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Efficacy and Safety of Ruxolitinib Cream for the Treatment of Atopic Dermatitis:  
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PII: S0190-9622(21)00931-2

DOI: <https://doi.org/10.1016/j.jaad.2021.04.085>

Reference: YMJD 15983

To appear in: *Journal of the American Academy of Dermatology*

Received Date: 6 November 2020

Revised Date: 16 April 2021

Accepted Date: 21 April 2021

Please cite this article as: Papp K, Szepietowski JC, Kircik L, Toth D, Eichenfield LF, Leung DYM, Forman SB, Venturanza ME, Sun K, Kuligowski ME, Simpson EL, Efficacy and Safety of Ruxolitinib Cream for the Treatment of Atopic Dermatitis: Results From Two Phase 3, Randomized, Double-Blind Studies, *Journal of the American Academy of Dermatology* (2021), doi: <https://doi.org/10.1016/j.jaad.2021.04.085>.

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## Capsule Summary

- Ruxolitinib cream, a Janus kinase inhibitor, demonstrated potent anti-inflammatory effects versus vehicle with rapid and sustained itch control in these phase 3 studies in patients with atopic dermatitis, confirming phase 2 data.
- These results support the potential of ruxolitinib cream as an effective and well-tolerated topical treatment for atopic dermatitis.

# **Efficacy and Safety of Ruxolitinib Cream for the Treatment of Atopic Dermatitis: Results From Two Phase 3, Randomized, Double-Blind Studies**

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**Abstract word count: 200**

**Capsule summary: 50**

**Word count: 2499 (limit, 2500)**

**Table/Figure count: 4**

**Reference count: 28**

**Clinical trials registration:** NCT03745638 and NCT03745651

**IRB approval statement:** The study protocol was approved by each site's institutional review board.

**Funding sources:** Incyte Corporation

**Conflict of Interest Statement:**

KP 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, Incyte Corporation, 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.

JCS has served as an advisor for AbbVie, LEO Pharma, Novartis, Pierre Fabre, Menlo Therapeutics, and Trevi; has received speaker honoraria from AbbVie, Janssen-Cilag, LEO Pharma, Novartis, Sanofi-Genzyme, Sun Pharma, and Eli Lilly; and has received clinical trial funding from AbbVie, Almirall, Amgen, Galapagos, Holm, Incyte Corporation, InflaRX, Janssen-Cilag, Menlo Therapeutics, Merck, Novartis, Pfizer, Regeneron, Trevi, and UCB.

LK has served as an investigator, consultant, or speaker for AbbVie, Amgen, Anaptys, Arcutis, Dermavant, Eli Lilly, Glenmark, Incyte Corporation, Kamedis, LEO Pharma, L'Oréal, Menlo, Novartis, Ortho Dermatologics, Pfizer, Regeneron, Sanofi, Sun Pharma, and Taro.

DT has served as an investigator for AbbVie, Avillion, Amgen, Arcutis, Astellas, Astion, Boehringer Ingelheim, Celgene, Dermira, DS BioPharma, Dow Pharmaceuticals, Eli Lilly, F. Hoffmann-La Roche Ltd, Galderma, GlaxoSmithKline, Incyte Corporation, Isotechnika, Janssen, LEO Pharma, Merck, Novartis, Pfizer, Regeneron, and UCB Biopharma.

LFE has served as an investigator, consultant, speaker, or data safety monitoring board member for AbbVie, Almirall, Arcutis, Dermira, Eli Lilly, Forte Biosciences, Galderma, Ichnos/Glenmark, Incyte Corporation, Janssen, LEO Pharma, Novartis, Ortho Dermatologics, Otsuka, Pfizer, Regeneron, and Sanofi Genzyme.

DYML has served as an advisor, investigator, or speaker for Incyte Corporation, LEO Pharma, Boehringer Ingelheim, Genentech, Aimimmune, Novartis, Sanofi, and Regeneron.

SBF has received honoraria, clinical research grants, or fees as a consultant, speaker, advisory board member, and/or investigator for AbbVie, Aclaris Therapeutics, Asana BioSciences, AstraZeneca, Athenex, Celgene Corporation, Cutanea Life Sciences, Eli Lilly, Incyte Corporation, Innovaderm Research, Novartis, Pfizer, Promius Pharma, Regeneron, UCB, Valeant Pharmaceuticals North America, and XBiotech.

MEV, KS, and MEK are employees and shareholders of Incyte Corporation.

ELS is an investigator for AbbVie, Eli Lilly, Galderma, Kyowa Hakko Kirin, LEO Pharma, Merck, Pfizer, and Regeneron and is a consultant with honorarium for AbbVie, Eli Lilly, Forte Bio, Galderma, Incyte Corporation, LEO Pharma, Menlo Therapeutics, Novartis, Pfizer, Regeneron, Sanofi Genzyme, and Valeant.

## Abstract

**Background:** Ruxolitinib (RUX) cream demonstrated potent anti-inflammatory and antipruritic efficacy in a phase 2 study in adults with atopic dermatitis (AD).

**Objective:** To evaluate 8-week efficacy and safety in two phase 3 studies of RUX cream in patients with AD

**Methods:** TRuE-AD1 (NCT03745638) and TRuE-AD2 (NCT03745651) enrolled patients aged  $\geq 12$  years with AD for  $\geq 2$  years, an IGA score of 2/3, and 3% to 20% affected body surface area. Patients were randomized 2:2:1 to twice-daily 0.75% RUX cream, 1.5% RUX cream, or vehicle cream for 8 continuous weeks. The primary endpoint was IGA treatment success (IGA-TS) at Week 8 (IGA score of 0/1 and  $\geq 2$ -grade improvement from baseline).

**Results:** In TRuE-AD1/TRuE-AD2, 631/618 patients were randomized (631/577 analyzed for efficacy). Significantly more patients achieved IGA-TS with 0.75% RUX cream (50.0%/39.0%) and 1.5% RUX cream (53.8%/51.3%) versus vehicle (15.1%/7.6%;  $P < 0.0001$ ) at Week 8. Significant itch reductions versus vehicle were reported within 12 hours of first application of 1.5% RUX ( $P < 0.05$ ). Application site reactions were infrequent ( $< 1\%$ ) and lower with RUX versus vehicle; none were clinically significant.

**Limitations:** Longer-term safety data are not yet available.

**Conclusions:** RUX cream showed anti-inflammatory and prompt antipruritic effects with superior efficacy versus vehicle and was well tolerated.

## Capsule Summary

- Ruxolitinib cream, a Janus kinase inhibitor, demonstrated potent anti-inflammatory effects versus vehicle with rapid and sustained itch control in these phase 3 studies in patients with atopic dermatitis, confirming phase 2 data.
- These results support the potential of ruxolitinib cream as an effective and well-tolerated topical treatment for atopic dermatitis.

## Keywords

atopic dermatitis, itch, JAK inhibitor, Janus kinase, ruxolitinib, topical

## Introduction

Atopic dermatitis (AD) is a chronic, highly pruritic, relapsing, inflammatory skin disease that substantially impacts patient quality of life (QoL).<sup>1-3</sup> AD often manifests in early childhood, affecting approximately 10%–20% of children and 5%–10% of adults, with rates varying geographically.<sup>3-5</sup> The extent of QoL impairment in patients with AD is similar to that of other chronic diseases<sup>6,7</sup>; even patients with milder forms of AD show considerable disease burden.<sup>8,9</sup> Sleep impairment resulting from chronic itch is an important factor contributing to the diminished QoL and overall well-being in patients with AD.<sup>10,11</sup>

Topical treatments, including corticosteroids and calcineurin inhibitors, are considered standard-of-care therapy for most patients with AD; however, their clinical benefit is often limited by their anatomic use restrictions and local adverse events (AEs), including skin atrophy, striae, and/or application site reactions (eg, stinging and burning).<sup>12-14</sup> Long-term application of these drugs, particularly in sensitive areas, is not recommended owing to safety/tolerability issues,<sup>12</sup> and concerns about adverse reactions can reduce patient adherence to treatment.<sup>15</sup> Thus, there remains an unmet need for a nonsteroidal topical therapy that is highly effective, well tolerated, and provides rapid and durable resolution of inflammatory lesions and pruritus.

Inflammation in AD is driven largely by type 2 cytokines that are modulated by Janus kinases (JAKs), JAK1 and JAK2.<sup>16</sup> JAK signaling may also directly mediate itch responses by acting directly on sensory nerve fibers<sup>17</sup> and contribute to skin barrier function through regulation of epidermal protein expression.<sup>18</sup>



A topical formulation of ruxolitinib (RUX), a selective inhibitor of JAK1 and JAK2,<sup>19</sup> was developed to optimally deliver drug directly to the affected skin to accelerate the onset of action and reduce the potential of AEs typically observed with oral administration. In a phase 2 study in adult patients (NCT03011892), RUX cream provided rapid and sustained improvements in AD (antipruritic and anti-inflammatory modes of action) without any clinically significant AEs.<sup>20,21</sup> Here, we report the efficacy and safety of RUX cream in adolescents and adults with AD from 2 large, confirmatory phase 3 studies.

## Methods

### *Study design and patients*

The TRuE-AD clinical studies comprised 2 randomized, double-blind, vehicle-controlled (VC) phase 3 studies of identical design (TRuE-AD1 [NCT03745638]; TRuE-AD2 [NCT03745651]). TRuE-AD1 was conducted across 79 centers in 7 countries (Canada, France, Germany, Hungary, Italy, Poland, United States). TRuE-AD2 was conducted across 66 centers in 7 countries (Bulgaria, Canada, Czechia, Germany, Poland, Spain, United States). Key inclusion criteria included age  $\geq 12$  years, diagnosis of AD for  $\geq 2$  years, Investigator's Global Assessment (IGA) score of 2/3, and body surface area (BSA) involvement of 3%–20% (excluding scalp). Key exclusion criteria included investigator-determined unstable course of AD (ie, spontaneous improvement and/or rapid deterioration), other types of eczema, immunocompromised status, and use of AD treatment during the washout period before baseline (biologics, 5 half-lives or 12 weeks; systemic corticosteroids or other immunomodulating agents, 4 weeks; topical drugs, 1 week) and during the study.

Patients were randomized 2:2:1 to twice-daily (BID), continuous treatment of the initially affected areas with 0.75% RUX cream, 1.5% RUX cream, or vehicle cream in the initial 8-week portion of the study (VC period) stratified by baseline IGA score (2 or 3) and region (North America or Europe). Rescue treatment was not permitted. All patients were assigned to study treatment using an interactive response technology system. Patients and study site personnel were blinded to individual treatment assignments. At Week 8, eligible patients continued treatment for an additional 44 weeks with 0.75% or 1.5% RUX cream in the long-term safety period (Weeks 8–52 [not reported here]). Patients initially randomized to vehicle were rerandomized (blinded) 1:1 at the Week 8 study visit to either RUX cream regimen, and patients initially randomized to RUX cream remained on their regimen.

These studies were conducted in accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki. All patients provided written informed consent before enrollment. The protocols were approved by the relevant institutional review board or ethics committee at each study center.

### *Assessments*

The assessments were the same in both studies. The primary endpoint was the proportion of patients achieving IGA treatment success (IGA-TS), defined as a score of 0 (clear [minor residual discoloration]) or 1 (almost clear [faint pink erythema with almost no induration/papulation and no oozing/crusting]) with  $\geq 2$ -grade improvement from baseline at Week 8. Key secondary endpoints included the proportion of patients achieving  $\geq 75\%$  improvement in Eczema Area and Severity Index (EASI-75) score at Week 8 versus baseline, clinically relevant reduction in itch defined as the proportion of

patients with a  $\geq 4$ -point reduction in itch numerical rating scale score (NRS4; measured with worst itch level) from baseline to Week 8, and the proportion of patients with a clinically meaningful improvement ( $\geq 6$ -point improvement from baseline) in the Patient-Reported Outcomes Measurement Information System (PROMIS) Short Form–Sleep Disturbance<sup>22</sup> (8b) score at Week 8 (24-hour recall completed daily with an electronic diary). For itch NRS assessment, patients completed an electronic diary each evening, reporting their worst level of itch during each 24-hour period from 0 (no itch) to 10 (worst imaginable itch). Other secondary endpoints included safety and tolerability (ie, treatment-emergent AEs [TEAEs] and clinical laboratory assessments), mean change from baseline in itch NRS score, mean percentage change from baseline in EASI score, the proportion of patients achieving  $\geq 90\%$  improvement in EASI (EASI-90), and plasma concentrations of RUX. The whole blood (WB) half-maximal inhibitory concentration ( $IC_{50}$ ) for RUX-mediated inhibition of thrombopoietin (TPO)–stimulated phosphorylation of signal transducer and activator of transcription 3 (pSTAT3; 281 nM), which is driven by JAK2,<sup>19</sup> was used as a proxy parameter to assess JAK-related myelosuppression in the bone marrow. The proportion of patients achieving itch NRS4 daily was an additional endpoint.

### *Statistical analyses*

The primary and key secondary endpoints were analyzed by exact logistic regression. The Bonferroni method was used for pairwise comparison between either active arm versus vehicle. Each comparison was conducted at a 2-sided alpha of 0.025 in a fixed sequence; the endpoint was tested only if the null hypothesis of the associated primary endpoint (and secondary in previous steps) was rejected. Statistical pairwise

comparisons for endpoints other than primary and key secondary were limited to 1.5% RUX cream versus vehicle; multiplicity control was not applied. For response endpoints, patients with missing postbaseline values were imputed as nonresponders. Change from baseline and percentage change from baseline were analyzed by the mixed-effect model with repeat measures. The efficacy population consisted of all randomized patients in TRuE-AD1; in TRuE-AD2, patients from 1 study site were excluded for quality issues. All patients who were treated with  $\geq 1$  application of treatment were included in the safety population. Safety was assessed using pooled data from both studies.

## Results

### *Patients*

Between December 20, 2018, and October 23, 2019, 631 patients were randomized in TRuE-AD1 (vehicle, n=126; 0.75% RUX, n=252; 1.5% RUX, n=253); TRuE-AD2 (December 20, 2018, to September 25, 2019) comprised 618 randomized patients (vehicle, n=124; 0.75% RUX, n=248; 1.5% RUX, n=246). In total, 558 (88.4%) and 561 (90.8%) patients, respectively, completed the 8-week VC period (**Supplemental Figure S1**; <http://dx.doi.org/10.17632/ffx6nd5zyb.1>). For efficacy analyses, TRuE-AD1 included all 631 patients; TRuE-AD2 included 577 patients (sensitivity analysis demonstrated no effect on efficacy outcomes with 1 study site excluded [n=41]). All randomized patients were included in the safety analysis for both studies. Distribution of baseline demographics was similar across treatment groups (**Table I**). The median (interquartile range) age of patients was 32.0 (19–49) and 33.0 (20–52) years in TRuE-AD-1 and TRuE-AD2, respectively; 19.5% and 19.7% of the population were adolescents (aged

<18 years). Patients in both studies had mean baseline itch NRS scores of 5.1; most patients had a score  $\geq 4$  at baseline (TRuE-AD1, n=395 [62.6%]; TRuE-AD-2, n=403 [65.2%]). Head/neck involvement at baseline was noted in 60.7% and 50.6% of patients, respectively (**Table I**).

### *Efficacy*

Significantly more patients in TRuE-AD1 and TRuE-AD2 achieved the primary endpoint of IGA-TS at Week 8 with 0.75% RUX (50.0% and 39.0%, respectively) and 1.5% RUX (53.8% and 51.3%) versus vehicle (15.1% and 7.6%; all  $P<0.0001$ ); responses were time and treatment strength dependent (**Table II** and **Supplemental Figure S2** [<http://dx.doi.org/10.17632/ffx6nd5zyb.1>]). Representative clinical images are shown in **Supplemental Figure S3** (<http://dx.doi.org/10.17632/ffx6nd5zyb.1>), and additional efficacy endpoints are provided in **Table II** and **Supplemental Figures S4–S8** (<http://dx.doi.org/10.17632/ffx6nd5zyb.1>). Both strengths of RUX cream showed substantially greater improvement in mean percentage change in EASI scores versus vehicle at Week 2 and later. Additionally, significantly more patients in TRuE-AD1 and TRuE-AD2 achieved EASI-75 at Week 8 with 0.75% RUX (56.0% and 51.5%, respectively) and 1.5% RUX (62.1% and 61.8%) versus vehicle (24.6% and 14.4%; all  $P<0.0001$ ); responses were time and treatment strength dependent. Similarly, more patients in both studies achieved EASI-90 at Week 8 with RUX cream versus vehicle ( $P<0.0001$ ; **Table II**). Significantly greater reductions in itch NRS scores versus vehicle were observed within 12 hours of the first application of 1.5% RUX cream ( $P<0.05$ ); further reductions were observed over 8 weeks (**Figure 1**). In patients with an itch NRS score  $\geq 4$  at baseline, clinically relevant reductions in itch (NRS4) were achieved at

Week 8 by significantly more patients in TRuE-AD1 and TRuE-AD2 who applied 0.75% RUX (40.4% and 42.7%, respectively) and 1.5% RUX (52.2% and 50.7%) versus vehicle (15.4% and 16.3%; all  $P<0.001$ ). On Day 2 (approximately 36 hours after the first application), the proportion of patients achieving itch NRS4 was higher with 1.5% RUX (11.6% and 10.8% in TRuE-AD1 and TRuE-AD2, respectively) versus vehicle (2.9% in TRuE-AD1 [ $P=0.048$ ]; 1.3% in TRuE-AD2 [ $P=0.015$ ]). Significantly more patients reported clinically meaningful improvement in the PROMIS sleep disturbance questionnaire ( $\geq 6$ -point improvement from baseline) at Week 8 with RUX cream versus vehicle ( $P<0.01$ ) in TRuE-AD1. In TRuE-AD2, the response rates were also higher with RUX cream versus vehicle, although the differences were not statistically significant.

#### *Plasma Concentrations of Ruxolitinib*

Mean steady state plasma concentrations of RUX following applications of 1.5% RUX cream were  $<15\%$  of the WB  $IC_{50}$  for TPO-stimulated pSTAT3 (281 nM).<sup>19</sup> Approximately 6% of the externally applied RUX cream became bioavailable.

#### *Safety*

The safety profile of RUX cream was similar among treatment groups across both studies (**Table III**). Application site reactions suggestive of skin tolerability issues (eg, stinging/burning sensation) were infrequent with RUX cream. The most common treatment-related AE was application site burning sensation, which was observed primarily with vehicle ( $n=11$  [4.4%]; 0.75% RUX,  $n=3$  [0.6%]; 1.5% RUX,  $n=4$  [0.8%]). During the 8-week VC period, 15 patients discontinued from both studies because of a TEAE (vehicle,  $n=8$  [3.2%]; 0.75% RUX,  $n=4$  [0.8%]; 1.5% RUX,  $n=3$  [0.6%]). Serious TEAEs were reported in 0.8% and 0.6% of patients who applied 0.75% and 1.5% RUX,

respectively, and in 0.8% who applied vehicle; none were considered related to treatment with RUX cream. No specific pattern of changes in hematologic laboratory parameters was reported, except for a small and transient elevation in platelet counts (within the normal range) at Week 2 (**Supplemental Figure S9**; <http://dx.doi.org/10.17632/ffx6nd5zyb.1>).

## Discussion

At Week 8, significantly higher IGA-TS rates (primary endpoint) were seen among patients treated with RUX cream in TRuE-AD1 and TRuE-AD2 (0.75% RUX, 50.0% and 39.0%, respectively; 1.5% RUX, 53.8% and 51.3%) versus vehicle (15.1% and 7.6%; all  $P < 0.0001$ ). In addition, approximately 60% of patients who applied 1.5% RUX cream achieved EASI-75 at Week 8. Statistically significant reductions in itch occurred within 12 hours of the first application of 1.5% RUX cream versus vehicle; clinically relevant reductions (NRS4) among patients treated with RUX cream regimens (strength dependent) were reported early and continued to improve during the VC period. This effect is likely related to JAK1-mediated inhibition of itch transmission in sensory neurons.<sup>17</sup> Improvement in sleep (as measured by PROMIS 8b) was also observed with RUX cream, which may have positive ramifications regarding overall QoL and mental health.<sup>23</sup> The low discontinuation rate (~6.4% among patients who applied 1.5% RUX) during the 8-week studies was likely due to, in part, rapid itch relief. Overall, these data indicate that RUX cream is a topical treatment that has direct antipruritic and anti-inflammatory effects, indicating a dual mode of action.

During the 8-week VC period, RUX cream was well tolerated and showed an unremarkable safety profile for both strengths versus vehicle; long-term safety was still

under evaluation during manuscript preparation. RUX cream was well tolerated on all lesions irrespective of their location. Application site reactions, such as stinging/burning, were infrequent (<1%) and lower in both strengths of RUX cream compared with vehicle; none were clinically significant. Treatment with oral JAK inhibitors, depending on their JAK2 specificity, may result in cytopenias, reflecting bone marrow suppression.<sup>24,25</sup> The occurrence and magnitude of cytopenias also depends on the duration of exposure (ie, the time that the plasma concentrations of JAK inhibitor exceeded the WB IC<sub>50</sub> for TPO-pSTAT3). In these two phase 3 AD studies, mean plasma concentrations of RUX were low (<15% of the WB IC<sub>50</sub> for JAK2 inhibition) and did not lead to any clinically meaningful changes in hematologic parameters. The relatively low bioavailability following topical application of RUX cream allows for a targeted delivery of the active drug to AD skin lesions while reducing the safety issues associated with oral administration of JAK inhibitors.<sup>25</sup>

The patient population in TRuE-AD1 and TRuE-AD2 included a range of disease severities based on severity strata using objective (IGA, EASI, BSA) and subjective (itch NRS) assessment tools.<sup>26-28</sup> Responses observed in these studies suggest that RUX cream may not only be effective in a broad patient population with AD irrespective of baseline disease severity but also provide an additional treatment option before consideration of systemic therapy. The efficacy and safety reported in these studies suggest that RUX cream has the potential to become the new standard for topical nonsteroidal therapy.

Regarding study limitations, longer-term safety evaluations of RUX cream are not yet completed; data for the 8-week VC period are reported in this analysis. Fewer Asian



patients versus other racial groups was an additional limitation. There was no active comparator in these studies; therefore, the studies did not directly compare these results to an approved treatment. However, a phase 2 study with RUX cream demonstrated greater improvements in IGA response and mean change from baseline in EASI score at Week 4, as well as more pronounced itch control for 1.5% RUX cream BID versus 0.1% triamcinolone acetonide cream BID.<sup>20,21</sup>

## Conclusions

The results of the two phase 3 TRuE-AD studies showed that application of RUX cream exhibits antipruritic and anti-inflammatory effects in AD. This unique dual mode of action combined with targeted and optimized delivery to the skin results in impressive efficacy that is both rapid and sustained. Treatment with RUX cream showed superior and clinically relevant treatment effects versus vehicle in all efficacy endpoints, particularly in prompt itch reduction. Reductions in itch levels were rapid, and substantial reductions were sustained throughout the VC period. RUX cream was well tolerated with no safety findings suggestive of systemic JAK inhibition. Importantly, there were no differences in its tolerability based on lesion location. These results show the potential of RUX cream as an important addition to the topical armamentarium for AD that addresses some of the limitations with current topical therapies.

## Acknowledgments

The authors thank the patients, investigators, and investigational sites whose participation made the study possible. This study was funded by Incyte Corporation

336 (Wilmington, DE, USA). Writing assistance was provided by Mayur Kapadia, MD, an  
337 employee of ICON (North Wales, PA, USA), and was funded by Incyte Corporation. Dr  
338 Leung thanks Rupam Brar, Mark Boguniewicz, Patricia Taylor, and Shirley Palombi for  
339 their assistance in performing this study at National Jewish Health (Denver, CO, USA).

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## Abbreviations

AD, atopic dermatitis

AE, adverse event

BSA, body surface area

EASI, Eczema Area and Severity Index

EASI-75,  $\geq 75\%$  improvement in Eczema Area and Severity Index from baseline

EASI-90,  $\geq 90\%$  improvement in Eczema Area and Severity Index from baseline

IC<sub>50</sub>, half-maximal inhibitory concentration

IGA, Investigator's Global Assessment

IGA-TS, Investigator's Global Assessment treatment success

JAK, Janus kinase

NRS, numerical rating scale

NRS4,  $\geq 4$ -point improvement in itch numerical rating scale score vs baseline

OR, odds ratio

PROMIS, Patient-Reported Outcomes Measurement Information System

QoL, quality of life

RUX, ruxolitinib

pSTAT3, phosphorylation of signal transducer and activator of transcription 3

TEAE, treatment-emergent adverse event

TPO, thrombopoietin

VC, vehicle-controlled

WB, whole blood

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**Table I. Patient Demographics and Baseline Clinical Characteristics**

Characteristic	TRuE-AD1				TRuE-AD2			
	0.75% RUX		1.5% RUX	Total (N=631)	0.75% RUX		1.5% RUX	Total (N=618)
	Vehicle (n=126)	Cream (n=252)	Cream (n=253)		Vehicle (n=124)	Cream (n=248)	Cream (n=246)	
Age, median (IQR), y	31.5 (20.0–49.0)	34.0 (19.0–51.0)	30.0 (19.0–47.0)	32.0 (19.0–49.0)	37.5 (21.5–53.5)	33.0 (19.0–52.0)	32.0 (21.0–49.0)	33.0 (20.0–52.0)
Age category, n (%)								
12–17 y	23 (18.3)	53 (21.0)	47 (18.6)	123 (19.5)	22 (17.7)	55 (22.2)	45 (18.3)	122 (19.7)
≥18 y	103 (81.7)	199 (79.0)	206 (81.4)	508 (80.5)	102 (82.3)	193 (77.8)	201 (81.7)	496 (80.3)
Female, n (%)	79 (62.7)	154 (61.1)	158 (62.5)	391 (62.0)	80 (64.5)	150 (60.5)	150 (61.0)	380 (61.5)
Race, n (%)								
White	85 (67.5)	171 (67.9)	177 (70.0)	433 (68.6)	85 (68.5)	174 (70.2)	178 (72.4)	437 (70.7)
Black	29 (23.0)	55 (21.8)	56 (22.1)	140 (22.2)	32 (25.8)	63 (25.4)	57 (23.2)	152 (24.6)
Asian	8 (6.3)	10 (4.0)	14 (5.5)	32 (5.1)	2 (1.6)	6 (2.4)	6 (2.4)	14 (2.3)
Other	4 (3.2)	16 (6.3)	6 (2.4)	26 (4.1)	5 (4.0)	5 (2.0)	5 (2.0)	15 (2.4)
Region, n (%)								
North America	88 (69.8)	176 (69.8)	176 (69.6)	440 (69.7)	84 (67.7)	166 (66.9)	165 (67.1)	415 (67.2)
Europe	38 (30.2)	76 (30.2)	77 (30.4)	191 (30.3)	40 (32.3)	82 (33.1)	81 (32.9)	203 (32.8)
BSA, mean ± SD, %	9.2±5.1	9.9±5.4	9.3±5.2	9.5±5.3	10.1±5.8	10.1±5.3	9.9±5.4	10.0±5.4
Baseline EASI, mean ± SD	7.4±4.3	8.2±4.8	7.9±4.6	7.9±4.6	8.2±5.2	8.1±5.0	7.8±4.9	8.0±5.0
Head/neck region score >0	79 (62.7)	151 (59.9)	153 (60.5)	383 (60.7)	62 (50.0)	129 (52.0)	122 (49.6)	313 (50.6)



Characteristic	TRuE-AD1				TRuE-AD2			
	0.75% RUX		1.5% RUX	Total (N=631)	0.75% RUX		1.5% RUX	Total (N=618)
	Vehicle (n=126)	Cream (n=252)	Cream (n=253)		Vehicle (n=124)	Cream (n=248)	Cream (n=246)	
Baseline IGA, n (%)								
2	31 (24.6)	61 (24.2)	60 (23.7)	152 (24.1)	33 (26.6)	64 (25.8)	63 (25.6)	160 (25.9)
3	95 (75.4)	191 (75.8)	193 (76.3)	479 (75.9)	91 (73.4)	184 (74.2)	183 (74.4)	458 (74.1)
Itch NRS score, mean $\pm$ SD	5.1 $\pm$ 2.5	5.1 $\pm$ 2.3	5.2 $\pm$ 2.5	5.1 $\pm$ 2.4	5.1 $\pm$ 2.4	5.2 $\pm$ 2.5	4.9 $\pm$ 2.5	5.1 $\pm$ 2.5
$\geq 4$ , n (%)	78 (61.9)	156 (61.9)	161 (63.6)	395 (62.6)	81 (65.3)	168 (67.7)	154 (62.6)	403 (65.2)
Duration of disease, median (range), y	17.9 (1.9–79.1)	14.1 (1.0–68.8)	16.0 (0–69.2)	15.3 (0–79.1)	15.9 (0.8–70.7)	15.9 (0.1–68.6)	16.6 (0–68.8)	16.0 (0–70.7)
Number of flares in the past 12 mo, mean $\pm$ SD	9.4 $\pm$ 35.2	5.3 $\pm$ 7.5	6.0 $\pm$ 23.3	6.4 $\pm$ 22.1	5.1 $\pm$ 8.1	5.1 $\pm$ 5.8	5.9 $\pm$ 8.5	5.4 $\pm$ 7.4

BSA, body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; IQR, interquartile range; NRS, numerical rating scale; RUX, ruxolitinib.

**Table II. Summary of Efficacy Outcomes**

Endpoint	TRuE-AD1			TRuE-AD2		
	Vehicle (n=126)	0.75% RUX Cream (n=252)	1.5% RUX Cream (n=253)	Vehicle (n=118)	0.75% RUX Cream (n=231)	1.5% RUX Cream (n=228)
Patients achieving IGA-TS, % (SE) <sup>†,‡</sup>						
Week 2	3.2 (1.6)	22.2 (2.6)	27.3 (2.8)	4.2 (1.9)	17.3 (2.5)	25.0 (2.9)
Week 4	6.3 (2.2)	42.5 (3.1)	46.6 (3.1)	5.9 (2.2)	35.5 (3.2)	43.4 (3.3)
Week 8	15.1 (3.2)	50.0 (3.2)****	53.8 (3.1)****	7.6 (2.4)	39.0 (3.2)****	51.3 (3.3)****
OR (95% CI)	NA	6.4 (3.6, 11.9)	7.5 (4.2, 14.0)	NA	8.8 (4.1, 21.2)	15.8 (7.4, 38.1)
Difference vs vehicle, % (95% CI)	NA	34.9 (26.1, 43.7)	38.7 (29.9, 47.4)	NA	31.3 (23.4, 39.2)	43.7 (35.6, 51.8)
Patients achieving EASI-75 score, % (SE) <sup>‡</sup>						
Week 2	5.6 (2.0)	30.2 (2.9)	36.0 (3.0)	4.2 (1.9)	25.5 (2.9)	31.6 (3.1)
Week 4	14.3 (3.1)	51.6 (3.2)	58.5 (3.1)	10.2 (2.8)	42.0 (3.3)	50.4 (3.3)
Week 8	24.6 (3.8)	56.0 (3.1)****	62.1 (3.1)****	14.4 (3.2)	51.5 (3.3)****	61.8 (3.2)****
OR (95% CI)	NA	4.0 (2.4, 6.8)	5.2 (3.1, 8.8)	NA	6.8 (3.7, 13.2)	10.7 (5.8, 20.7)
Difference vs vehicle, % (95% CI)	NA	31.4 (21.7, 41.1)	37.5 (27.8, 47.1)	NA	37.1 (28.1, 46.2)	47.4 (38.5, 56.4)
Patients achieving EASI-90 score, % (SE) <sup>‡</sup>						
Week 2	2.4 (1.4)	12.7 (2.1)	19.8 (2.5)	0.8 (0.8)	10.8 (2.0)	15.8 (2.4)
Week 4	4.0 (1.7)	30.6 (2.9)	36.4 (3.0)	2.5 (1.5)	25.5 (2.9)	32.5 (3.1)
Week 8	9.5 (2.6)	38.1 (3.1)****	44.3 (3.1)****	4.2 (1.9)	35.1 (3.1)****	43.4 (3.3)****
OR (95% CI)	NA	6.0 (3.1, 12.7)	7.8 (4.0, 16.4)	NA	13.1 (5.1, 43.0)	19.0 (7.4, 62.4)

Difference vs vehicle, % (95% CI)	NA	28.6 (20.7, 36.5)	34.7 (26.8, 42.7)	NA	30.8 (23.7, 38.0)	39.2 (31.8, 46.6)
Mean percentage change from baseline in EASI score, % (95% CI)						
Week 2	-16.1 (-24.6, -7.5)	-51.9 (-56.3, -47.5)****	-56.6 (-61.0, -52.2)****	-13.5 (-20.5, -6.5)	-45.6 (-50.0, -41.2)****	-49.5 (-56.5, -42.5)****
Week 4	-23.5 (-35.5, -11.4)	-68.4 (-72.3, -64.4)****	-71.2 (-75.9, -66.6)****	-21.1 (-31.3, -10.9)	-65.3 (-69.2, -61.3)****	-66.2 (-71.2, -61.3)****
Week 8	-40.5 (-52.0, -29.0)	-72.2 (-76.4, -67.9)****	-77.2 (-80.9, -73.4)****	-28.9 (-39.1, -18.6)	-74.8 (-78.5, -71.1)****	-74.7 (-79.5, -69.8)****
Patients achieving NRS4, % (SE) <sup>†,§</sup>						
Week 2	5.1 (2.5)	26.3 (3.5)	33.5 (3.7)	5.0 (2.4)	27.4 (3.6)	32.2 (3.9)
Week 4	11.5 (3.6)	38.5 (3.9)	51.6 (3.9)	12.5 (3.7)	38.2 (3.9)	45.2 (4.1)
Week 8	15.4 (4.1)	40.4 (3.9)***	52.2 (3.9)****	16.3 (4.1)	42.7 (4.0)****	50.7 (4.1)****
OR (95% CI)	NA	3.7 (1.8, 8.1)	6.0 (2.9, 13.2)	NA	4.2 (2.0, 9.0)	5.8 (2.8, 12.7)
Difference vs vehicle, % (95% CI)	NA	25.0 (13.9, 36.1)	36.8 (25.7, 47.9)	NA	26.4 (15.2, 37.6)	34.4 (23.0, 45.9)
Patients achieving ≥6-point improvement in PROMIS 8b, % (SE) <sup>†,  </sup>						
Week 2	5.2 (2.1)	13.7 (2.3)	14.7 (2.3)	10.0 (2.9)	14.6 (2.4)	18.0 (2.7)
Week 4	6.9 (2.4)	19.3 (2.6)	21.0 (2.6)	12.7 (3.2)	16.9 (2.6)	18.0 (2.7)
Week 8	9.5 (2.7)	21.0 (2.7)**	22.3 (2.7)**	19.1 (3.8)	20.7 (2.8)	25.6 (3.0)
OR (95% CI)	NA	2.6 (1.2, 5.7)	2.7 (1.3, 6.1)	NA	1.1 (0.6, 2.1)	1.5 (0.8, 2.7)
Difference vs	NA	11.5	12.8	NA	1.6	6.5

vehicle, %	(4.1, 19.0)	(5.3, 20.3)	(-7.6, 10.7)	(-2.9, 15.9)
(95% CI)				

EASI-75 (-90),  $\geq 75\%$  ( $\geq 90\%$ ) improvement in Eczema Area and Severity Index; IGA-TS, Investigator's Global Assessment treatment success; NA, not applicable; NRS4,  $\geq 4$ -point improvement in itch numerical rating scale score vs baseline; OR, odds ratio; PROMIS 8b, Patient-Reported Outcomes Measurement Information System Short Form – Sleep Disturbance (8b); RUX, ruxolitinib; SE, standard error.

\*\*  $P < 0.01$ ; \*\*\*  $P < 0.001$ ; \*\*\*\*  $P < 0.0001$ .

† Defined as patients achieving an Investigator's Global Assessment score of 0 or 1 with an improvement of  $\geq 2$  points from baseline.

‡ Patients with missing postbaseline values were imputed as nonresponders at Weeks 2, 4, and 8.

§ Patients in the analysis had an NRS score  $\geq 4$  at baseline.

|| Defined as a  $\geq 6$ -point improvement from baseline in the PROMIS Sleep Disturbance 8(b) raw score.

**Table III. Pooled TEAEs From TRuE-AD1 and TRuE-AD2 During the 8-Week Vehicle-Controlled Period**

<b>n (%)</b>	<b>Vehicle (n=250)</b>	<b>0.75% RUX Cream (n=500)</b>	<b>1.5% RUX Cream (n=499)</b>
Patients with TEAE	83 (33.2)	145 (29.0)	132 (26.5)
Most common TEAEs*			
Nasopharyngitis	2 (0.8)	15 (3.0)	13 (2.6)
Upper respiratory tract infection	5 (2.0)	7 (1.4)	12 (2.4)
Headache	5 (2.0)	4 (0.8)	11 (2.2)
Application site burning <sup>†</sup>	12 (4.8)	3 (0.6)	4 (0.8)
Application site pruritus <sup>†</sup>	7 (2.8)	5 (1.0)	1 (0.2)
AD	11 (4.4)	1 (0.2)	2 (0.4)
Patients with treatment-related AE	28 (11.2)	23 (4.6)	24 (4.8)
Most common treatment-related AEs <sup>‡</sup>			
Application site burning <sup>†</sup>	11 (4.4)	3 (0.6)	4 (0.8)
Application site pruritus <sup>†</sup>	6 (2.4)	4 (0.8)	0
Discontinuation due to a TEAE	8 (3.2)	4 (0.8)	4 (0.8)
Patients with serious TEAE <sup>§</sup>	2 (0.8)	4 (0.8)	3 (0.6)

AD, atopic dermatitis; AE, adverse event; RUX, ruxolitinib; TEAE, treatment-emergent adverse event.

\* Occurring in >1% of the total pooled patient population.

<sup>†</sup> Patient-reported tolerability was not lesion specific and was reported for all treated areas.

<sup>‡</sup> Occurring in >0.5% of the total pooled patient population.

<sup>§</sup> None of the following serious TEAEs were related to treatment with RUX cream: acute abdomen (n=1, 1.5% RUX), AD (n=1, vehicle), arrhythmia (n=1, 1.5% RUX), cerebrovascular accident (n=2, 0.75% RUX and 1.5% RUX [1 each]), cholangitis (n=1, 1.5% RUX), jaundice cholestatic (n=1, 1.5% RUX), nasal sinus cancer (n=1, vehicle), pneumonia (n=2, 0.75% RUX), tooth infection (n=1, 0.75% RUX); 2 patients each experienced 2 serious TEAEs.

## Figure Legend

**Figure 1.** Change from baseline in daily itch NRS score. B, baseline; NRS, numerical rating scale; RUX, ruxolitinib cream. \*  $P<0.05$ ; \*\*\*\*  $P<0.0001$ . Mean  $\pm$  SD itch NRS scores at baseline and Day 56 were as follows: TRuE-AD1: vehicle,  $5.1\pm2.5$  and  $3.3\pm2.7$ ; 0.75% RUX,  $5.1\pm2.3$  and  $2.1\pm2.3$ ; 1.5% RUX,  $5.2\pm2.5$  and  $1.7\pm2.1$ . TRuE-AD2: vehicle,  $5.3\pm2.4$  and  $3.6\pm2.8$ ; 0.75% RUX,  $5.2\pm2.5$  and  $1.8\pm1.9$ ; 1.5% RUX,  $5.0\pm2.5$  and  $1.9\pm2.4$ .

