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Journal

Dermatology and Therapy, 14(11)

ISSN

2193-8210

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Publication Date

2024-11-01

DOI

10.1007/s13555-024-01272-3

Peer reviewed

Dermatol Ther (Heidelb) (2024) 14:3161–3174
https://doi.org/10.1007/s13555-024-01272-3

BRIEF REPORT

Efficacy and Safety of Ruxolitinib Cream in Atopic Dermatitis Based on Previous Medication History

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Received: August 1, 2024 / Accepted: September 2, 2024 / Published online: October 7, 2024

ABSTRACT

Introduction: For some patients with atopic dermatitis (AD), topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), and systemic therapies are inadequate to control disease or are associated with adverse events (AEs). Ruxolitinib cream monotherapy demonstrated anti-inflammatory and anti-pruritic effects among patients enrolled in two pivotal phase 3 studies (TRuE-AD1/TRuE-AD2); most patients had long-term disease control with as-needed use during the 44-week long-term safety (LTS) period. This post hoc analysis explored efficacy and safety of 1.5% ruxolitinib cream by previous medication use.

Methods: Patients aged ≥ 12 years enrolled in TRuE-AD1/TRuE-AD2 were randomized 2:2:1 to twice-daily 0.75% or 1.5% ruxolitinib cream or vehicle cream for 8 weeks, followed by a 44-week LTS period; patients initially on vehicle were re-randomized 1:1 to either ruxolitinib cream strength.

Results: Within 12 months of enrollment ($N = 1249$), previous AD therapies were used by 89.4% of efficacy-evaluable patients applying vehicle or ruxolitinib cream ($n = 725$); of these, 80.4% received TCS ($n = 583$), 22.2% TCI ($n = 161$), 20.3% TCS + TCI ($n = 147$), and 18.9% systemic therapies ($n = 137$). Across previous medication subgroups, achievement of Investigator's Global Assessment (IGA)-treatment success (IGA 0/1 with ≥ 2-grade improvement from baseline), ≥ 75% improvement in Eczema Area and Severity Index from baseline, and ≥ 4-point improvement in Itch numerical rating scale score from baseline at Week 8 did not substantially differ among patients who applied ruxolitinib cream. Outcomes were similar to those in the overall study population. At all study

Prior Presentation Data included in this manuscript have previously been presented at: American Academy of Dermatology Virtual Meeting, San Francisco, CA, USA, April 23–25, 2021, and at Revolutionizing Atopic Dermatitis Virtual Conference, June 13, 2021, with encores at 30th European Academy of Dermatology and Venereology (EADV) Virtual Congress, September 29–October 2, 2021, and at Fall Clinical Dermatology Conference, Las Vegas, NV, USA, October 21–24, 2021.

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visits during the LTS period, > 70% of patients in each subgroup had IGA 0/1 and a low percentage (generally < 3%) of affected body surface area. Treatment-related AEs across subgroups were reported in 7.3% ($n = 35/481$) to 17.4% ($n = 19/109$) of patients.

Conclusions: Continuous-use ruxolitinib cream monotherapy for 8 weeks followed by as-needed use was effective and well tolerated, regardless of previous topical or systemic therapy, with outcomes similar to those achieved in the overall study population.

Trial Registration: ClinicalTrials.gov Identifier, NCT03745638/NCT03745651.

PLAIN LANGUAGE SUMMARY

Atopic dermatitis (AD) is a skin condition resulting in itchy, dry, and inflamed skin. For some patients, medication applied to the skin (topical treatment) or medication taken by mouth or injection (systemic treatment) may not control disease or may have side effects. In the TRuE-AD1/TRuE-AD2 trials in patients with mild to moderate AD aged 12 years and older, ruxolitinib cream used twice daily for 8 weeks reduced itch and redness. As-needed ruxolitinib cream use for another 44 weeks maintained long-term disease control. Here, we assessed disease control with 1.5% ruxolitinib cream in patients with AD based on their previous AD treatments. Of the 725 patients who had used previous AD treatments, most (80.4%) used topical corticosteroids (TCS). After 8 weeks, disease control outcomes were similar across all previous treatment subgroups (i.e., TCS, topical calcineurin inhibitors [TCI], TCS + TCI, systemic treatments) and were similar to the outcomes in the overall study population. After 44 weeks of as-needed ruxolitinib cream use, over two-thirds of patients still had clear or almost clear skin. The percentage of affected body surface area also remained low. Regardless of the AD treatments previously used, twice-daily ruxolitinib cream use for 8 weeks and then as needed for 44 weeks was generally well tolerated. These results show that twice-daily 1.5% ruxolitinib cream for 8 weeks, followed by as-needed treatment for 44 weeks, provides long-term control of AD in patients regardless of previous topical or systemic treatment received.

Keywords: Atopic dermatitis; Eczema; Janus kinases; Ruxolitinib cream; Treatment outcome

Key Summary Points
Although topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) have been traditionally used as first-line treatments for patients with mild to moderate atopic dermatitis (AD), a significant unmet need remains for treatments for long-term disease control without concerns regarding tolerability or long-term use.
Nearly 90% of adults and adolescents enrolled in the phase 3 studies of ruxolitinib cream had received other therapies for AD in the previous 12 months, including 80% who received TCS.
Ruxolitinib cream monotherapy demonstrated safety, efficacy, and tolerability, regardless of previous therapy use, in adolescents and adults with mild to moderate AD.

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by itching, dryness, and redness [1]. Therapies for AD include topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), topical Janus kinase (JAK) inhibitors, and systemic immunomodulatory agents [1]. In some patients, TCS and TCI may be insufficient because of inadequate efficacy, delayed onset of effect, duration-of-use limitations, anatomic use restrictions, poor tolerability, and/or adverse

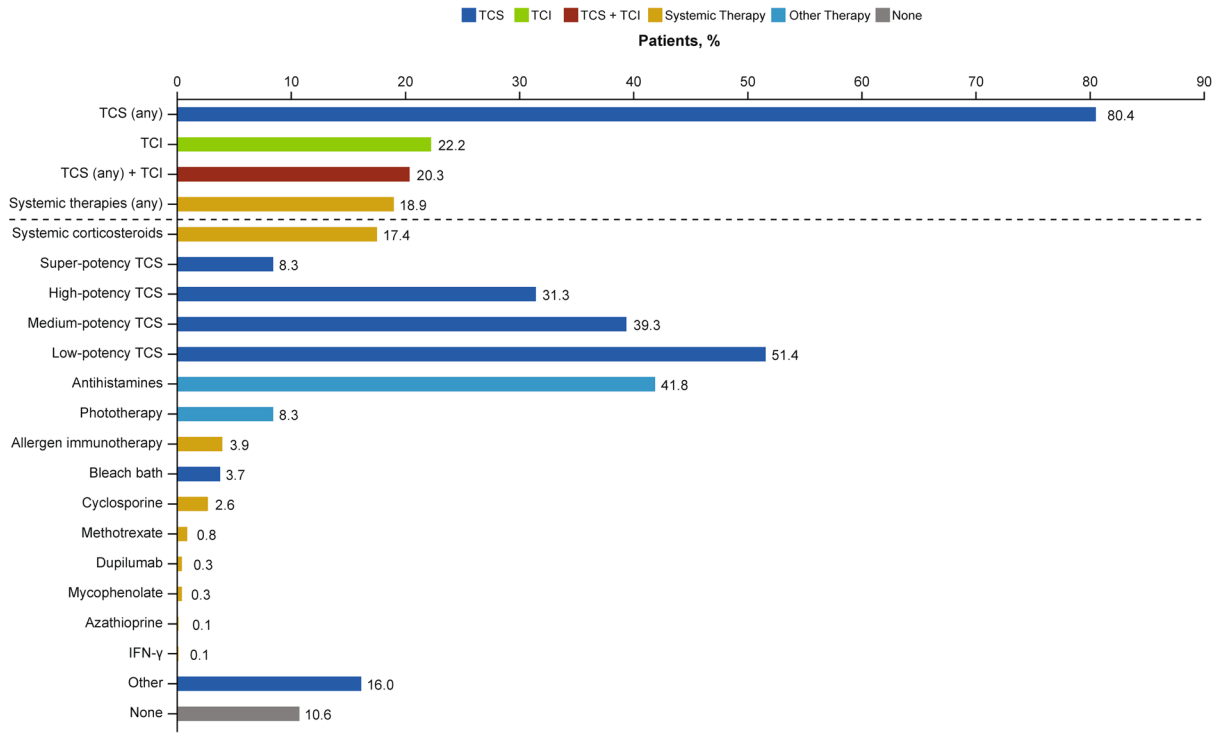

Fig. 1 Previous therapies at baseline among efficacy-evaluable patients randomized to vehicle or 1.5% ruxolitinib cream in TRuE-AD1 and TRuE-AD2 ($n = 725$). *IFN-γ* interferon-gamma, *TCI* topical calcineurin inhibitor, *TCS* topical corticosteroid

reactions such as striae [1–3]. Systemic therapies are indicated for patients whose AD is refractory to topical therapies and for whom phototherapy is not an option [4]. However, use of systemic therapies may be limited by comorbidities, age, and risk of severe adverse events (AEs); use of some systemic therapies is also restricted to short- or limited-term use [4, 5].

A cream formulation of ruxolitinib, a selective inhibitor of JAK1 and JAK2 [6], demonstrated anti-pruritic and anti-inflammatory action with twice-daily (BID) use versus vehicle and was well tolerated in adults and adolescents with AD in 2 identical phase 3 studies (TRuE-AD1 [NCT03745638]/TRuE-AD2 [NCT03745651]) [7]. Ruxolitinib cream also demonstrated effective disease control with as-needed use during the 44-week long-term safety (LTS) period [8]. Patients who have inadequate response to TCS and TCI or whose condition may not be suitable for these therapies may benefit from using ruxolitinib cream before progressing to systemic therapies. Here, efficacy, disease control, safety, and tolerability of ruxolitinib cream monotherapy were analyzed based on previous treatment history using pooled data from the two phase 3 studies.

METHODS

Details regarding study design of the TRuE-AD studies were previously reported [7, 8]. Studies were conducted in accordance with Good Clinical Practice guidelines and 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.

Information on AD therapies used in the 12 months before screening was captured, and patients were grouped by previous medication

Table 1 Baseline demographics and clinical characteristics by previous medication

Characteristic	Vehicle (*n* = 250)	1.5% Ruxolitinib cream (*n* = 499)
TCS	***n* = 205**	***n* = 401**
Age, median (range), years	34.0 (12–82)	32.0 (12–85)
Female, *n* (%)	130 (63.4)	243 (60.6)
Race, *n* (%)		
White	145 (70.7)	297 (74.1)
Black	45 (22.0)	82 (20.4)
Asian	7 (3.4)	15 (3.7)
Other	8 (3.9)	7 (1.7)
BSA, mean (SD), %	9.8 (5.6)	9.8 (5.4)
EASI, mean (SD)	8.1 (4.9)	8.2 (4.7)
IGA, *n* (%)		
2	43 (21.0)	88 (21.9)
3	162 (79.0)	313 (78.1)
Itch NRS score, mean (SD)[a]	5.2 (2.4)	5.2 (2.4)
≥ 4, *n* (%)	131 (63.9)	259 (64.6)
Disease duration, mean (SD), years	21.3 (16.9)	20.1 (14.7)
Facial involvement, *n* (%)[b]	80 (39.0)	167 (41.6)
Number of flares in last 12 months, mean (SD)[b]	7.6 (28.2)	6.1 (19.4)
TCI	***n* = 60**	***n* = 101**
Age, median (range), years	29.0 (12–75)	24.0 (13–77)
Female, *n* (%)	39 (65.0)	62 (61.4)
Race, *n* (%)		
White	57 (95.0)	94 (93.1)
Black	0	3 (3.0)
Asian	1 (1.7)	2 (2.0)
Other	2 (3.3)	2 (2.0)
BSA, mean (SD), %	10.9 (5.4)	12.2 (5.4)
EASI, mean (SD)	9.3 (5.0)	10.2 (5.6)
IGA, *n* (%)		
2	13 (21.7)	7 (6.9)
3	47 (78.3)	94(93.1)
Itch NRS score, mean (SD)[c]	4.8 (2.5)	4.9 (2.6)
≥ 4, *n* (%)	39 (65.0)	61 (60.4)

Table 1 continued

Characteristic	Vehicle (*n* = 250)	1.5% Ruxolitinib cream (*n* = 499)
Disease duration, mean (SD), years	24.9 (17.5)	20.8 (12.5)
Facial involvement, *n* (%)[b]	43 (71.7)	76 (75.2)
Number of flares in last 12 months, mean (SD)[b]	4.4 (10.1)	3.1 (3.5)
TCS + TCI	***n* = 57**	***n* = 90**
Age, median (range), years	29.0 (12–75)	24.5 (13–77)
Female, *n* (%)	37 (64.9)	57 (63.3)
Race, *n* (%)		
White	54 (94.7)	84 (93.3)
Black	0	3 (3.3)
Asian	1 (1.8)	2 (2.2)
Other	2 (3.5)	1 (1.1)
BSA, mean (SD), %	11.0 (5.5)	12.2 (5.4)
EASI, mean (SD)	9.6 (5.0)	10.5 (5.5)
IGA, *n* (%)		
2	11 (19.3)	4 (4.4)
3	46 (80.7)	86 (95.6)
Itch NRS score, mean (SD)[d]	4.9 (2.4)	5.0 (2.5)
≥ 4, *n* (%)	38 (66.7)	56 (62.2)
Disease duration, mean (SD), years	25.2 (17.7)	21.3 (12.8)
Facial involvement, *n* (%)[b]	41 (71.9)	71 (78.9)
Number of flares in last 12 months, mean (SD)[b]	4.2 (10.2)	3.3 (3.7)
Systemic therapies	***n* = 46**	***n* = 95**
Age, median (range), years	33.5 (12–82)	35.0 (12–77)
Female, *n* (%)	27 (58.7)	58 (61.1)
Race, *n* (%)		
White	40 (87.0)	80 (84.2)
Black	3 (6.5)	8 (8.4)
Asian	2 (4.3)	4 (4.2)
Other	1 (2.2)	3 (3.2)
BSA, mean (SD), %	11.9 (6.0)	12.9 (5.5)
EASI, mean (SD)	10.5 (6.0)	10.3 (5.2)
IGA, *n* (%)		
2	8 (17.4)	8 (8.4)
3	38 (82.6)	87 (91.6)

Table 1 continued

Characteristic	Vehicle ($n = 250$)	1.5% Ruxolitinib cream ($n = 499$)
Itch NRS score, mean (SD)[c]	5.7 (2.3)	5.6 (2.3)
≥ 4, *n* (%)	34 (73.9)	68 (71.6)
Disease duration, mean (SD), years	21.7 (16.7)	24.9 (17.1)
Facial involvement, *n* (%)[b]	26 (56.5)	58 (61.1)
Number of flares in last 12 months, mean (SD)[b]	4.5 (6.1)	4.4 (5.0)

BSA body surface area, *EASI* Eczema Area and Severity Index, *IGA* Investigator's Global Assessment, *NRS* numerical rating scale, *TCI* topical calcineurin inhibitor, *TCS* topical corticosteroid

[a]Data missing from 27 patients (vehicle, $n = 12$; 1.5% ruxolitinib cream, $n = 15$)

[b]Patient-reported

[c]Data missing from 2 patients (vehicle, $n = 1$; 1.5% ruxolitinib cream, $n = 1$)

[d]Data missing from 1 patient (vehicle, $n = 1$)

[e]Data missing from 6 patients (vehicle, $n = 3$; 1.5% ruxolitinib cream, $n = 3$)

history as follows: TCS, TCI, TCS + TCI, or systemic therapies (see Fig. 1). The washout period for previous therapies was 1 week for topical AD treatments, 4 weeks for systemic corticosteroids or other immunomodulating agents, and 12 weeks or 5 half-lives for biologics. During the 8-week vehicle-controlled (VC) period of continuous BID use, efficacy endpoints included percentages of patients achieving Investigator's Global Assessment (IGA)-treatment success (IGA-TS; score of 0/1 [clear or almost clear skin] with ≥ 2-grade improvement from baseline), ≥ 75% improvement in Eczema Area and Severity Index (EASI) from baseline (EASI75), and ≥ 4-point improvement in Itch numerical rating scale (NRS) score from baseline (NRS4). IGA, EASI, and percentage affected body surface area (BSA) were assessed at Weeks 2, 4, and 8; Itch NRS was collected daily through Week 8. Efficacy endpoints at Week 8 were analyzed for patients originally randomized to vehicle or 1.5% ruxolitinib cream, except for 24 randomized patients from one study site, who were excluded for quality issues. Disease-control endpoints during the as-needed use LTS period included the percentage of patients who had IGA 0/1 and quantification of affected BSA at each visit every 4 weeks. These were analyzed from baseline through Week 52 for efficacy-evaluable patients who continued into the LTS period and applied 1.5% ruxolitinib cream, including those who switched from vehicle.

Safety and tolerability assessments included the frequency of reported treatment-emergent AEs (TEAEs), treatment-related AEs (TRAEs), and TEAEs leading to treatment discontinuation. Safety data were adjusted for exposure for the 52-week analysis. Patients who applied vehicle during the VC period and all patients who applied 1.5% ruxolitinib cream at any time during the study were included in the safety analysis.

IGA-TS, EASI75, and Itch NRS4 data from the VC period were analyzed by logistic regression and reported descriptively. Only patients with baseline Itch NRS ≥ 4 were included in Itch NRS4 analyses. Other data were summarized using descriptive statistics.

RESULTS

Of 1072 patients who were enrolled and continued into the LTS period, 446 were initially randomized to 1.5% ruxolitinib cream, and 99 who were initially randomized to vehicle switched to 1.5% ruxolitinib cream [7, 8]. Pooled patient demographics and baseline clinical characteristics were comparable between treatment groups

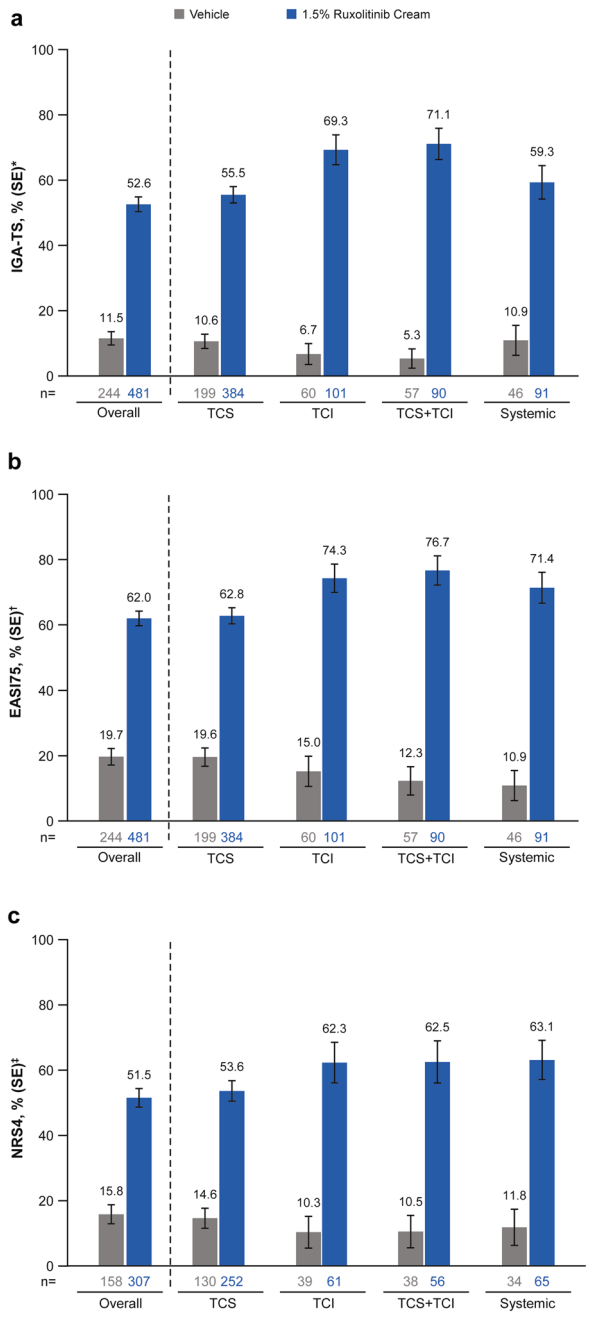

Fig. 2 Percentage of patients achieving **a** IGA-TS, **b** EASI75, or **c** Itch NRS4 at Week 8 by previous medication history. *Patients achieving an IGA score of 0 or 1 with an improvement of ≥ 2 points from baseline. Patients with missing post-baseline values were imputed as nonresponders at Week 8. †Patients with missing EASI post-baseline values were imputed as nonresponders at Week 8. ‡Patients in the analysis had an Itch NRS score ≥ 4 at baseline. Patients with missing post-baseline values were imputed as nonresponders at Weeks 2, 4, and 8. *EASI75* ≥ 75% improvement in Eczema Area and Severity Index from baseline, *IGA-TS* Investigator's Global Assessment–treatment success, *NRS* numerical rating scale, *NRS4* ≥ 4-point improvement in Itch NRS score versus baseline, *TCI* topical calcineurin inhibitor, *TCS* topical corticosteroid

[8] and previous medication subgroups (Table 1). Previous AD therapy with ≥ 1 treatment within the previous 12 months was reported in 89.4% (n = 648/725) of efficacy-evaluable patients who applied vehicle or 1.5% ruxolitinib cream. The most common previous AD therapies included TCS (80.4% [n = 583]; low-potency, 51.4% [n = 373]; medium-potency, 39.3% [n = 285]; high-potency, 31.3% [n = 227]; super-potency, 8.3% [n = 60]), antihistamines (41.8% [n = 303]), TCI (22.2% [n = 161]), systemic therapies (18.9% [n = 137], including 17.4% [n = 126] receiving systemic corticosteroids), and phototherapy (8.3% [n = 60]; Fig. 1). The combination of TCS + TCI was previously received by 20.3% (n = 147).

In the overall patient population, significantly higher percentages of patients who applied 1.5% ruxolitinib cream versus vehicle in the continuous-use VC period achieved IGA-TS (52.6% [n = 253/481] vs 11.5% [n = 28/244]; P < 0.0001; Fig. 2a), EASI75 (62.0% [n = 298/481] vs 19.7% [n = 48/244]; P < 0.0001; Fig. 2b), and Itch NRS4 (51.5% [n = 158/307] vs 15.8% [n = 25/158]; P < 0.0001; Fig. 2c) at Week 8. Across previous medication subgroups, IGA-TS was achieved in 55.5% (n = 213/384), 69.3% (n = 70/101), 71.1% (n = 64/90), and 59.3% (n = 54/91) of patients who previously used TCS, TCI, TCS + TCI, and systemic therapies, respectively (Fig. 2a). EASI75 was achieved in 62.8% (n = 241/384), 74.3% (n = 75/101), 76.7% (n = 69/90), and 71.4% (n = 65/91), respectively (Fig. 2b); Itch NRS4 was achieved in 53.6% (n = 135/252), 62.3% (n = 38/61), 62.5% (n = 35/56), and 63.1% (n = 41/65; Fig. 2c).

At all visits during the as-needed use LTS period, > 75% of patients in each subgroup who applied 1.5% ruxolitinib cream from Day 1 had IGA 0/1 (clear or almost clear; Fig. 3a). Mean affected BSA throughout the LTS period was low (generally < 3%) in all previous medication subgroups (Fig. 3b). Similar responses were observed at Week 12 after 4 weeks of as-needed ruxolitinib cream for patients who switched from vehicle (approximately > 70% through Week 52; Fig. 4a, b).

TEAEs during the entire 52-week period were reported in 59.0% (n = 284/481), 70.2% (n = 85/121), 73.4% (n = 80/109), and 70.2% (n = 80/114) of patients applying 1.5%

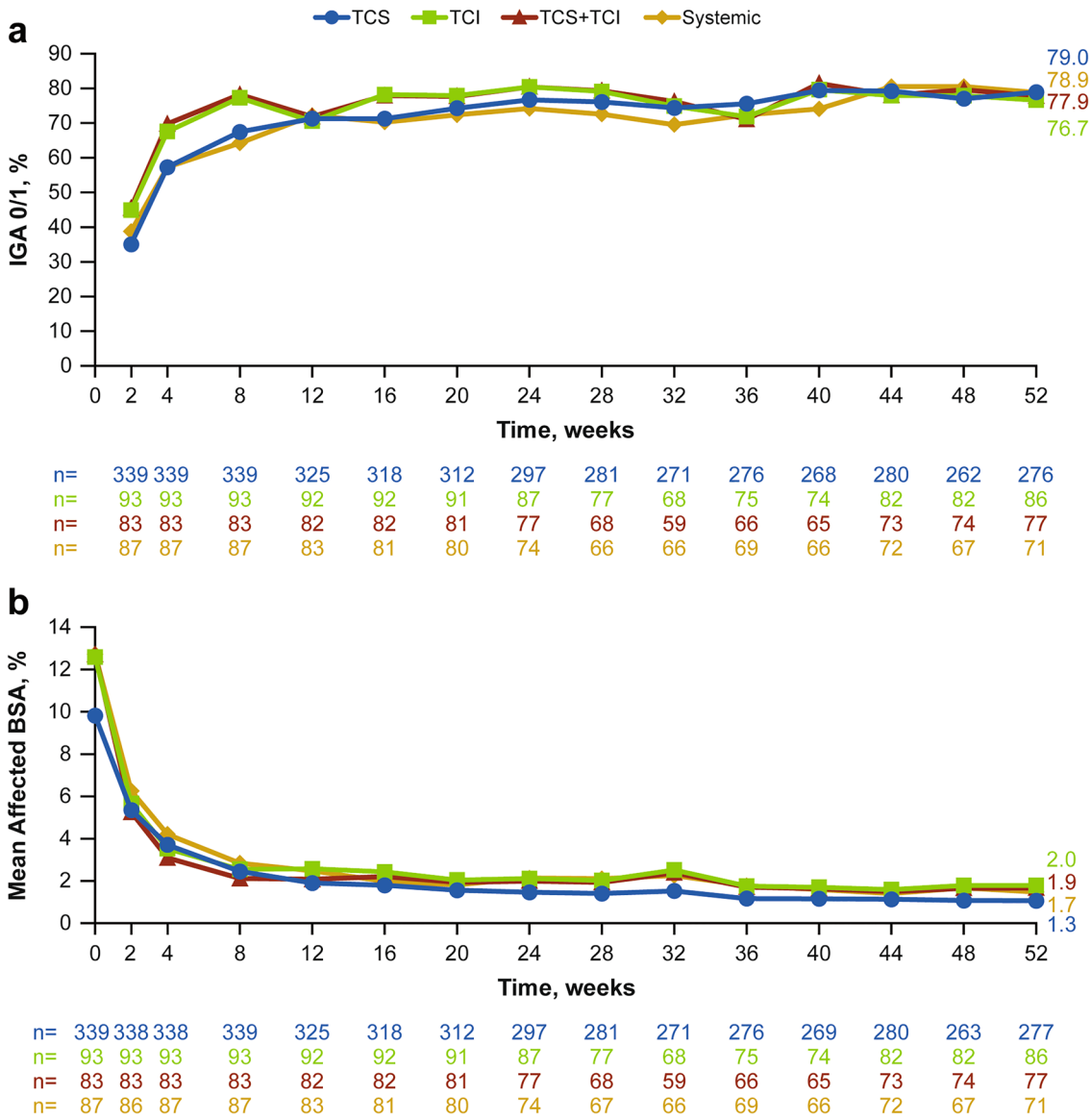

Fig. 3 **a** Percentage of patients achieving IGA 0/1 and **b** mean affected BSA by previous therapy among patients who applied 1.5% ruxolitinib cream from Day 1. *BSA* body surface area, *IGA* Investigator's Global Assessment, *TCI* topical calcineurin inhibitor, *TCS* topical corticosteroid

ruxolitinib cream at any time who had previously used TCS, TCI, TCS + TCI, and systemic therapies, respectively (Table 2). TRAEs occurred in 7.3% ($n = 35/481$), 15.7% ($n = 19/121$), 17.4% ($n = 19/109$), and 13.2% ($n = 15/114$) of patients, respectively. The most common TRAE, neutropenia, occurred in 1.5% ($n = 7/481$), 4.1% ($n = 5/121$), 4.6% ($n = 5/109$), and 1.8% ($n = 2/114$), respectively. Across these previous medication subgroups, the frequency of application site reactions was low: 1.9% ($n = 9/481$), 3.3% ($n = 4/121$); 3.7% ($n = 4/109$), and 3.5% ($n = 4/114$), respectively. Serious AEs occurred in 2.1% ($n = 10/481$),

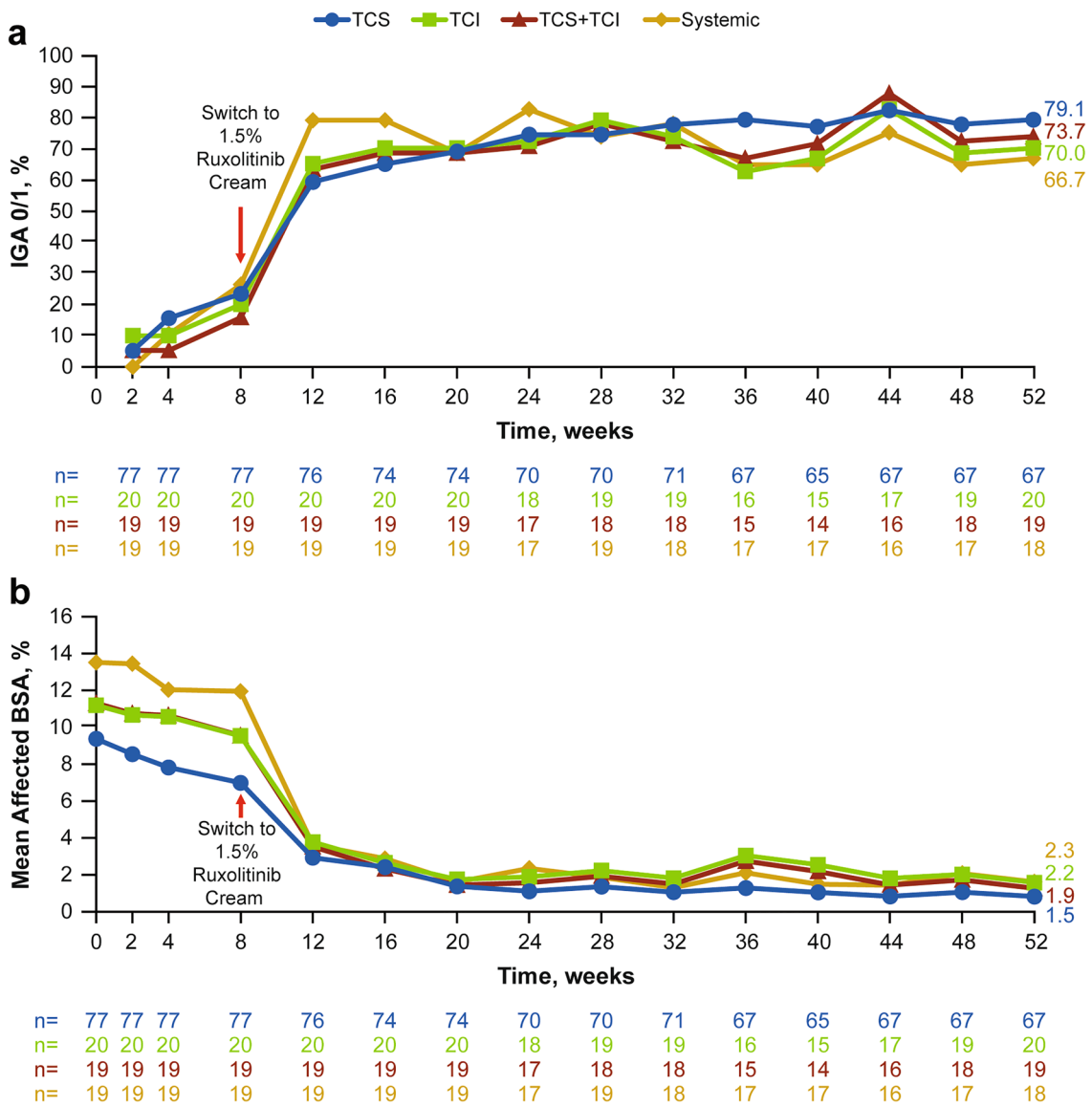

Fig. 4 **a** Percentage of patients achieving IGA 0/1 and **b** mean affected BSA by previous therapy among patients who applied 1.5% ruxolitinib cream after switching from vehicle cream after Week 8. *BSA* body surface area, *IGA* Investigator's Global Assessment, *TCI* topical calcineurin inhibitor, *TCS* topical corticosteroid

1.7% ($n=2/121$), 1.8% ($n=2/109$), and 0.9% ($n=1/114$) of patients, respectively; none were considered treatment related. Across previous medication subgroups, discontinuations due to a TEAE were observed in 0.8% ($n=4/481$), 0.8% ($n=1/121$), 0.9% ($n=1/109$), and 0.9% ($n=1/114$). Exposure-adjusted rates for overall TEAEs, TRAEs, application site reactions, and discontinuations due to a TEAE were generally higher for vehicle versus ruxolitinib cream and comparable across subgroups (Table 3).

Table 2 TEAEs in patients who applied 1.5% ruxolitinib cream at any time during the 52-week study period

n (%)	1.5% Ruxolitinib cream (*n* = 598)
Previous TCS	***n* = 481**
TEAE	284 (59.0)
Application site reaction	9 (1.9)
Serious TEAE	10 (2.1)
Discontinuation due to a TEAE	4 (0.8)
Treatment-related AE[a]	35 (7.3)
Most common treatment-related AEs[a]	
Neutropenia	7 (1.5)
Application site pain	3 (0.6)
Previous TCI	***n* = 121**
TEAE	85 (70.2)
Application site reaction	4 (3.3)
Serious TEAE	2 (1.7)
Discontinuation due to a TEAE	1 (0.8)
Treatment-related AE	19 (15.7)
Most common treatment-related AE[a]	
Neutropenia	5 (4.1)
Previous TCS and TCI	***n* = 109**
TEAE	80 (73.4)
Application site reaction	4 (3.7)
Serious TEAE	2 (1.8)
Discontinuation due to a TEAE	1 (0.9)
Treatment-related AE	19 (17.4)
Most common treatment-related AE[a]	
Neutropenia	5 (4.6)
Previous systemic therapy	***n* = 114**
TEAE	80 (70.2)
Application site reaction	4 (3.5)
Serious TEAE	1 (0.9)
Discontinuation due to a TEAE	1 (0.9)
Treatment-related AE[b]	15 (13.2)

AE adverse event, *TCI* topical calcineurin inhibitor, *TCS* topical corticosteroid, *TEAE* treatment-emergent adverse event

[a]For ≥ 3 patients

[b]No treatment-related AE occurred in ≥ 3 patients. Neutropenia occurred in 2 patients (1.8%)

DISCUSSION

Nearly all patients with mild to moderate AD in these two phase 3 studies of ruxolitinib cream, whose mean disease duration was approximately 15 years, had a history of AD treatments in the previous 12 months, including topical (with one-third receiving high-potency TCS and 8.3% receiving super-high potency TCS) and systemic therapies, highlighting the considerable disease burden in this population. Patient subgroups based on previous treatments experienced similar efficacy, safety, tolerability, and long-term disease control as the total study population, regardless of type of previous treatment [7, 8]. Long-term, as-needed use of ruxolitinib cream beyond the continuous-use period was well tolerated [8]. Thus, patients who had inadequate response on TCS and TCI or experienced intolerable AEs may benefit from using ruxolitinib cream before progressing to systemic therapies.

An important study limitation was that the use of previous AD medication could have been physician- or patient-reported, and verification was not required. Additionally, the number of patients in some subgroups was substantially lower than in others. Furthermore, patients could have received more than one previous AD medication or TCS therapy of different potencies over time; therefore, detailed analysis of efficacy outcomes based on specific previous therapy received was not feasible.

CONCLUSIONS

Ruxolitinib cream monotherapy was associated with rapid reductions in signs and symptoms of mild to moderate AD and long-term disease control, irrespective of previous therapy. This supports ruxolitinib cream as an important addition to the AD therapeutic armamentarium to address unmet needs from traditional topical therapies.

Table 3 Exposure-adjusted TEAEs during the 52-week study period

Characteristic, *n* (exposure-adjusted IR per 100 PY)	Vehicle[a] (*n* = 250)	1.5% Ruxolitinib cream[b] (*n* = 598)
Previous TCS	***n* = 205**	***n* = 481**
TEAE	68 (240.5)	284 (75.8)
Application site reaction	14 (49.5)	9 (2.4)
Serious TEAE	2 (7.1)	10 (2.7)
Discontinuation due to a TEAE	8 (28.3)	4 (1.1)
Treatment-related AE[c]	22 (77.8)	35 (9.3)
Most common treatment-related AEs[c]		
Application site pain	10 (35.4)	3 (0.8)
Neutropenia	0	7 (1.9)
Application site pruritus	5 (17.7)	0
Previous TCI	***n* = 60**	***n* = 121**
TEAE	23 (277.8)	85 (79.9)
Application site reaction	6 (72.5)	4 (3.8)
Serious TEAE	1 (12.1)	2 (1.9)
Discontinuation due to a TEAE	4 (48.3)	1 (0.9)
Treatment-related AE	11 (132.9)	19 (17.9)
Most common treatment-related AEs[c]		
Neutropenia	0	5 (4.7)
Application site pain	5 (60.4)	1 (0.9)
Atopic dermatitis	3 (36.2)	1 (0.9)
Previous TCS and TCI	***n* = 57**	***n* = 109**
TEAE	22 (281.5)	80 (83.6)
Application site reaction	6 (76.8)	4 (4.2)
Serious TEAE	1 (12.8)	2 (2.1)
Discontinuation due to a TEAE	4 (51.2)	1 (1.0)
Treatment-related AE	11 (140.7)	19 (19.9)
Most common treatment-related AEs[c]		
Neutropenia	0	5 (5.2)
Application site pain	5 (64.0)	1 (1.0)
Atopic dermatitis	3 (38.4)	1 (1.0)

Table 3 continued

Characteristic, *n* (exposure-adjusted IR per 100 PY)	Vehicle[a] (*n* = 250)	1.5% Ruxolitinib cream[b] (*n* = 598)
Previous systemic therapy	***n* = 46**	***n* = 114**
TEAE	20 (333.0)	80 (81.6)
Application site reaction	7 (116.5)	4 (4.1)
Serious TEAE	1 (16.6)	1 (1.0)
Discontinuation due to a TEAE	5 (83.2)	1 (1.0)
Treatment-related AE	11 (183.1)	15 (15.3)
Most common treatment-related AEs[c]		
Application site pain	5 (83.2)	1 (1.0)

AE adverse event, *IR*incidence rate, *PY* patient-year, *TCI* topical calcineurin inhibitor, *TCS* topical corticosteroid, *TEAE* treatment-emergent adverse event

[a]TEAE data from patients applying vehicle cream were collected up to 8 weeks; data in this table are adjusted for exposure

[b]Patients in the 1.5% ruxolitinib cream groups had up to 52 weeks of exposure depending on whether they were initially randomized to ruxolitinib cream in the vehicle-controlled period or switched from vehicle to 1.5% ruxolitinib cream at the start of the long-term safety period; data in this table are adjusted for exposure

[c]For ≥ 3 patients in either treatment group

ACKNOWLEDGEMENTS

The authors thank the patients, investigators, and investigational sites whose participation made the study possible. The authors thank Jonathan I. Silverberg, MD, PhD, MPH (George Washington University, Washington, DC, USA) for his critical review of this manuscript.

Medical Writing and Editorial Assistance. Medical writing assistance was provided by Joshua Solomon, PhD, an employee of ICON (Blue Bell, PA, USA), and was funded by Incyte Corporation (Wilmington, DE, USA), in accordance with Good Publication Practice (GPP) guidelines.

Author Contributions. Conceptualization: Andrew Blauvelt, Howard Kallender, Daniel Sturm, Lawrence F. Eichenfield. Methodology: Andrew Blauvelt, Howard Kallender, Daniel Sturm, Lawrence F. Eichenfield. Formal analysis and investigation: Qian Li, Haobo Ren. Writing – original draft preparation: Andrew Blauvelt, Howard Kallender, Daniel Sturm, Lawrence F. Eichenfield. Writing – review, editing, and approval: all authors.

Funding. This study was funded by Incyte Corporation (Wilmington, DE, USA) and the Rapid Service Fee was provided by Incyte.

Data Availability. Incyte Corporation (Wilmington, DE, USA) is committed to data sharing that advances science and medicine while protecting patient privacy. Qualified external scientific researchers may request anonymized datasets owned by Incyte for the purpose of conducting legitimate scientific research. Researchers may request anonymized datasets from any interventional study (except Phase 1 studies) for which the product and indication have been approved on or after 1 January 2020 in at least one major market (e.g. US, EU, JPN). Data will be available for request after the primary publication or 2 years after the study has ended. Information on Incyte's clinical trial data sharing policy and

instructions for submitting clinical trial data requests are available at: https://www.incyte.com/Portals/0/Assets/Compliance%20and%20Transparency/clinical-trial-data-sharing.pdf?ver=2020-05-21-132838-960.

Declarations

Conflicts of Interest. Andrew Blauvelt (currently Blauvelt Consulting) has served as a speaker (received honoraria) for AbbVie, Eli Lilly and Company, Pfizer, and UCB; served as a scientific advisor (received honoraria) for AbbVie, Abcentra, Aclaris, Affibody, Aligos, Almirall, Alumis, Amgen, AnaptysBio, Apogee, Arcutis, Arena, Aslan, Athenex, Bluefin Biomedicine, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, CTI BioPharma, Dermavant, EcoR1, Eli Lilly and Company, Escient, Evelo, Evommune, Forte, Galderma, HighlightII Pharma, Incyte, InnoventBio, Janssen, Landos, LEO, Lipidio, Microbion, Merck, Monte Rosa Therapeutics, Nektar, Novartis, Overtone Therapeutics, Paragon, Pfizer, Q32 Bio, Rani, Rapt, Regeneron, Sanofi Genzyme, Spherix Global Insights, Sun Pharma, Takeda, TLL Pharmaceutical, TrialSpark, UCB Pharma, Union, Ventyx, Vibliome, and Xencor; and has acted as a clinical study investigator (institution has received clinical study funds) for AbbVie, Acelyrin, Allakos, Almirall, Alumis, Amgen, Arcutis, Athenex, Boehringer Ingelheim, Bristol Myers Squibb, Concert, Dermavant, Eli Lilly and Company, Evelo, Evommune, Galderma, Incyte, Janssen, LEO, Merck, Novartis, Pfizer, Regeneron, Sanofi, Sun Pharma, UCB Pharma, and Ventyx. Howard Kallender, Daniel Sturm, Qian Li, and Haobo Ren are employees and shareholders of Incyte Corporation. Lawrence F. Eichenfield has served as an investigator, consultant, speaker, or data safety monitoring board member for AbbVie, Amgen, Arcutis, Aslan, Castle Biosciences, Dermavant, Eli Lilly, Forte Biosciences, Galderma, Incyte, Janssen, LEO Pharma, Novartis, Ortho Dermatologics, Otsuka, Pfizer, Regeneron, and Sanofi Genzyme.

Ethical Approval. Studies were conducted in accordance with Good Clinical Practice guidelines and 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.

REFERENCES

1. Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. Lancet. 2020;396(10247):345–60.

2. Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: 2. Management and treatment of atopic dermatitis with topical therapies. J Am Acad Dermatol. 2014;71(1):116–32.

3. Sidbury R, Alikhan A, Bercovitch L, et al. Guidelines of care for the management of atopic dermatitis in adults with topical therapies. J Am Acad Dermatol. 2023;89(1):e1–20.

4. Simpson EL, Bruin-Weller M, Flohr C, et al. When does atopic dermatitis warrant systemic therapy? Recommendations from an expert panel of the International Eczema Council. J Am Acad Dermatol. 2017;77(4):623–33.

5. Davis DMR, Drucker AM, Alikhan A, et al. Guidelines of care for the management of atopic dermatitis in adults with phototherapy and

systemic therapies. J Am Acad Dermatol. 2024; 90(2):e43–56.

6. Quintas-Cardama A, Vaddi K, Liu P, et al. Preclinical characterization of the selective JAK1/2 inhibitor INCB018424: therapeutic implications for the treatment of myeloproliferative neoplasms. Blood. 2010;115(15):3109–17.

7. Papp K, Szepietowski JC, Kircik L, et al. Efficacy and safety of ruxolitinib cream for the treatment of atopic dermatitis: results from two phase 3, randomized, double-blind studies. J Am Acad Dermatol. 2021;85(4):863–72.

8. Papp K, Szepietowski JC, Kircik L, et al. Long-term safety and disease control with ruxolitinib cream in atopic dermatitis: results from two phase 3 studies. J Am Acad Dermatol. 2023;88(5):1008–16.