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REVIEW

Management of Atopic Dermatitis: Clinical Utility of Ruxolitinib

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Abstract: Atopic dermatitis (AD) is a common chronic, pruritic inflammatory skin disease that profoundly impacts patients' quality of life. As the first FDA-approved topical JAK inhibitor, ruxolitinib 1.5% cream represents a novel therapeutic topical agent for the treatment of AD. The objective of this review is to summarize the efficacy and safety of ruxolitinib cream in patients with AD based on the available evidence. Overall, ruxolitinib cream demonstrated high efficacy and a favorable safety profile for treating atopic dermatitis.

Keywords: atopic dermatitis, eczema, ruxolitinib, JAK inhibitor, topical, itch

Introduction

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin condition characterized by dry skin, severe itching, and eczematous lesions. The disease is estimated to affect at least 10–20% of children and 5–10% of adults globally,[1] and its prevalence is increasing.[2] It can be severely debilitating, causing sleep disturbance, poor quality of life, and mental health impairment.[2] Increased health care resource utilization related to AD is also associated with substantial expenses in the long term; combined direct and indirect costs related to AD in 2015 summed to approximately 5.3 billion US dollars, likely an underestimate in the present day.[3]

The pathogenesis of AD is complex, with immunologic dysregulation, impaired epidermal barrier function, and cutaneous inflammation all contributing to the disease process.[4] Moreover, the disease is clinically and immunologically heterogeneous,[5] necessitating varied treatment approaches. In recent years, better understanding of AD pathogenesis has led to a surge of new therapeutic options, including systemic and biologic drugs, which have revolutionized the treatment for patients with moderate-to-severe disease. However, there remains a need for therapeutic advances for patients with mild-to-moderate disease. Topical steroids, topical calcineurin inhibitors, and topical phosphodiesterase 4 inhibitors have continued as available topical treatments, associated with side effects with long-term use and variable efficacy.[6,7] Continued efforts to develop novel therapeutics that are safe and effective are thus paramount.

Janus kinase inhibitors (JAKi) have emerged as a promising therapeutic approach in treating AD. JAKs are small intracellular signaling enzymes that mediate the downstream signaling of proinflammatory cytokines. The JAK family consists of four members, including JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2), which are expressed fairly ubiquitously throughout the body.[8] Growing evidence has demonstrated the substantial contribution of JAK-dependent cytokines to the pathogenesis of AD. JAK signaling may also play a role in the itch response by acting directly on sensory nerve fibers.[9]

Ruxolitinib is a selective JAK1/2 inhibitor available in topical and oral formulations. Ruxolitinib 1.5% topical cream is the first topical JAKi to receive US Food and Drug Administration (FDA) approval in adolescents and adults (≥12 years) with mild-to-moderate AD. The approval was based on the Topical Ruxolitinib Evaluation in Atopic Dermatitis Study (TRuE-AD) clinical trials, which demonstrated significant improvement in AD with no tolerability issues.[10] This review aims to summarize the efficacy and safety findings of topical ruxolitinib cream in treating AD based on the

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current literature. Here we present the results from Phase I, Phase II, and Phase III studies investigating the efficacy and safety of ruxolitinib cream in AD.

Efficacy

This section reviews the efficacy of ruxolitinib cream in clinical trials in patients with atopic dermatitis, including a Phase I open-label maximum use trial, a phase II, randomized, double-blind, dose-ranging, vehicle- and active-controlled trial, and two phase III randomized, double-blind, vehicle-controlled trials of identical design known as TRuE-AD1 and TRuE-AD2. A summary of efficacy data is presented in Table 1.

Phase I

A multicenter phase I, open-label, maximum-use trial (NCT03920852) was conducted in adolescents and adults with AD to evaluate the tolerability and safety of ruxolitinib cream.[11] Such trials involve application of a topical drug product under maximal use conditions, as in the case of large surface areas treated for extended periods of time.[12] While the principal focus of this trial was the reporting of safety measures, which are a later section, exploratory efficacy endpoints were also evaluated. Patients meeting the following criteria were eligible for enrollment: age 12 to 65 years, AD duration of ≥2 years, International Global Assessment (IGA) score ≥2, and body surface area (BSA) involvement ≥25%.

Patients were instructed to apply ruxolitinib 1.5% cream twice daily (BID) for 28 days on all AD lesions present at baseline (scalp lesions excluded), with continued application to these same areas regardless of clinical response. Patients with no safety concerns at day 28 could continue applying ruxolitinib cream BID for an additional 28 days to active lesions only. Forty-one patients (21 males, 20 females) in total, with a median interquartile range (IQR) age of 17 (15–36) years and consisting of 68.3% Caucasians, were enrolled.[11] Two patients discontinued the study for reasons unrelated to the treatment. Of the 39 patients who completed the initial 28 days of treatment, 37 elected to continue ruxolitinib cream during the extension period (days 28–56).[11]

IGA treatment success (IGA-TS, defined as an IGA score of 0/1 with a ≥2-point improvement from baseline) was achieved by 20.0% of patients on day 15, with further increases to 35.9% and 56.8% by days 28 and 56, respectively. From a mean (±SD) affected BSA of 38.1% (±16.3%) at baseline, there was a progressive improvement by days 15, 28,

Table 1 Summary of Efficacy Outcomes for Ruxolitinib 1.5% Cream BID vs Vehicle BID (if Applicable) at Week 8 in Phase I–III Studies

	IGA-TS (%)[a]	EASI-75 (%)[b]	NRS4 (%)[c]	% Reduction in EASI	% Reduction in Itch NRS
Phase I					
Ruxolitinib 1.5% (n=41)	56.8	94.6	90.5	− 93.75	N/A
Phase II					
Ruxolitinib 1.5% (n=50)	48.0*	N/A	N/A	− 78.5*	− 68.5**
Vehicle (n=52)	9.6	N/A	N/A	− 26.9	− 17.6
Phase III (TRuE-AD1)					
Ruxolitinib 1.5% (n=253)	53.8**	62.1**	52.2**	− 77.2**	− 67.3**
Vehicle (n=126)	15.1	24.6	15.4	− 40.5	− 35.3
Phase III (TRuE-AD2)					
Ruxolitinib 1.5% (n=228)	51.3**	61.8**	50.7**	− 74.7**	− 62.0**
Vehicle (n=118)	7.6	14.4	16.3	− 28.9	− 32.1

Notes: *p<0.001 vs vehicle, **p<0.0001 vs vehicle. [a]Proportion of patients who achieved IGA treatment success, defined as IGA score of 0/1 with a ≥2-grade improvement from baseline, [b]Proportion of patients with a ≥75% improvement in the Eczema Area and Severity Index, [c]Proportion of patients with a ≥4-point improvement in the itch Numerical Rating Scale score.

Abbreviations: BID, twice daily; EASI, Eczema Area and Severity Index; IGA-TS, Investigator's Global Assessment – Treatment Success; N/A, not applicable; NRS, Numerical Rating Scale; TRuE-AD1, Topical Ruxolitinib Evaluation in Atopic Dermatitis Study 1; TRuE-AD2, Topical Ruxolitinib Evaluation in Atopic Dermatitis Study 2.

and 56 to 15.8% (11.4%), 6.5% (8.2%), and 3.1% (5.4%), respectively. Of note, patients reported rapid onset of itch relief with ruxolitinib cream, with mean itch numerical rating scale (NRS) improving by 1.9 from baseline as early as day 1 (12 h after first application of the cream). By day 20, patients reported further decreases in itch, with the mean improvement from baseline in itch NRS of 5.3; these reductions were maintained until study termination. Increasingly greater proportions of patients achieved NRS4 as the study progressed: 58.6%, 82.6%, and 90.5% on days 15, 28, and 56, respectively. A similar trend was seen in the proportion of patients who achieved Eczema Area and Severity Index (EASI) responses of EASI-75 (75% improvement in EASI), with 30.0%, 79.5%, and 94.6% achieving EASI-75 by days 15, 28, and 56, respectively, and mean EASI scores decreasing from 20.8 (±9.2) at baseline to 6.3 (±5.2), 2.4 (±2.3), and 1.3 (±2.2) at days 15, 28, and 56, respectively.[11]

Phase II

A multicenter phase II, randomized, double-blind, dose-ranging, vehicle- and active-controlled trial (NCT03011892) investigated the efficacy and safety of ruxolitinib cream in adult AD patients. This section will review efficacy endpoints observed in the trial, with reported safety data detailed in a later section. Patients with active AD, 18–70 years of age, disease duration of ≥2 years, an IGA score of either 2 or 3, and BSA involvement of 3–20% were eligible for enrollment, and randomized in equal numbers to receive treatment with ruxolitinib cream (0.15% once daily [QD], 0.5% QD, 1.5% QD, or 1.5% BID), vehicle cream BID, or active control (triamcinolone 0.1% cream BID). Patients in the ruxolitinib and vehicle cream groups remained on their respective regimens for 8 weeks of double-blind treatment, while those in the triamcinolone cream group transitioned to vehicle cream after 4 weeks. Following the double-blind period, all patients had the option of receiving 4 additional weeks of open-label treatment with ruxolitinib 1.5% cream BID. The primary endpoint was the mean percentage decrease in EASI score from baseline after 4 weeks of treatment in patients receiving ruxolitinib 1.5% BID versus vehicle cream BID.[7,13]

In total, 307 patients (139 males, 168 females), with a median (IQR) age of 35 (25–51) years and consisting of 56.0% Caucasians, were randomized. At baseline, the mean (±SD) EASI score was 8.4 (±4.7) and itch NRS score was 6.0 (±2.1). In total, 260 patients completed the 8-week double-blind treatment, and 240 participated in 4 weeks of additional open-label treatment with ruxolitinib 1.5% cream BID. All ruxolitinib cream regimens caused statistically significant reductions from baseline EASI scores versus vehicle cream at weeks 2, 4, and 8, with dose-dependent responses. At week 4, more patients using ruxolitinib 1.5% cream BID achieved EASI-50, −75, and −90 (78.0%, 56.0%, 26.0%) than with triamcinolone (66.7%, 47.1%, 13.7%) and with vehicle (23.1%, 17.3%, 5.8%). Patients treated with ruxolitinib 1.5% cream BID exhibited a 71.6% reduction in EASI score from baseline after 4 weeks versus a 15.5% reduction with vehicle cream (primary endpoint; $p<0.0001$), with further reductions seen in ruxolitinib 1.5% cream BID-treated patients at week 8. Both the ruxolitinib 1.5% cream QD and BID groups also demonstrated greater reductions from baseline EASI scores (67.0% and 71.6%, respectively) than the triamcinolone group (59.8%) after 4 weeks, though these differences lacked statistical significance; no comparison to triamcinolone was available at week 8 as triamcinolone was stopped after 4 weeks. In patients applying ruxolitinib 1.5% cream BID, IGA responses were achieved by 38.0% and 48.0% at weeks 4 and 8, respectively, versus 7.7% and 9.6% at weeks 4 and 8 with vehicle cream (both $p<0.001$). A greater, though nonsignificant, proportion of IGA responses were also seen with ruxolitinib 1.5% cream BID than triamcinolone at week 4 (38.0% vs 25.5%). By week 8, IGA responses were also seen in significantly more patients applying ruxolitinib 0.5% cream QD (31.4%; $p<0.01$) and ruxolitinib 1.5% cream QD (30.8%; $p<0.05$) than vehicle (9.6%). Those treated with ruxolitinib 1.5% cream BID during the first 8 weeks who elected to continue the same treatment open-label for 4 additional weeks experienced a further mean percentage reduction in EASI score from 79.4% to 84.9% by week 12. All other treatment groups who transitioned to 4 weeks of open-label treatment with ruxolitinib 1.5% cream BID experienced improvements in EASI scores and IGA response in the open-label period.[7]

Notably, ruxolitinib 1.5% cream rapidly ameliorated pruritus in AD patients. Results from daily patient-reported itch NRS scores demonstrated significant decreases in itch NRS scores with ruxolitinib 1.5% cream BID compared to vehicle just 36 hours after the first application (−1.8 vs −0.2; $p<0.0001$). All concentrations/regimens of ruxolitinib cream decreased itch NRS scores in a dose-dependent manner within 2 weeks, and these reductions in pruritus were maintained for the remainder of the double-blind period. Both the QD and BID regimens of ruxolitinib 1.5% cream resulted in

greater reductions in itch NRS than triamcinolone at week 4, with the BID regimen resulting in a significantly greater reduction in itch versus triamcinolone (−4.0 vs −2.5, respectively; p=0.003). By week 8, patients in the ruxolitinib 1.5% cream BID group demonstrated a 68.5% mean reduction from baseline in itch NRS scores versus 17.6% in the vehicle group (p<0.0001). In those initially randomized to 8 weeks of ruxolitinib 1.5% cream BID who elected to continue their treatment in the open-label period, reductions in itch NRS were maintained at the conclusion of open-label treatment (76.1% mean reduction from baseline at week 12). Those who transitioned from the other treatment groups to ruxolitinib 1.5% cream BID for weeks 8 through 12 demonstrated continued reductions in itch NRS in the open-label period.[13]

Itch (NRS scores) was found to be correlated with quality of life (QoL[Skindex-16 scores]) at baseline, with improvements in itch over the course of the study similarly correlated with improved QoL (Pearson correlation, 0.67; p<0.001). All ruxolitinib cream concentrations/regimens brought about significant improvements in QoL versus vehicle at weeks 2, 4, and 8 with ruxolitinib 1.5% cream BID exhibiting 63.5%, 73.7%, and 73.2% improvement, respectively, from baseline in Skindex-16 versus 10.5%, 20.2%, and 19.7% improvements, respectively, with vehicle cream (all p<0.001). At week 4, QoL was also significantly improved from baseline in the ruxolitinib 1.5% cream BID group compared to triamcinolone (73.7% vs 59.7%, p=0.02).[13]

An exploratory biomarker analysis of sera collected from patients at baseline and week 8 demonstrated that baseline thymus and activation-regulated chemokine (TARC/CCL17) levels were associated with baseline EASI scores (p=0.003), and that TARC/CCL17 levels were significantly lower in the ruxolitinib 1.5% cream BID group compared to vehicle at week 8 (p<0.01). In addition, while no association was found between IgE levels and baseline EASI scores, IgE levels at week 8 were reduced, though not significantly, in patients treated with either ruxolitinib 1.5% cream BID or QD versus vehicle.[7]

A proteomic analysis of sera from 89 patients in the Phase II trial evaluated the association between circulating inflammatory mediators and an itch-free state (NRS itch score of 0/1) after treatment with ruxolitinib cream. Sera from itch-free patients (n=22) and non-itch-free patients (NRS itch score >1; n=67) after 8 weeks of treatment were evaluated for expression of 1012 proteins using the OLINK proximity extension assay. It was found that reduced itch after treatment with ruxolitinib cream was correlated with changes in expression of inflammatory mediators.[14]

Phase III

Two multicenter Phase III, randomized, double-blind, vehicle-controlled trials of identical design (TRuE-AD1 [NCT03745638] and TRuE-AD2 [NCT03745651]) evaluated the efficacy and safety of ruxolitinib cream in adult and adolescent patients with AD. Patients with AD who were ≥12 years of age, had a disease duration of ≥2 years, an IGA score of either 2 or 3, and BSA involvement of 3% to 20% (scalp excluded) were included. Participants were randomized in a 2:2:1 ratio to double-blind treatment of all lesional areas present at baseline with 0.75% ruxolitinib cream BID, ruxolitinib 1.5% cream BID, or vehicle cream BID for 8 weeks. The studies' primary endpoint was the percentage of patients in each treatment group who achieved IGA treatment success (IGA-TS, defined as an IGA score of 0 or 1 with a ≥2-point improvement from baseline) by week 8. Secondary endpoints included the proportion of patients who achieved EASI-75, proportion of patients who achieved a ≥4-point reduction in their itch NRS score (NRS4), and proportion of patients with a ≥6-point increase in the Patient-Reported Outcomes Measurement Information System short form 8b questionnaire[15] score (PROMIS-8b; measure of sleep disturbance). Additional secondary endpoints included mean change in EASI scores and itch NRS scores from baseline, percentage of patients achieving EASI-90, as well as safety and tolerability endpoints (ie, treatment-emergent adverse events, ruxolitinib plasma concentrations, clinical laboratory results) detailed in a later section.[9]

In TRuE-AD1, 631 patients (240 males, 391 females) with a median (IQR) age of 32 (19–49) years were randomized, and an additional 618 patients (238 males, 380 females) were randomized in TRuE-AD2 with a median (IQR) age of 33 (20–52) years (total patients = 1249); 558 and 561 (total patients = 1119), respectively, completed the 8-week study. Patients enrolled in TRuE-AD1 had a baseline mean (±SD) EASI score of 7.9 (±4.6) and BSA involvement of 9.5% (±5.3%); those enrolled in TRuE-AD2 had a baseline mean (SD) EASI score of 8.0 (±5.0) and BSA involvement of 10.0% (±5.0%). In both studies, the primary endpoint was met and IGA responses were found to be dose-dependent. Greater proportions of patients in TRuE-AD1 and TRuE-AD2 achieved IGA-TS at week 8 with both ruxolitinib 0.75% (TRuE-AD1: 50.0%, TRuE-AD2: 39.0%) and ruxolitinib 1.5% (TRuE-AD1: 53.8%, TRuE-AD2: 51.3%) compared to

vehicle (TRuE-AD1: 15.1%, TRuE-AD2: 7.6%; all p<0.0001). Both ruxolitinib 0.75% and 1.5% cream regimens brought about significantly greater percentage improvements in EASI scores versus vehicle cream at weeks 2, 4, and 8. By week 8, more patients had achieved EASI-75 with ruxolitinib 0.75% cream (TRuE-AD1: 56.0%, TRuE-AD2: 51.5%) and ruxolitinib 1.5% cream (TRuE-AD1: 62.1%, TRuE-AD2: 61.8%) versus vehicle cream (TRuE-AD1: 24.6%, TRuE-AD2: 14.4%; all p<0.0001). In both studies, EASI-90 was also achieved by significantly more patients in both ruxolitinib cream regimen groups than vehicle at week 8 (p<0.0001).[9]

Rapid reductions in pruritus were seen with ruxolitinib cream through daily patient-reported itch NRS scores. Within 12 hours after the first application, ruxolitinib 1.5% cream caused significantly greater reductions in itch NRS scores compared to vehicle cream (p<0.05), with additional reductions observed at weeks 2, 4, and 8. By day 2, significantly more patients had achieved itch NRS4 with ruxolitinib 1.5% cream (TRuE-AD1: 11.6%, TRuE-AD2: 10.8%) than vehicle (TRuE-AD1: 2.9%, TRuE-AD2: 1.3%; both p<0.05). After 8 weeks of treatment, significantly greater proportions of patients had achieved NRS4 with both ruxolitinib 0.75% cream (TRuE-AD1: 40.4%, TRuE-AD2: 42.7%) and ruxolitinib 1.5% cream (TRuE-AD1: 52.2%, TRuE-AD2: 50.7%) versus vehicle cream (TRuE-AD1: 15.4%, TRuE-AD2: 16.3%; all p<0.001).[9] A combined analysis of patients from both studies showed that more patients treated with ruxolitinib 0.75% and ruxolitinib 1.5% versus vehicle reported no days of itch at week 8 (0.75%: 28.0%; 1.5%: 32.7%; vehicle: 9.0%), as evaluated by the Patient-Oriented Eczema Measure Q1. The median time to attainment of itch NRS4 was shorter for ruxolitinib compared to vehicle (0.75%: 15 days; 1.5% 13 days; vehicle: not reached).[16]

In TRuE-AD1, significantly more patients had achieved a ≥6-point improvement in PROMIS-8b score (representative of a clinically meaningful improvement in sleep disturbance) using ruxolitinib 0.75% cream (21.0%) and ruxolitinib 1.5% cream (22.3%) versus vehicle (9.5%; both p<0.01) at week 8,[9] although corresponding improvement in TRuE-AD2 was not statistically significant. PROMIS short form 8a questionnaire scores (PROMIS-8a; measure of sleep-related impairment) were also assessed as an exploratory outcome. In a combined analysis of both studies, significantly greater proportions of patients achieved a ≥6-point improvement in PROMIS-8a (representative of a clinically meaningful improvement in sleep-related impairment) at week 8 with ruxolitinib 0.75% cream (20.1%) and ruxolitinib 1.5% cream (22.3%) versus vehicle cream (13.3%; both p<0.05).[17]

Additional patient-reported outcomes from TRuE-AD1 and TRuE-AD2 were assessed as exploratory endpoints at week 8. Significantly greater reductions in the Patient-Oriented Eczema Measure (POEM) were seen in patients treated with ruxolitinib 0.75% cream (−10.5) and ruxolitinib 1.5% cream (−11.0) than vehicle (−4.2; both p<0.0001). Dermatology Life Quality Index (DLQI) improved by a mean of 7.2 points with ruxolitinib 0.75% cream and 7.1 points with ruxolitinib 1.5% cream versus 3.1 points with vehicle (both p<0.0001). Children's DLQI similarly saw significantly greater improvements with both ruxolitinib cream regimens compared to vehicle. After 8 weeks, the proportion of patients reporting either much or very much improvement in their Patient Global Impression of Change was significantly greater with ruxolitinib 0.75% cream (80.0%) and ruxolitinib 1.5% cream (84.9%) versus vehicle (41.3%; both p<0.0001).

An efficacy analysis of only adolescent patients (ages 12–17) in TRuE-AD1 and TRuE-AD2 (n=245) revealed that greater proportions of adolescents achieved IGA-TS, EASI-75, and itch NRS4 with either ruxolitinib[9] cream regimen compared to vehicle; of note, p-values were not reported for these analyses. IGA-TS was achieved by 47.2% and 50.6% of the adolescents treated with ruxolitinib 0.75% cream and ruxolitinib 1.5% cream, respectively, versus 14.0% of the adolescents treated with vehicle. EASI-75 was achieved by 54.7% and 60.9% of the adolescents treated with ruxolitinib 0.75% cream and ruxolitinib 1.5% cream, respectively (vehicle, 34.9%). Itch NRS4 was achieved by 41.4% and 52.1% of those treated with ruxolitinib 0.75% and 1.5% cream, respectively, compared to 17.4% with vehicle.[18]

Clinically relevant rates of IGA-TS were seen in patients treated with ruxolitinib 1.5% cream regardless of baseline AD severity. Patients in the two phase III studies who received treatment with ruxolitinib 1.5% cream (n=481) were stratified by baseline IGA scores, EASI scores, itch NRS scores, and affected BSA to evaluate the relative efficacy of ruxolitinib cream in patient subgroups with different baseline AD characteristics. At week 8, IGA-TS was achieved in clinically meaningful proportions of patients with baseline IGA scores of 2 and 3 (25.2% and 62.0%, respectively), EASI scores of ≤7 and >7 (44.8% and 60.3%, respectively), itch NRS scores of <4 and ≥4 (51.0% and 53.7%, respectively), and affected BSA of <10% and ≥10% (48.4% and 58.8%, respectively).[19]

The Work Productivity and Activity Impairment Questionnaire-Specific Health Problem version 2.0 (WPAI:SHP v2.0) was used to assess absenteeism (percentage of work time missed) and presenteeism (score representing impairment while working) in employed AD patients enrolled the two phase III trials. At week 8, patients treated with ruxolitinib 0.75% and 1.5% cream reported 7.7% and 7.5% absenteeism, respectively, compared to 12.7% with vehicle. Similarly, ruxolitinib 0.75% and 1.5% cream resulted in 19.2 and 19.8-point reductions, respectively, in presenteeism versus a 12.3-point reduction with vehicle cream ($p<0.0001$). Daily activity impairment scores were also significantly reduced with ruxolitinib 0.75% cream (−20.6) and ruxolitinib 1.5% cream (−21.5) versus vehicle (−10.6; both $p<0.0001$) at week 8.[20]

Patients in the phase III studies who did not achieve IGA-TS at week 8 (n=584) still achieved clinically relevant improvements at significantly higher rates with both ruxolitinib creams than with vehicle. As an exploratory outcome, the proportions of patients not achieving IGA-TS who still achieved clinically meaningful responses were determined for each treatment group. A clinically meaningful response was considered either a ≥2-point reduction in itch NRS, ≥4-point reduction in DLQI, ≥6-point reduction in children's DLQI, or attainment of EASI-50 by week 8. In the subset of patients not achieving IGA-TS by week 8, 88.3% and 85.3% of those treated with ruxolitinib 0.75% and 1.5% cream, respectively, still achieved clinically meaningful responses versus 63.2% with vehicle (both $p<0.0001$).[21]

Stratification of patients by their previous use of AD drugs, including topical corticosteroids (TCS, n=966), topical calcineurin inhibitors (TCI, n=267), or systemic therapies (n=228), demonstrated that ruxolitinib cream was clinically effective and superior to vehicle cream regardless of patients' previous history of topical or systemic therapies. In those with a history of TCS use, patients treated with ruxolitinib 0.75% and 1.5% cream achieved IGA-TS at higher rates than with vehicle at week 8 (0.75%: 46.2%; 1.5%: 55.5%; vehicle: 10.6%). Patients previously treated with TCI (0.75%: 62.3%; 1.5%: 69.3%; vehicle: 6.7%) and systemic therapies (0.75%: 56.0%; 1.5%: 59.3%; vehicle: 10.9%) similarly achieved IGA-TS more often with both strengths of ruxolitinib cream than with vehicle.[22]

Ruxolitinib 1.5% cream was found to be effective in the phase III trials regardless of patients' demographic characteristics. Clinically relevant proportions of patients achieved IGA-TS in all patient subpopulations stratified by sex, age group, race, and geographic region, with 55.9% of the men treated with ruxolitinib 1.5% achieved IGA-TS versus 17.8% of the men with vehicle (women: 50.5% and 7.8%, respectively). Participants in Europe and North America achieved higher rates of IGA-TS with ruxolitinib 1.5% than with vehicle (ruxolitinib 1.5% vs vehicle: Europe, 66.4% vs 9.7%; North America, 46.9% vs 12.2%). Patients in age groups 12–17 (50.6% vs 14.0%), 18–64 (52.2% vs 10.3%), and ≥65 (60.5% vs 15.4%) also achieved IGA-TS at higher proportions with ruxolitinib 1.5% versus vehicle. Black, white, and Asian/other patients similarly all achieved higher rates of IGA-TS with ruxolitinib 1.5% versus vehicle (black, 38.1% vs 11.5%; white, 57.3% vs 12.3%; Asian/other, 56.3% vs 5.0%).[23]

An analysis of efficacy in patients who had relatively more severe AD at baseline, defined as BSA involvement of ≥10% and EASI score of ≥16, revealed that this subpopulation of patients (n=81; in whom systemic therapies may be applicable) exhibited high rates of clinical response with ruxolitinib cream. At week 8, these patients achieved higher response rates with either ruxolitinib 0.75% or 1.5% versus vehicle for IGA-TS (0.75%: 50.0%; 1.5%: 59.4%; vehicle: 0%), EASI-75 (0.75% 75.0%; 1.5%: 71.9%; vehicle: 7.7%), and itch NRS4 (0.75% 50.0%; 1.5%: 61.1%; vehicle: 27.3%).[24]

Safety

This section reviews the safety of ruxolitinib cream in clinical trials in patients with AD, including a phase I open-label maximum-use trial, a phase II, randomized, double-blind, dose-ranging, vehicle-and active-controlled trial, and two phase III randomized, double-blind, vehicle-controlled trials of identical design (TRuE-AD1 and TRuE-AD2). A summary of safety data is presented in Table 2.

Phase I

One of the primary endpoints in this open-label, phase I, maximum-use condition study was the safety of ruxolitinib 1.5% cream BID, which was measured using the frequency, duration, and severity of the treatment-emergent adverse events (TEAEs) in all 41 AD patients enrolled. Thirty-seven (90.2%) patients participated in the extended period (28 days), thus completing the study.[11]

Table 2 TEAEs for Ruxolitinib 1.5% Cream BID vs Vehicle BID (if Applicable) in Phase I–III Studies

	Phase I	Phase II[a]		Phase III[b]	
	Ruxolitinib 1.5%	Vehicle	Ruxolitinib 1.5%	Vehicle	Ruxolitinib 1.5%
Total number of patients (n)	41	52	50	250	499
Patients with TEAEs, n (%)	13 (31.7)	17 (32.7)	12 (24.0)	83 (33.2)	132 (26.5)
Most common TEAEs					
Nasopharyngitis, n (%)	1 (2.4)	4 (7.7)	2 (4.0)	2 (0.8)	13 (2.6)
URI, n (%)	2 (4.9)	3 (5.8)	1 (2.0)	5 (2.0)	12 (2.4)
Headache, n (%)	N/A	2 (3.8)	2 (4.0)	5 (2.0)	11 (2.2)
Application site pain, n (%)[c]	N/A	2 (3.8)	1 (2.0)	12 (4.8)	4 (0.8)
Application site pruritus, n (%)	1 (2.4)	N/A	N/A	7 (2.8)	1 (0.2)
AD, n (%)	N/A	4 (7.7)	0	11 (4.4)	2 (0.4)
Serious TEAE, n (%)	1 (2.4)	0	0	2 (0.8)	3 (0.6)
Discontinuation due to TEAE, n (%)	1 (2.4)	1 (1.9)	0	8 (3.2)	4 (0.8)
Treatment-related AEs, n (%)	4 (9.8)	5 (9.6)	3 (6.0	28 (11.2)	24 (4.8)
Most common treatment-related AEs					
Application site pain, n (%)[c]	N/A	2 (3.8)	1 (2.0)	11 (4.4)	4 (0.8)
Application site pruritus, n (%)	N/A	N/A	N/A	6 (2.4)	0

Notes: [a]Results from the double-blind period. [b]Pooled TEAEs from TRuE-AD1 and TRuE-AD2 during the 8-week vehicle-controlled period. [c]Application site burning was counted towards application site pain.

Abbreviations: AD, atopic dermatitis; AEs, adverse events; BID, twice daily; N/A, not applicable; TEAEs, treatment-emergent adverse events; TRuE-AD1, Topical Ruxolitinib Evaluation in Atopic Dermatitis Study 1; TRuE-AD2, Topical Ruxolitinib Evaluation in Atopic Dermatitis Study 2; URI, upper respiratory infection.

Overall, ruxolitinib was well-tolerated, with no fatal TEAEs. Thirteen (31.7%) patients experienced TEAEs, most mild-to-moderate in severity. Among these, four patients (9.8%) experienced TEAEs that were determined to be potentially related to treatment (neutropenia, n = 1; aspartate aminotransferase elevation, n = 2; alanine aminotransferase elevation, n = 1; dyspnea [likely from applying ruxolitinib on face], n = 1; hemoglobin decrease, n = 1]). Notably, those with low neutrophil or hemoglobin counts presented with low counts at baseline. Furthermore, all of these patients had a plasma concentration of ruxolitinib below the half-maximal inhibitory concentration (IC50) needed to inhibit thrombopoietin (TPO)-stimulated phosphorylation of signal transducer and activator of transcription 3 (STAT3) in whole blood (281 nM). Although there was a small increase in platelet counts on day 15, it spontaneously returned to baseline by day 28.[11]

Phase II

A multicenter phase II, randomized, double-blind, dose-ranging, vehicle-controlled and active-controlled trial (NCT03011892) investigated the safety and tolerability of ruxolitinib cream in 307 adult AD patients by monitoring the frequency, duration, and severity of AEs. Patients were randomized to vehicle cream BID, active control (triamcinolone 0.1% cream BID for 4 weeks followed by vehicle cream for four additional weeks), or ruxolitinib cream (0.15% QD, 0.5% QD, 1.5% QD, or 1.5% BID) for 8 weeks of double-blinded period. Protocol-compliant patients with no safety issues were eligible for an additional 4 weeks of non-blinded treatment with ruxolitinib 1.5% cream BID, which was proceeded by a 4-week safety follow-up period. Ruxolitinib was not applied on the face in this trial.[7]

Ruxolitinib cream demonstrated a safe profile and was well tolerated in the phase II study. All treatment-related AEs were mild or moderate in severity, and no patient experienced a serious TEAEs. The most common treatment-related AE

was site application pain across all ruxolitinib cream treatment groups (0.15% QD, n=1 [2.0%]; 1.5% QD, n=2 [3.9%]; 1.5% BID, n=1 [2.0%]) and in the vehicle group (n=2 [3.8%]). Notably, the frequency and severity of TEAEs were comparable to those observed with vehicle application. No patient in the open-label period discontinued the study due to TEAEs, and no more than one patient reported treatment-related AD in any of the groups. Three patients discontinued the study in the double-blinded period due to treatment-unrelated TEAEs. A transient increase in platelet count (~10%) was noted in patients treated with ruxolitinib 1.5% cream (QD or BID), peaking at 2 weeks of treatment, similar to findings observed in the phase I study. No other significant clinical hematological changes occurred.[7]

Phase III

Two multicenter phase III, randomized, double-blind, vehicle-controlled trialsof identical design (TRuE-AD1 [NCT03745638] and TRuE-AD2 [NCT03745651]) evaluated the safety and tolerability of ruxolitinib cream (secondary endpoints) in all 1249 randomized AD patients, ages 12 years and older.[9] A separate study analyzed the safety of ruxolitinib cream in AD adolescents based on the data from both phase III trials (n=245; 19.6%). TRuE-AD1 and TRuE-AD2 comprised 19.5% and 19.7% of the adolescents (ages 12–18 years), respectively.[18]

Safety of Ruxolitinib Cream in AD Patients Ages 12 Years and Older

The safety profiles of ruxolitinib 0.75% and 1.5% cream were similar across all treatment groups in both phase III trials. Ruxolitinib cream was well tolerated on all AD lesions, irrespective of location. Application site reactions, such as stinging and burning, were infrequent (<1.0%). The most common treatment-related TEAE was burning sensation at site application which was reported mostly with vehicle use (vehicle [4.4%]; ruxolitinib 0.75% [0.6%] and ruxolitinib 1.5% [0.8%]). In total, 15 patients discontinued the studies during the 8-week vehicle-controlled period due to TEAEs (vehicle, n = 8 [3.2%]; 0.75% RUX, n = 4 [0.8%]; 1.5% RUX, n = 3 [0.6%]). All serious TEAEs were considered unrelated to treatment (vehicle [0.8%]; ruxolitinib 0.75% [0.8%] and ruxolitinib 1.5% [0.6%]). Paralleling results from the phase I and II trials, there was a slight transient increase from baseline in plasma platelet counts at week 2; however, no other significant pattern in hematologic laboratory values (or changes in platelet volume)[1] was observed.[9] There were no findings suggestive of systemic JAK inhibition.[9]

Safety of Ruxolitinib Cream in AD Patients Ages 12–18 Years

The safety profile of ruxolitinib cream among AD adolescents was comparable to the overall population's safety profile. Ruxolitinib cream was well tolerated in the adolescents, including on sensitive skin areas. Treatment-related AEs were reported in 4.6% and 3.3% of the adolescent patients who applied ruxolitinib 0.75% and 1.5% cream, respectively, in contrast to 11.1% who applied vehicle cream. No serious treatment-related AEs occurred. No adolescent patient discontinued the study due to AEs. No findings suggested local or systemic safety signals.[18]

Pharmacokinetics

This section reviews the pharmacokinetics (PK) of ruxolitinib cream in clinical trials in patients with AD, including a phase I open-label maximum-use trial, a phase II, randomized, double-blind, dose-ranging, vehicle- and active-controlled trial, and two phase III randomized, double-blind, vehicle-controlled trials of identical design (TRuE-AD1 and TRuE-AD2).

Phase I

Ruxolitinib's mean (standard deviation [±SD]) Css was 104 (±309) nM during the first 28 days of the study. On day 1, ruxolitinib's mean plasma concentration peaked at 241 nM 4 hours after the drug's application; lower values were observed in those with <40% affected BSA. Ruxolitinib's plasma concentration also trended lower in adolescents than adults, consistent with the smaller surface area treated and amount of drug applied in adolescents. The median pre-dose trough concentration (C_{trough}) remained stable during the first 28-day period but lowered by day 56; this observation likely reflects a decrease in the number of active lesions since only active lesions were treated during the extended period (days 29–56).[11]

Five patients with the highest mean Css underwent further studies. Two patients had a baseline affected BSA > 40% (45% and 90%, respectively) and exhibited Css levels above the IC50 for TPO-stimulated STAT3 on days 1, 15, and 28. One of the five patients experienced a 57% reduction in platelet count on day 28 but remained within the average platelet range for the entirety of the study. A different patient experienced a treatment-related elevation in liver function enzymes (alanine aminotransferase [baseline, 18 IU/L; day 15, 94 IU/L] and aspartate aminotransferase [baseline, 30 IU/L; day 15, 67 IU/L]), which resolved without ruxolitinib dosage adjustments. None of the five patients experienced any hematological AEs during the study period.[11]

Ruxolitinib's mean systemic bioavailability (±SD) was 2.5% (±3.6%). There was no increase in ruxolitinib's peak plasma concentration (C_{max}) at 12 hours post-application or area under the curve between hours 0 to 12 on days 1 through 28, suggesting that ruxolitinib 1.5% cream does not accumulate in plasma when dosed BID for 28 days. Furthermore, no pattern between hematologic laboratory values and plasma concentrations was observed.[11]

Phase II

One hundred eighty-eight patients from one of the four ruxolitinib treatment groups contributed to the phase II PK population. Ruxolitinib's topical bioavailability was neither dose- nor strength- dependent.[1,7] The drug's 1.5% cream bioavailability (±SD%) was 5.68% (± 5.58%), significantly lower than the expected bioavailability of oral ruxolitinib. Notably, ruxolitinib 1.5% cream BID mean steady-state C_{trough} was estimated at <20% of the IC50 value necessary for JAK2 inhibition, indicating a low risk for systemic AEs associated with JAK1/JAK2 inhibition (ie, myelosuppression suppression). Lastly, the plasma PK profile of ruxolitinib cream in AD patients was similar to that observed in psoriasis patients.[1]

Phase III

Nine hundred and fifty-one patients pooled from both TRuE-AD1 and TRuE-AD2 studies (from either ruxolitinib treatment groups [0.75% and 1.5%]) constituted the PK population. The mean (±SD) Css of ruxolitinib 0.75% and 1.5% cream BID in the vehicle-controlled period were 23.8 (±35.0) nM (n = 472) and 35.7 (±55.0) nM (n = 479), respectively – a fraction of the whole blood IC50 needed for TPO-stimulated phosphorylation of STAT 3 (281 nM). No correlation between Css and changes in hematological parameters was observed. There was also no difference in topical ruxolitinib's bioavailability across the different strength groups (ruxolitinib 0.75%, 7.68%; ruxolitinib 1.5%, 6.22%), a finding analogous to that observed in ruxolitinib's phase II trial.[1]

Conclusion

As the first FDA-approved topical JAK inhibitor, ruxolitinib 1.5% cream represents a novel therapeutic targeting approach for AD. Based on currently available studies, ruxolitinib 1.5% cream has been demonstrated to provide strong efficacy with an acceptable safety profile for the treatment of AD. Patients in Phase I–III studies saw significant clinical improvements with ruxolitinib cream versus vehicle, with large proportions achieving EASI-75 and EASI-90 with treatment. The rapid and sustained onset of itch relief brought about by ruxolitinib cream, as observed in each clinical trial reported here, is of significant additional clinical value given the significant role that itch plays in the AD disease process. Furthermore, no significant adverse events have been identified in connection to the use of topical ruxolitinib, and systemic absorption of the drug has been shown to produce levels in blood that are of little clinical concern. In sum, topical ruxolitinib 1.5% cream is an effective and safe treatment option for mild-to-moderate adolescent and adult AD patients.

Abbreviations

AD, atopic dermatitis; BID, twice daily; BSA, body surface area; Css, concentration of drug in plasma at steady state; C_{trough}, pre-dose trough concentration; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EASI-75, 75% improvement in EASI; IC50 ex vivo half-maximal inhibitory concentration; IGA, International Global Assessment; IGA-TS IGA treatment success; JAK, Janus kinase; JAKi, Janus kinase inhibitors; NRS, numerical rating scale; SD, standard deviation; NRS4, ≥4-point reduction in NRS score; PROMIS-8b, Patient-Reported Outcomes

Measurement Information System short form 8b questionnaire; (PK) pharmacokinetics; POEM, Patient-Oriented Eczema Measure; PROMIS-8a, PROMIS short form 8a questionnaire scores; QD, once daily; QoL, quality of life; IQR, interquartile range; STAT 3, signal transducer and activator of transcription 3; TARC/CCL17, thymus and activation-regulated chemokine; TEAE, treatment-emergent adverse event; TPO, thrombopoietin; TRuE-AD1, Topical Ruxolitinib Evaluation in Atopic Dermatitis Study 1; TRuE-AD2, Topical Ruxolitinib Evaluation in Atopic Dermatitis Study 2; WPAI:SHP v2.0, The Work Productivity and Activity Impairment Questionnaire-Specific Health Problem version 2.0.

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References

1. Gong X, Chen X, Kuligowski ME, et al. Pharmacokinetics of ruxolitinib in patients with atopic dermatitis treated with ruxolitinib cream: data from phase ii and iii studies. *Am J Clin Dermatol*. 2021;22(4):555–566. doi:10.1007/s40257-021-00610-x
2. Chan LS, Shi VY. *Atopic Dermatitis: Inside Out or Outside*. 1st ed. Elsevier; 2022.
3. Smith Begolka W, Chovatiya R, Thibau IJ, Silverberg JI. Financial burden of atopic dermatitis out-of-pocket health care expenses in the United States. *Dermatitis*. 2020;32(1S):S62–S70. doi:10.1097/DER.0000000000000715
4. Laughter MR, Maymone MBC, Mashayekhi S, et al. The global burden of atopic dermatitis: lessons from the Global Burden of Disease Study 1990–2017. *Br J Dermatol*. 2021;184(2):304–309. doi:10.1111/bjd.19580
5. Czarnowicki T, He H, Krueger JG, Guttman-Yassky E. Atopic dermatitis endotypes and implications for targeted therapeutics. *J Allergy Clin Immunol*. 2019;143(1):1–11. doi:10.1016/j.jaci.2018.10.032
6. Freitas E, Gooderham M, Torres T. New topical therapies in development for atopic dermatitis. *Drugs*. 2022;82(8):843–853. doi:10.1007/s40265-022-01722-2
7. Kim BS, Howell MD, Sun K, Papp K, Nasir A, Kuligowski ME. Treatment of atopic dermatitis with ruxolitinib cream (JAK1/JAK2 inhibitor) or triamcinolone cream. *J Allergy Clin Immunol*. 2020;145(2):572–582. doi:10.1016/j.jaci.2019.08.042
8. Chapman S, Gold LS, Lim HW. Janus kinase inhibitors in dermatology: part II. A comprehensive review. *J Am Acad Dermatol*. 2022;86(2):414–422. doi:10.1016/j.jaad.2021.06.873
9. Papp K, Szepietowski JC, Kircik L, et al. Efficacy and safety of ruxolitinib cream for the treatment of atopic dermatitis: results from 2 Phase 3, randomized, double-blind studies. *J Am Acad Dermatol*. 2021;85(4):863–872. doi:10.1016/j.jaad.2021.04.085
10. Ruxolitinib (Opzelura) for atopic dermatitis. *Med Lett Drugs Ther*. Available from: https://secure.medicalletter.org/TML-article-1642d. Accessed 21 October 2022.
11. Bissonnette R, Call RS, Raoof T, et al. A maximum-use trial of ruxolitinib cream in adolescents and adults with atopic dermatitis. *Am J Clin Dermatol*. 2022;23(3):355–364. doi:10.1007/s40257-022-00690-3
12. Bashaw ED, Tran DC, Shukla CG, Liu X. Maximal usage trial: an overview of the design of systemic bioavailability trial for topical dermatological products. *Ther Innov Regul Sci*. 2015;49(1):108–115. doi:10.1177/2168479014539157
13. Kim BS, Sun K, Papp K, Venturanza M, Nasir A, Kuligowski ME. 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. *J Am Acad Dermatol*. 2020;82(6):1305–1313. doi:10.1016/j.jaad.2020.02.009
14. Owens S, Jones H, Kuligowski ME, Howell MD. 18263 Association between an itch-free state in atopic dermatitis treated with ruxolitinib cream and systemic inflammatory mediators. *J Am Acad Dermatol*. 2020;83(6):AB95–AB95. doi:10.1016/j.jaad.2020.06.469
15. Buysse DJ, Lan YU, Moul DE, et al. Development and validation of patient-reported outcome measures for sleep disturbance and sleep-related impairments. *Sleep*. 2010;33(6):781–792. doi:10.1093/sleep/33.6.781
16. Blauvelt A, Szepietowski JC, Papp K, et al. 26884 Ruxolitinib cream rapidly decreases pruritus in atopic dermatitis: pooled results from two phase 3 studies. *J Am Acad Dermatol*. 2021;85(3):AB121–AB121. doi:10.1016/j.jaad.2021.06.501
17. Simpson EL, Boguniewicz M, Thaçi D, et al. 26887 Effect of ruxolitinib cream on sleep disturbance and sleep impairment: pooled analysis from two randomized phase 3 studies. *J Am Acad Dermatol*. 2021;85(3):AB121–AB121. doi:10.1016/j.jaad.2021.06.502
18. Eichenfield LF, Simpson EL, Siegfried EC, et al. 27633 Efficacy and safety of ruxolitinib cream among adolescents with atopic dermatitis: pooled Results from two phase 3 studies. *J Am Acad Dermatol*. 2021;85(3):AB158–AB158. doi:10.1016/j.jaad.2021.06.644
19. Papp K, Szepietowski JC, Kircik L, et al. 27716 Efficacy of ruxolitinib cream for the treatment of atopic dermatitis by baseline clinical characteristics: pooled subgroup analysis from two randomized phase 3 studies. *J Am Acad Dermatol*. 2021;85(3):AB160–AB161. doi:10.1016/j.jaad.2021.06.653
20. Eichenfield LF, Silverberg JI, Kuligowski ME, Venturanza ME, Sun K, Augustin M. 28200 Effects of ruxolitinib cream on work productivity and activity impairment in patients with atopic dermatitis: pooled results from two phase 3 studies. *J Am Acad Dermatol*. 2021;85(3):AB179–AB179. doi:10.1016/j.jaad.2021.06.728
21. Simpson EL, Kircik L, Blauvelt A, et al. 24916 Efficacy of ruxolitinib cream in patients with atopic dermatitis who demonstrated partial responses: pooled analysis from two randomized phase 3 studies. *J Am Acad Dermatol*. 2021;85(3):AB50–AB50. doi:10.1016/j.jaad.2021.06.226

22. Blauvelt A, Eichenfield LF, Kuligowski ME, Venturanza ME, Sun K, Silverberg JI. 27482 Efficacy of ruxolitinib cream among patients with atopic dermatitis based on previous medication history: pooled results from two phase 3 studies. *J Am Acad Dermatol*. 2021;85(3):AB148–AB148. doi:10.1016/j.jaad.2021.06.605
23. Papp K, Szepietowski JC, Kircik L, et al. 27496 Efficacy of ruxolitinib cream for the treatment of atopic dermatitis by baseline patient demographics: pooled subgroup analysis from two randomized phase 3 studies. *J Am Acad Dermatol*. 2021;85(3):AB149–AB149. doi:10.1016/j.jaad.2021.06.609
24. Simpson EL, Kircik L, Blauvelt A, et al. 27620 Effects of ruxolitinib cream in patients with atopic dermatitis with baseline body surface area ≥10% and Eczema Area and Severity Index score ≥16: pooled results from two phase 3 studies. *J Am Acad Dermatol*. 2021;85(3):AB157–AB157. doi:10.1016/j.jaad.2021.06.640