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Kim, Brian S; Sun, Kang; Papp, Kim; Venturanza, May; Nasir, Adnan; and Kuligowski, Michael E., "Effects of ruxolitinib cream on pruritus and quality of life in atopic dermatitis: Results from a phase 2, randomized, dose-ranging, vehicle- and active-controlled study." *Journal of the American Academy of Dermatology*. 82, 6. 1305 - 1313. (2020).

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Effects of ruxolitinib cream on pruritus and quality of life in atopic dermatitis: Results from a phase 2, randomized, dose-ranging, vehicle- and active-controlled study



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St Louis, Missouri; Wilmington, Delaware; Waterloo, Ontario, Canada; and Raleigh, North Carolina

Background: Atopic dermatitis (AD), a chronic, highly pruritic skin disorder, impairs quality of life (QoL). Janus kinase inhibitors suppress inflammatory and pruritus-associated cytokine signaling in AD.

Objective: To report the effects of ruxolitinib (RUX) cream on itch and QoL in AD.

Methods: A total of 307 adult patients with an Investigator's Global Assessment (score of 2 or 3) and 3% to 20% affected body surface area were randomly assigned for 8 weeks to receive double-blind treatment with RUX (1.5% twice daily, 1.5% once daily, 0.5% once daily, or 0.15% once daily), vehicle twice daily, or triamcinolone cream (0.1% twice daily for 4 weeks then vehicle for 4 weeks). Itch was measured by using the numerical rating scale, and patient QoL was assessed with Skindex-16.

Results: Improvements in itch numerical rating scale and Skindex-16 were observed with RUX cream. Overall, 42.5% of patients who applied 1.5% RUX twice daily experienced minimal clinically important difference in itch within 36 hours of treatment (vehicle, 13.6%; $P < .01$); near-maximal improvement was observed by week 4. Itch reduction was associated with improved QoL burden (Pearson correlation, 0.67; $P < .001$). Significant improvements in Skindex-16 overall scores were noted at week 2.

Limitations: Facial AD lesions were not treated.

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Funding sources: Supported by Incyte Corporation.

Disclosure: Dr Kim has served as a consultant to AbbVie, Cara Therapeutics, 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 JAK inhibitors in chronic itch; and is founder and chief scientific officer of Nuogen Pharma. Dr Papp has received honoraria or clinical research grant 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. Dr 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, Bristol-Myers Squibb, Trevi, Aclaris, Gage, and Brickell. Drs Sun, Venturanza, and Kuligowski are employees and shareholders of Incyte Corporation.

Presented at the American Academy of Dermatology meeting, Washington, DC, March 1-5, 2019, and the Revolutionizing Atopic Dermatitis meeting, Chicago, IL, April 6-7, 2019.

IRB approval status: Reviewed and approved by each site's institutional review board.

Accepted for publication February 3, 2020.

Reprints not available from the authors.

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Published online February 11, 2020.

0190-9622

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<https://doi.org/10.1016/j.jaad.2020.02.009>

Conclusion: RUX cream provides a clinically meaningful reduction in itch and QoL burden. (J Am Acad Dermatol 2020;82:1305-13.)

Key words: atopic dermatitis; burden of disease; itch; JAK inhibitor; Janus kinase; pruritus; quality of life; ruxolitinib; Skindex-16.

Atopic dermatitis (AD) is a common, chronic, and relapsing inflammatory skin disease in which itch has a substantial and negative impact on the quality of life (QoL) of both patients and their caregivers.¹⁻⁴ QoL burden in AD is similar to that of other chronic diseases, such as psoriasis and asthma, even in patients with mild to moderate disease.⁵⁻⁹ In fact, itch has been reported as the central and most burdensome symptom of AD.³ Many patients experience bursts of intense itch, which directly interfere with activities of daily living.^{2,10} Nighttime itch disrupts sleep, resulting in fatigue, daytime sleepiness, and insomnia.¹¹ Moreover, AD is associated with a variety of negative effects on vitality, social functioning, and mental functioning.⁹ Despite our increasing understanding of itch in AD, treatments for AD have not been primarily focused on treating the associated pruritus.

Currently, the management of AD includes topical treatments such as emollients, corticosteroids, calcineurin inhibitors, and a recently approved phosphodiesterase 4 inhibitor (crisaborole) that are designed to restore skin barrier function and/or suppress inflammation.^{12,13} However, current topical therapies may be limited by local tolerability issues, restrictions for use on sensitive skin areas, and/or insufficient efficacy. In addition, topical corticosteroids and calcineurin inhibitors are not approved for long-term use, although calcineurin inhibitors have been used in so-called proactive treatment regimens to provide more effective, longer-term disease control and to decrease topical corticosteroid use.^{12,13} Furthermore, many current topical agents do not appear to have direct anti-itch properties.¹² Thus, there is a need for the development of novel topical therapies for AD that are tolerable, are amenable to long-term use, and show rapid and sustained improvement in itch and associated QoL.

Increased expression of epithelial cell–derived and type 2 cytokines in the skin of patients with AD

drive disease pathogenesis.^{14,15} The expressions of key skin barrier proteins are impeded by inflammatory cytokines, which may further augment allergic sensitization and responses, impair protective innate immune responses, and trigger scratching, thereby damaging the skin and perpetuating the itch-scratch cycle.^{14,16-19} Janus kinases (JAKs) mediate type 2 and other cytokine

signaling involved in the pathogenesis of AD.^{20,21} In addition, JAK inhibition also occurs directly on sensory neurons²² and may also improve skin barrier function.²³ Thus, JAK inhibitors are uniquely suited for the treatment of AD through their beneficial effect on inflammation and restoration of the epithelial barrier.²⁰

Ruxolitinib (RUX), a potent, selective inhibitor of JAK1 and JAK2, has a low molecular weight and is amenable to formulation in water-containing vehicles.²⁴ Previously, we showed that RUX cream provides dose-dependent efficacy in patients with AD and was not associated with clinically significant application site reactions or notable adverse events.²⁵ Here, we report the effects of RUX cream on pruritus and QoL from a phase 2 study in patients with AD.

METHODS

Study design and treatment

This phase 2 study was conducted in the United States and Canada at 52 study sites ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03011892) identifier NCT03011892). Patients were stratified by Eczema Area and Severity Index score (≤ 7 or > 7) and equally randomly assigned for 8 weeks of double-blind treatment with vehicle control (cream) twice daily, 0.1% triamcinolone acetonide cream twice daily (active control; 4 weeks followed by 4 weeks of vehicle), or RUX cream (1.5% twice daily, 1.5% once daily, 0.5% once daily, or 0.15% once daily); vehicle was applied in the evenings for patients randomly assigned to receive RUX cream

CAPSULE SUMMARY

- Ruxolitinib cream showed significant improvements in Eczema Area and Severity Index and Investigator's Global Assessment scores with rapid and sustained improvement in itch.
- Rapid and clinically meaningful decrease in itch with ruxolitinib cream correlates with improved quality of life.

Abbreviations used:

AD:	atopic dermatitis
CRI:	clinically relevant improvement
JAK:	Janus kinase
MCID:	minimal clinically important difference
NRS:	numerical rating scale
QoL:	quality of life
RUX:	ruxolitinib

once daily to maintain blinding. After the blinded period, patients with no safety concerns who were compliant with the protocol could receive 4 weeks of open-label treatment with 1.5% RUX cream twice daily. Use of bland emollients and non-sedating antihistamines was permitted during the study. Treatment of the face with 2.5% hydrocortisone cream was permitted.

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

Patients

Key inclusion criteria included being aged 18 to 70 years with active AD and a history of AD of at least 2 years, having an Investigator's Global Assessment score of 2 or 3, and having body surface area involvement of 3% to 20%. Active infections, use of systemic immunosuppressive or immunomodulating drugs within 4 weeks or 5 half-lives of baseline (whichever was longer), and use of topical AD treatments (besides bland emollients) within 2 weeks of baseline were key exclusion criteria.

Assessments

The mean change from baseline in itch numerical rating scale (NRS) score was a secondary endpoint of the study. Itch NRS score was assessed daily by patients and recorded in an electronic diary. The itch NRS score is a single-question assessment tool with a scale of 0 (no itch) to 10 (worst imaginable itch).²⁶ Patients reported their worst level of itch (not average itch) during each 24-hour period. Clinically relevant improvement (CRI) in itch NRS was defined as a 4-point or greater reduction versus baseline. The minimal clinically important difference (MCID) in itch NRS was defined as a 2- to 3-point reduction versus baseline²⁷ (eg, in this study, this was defined as a 2-point or greater reduction). Change from

baseline in Skindex-16 was an exploratory endpoint of the study to assess patient QoL. Patients answered questions regarding the effect of various AD symptoms during the past week on a scale of 0 (never bothered) to 6 (always bothered). Patients were assessed at baseline and weeks 2, 4, 8, 10, and 12.

Statistics

To provide an adequate safety database and power for statistical comparisons in efficacy endpoints, 300 patients were needed for this study. Itch and QoL measures were evaluated with descriptive statistics. Cumulative incidence plots were created for the time to first itch response from baseline for each treatment group. A log-rank test was used for between-group comparisons.

RESULTS

Patients

Between January 24, 2017, and November 7, 2017, 307 patients were randomly assigned (vehicle, n = 52; triamcinolone, n = 51; 0.15% RUX once daily, n = 51; 0.5% RUX once daily, n = 51; 1.5% RUX once daily, n = 52; 1.5% RUX twice daily, n = 50) for treatment in the double-blind period; 260 (84.7%) patients completed double-blind treatment. The median age was 35 years (interquartile range, 25-51); 54.7% of patients were women. The mean \pm standard deviation itch NRS score was 6.0 ± 2.1 , and mean \pm standard deviation Skindex-16 overall score was 3.7 ± 1.3 at baseline. Patient demographics and baseline clinical characteristics were similar across treatment groups (Table 1).

Pruritus outcomes

Randomized double-blind period. Compared with vehicle, significant reductions in itch NRS scores were observed within 36 hours after first application of 1.5% RUX cream twice daily (-1.8 vs -0.2 ; $P < .0001$). Decreases in itch NRS scores noted within the first 2 weeks of treatment for all RUX cream regimens were sustained through the double-blind period. At week 4, both 1.5% RUX cream regimens produced a more pronounced alleviation in itch (mean percent change from baseline, -64.6 for 1.5% twice daily and -54.0 for 1.5% once daily) compared with triamcinolone (-50.3); the difference was statistically significant for 1.5% RUX twice daily versus triamcinolone by mean change from baseline (-4.0 vs -2.5 , respectively; $P = .003$). Improvements from baseline in itch NRS scores were treatment-regimen dependent, with 68.5% mean improvement in patients treated with 1.5% RUX cream twice daily at week 8,

Table I. Patient demographics and baseline clinical characteristics

Characteristics	Vehicle BID (n = 52)	0.1% TAC BID (n = 51)	RUX cream				Total (N = 307)
			0.15% QD (n = 51)	0.5% QD (n = 51)	1.5% QD (n = 52)	1.5% BID (n = 50)	
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)
Women, 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
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
Categorical itch NRS score, n (%)							
None	1 (1.9)	0	0	0	0	0	1 (0.3)
Mild	6 (11.5)	10 (19.6)	6 (11.8)	3 (5.9)	5 (9.6)	7 (14.0)	37 (12.1)
Moderate	18 (34.6)	20 (39.2)	20 (39.2)	22 (43.1)	18 (34.6)	19 (38.0)	117 (38.1)
Severe	23 (44.2)	14 (27.5)	20 (39.2)	23 (45.1)	25 (48.1)	21 (42.0)	126 (41.0)
Missing	4 (7.7)	7 (13.7)	5 (9.8)	3 (5.9)	4 (7.7)	3 (6.0)	26 (8.5)
Skindex-16 scores [†]							
Overall, mean ± SD	3.7 ± 1.2	3.6 ± 1.4	3.8 ± 1.5	3.5 ± 1.4	3.8 ± 1.3	3.9 ± 1.3	3.7 ± 1.3
Symptom subscale, mean ± SD	3.7 ± 1.3	3.5 ± 1.5	4.1 ± 1.4	3.8 ± 1.4	4.1 ± 1.2	3.7 ± 1.4	3.8 ± 1.4
Emotional subscale, mean ± SD	4.3 ± 1.3	4.4 ± 1.4	4.2 ± 1.6	4.0 ± 1.4	4.4 ± 1.4	4.5 ± 1.3	4.3 ± 1.4
Functional subscale, mean ± SD	2.7 ± 1.6	2.5 ± 2.0	2.9 ± 1.9	2.5 ± 1.8	2.6 ± 1.9	3.1 ± 1.7	2.7 ± 1.8

BID, Twice daily; BSA, body surface area; NRS, numerical rating scale; QD, once daily; RUX, ruxolitinib; SD, standard deviation; TAC, triamcinolone acetonide cream.

*Range of NRS, 0-10 (0, no itch; 10, worst imaginable itch).

[†]Range of Skindex-16, 0-6 (0, never bothered; 6, always bothered).

which was significantly better than vehicle (17.6%; $P < .0001$). In patients eligible for CRI analysis (baseline itch NRS of ≥ 4 ; $n = 232$), a higher proportion of patients using RUX cream achieved a CRI response after just a single day of therapy than those using vehicle (day 2 response rates for 1.5% RUX cream twice daily vs vehicle, 10.5% vs 2.9%; $P = .22$); day 4 response rates for 1.5% RUX cream twice daily and vehicle were 26.3% and 2.9%, respectively ($P < .05$). At week 2, significantly more patients achieved CRI with 1.5% RUX cream twice daily (47.5%; $P < .001$), 1.5% RUX once daily (32.4%; $P < .01$), and 0.5% RUX once daily (25.0%; $P < .05$) versus vehicle (5.4%) (Fig 1). Response rates observed with 1.5% RUX cream twice daily at week 2 were also significantly higher compared with triamcinolone (19.4%; $P < .05$). Cumulative incidence rates for time to first CRI response were substantially higher in all RUX cream groups (log-rank $P < .001$) versus vehicle. Shorter median time

to first response was noted in 1.5% RUX cream twice daily and once-daily treatment groups (8 and 12.5 days, respectively) versus vehicle (response not reached). Similarly, among patients eligible for MCID analysis (baseline itch NRS of ≥ 2 ; $n = 272$), higher rates of MCID were observed as early as day 2 (within 36 hours of treatment initiation) with 1.5% RUX cream twice daily (42.5%; $P < .01$) and once daily (37.2%; $P < .05$) versus vehicle (13.6%); significantly higher rates of MCID were also observed for 1.5% RUX cream twice daily compared with triamcinolone at day 2 (20.5%; $P < .05$).

Open-label treatment with 1.5% RUX cream twice daily. A total of 252 patients applied 1.5% RUX cream twice daily in the open-label period. For patients who were initially randomly assigned to 1.5% RUX cream twice daily and continued in the open-label period ($n = 43$), improvement in itch from the double-blind period was sustained (76.1% mean

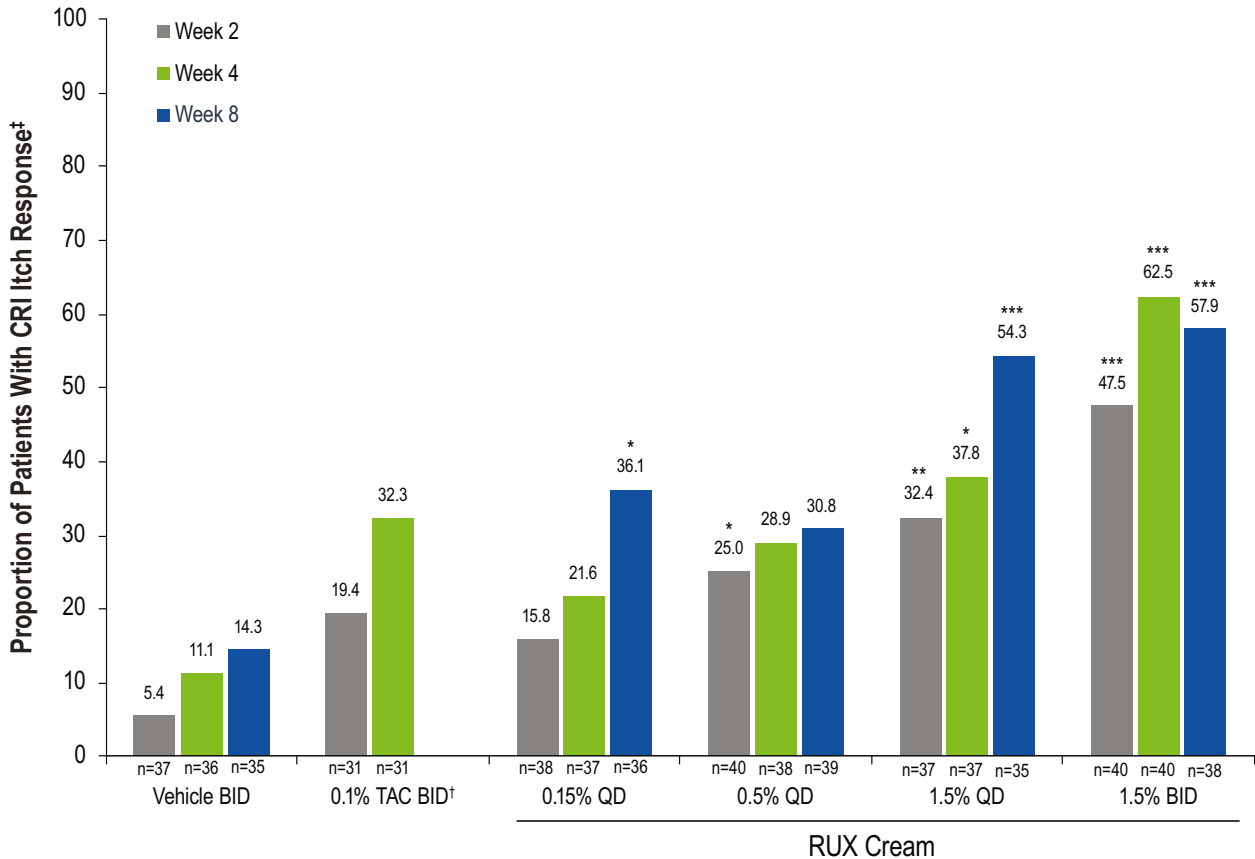


Fig 1. Itch CRI responders in the double-blind period. * $P < .05$ versus vehicle; ** $P < .01$ versus vehicle; *** $P < .001$ versus vehicle; †The TAC arm received 0.1% TAC cream through week 4 and vehicle thereafter. ‡CRI itch response was defined as a 4-point or greater reduction in itch NRS versus baseline. *BID*, Twice daily; *CRI*, clinically relevant improvement; *NRS*, numerical rating scale; *QD*, once daily; *RUX*, ruxolitinib; *TAC*, triamcinolone acetonide cream.

improvement from baseline at week 12). Patients who transitioned from their randomized groups to 1.5% RUX cream twice daily showed further reduction in itch NRS (Fig 2).

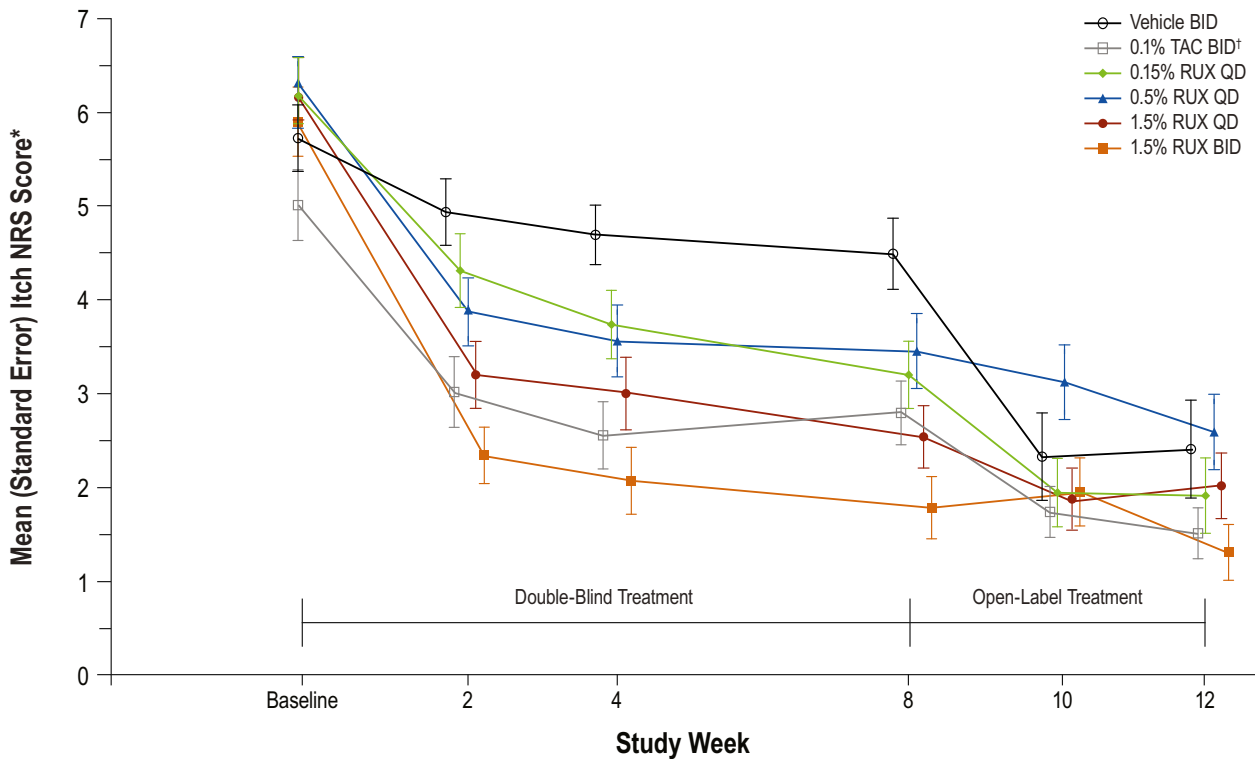
QoL outcomes

Representative visual improvement in AD lesions after 4 weeks of treatment with RUX cream is shown in Fig 3. Significant improvements in QoL were noted for all RUX cream regimens. The improvements were treatment-regimen dependent (Fig 4). The mean percent improvement from baseline in Skindex-16 overall scores in patients treated with 1.5% RUX cream twice daily was 63.5% at week 2 (vehicle, 10.5%; $P < .001$) and 73.2% at week 8 (vehicle, 19.7%; $P < .001$). At week 4, the mean percent improvement in overall score was significantly greater with 1.5% RUX cream twice daily (73.7%; $P = .02$) compared with triamcinolone (59.7%). Itch NRS scores and Skindex-16 scores were correlated at baseline.

Reduction in itch was positively associated with decreased QoL burden (Pearson correlation, 0.67; $P < .001$).

DISCUSSION

The results of this study show that all regimens of RUX cream provide a clinically meaningful decrease in itch level versus vehicle. MCID was achieved within 36 hours from the beginning of therapy with 1.5% RUX cream (twice daily and once daily), and significantly more patients achieved CRI at week 2. Compared with 0.1% triamcinolone cream, the current topical standard of care for patients with AD, considerably more patients who received 1.5% RUX cream twice daily achieved CRI at week 2. This improvement in itch was sustained throughout the double-blind period. All patients who switched at week 8 to 1.5% RUX cream twice daily noted further reductions in itch, and those who continued with 1.5% RUX cream twice daily showed additional



Number of Patients

Vehicle BID	37	39	38	35	31	30
0.1% TAC BID†	35	38	37	35	36	31
0.15% RUX QD	41	43	42	40	40	38
0.5% RUX QD	39	38	37	37	35	32
1.5% RUX QD	40	38	38	37	35	33
1.5% RUX BID	40	41	42	39	36	34

Fig 2. Itch NRS scores in patients who applied 1.5% RUX cream twice daily in the open-label period. *Range of NRS, 0-10 (0, no itch; 10, worst imaginable itch). †The TAC arm received 0.1% TAC cream through week 4 and vehicle thereafter. *BID*, Twice daily; *NRS*, numerical rating scale; *QD*, once daily; *RUX*, ruxolitinib; *TAC*, triamcinolone acetonide cream.

incremental improvement. The rapid and sustained alleviation of itch prompted by 1.5% RUX cream twice daily corresponded with reduced QoL burden, and marked improvements in QoL were observed with all RUX cream regimens. Although patients enrolled in this study presented with various degrees of disease severity,²⁵ all RUX cream treatment regimens resulted in significant improvements from baseline and versus vehicle, regardless of baseline disease severity. Collectively, these data show that RUX cream is efficacious in improving both itch and QoL in patients with AD.

These results show that topical JAK inhibition may offer a highly effective treatment for AD with unique anti-itch properties and beneficial effects on QoL. Indeed, improvement in QoL was directly correlated with reduction of itch in this study, further supporting the increasing evidence that itch is the cardinal symptom of AD. Itch data have been reported for

other topical JAK inhibitors.^{28,29} Itch reductions with RUX cream in this study were comparable to those reported in phase 3 trials of patients with AD treated with dupilumab (SOLO 1 and SOLO 2),³⁰ although the populations studied were different, and no direct comparisons could be made; baseline itch NRS scores were similar in our study and SOLO 1/SOLO 2. Future head-to-head studies would be required to definitively assess such differences in outcomes. Furthermore, the fast onset and magnitude of effect of RUX cream on itch may reflect its synergistic effect on the inhibition of pruritus transmission directly in sensory neurons and its anti-inflammatory activity. This combined effect suggests the possibility for the use of RUX cream in the treatment of itch in other inflammatory diseases beyond AD.^{15,31}

A limitation to this study was the fact that treatment of facial AD lesions with RUX cream was not permitted because of the safety restrictions for its



Fig 3. Representative clinical images at baseline and week 4 on treatment with RUX cream. QD, Once daily; RUX, ruxolitinib.

active control comparator (triamcinolone cream). Additionally, patients in our study were 18 years of age or older, which may not be representative of the AD population as a whole because AD is highly prevalent in children. Findings from this study will be verified in a larger population that includes younger

patients as part of the RUX cream phase 3 development program.

CONCLUSIONS

A clinically meaningful and prompt decrease in itch and marked improvements in QoL were

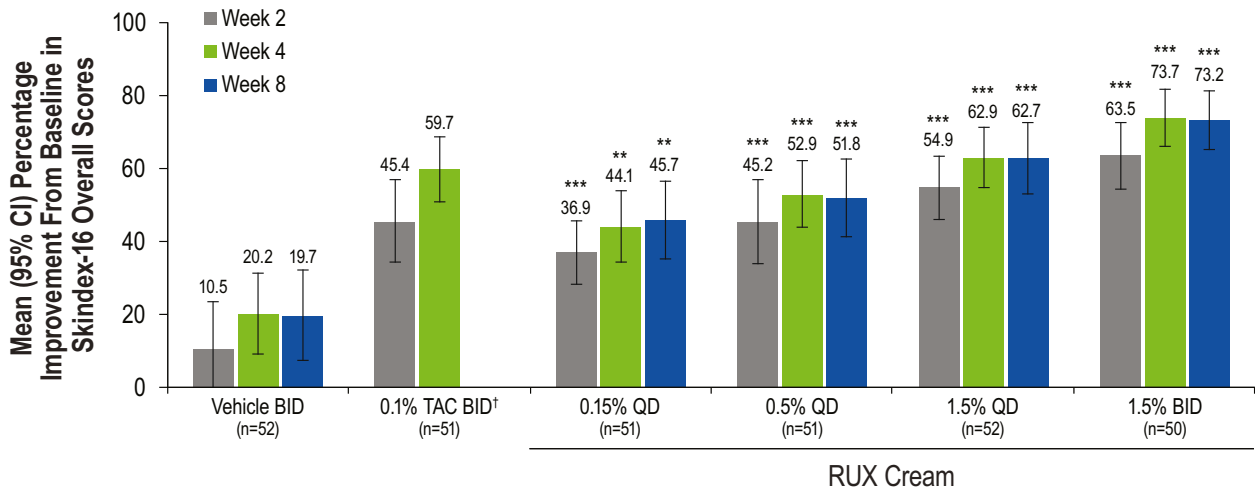


Fig 4. Skindex-16 overall scores in the double-blind period. $**P < .01$ vs vehicle; $***P < .001$ vs vehicle. [†]The TAC arm received 0.1% TAC cream through week 4 and vehicle thereafter. *BID*, Twice daily; *CI*, confidence interval; *QD*, once daily; *RUX*, ruxolitinib; *TAC*, triamcinolone acetonide cream.

observed with all RUX cream regimens compared with vehicle. Rapid and sustained alleviation in itch was observed with 1.5% RUX cream twice daily, which corresponded to reduced QoL burden.

Writing assistance was provided by Tania Iqbal, PhD, at Complete Healthcare Communications, LLC (North Wales, PA), a CHC Group company, and was funded by Incyte Corporation (Wilmington, DE).

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