 (38.5)	18 (36.0)	116 (37.8)
Baseline EASI, mean ± SD	8.6 ± 5.1	8.4 ± 4.7	8.2 ± 4.5	8.5 ± 4.8	8.4 ± 4.7	8.4 ± 4.7	8.4 ± 4.7
≤7, n (%)	24 (46.2)	24 (47.1)	25 (49.0)	24 (47.1)	25 (48.1)	25 (50.0)	147 (47.9)
>7, n (%)	28 (53.8)	27 (52.9)	26 (51.0)	27 (52.9)	26 (50.0)	25 (50.0)	159 (51.8)
Baseline IGA, n (%)*							
2	15 (28.8)	18 (35.3)	16 (31.4)	17 (33.3)	15 (29.4)	14 (28.0)	95 (30.9)
3	36 (69.2)	33 (64.7)	35 (68.6)	34 (66.7)	36 (70.6)	36 (72.0)	210 (68.4)
Itch NRS score,† mean ± SD	6.0 ± 2.1	5.2 ± 2.2	6.1 ± 2.2	6.2 ± 1.7	6.2 ± 2.1	5.9 ± 2.3	6.0 ± 2.1
Duration of disease (y), median (range)	19.5 (2.2-65.3)	24.8 (2.3-62.2)	22.3 (2.3-60.9)	19.8 (2.0-66.1)	20.2 (0.7-56.9)	21.2 (0.1-64.8)	20.8 (0.1-66.1)
No. of flares in last 12 mo, mean ± SD	10.6 ± 20.2	4.7 ± 6.0	4.3 ± 5.4	7.0 ± 8.8	4.4 ± 6.5	12.8 ± 51.7	7.3 ± 23.3

BSA, Body surface area; *TAC*, triamcinolone acetonide cream.
*Excludes 1 patient with an IGA of 4 at baseline.
†Range of NRS, 0-10 (0, no itch; 10, worst imaginable itch).

improvement in EASI score from baseline to week 12 was 84.9%. EASI-50, -75, and -90 at week 12 were achieved by 95.1% (n = 39), 73.2% (n = 30), and 56.1% (n = 23) of patients, respectively. At week 12, 58.5% of patients (n = 24) were IGA responders. Thus, transitioning patients from their initial treatment groups to 1.5% RUX cream BID in the open-label period was associated with additional improvement in EASI scores and IGA response (Fig 6).

For the biomarker analysis, sera were collected from 111 patients across all groups and analysis was conducted on 102 patients with matched baseline and week 8 samples from the vehicle BID (n = 17), triamcinolone BID (n = 18), and RUX cream (0.15% QD [n = 18], 0.5% QD [n = 19], 1.5% QD [n = 13], and 1.5% BID [n = 17]) arms. Baseline TARC/CCL17 levels correlated with baseline EASI scores ($P = .003$; Fig 7, *A*). At week 8, TARC/CCL17 levels were reduced ($P < .01$) in patients treated with 1.5% RUX cream BID versus vehicle (Fig 7, *B*). Total serum IgE levels did not correlate with EASI at baseline; however, these levels were numerically reduced in patients treated with 1.5% RUX cream (QD or BID), but the reduction did not reach statistical significance. No material differences in TARC/CCL17 or IgE were observed with 0.15% QD or 0.5% QD. Stratification of participants by TARC/CCL17 (≤522 vs >522 pg/mL) or total IgE subgroups (<200 vs ≥200 kU/L) did not differentiate the treatment response to RUX cream on adjusted mean change from baseline for EASI.

Safety

RUX cream was well tolerated and not associated with clinically significant application-site reactions (Table II). In the double-blind period, 3 patients discontinued from the study because of treatment-emergent adverse events (TEAEs) not related to treatment (vehicle BID, AD [n = 1]; triamcinolone, uvulitis [n = 1]; 0.15% RUX cream QD, eczema [n = 1]). One patient who applied triamcinolone experienced a serious TEAE (myocardial infarction) unrelated to treatment. All treatment-related AEs were mild or moderate in severity. Application-site pain was the most common treatment-related AE in any RUX cream group (0.15% QD, n = 1 [2.0%]; 1.5% QD, n = 2 [3.9%]; 1.5% BID, n = 1 [2.0%]) and was also reported in patients who applied vehicle (n = 2 [3.8%]). In the open-label period, no patients discontinued from the study because of a TEAE, and no treatment-related AE was reported by more than 1 patient in any treatment group. No clinically significant laboratory changes were observed. A small (~10%) and temporary increase in platelet counts was noted with a peak at 2 weeks of treatment with 1.5% RUX cream (QD and BID). RUX systemic exposure was low and corresponded to approximately 4% to 5% of the topical dose applied. Overall, RUX cream was well tolerated and did not demonstrate any additional safety concerns in the treatment arms versus vehicle.

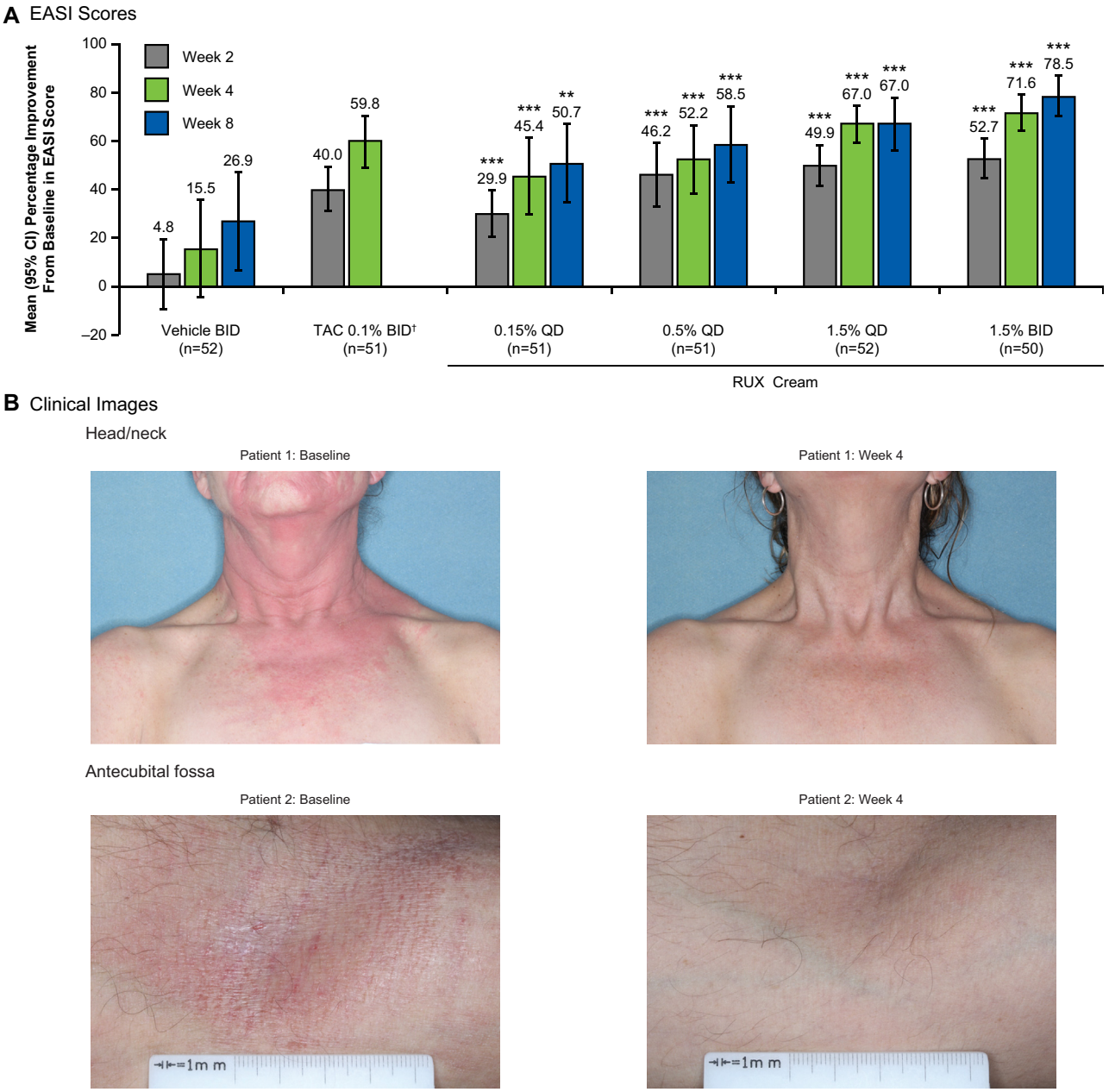

FIG 3. EASI scores (percentage improvement from baseline) in the double-blind period **(A)** and representative clinical images at baseline and week 4 on treatment with 1.5% RUX cream **(B)**. *TAC,* Triamcinolone acetonide cream. ***$P < .001$ vs vehicle. **$P < .01$ vs vehicle. †The TAC arm received TAC 0.1% cream through week 4 and vehicle thereafter.

DISCUSSION

In this study, all concentrations of RUX cream achieved rapid and sustained improvement in the signs and symptoms of AD versus vehicle. The primary end point was reached; application of 1.5% RUX cream BID significantly improved the mean percentage change from baseline in EASI score versus vehicle at week 4 (71.6% vs 15.5%; $P < .0001$). Notably, marked and lasting improvement in itch NRS was achieved with all treatment regimens; for 1.5% RUX cream BID, significant improvement in itch was observed within 36 hours of treatment. Improvements were consistent across all efficacy end points, including EASI-90 and IGA response. In general, RUX cream demonstrated increased improvement in EASI score, IGA response, and itch over time and with increasing strengths of the drug. RUX cream was well tolerated with no serious TEAEs reported.

Triamcinolone was selected as an active control because it is a midpotency corticosteroid that is often used as a first-line agent to treat AD.[36,37] The efficacy of triamcinolone was confirmed in this patient population and served as a

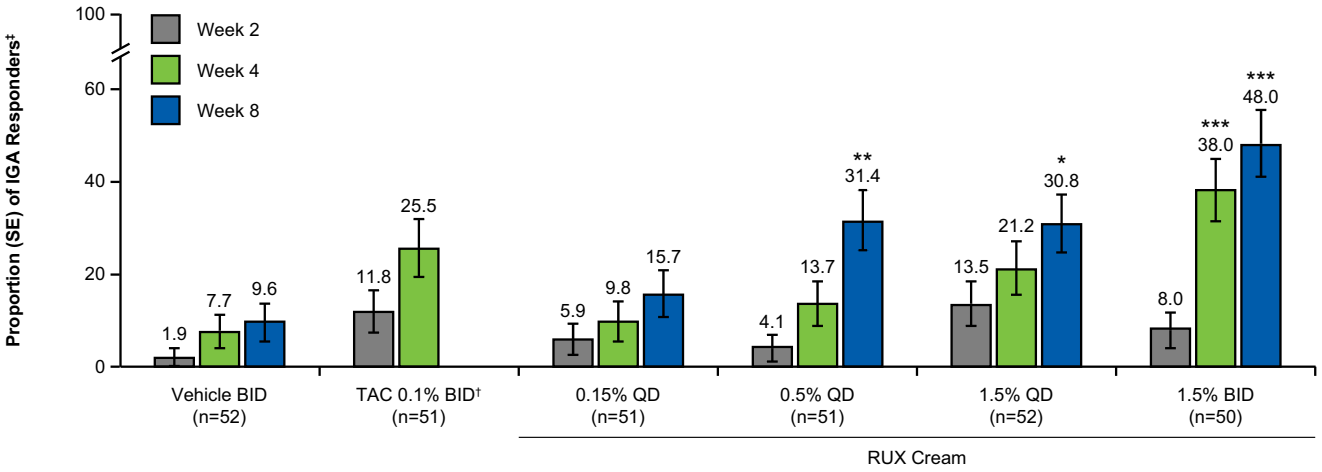

FIG 4. IGA response in the double-blind period. *TAC,* Triamcinolone acetonide cream. ***$P < .001$ vs vehicle. **$P < .01$ vs vehicle. *$P < .05$ vs vehicle. †The TAC arm received TAC 0.1% cream through week 4 and vehicle thereafter. ‡Defined as a patient achieving an IGA score of 0 to 1, with an improvement of 2 or more points from baseline. Patients who discontinued treatment were included as nonresponders.

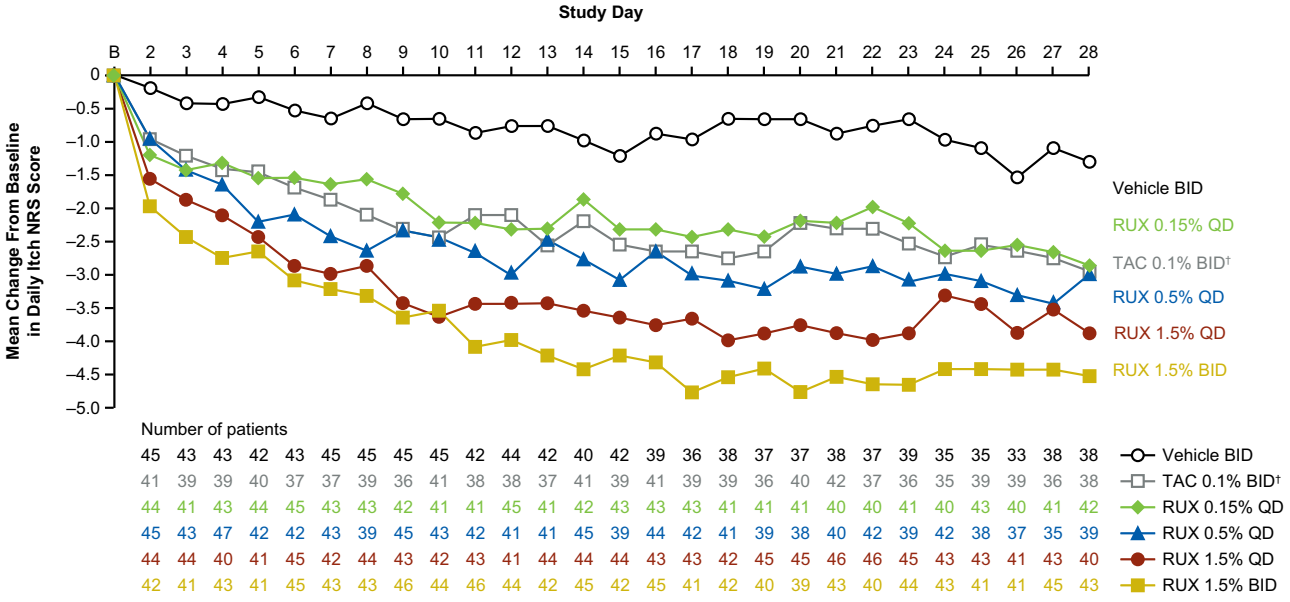

FIG 5. Itch NRS (mean change from baseline in daily score*) in the double-blind period. *B,* Baseline; *TAC,* triamcinolone acetonide cream. *Itch NRS scores (mean ± SD) at baseline were as follows: vehicle, 6.0 ± 2.1; TAC 0.1%, 5.2 ± 2.2; 0.15% RUX QD, 6.1 ± 2.2; 0.5% RUX QD, 6.2 ± 1.7; 1.5% RUX QD, 6.2 ± 2.1; 1.5% RUX BID, 5.9 ± 2.3. †The TAC arm received 0.1% cream through week 4 and vehicle thereafter.

benchmarking point of comparison. In the current study, triamcinolone was used as indicated (on-label) and thus not used beyond week 4.

Patients enrolled in this study presented with various degrees of disease severity (as defined by EASI and IGA scores, as well as body surface area). All active RUX cream treatment regimens brought about significant improvements over baseline and versus vehicle, irrespective of the baseline disease severity. Thus, our study suggests that the efficacy of RUX cream is not limited to specific subgroups as defined by baseline disease severity. Accordingly, RUX cream is expected to represent a broadly efficacious topical agent for a wide spectrum of patients with AD typically managed with topical therapy. Treatments with topical corticosteroids or calcineurin inhibitors may be associated with

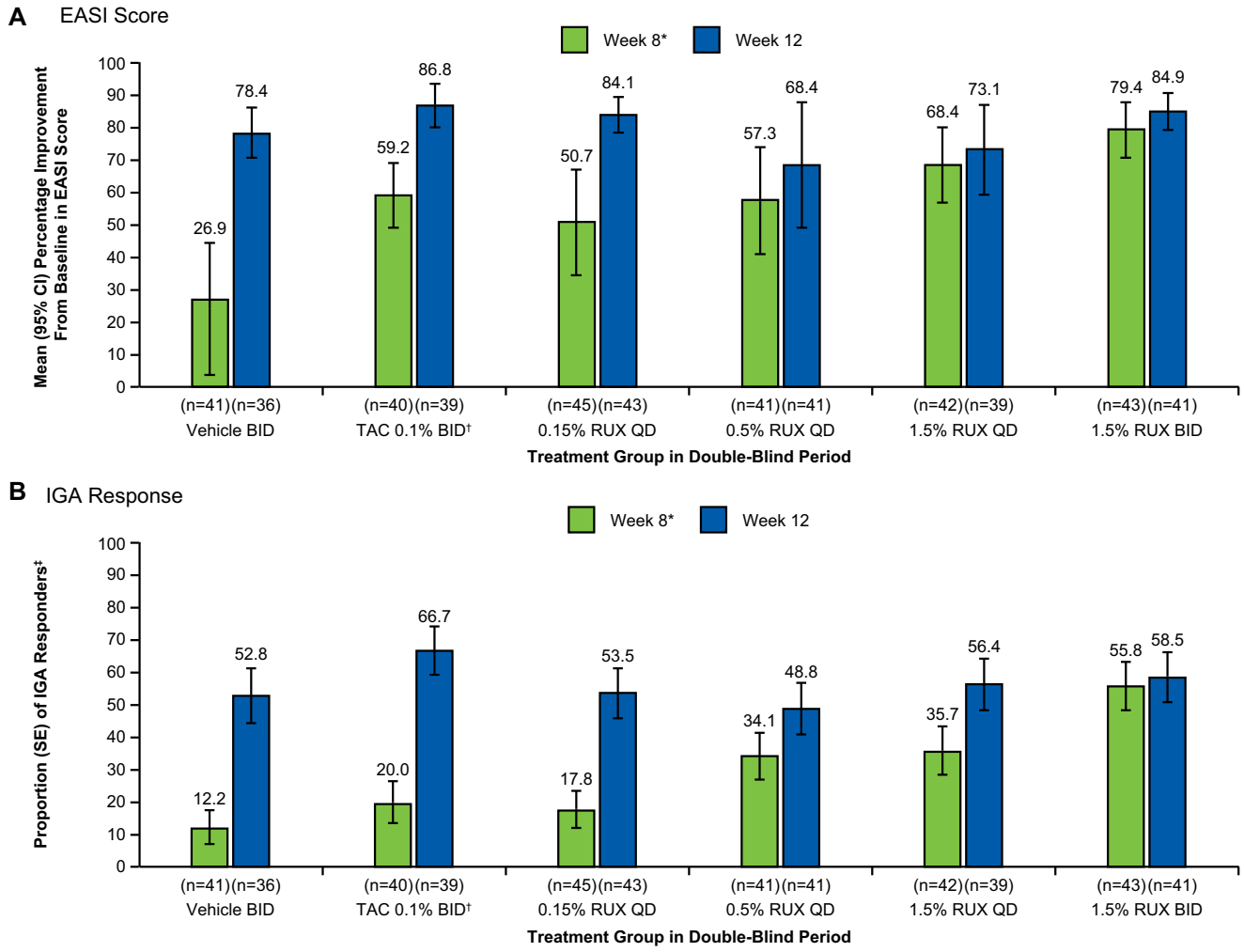

FIG 6. Improvement in EASI score (**A**) and IGA response (**B**) in patients who applied 1.5% RUX cream BID in the open-label period. *TAC,* Triamcinolone acetonide cream. *Patients switched to 1.5% RUX cream BID after week 8. †The TAC arm received TAC 0.1% cream through week 4 and vehicle through week 8. ‡Defined as a patient achieving an IGA score of 0 to 1 with an improvement of 2 or more points from baseline.

limited efficacy, concerns for safety, and/or application-site tolerability issues and are therefore not recommended for long-term use.[20,21] Thus, there is a significant unmet need for the treatment of patients with AD with a topical agent that has an optimal combination of favorable efficacy, safety, and tolerability.

Baseline mean itch severity was 6.0 ± 2.1. Patients were equally distributed both above and below an EASI score of 7. For the 1.5% RUX cream BID regimen, the improvement in itch severity was both significant and clinically meaningful. Furthermore, prompt improvement in itch was observed within 36 hours, consistent with recent studies indicating that JAK inhibitors may have direct antipruritic properties.[29,38,39]

Apart from the high level of efficacy seen with 1.5% RUX cream BID, serum levels of TARC/CCL17, a biomarker of disease severity,[40] were significantly reduced after 8 weeks of treatment. Given the low systemic bioavailability of RUX observed in this study, it is unlikely that this reduction is due to the systemic effect of RUX cream. These data suggest that 1.5% RUX cream improves the course of the disease through local effects on skin inflammation, which subsequently results in a reduction of systemic biomarkers.

In terms of safety, no serious TEAEs were observed in patients treated with RUX cream; the frequency and severity of TEAEs were comparable with those with vehicle. RUX cream was well tolerated (ie, not associated with any significant application-site reactions). Other agents, such as topical calcineurin inhibitors and phosphodiesterase 4 inhibitors, are well known to cause a burning/stinging sensation upon application. Although RUX cream was not applied to the face in this study, it was equally well tolerated in typical areas of AD skin lesions, as well as more sensitive skin areas, such as creases and folds. Thus,

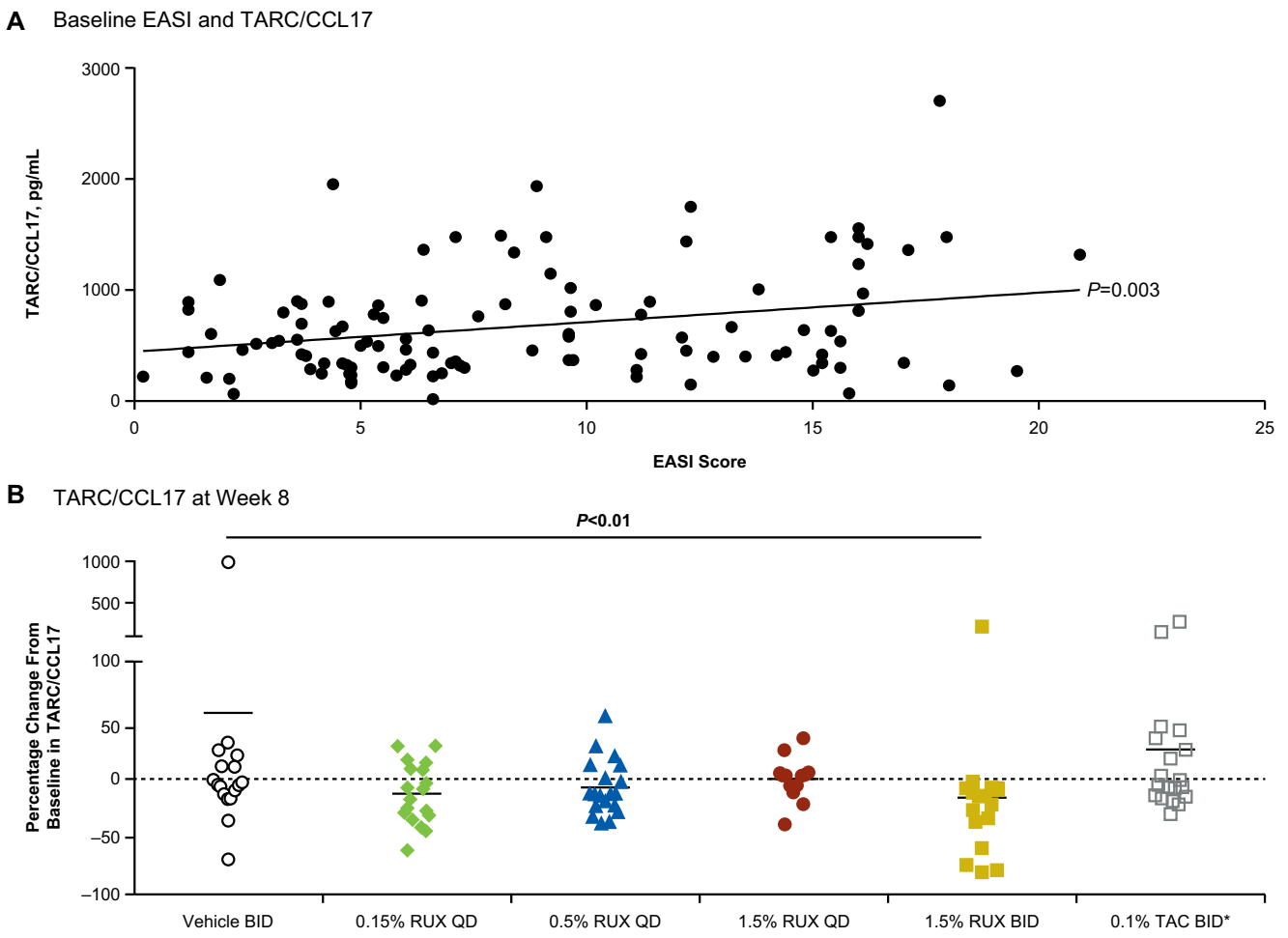

FIG 7. Correlation of TARC/CCL17 with EASI and percentage change from baseline at week 8. **A,** Correlation between baseline EASI score and baseline concentrations of TARC/CCL17 in patients who had paired baseline and week 8 samples (n = 102). Significance (P = .003) was determined using Pearson correlation coefficient (r = 0.28). **B,** Percentage change in circulating TARC/CCL17 levels from baseline to week 8. Statistical significance in the percentage change from baseline was determined by comparing each treatment group with the patients receiving vehicle using a nonparametric Mann-Whitney test. *TAC,* Triamcinolone acetonide cream. *The TAC arm received 0.1% cream through week 4 and vehicle thereafter.

RUX cream is unlikely to be associated with tolerability issues in the skin.

Improved efficacy versus placebo for oral JAK inhibitors in the treatment of AD has been reported[41-43]; however, as systemic agents, oral JAK inhibitors may be associated with additional safety concerns.[28] The results of our study provide evidence for the efficacy, safety, and good tolerability of topical JAK inhibition in the treatment of AD. There are several JAK inhibitors in development for the treatment of AD,[27] including topical formulations such as tofacitinib[38] (a JAK1/JAK3 inhibitor) and delgocitinib[39] (a pan JAK inhibitor), that have also demonstrated efficacy in the treatment of AD. However, this is the first study focusing on a selective topical JAK1/JAK2 inhibitor in patients with AD that includes a head-to-head comparison with a midpotency corticosteroid (0.1% triamcinolone). Given the concerns of limited efficacy, side effects, application-site reactions, and inability for prolonged use of the other currently available topical agents, RUX cream represents a novel therapeutic strategy in AD with a dual mechanism of action: anti-inflammatory and antipruritic.

Confirmation of these findings is needed in a larger patient population. Regarding study limitations, treatment of facial dermatitis with the study medication was not permitted in this study because of the restrictions on the use of triamcinolone on the face.

In conclusion, RUX cream provided rapid and sustained relief in signs of AD and itch with no notable safety findings. These data show that RUX cream may offer a novel and effective topical treatment for patients with AD.

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TABLE II. Study duration and TEAEs

Double-blind period	Vehicle BID (n = 52)	TAC 0.1% BID (n = 51)	RUX cream 0.15% QD (n = 51)	RUX cream 0.5% QD (n = 51)	RUX cream 1.5% QD (n = 51)	RUX cream 1.5% BID (n = 50)
Days in study, median (range)	56.0 (4.0-71.0)	56.0 (16.0-74.0)	56.0 (9.0-83.0)	56.0 (1.0-65.0)	56.0 (29.0-69.0)	56.0 (11.0-67.0)
Patients with TEAE, n (%)	17 (32.7)	17 (33.3)	19 (37.3)	11 (21.6)	17 (33.3)	12 (24.0)
Most common TEAEs, n (%)*						
Nasopharyngitis	4 (7.7)	0	3 (5.9)	1 (2.0)	4 (7.8)	2 (4.0)
AD	4 (7.7)	2 (3.9)	1 (2.0)	0	2 (3.9)	0
Upper respiratory tract infection	3 (5.8)	1 (2.0)	2 (3.9)	1 (2.0)	1 (2.0)	1 (2.0)
Application-site pain	2 (3.8)	0	1 (2.0)	0	2 (3.9)	1 (2.0)
Headache	2 (3.8)	0	1 (2.0)	1 (2.0)	0	2 (4.0)
Urinary tract infection	2 (3.8)	1 (2.0)	0	0	1 (2.0)	0
Treatment-related TEAE, n (%)	5 (9.6)	1 (2.0)	2 (3.9)	1 (2.0)	5 (9.8)	3 (6.0)
Most common treatment-related TEAEs, n (%)*						
Application-site pain	2 (3.8)	0	1 (2.0)	0	2 (3.9)	1 (2.0)
Discontinuation because of a TEAE, n (%)†	1 (1.9)	1 (2.0)	1 (2.0)	0	0	0
Serious TEAE, n (%)‡	0	1 (2.0)	0	0	0	0

Open-label period	Vehicle BID to 1.5% RUX BID (n = 41)	TAC 0.1% BID to 1.5% RUX BID (n = 40)	0.15% QD to 1.5% BID (n = 45)	0.5% QD to 1.5% BID (n = 41)	1.5% QD to 1.5% BID (n = 42)	Continued on 1.5% BID (n = 43)
Days in study, median (range)	28.0 (0-66.0)	28.0 (12.0-38.0)	29.0 (10.0-51.0)	28.0 (13.0-40.0)	28.0 (20.0-36.0)	84.0 (50.0-106.0)
Patients with TEAE, n (%)	5 (12.2)	11 (27.5)	11 (24.2)	8 (19.5)	11 (26.2)	17 (39.5)
Most common TEAEs, n (%)*						
Nasopharyngitis	1 (2.4)	1 (2.5)	4 (8.9)	1 (2.4)	2 (4.8)	4 (9.3)
Upper respiratory tract infection	1 (2.4)	2 (5.0)	0	1 (2.4)	2 (4.8)	1 (2.3)
AD	1 (2.4)	1 (2.5)	0	0	1 (2.4)	1 (2.3)
Headache	0	0	1 (2.2)	1 (2.4)	0	2 (4.7)
Treatment-related TEAE, n (%)	0	0	0	1 (2.4)	1 (2.4)	2 (4.7)
Discontinuation because of a TEAE, n (%)†	0	0	0	0	0	0
Serious TEAE, n (%)‡	0	0	0	0	0	0

TAC, Triamcinolone acetonide cream.
*Occurring in >1% of the total patient population.
†No AEs that resulted in discontinuation were related to treatment.
‡Unrelated to study drug.

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Clinical implications: Ruxolitinib cream significantly reduced signs of atopic dermatitis throughout the study and rapidly decreased itch. These data support possible addition of ruxolitinib cream to the topical armamentarium for atopic dermatitis.

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