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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

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Background

- Atopic dermatitis (AD) is a chronic, highly pruritic, inflammatory skin disease[1]
- AD is often stratified using objective (Investigator's Global Assessment [IGA], Eczema Area and Severity Index [EASI], body surface area [BSA]) and subjective (eg, itch numerical rating scale [NRS]) assessment tools[2-4]
  - In recent clinical studies with systemic therapies, including oral Janus kinase (JAK) inhibitors[5-7] and dupilumab,[8] BSA ≥10%, EASI ≥16, and a lack of adequate response to topical corticosteroids (TCS) were used as part of the inclusion criteria to identify patients with more severe AD
- JAKs act downstream of proinflammatory cytokines and itch mediators involved in the pathogenesis of AD[9,10]
- Ruxolitinib cream is a topical selective inhibitor of JAK1 and JAK2 in development for the treatment of AD[11]
- In two phase 3 AD studies of identical design (TRuE-AD1 [NCT03745638] and TRuE-AD2 [NCT03745651]), ruxolitinib cream demonstrated anti-inflammatory activity with rapid and sustained antipruritic action vs vehicle and was well tolerated[12]
- Although more severe AD may require systemic therapy, we aimed to evaluate treatment responses to ruxolitinib cream in a subpopulation that may meet minimal standard criteria for systemic treatment

Objective

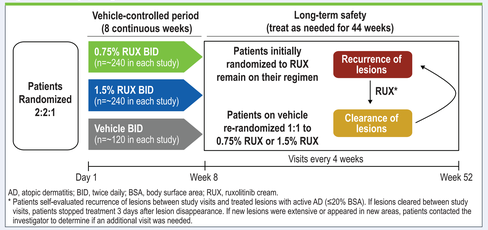
- To analyze the efficacy and safety of ruxolitinib cream in patients with AD who had a baseline BSA ≥10% and EASI ≥16 using pooled data from two phase 3 trials in adolescent and adult patients

Methods

Study Design and Patients

- Eligible patients were aged ≥12 years with AD for ≥2 years and had an IGA score of 2 or 3 and 3%–20% affected BSA (excluding scalp)
- Key exclusion criteria were unstable course of AD, other types of eczema, immunocompromised status, use of AD systemic therapies during the washout period and during the study, use of AD topical therapies (except bland emollients) during the washout period and during the study, and any serious illness or medical condition that could interfere with study conduct, interpretation of data, or patients' well-being
- TRuE-AD1 and TRuE-AD2 had identical study designs (**Figure 1**)
  - In both studies, patients were randomized (2:2:1) to 1 of 2 ruxolitinib cream strength regimens (0.75% twice daily [BID] or 1.5% BID) or vehicle cream BID for 8 weeks of double-blinded treatment
  - Patients on ruxolitinib cream subsequently continued treatment for 44 weeks; patients initially randomized to vehicle were re-randomized 1:1 (blinded) to either ruxolitinib cream strength

Figure 1. Study Design



AD, atopic dermatitis; BID, twice daily; BSA, body surface area; RUX, ruxolitinib cream.
* Patients self-evaluated recurrence of lesions between study visits and treated lesions with active AD (≤20% BSA). If lesions cleared between study visits, patients stopped treatment 3 days after lesion disappearance. If new lesions were extensive or appeared in new areas, patients contacted the investigator to determine if an additional visit was needed.

Assessments

- Efficacy endpoints from the vehicle-controlled period that were included in this subanalysis of patients with BSA ≥10% and EASI ≥16 at baseline were similar to the primary analysis of the overall population. They included the proportion of patients achieving IGA-treatment success (IGA-TS; score of 0 or 1 with ≥2-grade improvement from baseline); ≥50%, ≥75%, and ≥90% improvement in EASI score (EASI-50, EASI-75, and EASI-90, respectively) vs baseline; and a ≥4-point improvement in itch NRS score (NRS4) from baseline
- Safety and tolerability were assessed by treatment-emergent adverse events (AEs)

Statistical Analyses

- All analyses were conducted using the pooled data from both studies
- IGA-TS, EASI-75, and NRS4 were analyzed by logistic regression and reported descriptively
- All other endpoints were analyzed using descriptive statistics

Results

Patients

- Of 1249 randomized patients, 81 had BSA ≥10% and EASI ≥16 at baseline
- Distribution of baseline demographics and clinical characteristics was similar across treatment groups (**Table 1**)

Table 1. Patient Demographics and Baseline Clinical Characteristics

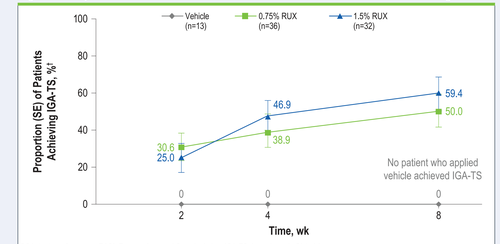
Characteristic	Vehicle (n=13)	0.75% RUX (n=36)	1.5% RUX (n=32)	Total (N=81)
Age, median (range), y	41.0 (12–63)	45.5 (12–75)	26.5 (13–85)	34.0 (12–85)
Female, n (%)	7 (53.8)	24 (66.7)	17 (53.1)	48 (59.3)
Race, n (%)				
White	11 (84.6)	27 (75.0)	27 (84.4)	65 (80.2)
Black	2 (15.4)	7 (19.4)	1 (3.1)	10 (12.3)
Asian	0	1 (2.8)	1 (3.1)	2 (2.5)
Other	0	1 (2.8)	3 (9.4)	4 (4.9)
Region, n (%)				
North America	7 (53.8)	15 (41.7)	8 (25.0)	30 (37.0)
Europe	6 (46.2)	21 (58.3)	24 (75.0)	51 (63.0)
BSA, mean (SD), %	17.7 (3.3)	16.6 (3.0)	18.0 (1.9)	17.3 (2.7)
EASI, mean (SD)	20.2 (2.9)	19.4 (3.4)	19.3 (2.9)	19.5 (3.1)
IGA, n (%)				
2	0	3 (8.3)	0	3 (3.7)
3	13 (100.0)	33 (91.7)	32 (100.0)	78 (96.3)
Itch NRS score, mean (SD)	6.9 (1.6)	5.5 (2.5)	5.1 (2.4)	5.6 (2.4)
≥4, n (%)	11 (84.6)	26 (72.2)	18 (56.3)	55 (67.9)
Duration of disease, median (range), y	30.1 (2.8–55.1)	17.0 (2.1–60.1)	18.2 (1.9–55.8)	18.1 (1.9–60.1)
Facial involvement, n (%)*	10 (76.9)	24 (66.7)	22 (68.8)	56 (69.1)
Number of flares in last 12 mo, mean (SD)*	4.1 (6.8)	4.4 (6.3)	2.7 (2.8)	3.7 (5.3)

BSA, body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; NRS, numerical rating scale; RUX, ruxolitinib cream.
* Patient reported.

Efficacy

- At Week 8, more patients achieved IGA-TS with 0.75% and 1.5% ruxolitinib creams vs vehicle (50.0% and 59.4% vs 0%, respectively; **Figure 2**)

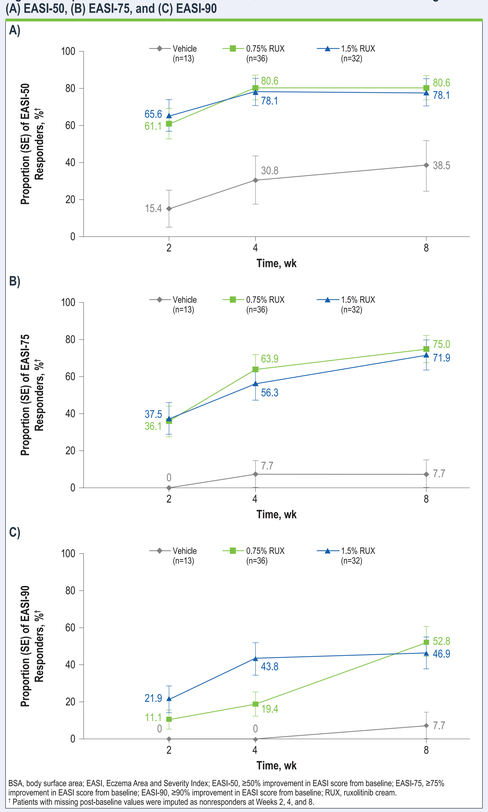
Figure 2. Proportion of Patients With BSA ≥10% and EASI ≥16 at Baseline Achieving IGA-TS



BSA, body surface area; EASI, Eczema Area and Severity Index; IGA-TS, Investigator's Global Assessment-treatment success; RUX, ruxolitinib cream.
† Defined as 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 Weeks 2, 4, and 8.

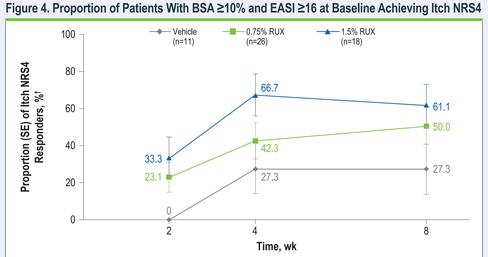
- More patients who applied 0.75% and 1.5% ruxolitinib cream vs vehicle achieved EASI-50 (80.6%/78.1% vs 38.5%), EASI-75 (75.0%/71.9% vs 7.7%), and EASI-90 (52.8%/46.9% vs 7.7%) at Week 8 (**Figure 3**)
- At Week 8, more patients achieved itch NRS4 with 0.75% and 1.5% ruxolitinib creams vs vehicle (50.0% and 61.1% vs 27.3%; **Figure 4**)

Figure 3. Proportion of Patients With BSA ≥10% and EASI ≥16 at Baseline Achieving (A) EASI-50, (B) EASI-75, and (C) EASI-90



BSA, body surface area; EASI, Eczema Area and Severity Index; EASI-50, ≥50% improvement in EASI score from baseline; EASI-75, ≥75% improvement in EASI score from baseline; EASI-90, ≥90% improvement in EASI score from baseline; RUX, ruxolitinib cream.
† Patients with missing post-baseline values were imputed as nonresponders at Weeks 2, 4, and 8.

Figure 4. Proportion of Patients With BSA ≥10% and EASI ≥16 at Baseline Achieving Itch NRS4



BSA, body surface area; EASI, Eczema Area and Severity Index; NRS4, ≥4-point improvement in itch numerical rating scale score; RUX, ruxolitinib cream.
† 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.

- Application of 0.75% and 1.5% ruxolitinib cream resulted in greater response rates vs vehicle at Week 8 using various criteria to define more severe AD (**Table 2**)

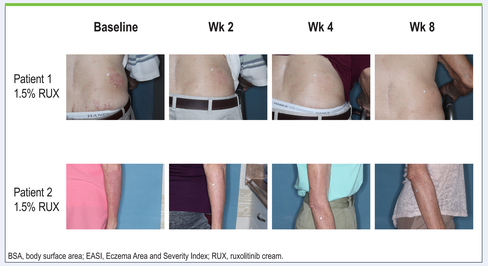
Table 2. Summary of Efficacy Analyses at Week 8 Using Various Criteria to Define More Severe AD

Criteria for More Severe AD	Efficacy Outcome*	Vehicle, n (%)	0.75% RUX, n (%)	1.5% RUX, n (%)
IGA=3		n=180	n=358	n=358
	IGA-TS	27 (15.0)	192 (53.6)	222 (62.0)
	EASI-50	68 (37.8)	269 (75.1)	291 (81.3)
	EASI-75	37 (20.6)	203 (56.7)	237 (66.2)
	EASI-90	10 (5.6)	141 (39.4)	170 (47.5)
	Itch NRS4†	21 (17.5)	113 (46.5)	126 (54.3)
IGA=3 and EASI ≥16		n=14	n=34	n=33
	IGA-TS	0	18 (52.9)	19 (57.6)
	EASI-50	5 (35.7)	27 (79.4)	26 (78.8)
	EASI-75	1 (7.1)	24 (70.6)	23 (69.7)
	EASI-90	1 (7.1)	17 (50.0)	15 (45.5)
	Itch NRS4‡	3 (25.0)	13 (50.0)	11 (57.9)
IGA=3 and EASI ≥16 and BSA ≥10		n=13	n=33	n=32
	IGA-TS	0	18 (54.5)	19 (59.4)
	EASI-50	5 (38.5)	26 (78.8)	25 (78.1)
	EASI-75	1 (7.7)	24 (72.7)	23 (71.9)
	EASI-90	1 (7.7)	17 (51.5)	15 (46.9)
	Itch NRS4§	3 (27.3)	12 (48.0)	11 (61.1)
IGA=3 and EASI ≥16 and BSA ≥10 and Itch NRS ≥4		n=11	n=25	n=18
	IGA-TS	0	11 (44.0)	12 (66.7)
	EASI-50	5 (45.5)	18 (72.0)	14 (77.8)
	EASI-75	1 (9.1)	16 (64.0)	13 (72.2)
	EASI-90	1 (9.1)	11 (44.0)	10 (55.6)

AD, atopic dermatitis; BSA, body surface area; EASI, Eczema Area and Severity Index; EASI-50, ≥50% improvement in EASI score from baseline; EASI-75, ≥75% improvement in EASI score from baseline; EASI-90, ≥90% improvement in EASI score from baseline; IGA, Investigator's Global Assessment; IGA-TS, IGA-treatment success; NRS, numerical rating scale; NRS4, ≥4-point improvement in itch NRS score from baseline; RUX, ruxolitinib cream.
* Patients with missing post-baseline values were imputed as nonresponders.
† Patients had an itch NRS score ≥4 at baseline (vehicle, n=120; 0.75% RUX, n=243; 1.5% RUX, n=232).
‡ Patients had an itch NRS score ≥4 at baseline (vehicle, n=12; 0.75% RUX, n=26; 1.5% RUX, n=19).
§ Patients had an itch NRS score ≥4 at baseline (vehicle, n=11; 0.75% RUX, n=25; 1.5% RUX, n=18).

- Clinical pictures illustrating the efficacy of ruxolitinib cream in patients with AD who had a baseline BSA ≥10% and EASI ≥16 are shown in **Figure 5**

Figure 5. Clinical Images Throughout Treatment in Patients With BSA ≥10% and EASI ≥16 at Baseline



BSA, body surface area; EASI, Eczema Area and Severity Index; RUX, ruxolitinib cream.

Safety

- Ruxolitinib cream was well tolerated and not associated with clinically significant application site reactions (**Table 3**); no safety findings were suggestive of systemic JAK inhibition
- No serious AEs related to ruxolitinib cream were reported

Table 3. Treatment-Emergent AEs During the 8-Week Vehicle-Controlled Period

n (%)	Vehicle (n=13)	0.75% RUX (n=36)	1.5% RUX (n=32)
Patients with TEAE	6 (46.2)	14 (38.9)	10 (31.3)
Patients with treatment-related AE	5 (38.5)	1 (2.8)	3 (9.4)
Most common treatment-related AEs*			
AD	2 (15.4)	1 (2.8)	0
Nasopharyngitis	0	2 (5.6)	1 (3.1)
Application site pain†	2 (15.4)	0	0
Dermatitis acneiform	0	0	2 (6.3)
Dysmenorrhea	0	2 (5.6)	0
Headache	0	0	2 (6.3)
Oral herpes	0	2 (5.6)	0
Seasonal allergy	0	0	2 (6.3)
Discontinuation due to a TEAE	1 (7.7)	0	0
Patients with serious TEAE	1 (7.7)	0	0

AD, atopic dermatitis; AE, adverse event; RUX, ruxolitinib cream; TEAE, treatment-emergent AE.
* Occurring in ≥2 patients in any group.
† Patient-reported tolerability was not lesion specific and was reported for all treated areas.

Conclusions

- **In the analyzed subset of patients with AD who are typically eligible for both topical and systemic therapies, substantially higher rates of clinical responses were observed with ruxolitinib cream vs vehicle**
  - **Results were similar using different definitions for more severe AD**
- **Ruxolitinib cream was well tolerated in this subset of patients**
- **In patients with more severe AD, ruxolitinib cream appears to be highly efficacious. It may delay or prevent the need for systemic therapy in these patients**
  - **Although these patients met minimal standard criteria for systemic use, baseline severity in this analysis was lower than the baseline severity in studies with systemic treatments.[5-8] Thus, the data may not be directly comparable**

Disclosures

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. LK has served as an investigator, consultant, or speaker for AbbVie, Amgen, Anaptys, Arcutis, Dermavant, Eli Lilly, Glenmark, Incyte Corporation, Kamedis, LEO Pharma, L'Oreal, Menlo, Novartis, Ortho Dermatologics, Pfizer, Regeneron, Sanofi, Sun Pharma, and Taro. AB has served as a scientific adviser and/or clinical study investigator for AbbVie, Aligos, Almirall, Amgen, Arcutis, Arena, Athenex, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant, Eli Lilly and Company, Evommune, Forte, Galderma, Incyte Corporation, Janssen, Landos, LEO Pharma, Novartis, Pfizer, Rapt, Regeneron, Sanofi Genzyme, Sun Pharma, and UCB Pharma. MEK, MEV, and KS are employees and shareholders of Incyte Corporation. LFE has served as an investigator, consultant, speaker, or data safety monitoring board member for AbbVie, Almirall, Arcutis, Asana, Dermavant, Eli Lilly, Forte Biosciences, Galderma, Ichnos/Glenmark, Incyte Corporation, Janssen, LEO Pharma, Novartis, Ortho Dermatologics, Otsuka, Pfizer, Regeneron, and Sanofi Genzyme.

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