Long-Term Safety and Disease Control With Ruxolitinib Cream in Patients With More Severe Atopic Dermatitis: Pooled Results From Two Phase 3 Studies

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Introduction

- Atopic dermatitis (AD) is a highly pruritic inflammatory skin disease[1]
- The severity of 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]
- Topical therapies are the standard of care for most patients with AD[5]
  - For patients with more severe AD, systemic therapies may be considered as monotherapy or in combination with topical therapies[6]
  - Failure of topical therapies represents one factor when considering systemic therapy; it is not known whether new, more effective nonsteroidal therapies could prevent some patients from starting systemic therapy
- Ruxolitinib cream is a topical formulation of ruxolitinib, a selective inhibitor of Janus kinase (JAK) 1/JAK2[7]
- In two phase 3 randomized studies of identical design (TRuE-AD1 [NCT03745638] and TRuE-AD2 [NCT03745651]), ruxolitinib cream demonstrated anti-inflammatory activity with antipruritic action vs vehicle and was well tolerated in patients with AD[7]

Objective

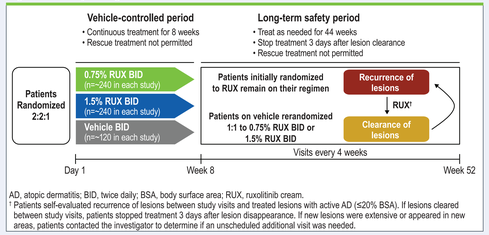
- To evaluate the long-term safety and disease control of ruxolitinib cream in a subpopulation of patients with more severe AD at baseline

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], 1.5% BID) or vehicle cream BID for 8 weeks of double-blinded continuous treatment (vehicle-controlled [VC] period); patients were instructed to continue treating lesions even if they improved
  - Patients on ruxolitinib cream subsequently continued treatment for 44 weeks (long-term safety [LTS] period); patients initially randomized to vehicle were rerandomized 1:1 (blinded) to either ruxolitinib cream regimen
    - During the LTS period, patients were instructed to treat skin areas with active AD only and stop treatment 3 days after clearance of lesions; patients were to restart treatment with ruxolitinib cream at the first sign of recurrence

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 unscheduled additional visit was needed.

- The definition of more severe AD (IGA score of 3, EASI ≥16, and affected BSA ≥10% at baseline) was based on IGA, EASI, and BSA thresholds for clinical trials of systemic therapies (ie, dupilumab[8] and oral JAK inhibitors[9-11])
  - Other definitions of more severe AD included in this analysis were BSA ≥10% alone and IGA=3 alone, as well as combined IGA=3, EASI ≥16, BSA ≥10%, and itch NRS score ≥4 at baseline

Assessments

- Disease control was assessed by the proportion of patients who achieved no or minimal skin lesions (IGA score of 0 or 1 [clear or almost clear skin]) and mean percentage of BSA affected by AD at each visit (every 4 weeks) during the LTS period
- Safety and tolerability assessments included the frequency of reported treatment-emergent adverse events (TEAEs), treatment-related adverse events, and adverse events (AEs) leading to treatment discontinuation

Statistical Analyses

- All analyses were conducted using the pooled data from both studies
  - The disease control analysis included patients who remained on their initial ruxolitinib cream strength regimen from the VC period through the LTS period; data are reported as observed
  - The safety analysis included patients who applied ruxolitinib cream in any period (VC or LTS)
- Data were summarized using descriptive statistics

Results

Patients

- A total of 1249 patients (median age, 32 years) were randomized in the VC period
- Distribution of baseline demographics and clinical characteristics of all randomized patients was similar across treatment groups (**Table 1**)

Table 1. Patient Demographics and Baseline Clinical Characteristics

Characteristic	Vehicle (n=250)	0.75% RUX (n=500)	1.5% RUX (n=499)	Total (N=1249)
Age, median (range), y	34.0 (12–82)	33.0 (12–85)	31.0 (12–85)	32.0 (12–85)
Female, n (%)	159 (63.6)	304 (60.8)	308 (61.7)	771 (61.7)
Race, n (%)				
White	170 (68.0)	345 (69.0)	355 (71.1)	870 (69.7)
Black	61 (24.4)	118 (23.6)	113 (22.6)	292 (23.4)
Asian	10 (4.0)	16 (3.2)	20 (4.0)	46 (3.7)
Other	9 (3.6)	21 (4.2)	11 (2.2)	41 (3.3)
Region, n (%)				
North America	172 (68.8)	342 (68.4)	341 (68.3)	855 (68.5)
Europe	78 (31.2)	158 (31.6)	158 (31.7)	394 (31.5)
BSA, mean (SD), %	9.6 (5.5)	10.0 (5.3)	9.6 (5.3)	9.8 (5.4)
EASI, mean (SD)	7.8 (4.8)	8.1 (4.9)	7.8 (4.8)	8.0 (4.8)
IGA, n (%)				
2	64 (25.6)	125 (25.0)	123 (24.6)	312 (25.0)
3	186 (74.4)	375 (75.0)	376 (75.4)	937 (75.0)
Itch NRS score, mean (SD)	5.1 (2.4)	5.2 (2.4)	5.1 (2.5)	5.1 (2.4)
≥4, n (%)	159 (63.6)	324 (64.8)	315 (63.1)	798 (63.9)
Duration of disease, median (range), y	16.5 (0.8–79.1)	15.1 (0.1–68.8)	16.1 (0–69.2)	15.8 (0–79.1)
Facial involvement, n (%)*	93 (37.2)	195 (39.0)	197 (39.5)	485 (38.8)
Number of flares in last 12 mo, mean (SD)*	7.3 (25.7)	5.2 (6.7)	6.0 (17.6)	5.9 (16.5)

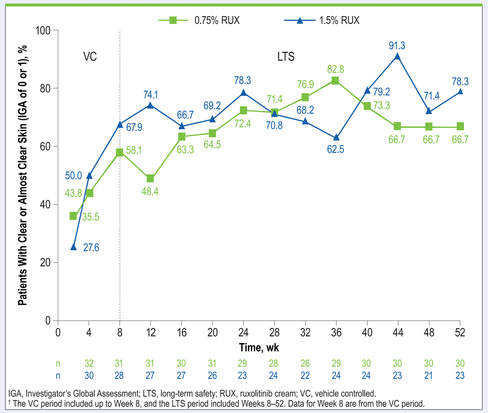
BSA, body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; NRS, numerical rating scale; RUX, ruxolitinib cream.
* Patient reported.

- Among patients with a baseline IGA score of 3, EASI ≥16, and BSA ≥10% in the pooled population, 31 and 28 patients continued from the VC to the LTS period in the 0.75% and 1.5% ruxolitinib cream arms, respectively, and were evaluated for disease control
  - 39 and 36 patients applied 0.75% or 1.5% ruxolitinib cream, respectively, in either study period (VC or LTS) and were evaluated for safety

Efficacy

- A substantial proportion of patients achieved clear or almost clear skin (IGA 0/1) during the LTS period (**Figure 2**); data were similar when different definitions were used to define more severe AD (**Table 2**)

Figure 2. Proportion of Patients With Clear or Almost Clear Skin (IGA 0/1) in the VC and LTS Periods in Patients With IGA=3, BSA ≥10%, and EASI ≥16 at Baseline†



IGA, Investigator's Global Assessment; LTS, long-term safety; RUX, ruxolitinib cream; VC, vehicle controlled.
† The VC period included up to Week 8, and the LTS period included Weeks 8–52. Data for Week 8 are from the VC period.

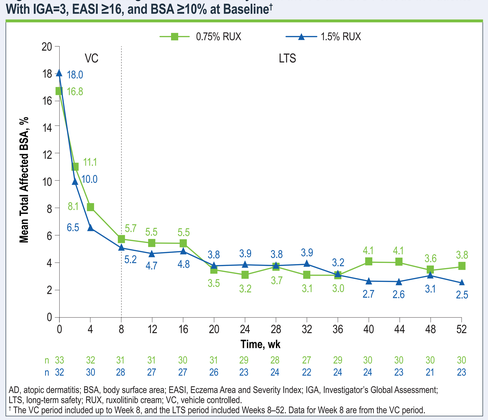
Table 2. Summary of Patients Achieving IGA 0/1 During the LTS Period Using Different Criteria to Define More Severe AD at Baseline

Criteria for More Severe AD	Week, %											
	12	16	20	24	28	32	36	40	44	48	52
BSA ≥10%*												
0.75% RUX	54.5	60.2	59.5	65.6	66.0	66.9	69.8	68.5	69.9	70.5	71.1
1.5% RUX	68.0	66.7	69.6	69.2	67.6	65.8	67.1	70.1	72.3	69.1	68.7
IGA=3†												
0.75% RUX	57.5	64.0	64.9	66.8	68.0	70.2	72.5	72.8	72.1	72.2	75.5
1.5% RUX	66.9	68.5	70.8	72.2	72.8	70.4	72.9	74.0	75.8	73.6	74.9
IGA=3, EASI ≥16, BSA ≥10%, itch NRS ≥4‡												
0.75% RUX	43.5	60.9	65.2	66.7	65.0	73.7	85.7	72.7	59.1	59.1	63.6
1.5% RUX	68.8	62.5	53.3	61.5	57.1	61.5	57.1	71.4	92.3	66.7	69.2

AD, atopic dermatitis; BSA, body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; LTS, long-term safety; NRS, numerical rating scale; RUX, ruxolitinib cream.
* n=182/n=182 for 0.75%/1.5% RUX at the start of the LTS period.
† n=309/n=328 for 0.75%/1.5% RUX at the start of the LTS period.
‡ n=23/n=17 for 0.75%/1.5% RUX at the start of the LTS period.

- Percentage of BSA affected by AD is shown in **Figure 3**; data were similar when different definitions were used to define more severe AD (**Table 3**)

Figure 3. Mean Percentage of BSA Affected by AD in the VC and LTS Periods in Patients With IGA=3, EASI ≥16, and BSA ≥10% at Baseline†



AD, atopic dermatitis; BSA, body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; LTS, long-term safety; RUX, ruxolitinib cream; VC, vehicle controlled.
† The VC period included up to Week 8, and the LTS period included Weeks 8–52. Data for Week 8 are from the VC period.

Table 3. Summary of Mean Percentage of BSA Affected by AD During the LTS Period Using Different Criteria to Define More Severe AD at Baseline

Criteria for More Severe AD	Week, mean %										
	12	16	20	24	28	32	36	40	44	48	52
BSA ≥10%*											
0.75% RUX	5.0	4.2	3.3	3.2	3.3	3.1	2.9	3.0	2.9	3.1	2.7
1.5% RUX	3.2	3.0	2.6	2.7	2.4	2.9	2.3	2.2	2.1	2.1	2.2
IGA=3†											
0.75% RUX	3.4	3.0	2.3	2.4	2.4	2.2	2.2	2.2	2.2	2.3	2.0
1.5% RUX	2.4	2.3	2.0	2.0	1.9	2.1	1.7	1.7	1.6	1.7	1.6
IGA=3, EASI ≥16, BSA ≥10%, itch NRS ≥4‡											
0.75% RUX	5.6	4.5	3.5	3.3	4.2	3.4	2.6	3.7	3.8	3.9	3.6
1.5% RUX	4.9	4.6	3.5	3.8	3.6	3.1	3.0	2.4	2.1	2.7	2.0

AD, atopic dermatitis; BSA, body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; LTS, long-term safety; NRS, numerical rating scale; RUX, ruxolitinib cream.
* n=182/n=182 for 0.75%/1.5% RUX at the start of the LTS period.
† n=309/n=328 for 0.75%/1.5% RUX at the start of the LTS period.
‡ n=23/n=17 for 0.75%/1.5% RUX at the start of the LTS period.

Safety

- In the overall population, the most common TEAEs through Week 52 were upper respiratory tract infection, nasopharyngitis, and headache
  - No AEs suggestive of a relationship to systemic exposure were observed
- Ruxolitinib cream was well tolerated and the frequency of application site reactions was low in this subset of patients with more severe AD (**Table 4**)

Table 4. Adverse Events Among Patients With IGA=3, EASI ≥16, and BSA ≥10% at Baseline Who Applied Ruxolitinib Cream in the Phase 3 Studies (VC or LTS Periods)

n (%)	0.75% RUX (n=39)	1.5% RUX (n=36)
Patients with TEAE	28 (71.8)	24 (66.7)
Patients with application site reaction	1 (2.6)	2 (5.6)
Patients with TRAE	6 (15.4)	6 (16.7)
Patients who discontinued due to a TEAE	0	0
Patients with serious TEAE*	1 (2.6)	1 (2.8)

LTS, long-term safety; RUX, ruxolitinib cream; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; VC, vehicle controlled.
* None were considered related to treatment with ruxolitinib cream.

Conclusions

- **The subset of patients meeting various thresholds for more severe disease at baseline achieved effective long-term disease control with ruxolitinib cream monotherapy during the 52-week study period**
- **Ruxolitinib cream was well tolerated in the long-term setting in this subset of patients who may be eligible for both systemic and topical therapies**
- **These data suggest that ruxolitinib cream may delay or prevent the need for systemic therapy in a subset of patients with more severe AD**
  - **Although these patients met various thresholds for more severe disease at baseline, failure of topical therapy was not a requirement for entering the studies**

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 Therapeutics, Novartis, Ortho Dermatologics, Pfizer, Regeneron, Sanofi, Sun Pharma, and Taro. AB has served as a scientific advisor and/or clinical study investigator for AbbVie, Abcentra, Aligos, Almirall, Amgen, Arcutis, Arena, Aslan, 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 was an employee and shareholder of Incyte Corporation at the time of development of the original presentation. 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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