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

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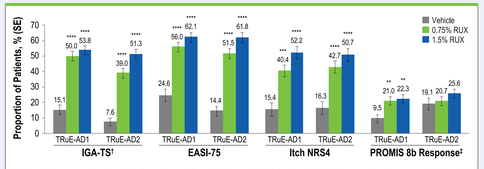
Kim Papp, MD, PhD,[1] Jacek C. Szepietowski, MD, PhD, FRCP (Edin),[2] Leon Kircik, MD,[3] Darryl Toth, MD,[4] Lawrence F. Eichenfield, MD,[5] Seth B. Forman, MD,[6] Michael E. Kuligowski, MD, PhD, MBA,[7] May E. Venturanza, MD,[7] Kang Sun, PhD,[7] Eric L. Simpson, MD, MCR[8]

[1]K. Papp Clinical Research and Probity Medical Research, Waterloo, ON, Canada; [2]Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, Wroclaw, Poland; [3]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [4]XLR8 Medical Research and Probity Medical Research, Windsor, ON, Canada; [5]Departments of Dermatology and Pediatrics, University of California San Diego, San Diego, CA, USA; [6]ForCare Clinical Research, Tampa, FL, USA; [7]Incyte Corporation, Wilmington, DE, USA; [8]Oregon Health & Science University, Portland, OR, USA

Introduction

- Atopic dermatitis (AD) is a highly pruritic inflammatory skin disease[1]
- The pathogenesis of AD involves Janus kinases (JAKs) acting downstream of proinflammatory cytokines and itch mediators[2,3]
- Ruxolitinib cream is a topical formulation of ruxolitinib, a selective inhibitor of JAK1 and JAK2[4]
- In two phase 3 randomized studies of identical design (TRueE-AD1 [NCT03745638] and TRueE-AD2 [NCT03745651]), ruxolitinib cream demonstrated anti-inflammatory activity with antipruritic action vs vehicle and was well tolerated in patients with AD[4] (**Figure 1**)

Figure 1. Primary and Key Secondary Endpoints at Week 8 of the Vehicle-Controlled Period in TRueE-AD1 and TRueE-AD2



EASI-75, ≥75% improvement from baseline in Eczema Area and Severity Index score; IGA-TS, Investigator's Global Assessment-treatment success; NRS4, ≥4-point improvement in itch numerical rating scale score from baseline; PROMIS, Patient-Reported Outcomes Measurement Information System; RUX, ruxolitinib cream.
** $P<0.01$ vs vehicle; *** $P<0.001$ vs vehicle; **** $P<0.0001$ vs vehicle.
† IGA score of 0 or 1 and ≥2-point improvement from baseline.
‡ ≥6-point improvement in PROMIS Short Form sleep disturbance score 8(b).

Objective

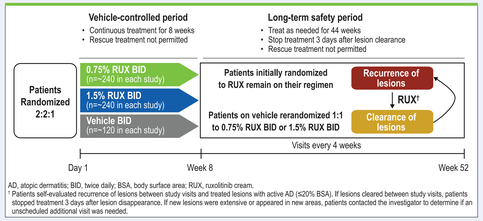
- To evaluate the long-term safety and disease control of ruxolitinib cream in patients with AD

Methods

Study Design and Patients

- Eligible patients were aged ≥12 years with AD for ≥2 years and had an Investigator's Global Assessment (IGA) score of 2 or 3 and 3%–20% affected body surface area (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
- TRueE-AD1 and TRueE-AD2 had identical study designs (**Figure 2**)
  - 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-blind 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 2. 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.

Assessments

- 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
- 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

Statistical Analyses

- Data were analyzed by descriptive statistics
- Disease control data (IGA 0/1 and BSA) are reported as observed

Results

Patients

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

Table 1. Patient Demographics and Baseline Clinical Characteristics

Characteristic	TRueE-AD1			TRueE-AD2		
	Vehicle (n=126)	0.75% RUX (n=252)	1.5% RUX (n=253)	Vehicle (n=124)	0.75% RUX (n=248)	1.5% RUX (n=246)
Age, median (range), y	31.5 (12–82)	34.0 (12–85)	30.0 (12–77)	37.5 (12–82)	33.0 (12–81)	32.0 (12–85)
Female, n (%)	79 (62.7)	154 (61.1)	158 (62.5)	80 (64.5)	150 (60.5)	150 (61.0)
Race, n (%)						
White	85 (67.5)	171 (67.9)	177 (70.0)	85 (68.5)	174 (70.2)	178 (72.4)
Black	29 (23.0)	55 (21.8)	56 (22.1)	32 (25.8)	63 (25.4)	57 (23.2)
Asian	8 (6.3)	10 (4.0)	14 (5.5)	2 (1.6)	6 (2.4)	6 (2.4)
Other	4 (3.2)	16 (6.3)	6 (2.4)	5 (4.0)	5 (2.0)	5 (2.0)
Region, n (%)						
North America	88 (69.8)	176 (69.8)	176 (69.6)	84 (67.7)	166 (66.9)	165 (67.1)
Europe	38 (30.2)	76 (30.2)	77 (30.4)	40 (32.3)	82 (33.1)	81 (32.9)
BSA, mean (SD), %	9.2 (5.1)	9.9 (5.4)	9.3 (5.2)	10.1 (5.8)	10.1 (5.3)	9.9 (5.4)
EASI, mean (SD)	7.4 (4.3)	8.2 (4.8)	7.9 (4.6)	8.2 (5.2)	8.1 (5.0)	7.8 (4.9)
IGA, n (%)						
2	31 (24.6)	61 (24.2)	60 (23.7)	33 (26.6)	64 (25.8)	63 (25.6)
3	95 (75.4)	191 (75.8)	193 (76.3)	91 (73.4)	184 (74.2)	183 (74.4)
Itch NRS score, mean (SD)	5.1 (2.5)	5.1 (2.3)	5.2 (2.5)	5.1 (2.4)	5.2 (2.5)	4.9 (2.5)
≥4, n (%)	78 (61.9)	156 (61.9)	161 (63.6)	81 (65.3)	168 (67.7)	154 (62.6)
Duration of disease, median (range), y	17.9 (1.9–79.1)	14.1 (1.0–68.8)	16.0 (0–69.2)	15.9 (0.8–70.7)	15.9 (0.1–68.6)	16.6 (0–68.8)
Facial involvement, n (%)*	52 (41.3)	112 (44.4)	118 (46.6)	41 (33.1)	83 (33.5)	79 (32.1)
Number of flares in last 12 mo, mean (SD)*	9.4 (35.2)	5.3 (7.5)	6.0 (23.3)	5.1 (8.1)	5.1 (5.8)	5.9 (8.5)

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

- In TRueE-AD1, 542 patients entered the LTS period, and 430 (79.3%) completed the study
  - The most common reasons for discontinuation were withdrawal by patient (n=49 [9.0%]) and lost to follow-up (n=41 [7.6%])
- In TRueE-AD2, 530 patients entered the LTS period, and 401 (75.7%) completed the study
  - The most common reasons for discontinuation were withdrawal by patient (n=78 [14.7%]) and lost to follow-up (n=25 [4.7%])
- The median (range) cumulative time off treatment due to lesion clearance was 91.0 (2–307) and 116.0 (2–286) days in TRueE-AD1 for 0.75% and 1.5% ruxolitinib cream, respectively, and 126.0 (3–308) and 145.5 (2–312) days in TRueE-AD2
- Among patients who achieved IGA 0 at the end of the VC period, median time to first retreatment was 6.5 and 11.0 days in TRueE-AD1 for 0.75% and 1.5% ruxolitinib cream, respectively, and 21.0 and 18.5 days in TRueE-AD2

Safety

- The safety profile of ruxolitinib cream in the LTS period was consistent with the VC period
- Ruxolitinib cream was well tolerated, and the frequency of application site reactions was low (**Table 2**)

Table 2. Adverse Events in the LTS Period (Pooled)

n, %	Vehicle to 0.75% RUX (n=101)	Vehicle to 1.5% RUX (n=99)	0.75% RUX (n=426)	1.5% RUX (n=446)
Patients with TEAE	54 (53.5)	57 (57.6)	256 (60.1)	240 (53.8)
Patients with treatment-related AE	2 (2.0)	6 (6.1)	20 (4.7)	13 (2.9)
Patients who discontinued due to a TEAE	0	0	9 (2.1)	0
Patients with serious TEAE	5 (5.0)	1 (1.0)	10 (2.3)	6 (1.3)

AE, adverse event; LTS, long-term safety; RUX, ruxolitinib cream; TEAE, treatment-emergent adverse event.

- No clinically meaningful changes or trends in hematologic parameters were noted over the 52-week period
- No AEs suggestive of a relationship to systemic exposure were observed
- The most common TEAEs (>2.0% in either ruxolitinib cream group) for the full 52-week study are shown in **Table 3**

Table 3. Most Common TEAEs for the 52-Week Study (Pooled)

TEAE, n (%)*	0.75% RUX (n=601)†	1.5% RUX (n=598)†
Upper respiratory tract infection	50 (8.3)	60 (10.0)
Nasopharyngitis	46 (7.7)	58 (9.7)
Headache	19 (3.2)	24 (4.0)
Bronchitis	16 (2.7)	20 (3.3)
Rhinitis	19 (3.2)	12 (2.0)
Atopic dermatitis	17 (2.8)	12 (2.0)
Influenza	8 (1.3)	18 (3.0)
Hypertension	16 (2.7)	11 (1.8)
Asthma	13 (2.2)	12 (2.0)
Sinusitis	17 (2.8)	8 (1.3)
Conjunctivitis	14 (2.3)	4 (0.7)

LTS, long-term safety; RUX, ruxolitinib cream; TEAE, treatment-emergent adverse event; VC, vehicle controlled.
* TEAE >2.0% in either RUX cream group.
† Includes patients who received ≥1 dose of RUX in the VC and/or LTS period.

- Exposure-adjusted TEAEs and application site reactions were lower for patients who applied ruxolitinib cream vs vehicle (**Table 4**)

Table 4. Exposure-Adjusted TEAEs

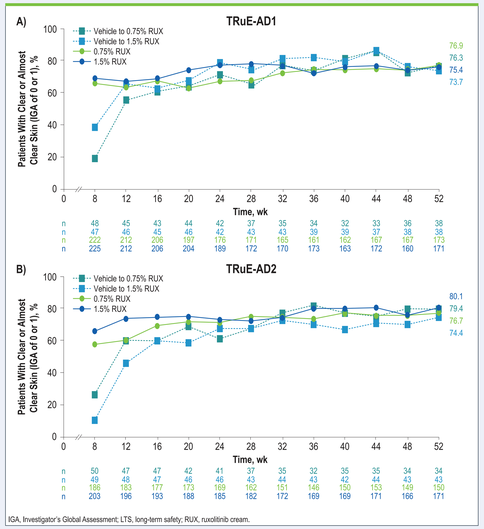
n (exposure-adjusted IR per 100 PY)	TRueE-AD1			TRueE-AD2		
	Vehicle (n=126)	0.75% RUX (n=300)	1.5% RUX (n=300)	Vehicle (n=124)	0.75% RUX (n=301)	1.5% RUX (n=298)
Any TEAE	44 (251.4)	171 (75.2)	172 (72.9)	39 (223.0)	197 (91.9)	173 (75.2)
Any application site reaction	8 (45.7)	8 (3.5)	5 (2.1)	11 (62.9)	10 (4.7)	5 (2.2)

IR, incidence rate; PY, patient-year; TEAE, treatment-emergent adverse event.

Disease Control

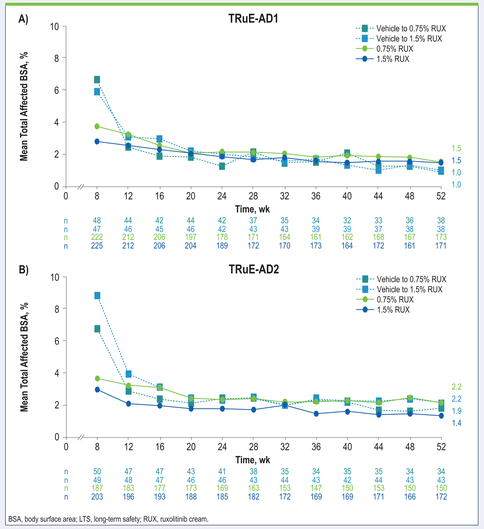
- The proportion of patients with clear or almost clear skin (IGA 0/1) increased during the LTS period with as-needed use of ruxolitinib cream (**Figure 3**)
- The proportion of patients who achieved an IGA score of 0/1 increased after switching from vehicle to either ruxolitinib cream strength in the LTS period (**Figure 3**)
- Mean affected BSA decreased during the LTS period with as-needed use of ruxolitinib cream (**Figure 4**)
- Affected BSA was substantially reduced after switching from vehicle to either ruxolitinib cream strength in the LTS period (**Figure 4**)

Figure 3. Proportion of Patients With Clear or Almost Clear Skin (IGA 0/1) in the LTS Period



IGA, Investigator's Global Assessment; LTS, long-term safety; RUX, ruxolitinib cream.

Figure 4. Affected BSA in the LTS Period



BSA, body surface area; LTS, long-term safety; RUX, ruxolitinib cream.

Conclusions

- **Over 75% of patients who entered the LTS period completed the study**
- **Ruxolitinib cream was well tolerated over 52 weeks, with a consistent safety profile throughout the study period**
  - **The incidence of application site reactions was low**
- **Disease control was observed with ruxolitinib cream monotherapy use as needed during the LTS period**
  - **A high proportion of patients maintained clear or almost clear skin using ruxolitinib cream as needed**
  - **Mean affected BSA decreased during the LTS period**
  - **Patients who previously applied vehicle exhibited disease control with ruxolitinib cream through achievement of clear or almost clear skin and reductions in affected BSA**

Disclosures

KP has received honoraria or clinical research grants as a consultant, speaker, scientific officer, advisory board member, and/or steering committee member for AbbVie, Akros, Amgen, Anacor, Arcutis, Astellas, Bausch Health/Valeant, Baxalta, Boehringer Ingelheim, Bristol Myers Squibb, Can-Fite, Celgene, Coherus, Dermira, Dow Pharmaceuticals, Eli Lilly, Galderma, Gilead, GlaxoSmithKline, Incyte Corporation, InflaRx, Janssen, Kyowa Hakko Kirin, LEO Pharma, Meiji Seika Pharma, Merck (MSD), Merck Serono, Mitsubishi Pharma, Moberg Pharma, Novartis, Pfizer, PRCL Research, Regeneron, Roche, Sanofi-Aventis/Genzyme, Sun Pharmaceuticals, Takeda, and UCB. JCS has served as an advisor for AbbVie, LEO Pharma, Menlo Therapeutics, Novartis, Pierre Fabre, and Trevi; has received speaker honoraria from AbbVie, Eli Lilly, Janssen-Cilag, LEO Pharma, Novartis, Sanofi Genzyme, and Sun Pharma; and has received clinical trial funding from AbbVie, Almirall, Amgen, Galapagos, Holm, Incyte Corporation, InflaRX, Janssen-Cilag, Menlo Therapeutics, Merck, Novartis, Pfizer, Regeneron, Trevi, and UCB. LK has served as an investigator, consultant, or speaker for AbbVie, Amgen, Anaptys, Arcutis, Dermavant, Eli Lilly, Glenmark, Incyte Corporation, Kamedis, LEO Pharma, L'Oreal, Menlo Therapeutics, Novartis, Ortho Dermatologics, Pfizer, Regeneron, Sanofi, Sun Pharma, and Taro. DT has served as an investigator for AbbVie, Amgen, Arcutis, Astellas, Astion, Avillion, Boehringer Ingelheim, Celgene, Dermira, Dow Pharmaceuticals, DS BioPharma, Eli Lilly, F. Hoffmann-La Roche Ltd, Galderma, GlaxoSmithKline, Incyte Corporation, Isotechnika, Janssen, LEO Pharma, Merck, Novartis, Pfizer, Regeneron, and UCB Biopharma. LFE has served as an investigator, consultant, speaker, or data safety monitoring board member for AbbVie, Almirall, Arcutis, Asana, Dermavant, Eli Lilly, Forte Biosciences, Galderma, Ichnos/Glenmark, Incyte Corporation, Janssen, LEO Pharma, Novartis, Ortho Dermatologics, Otsuka, Pfizer, Regeneron, and Sanofi Genzyme. SBF has received honoraria, clinical research grants, or fees as a consultant, speaker, advisory board member, and/or investigator for AbbVie, Aclaris Therapeutics, Asana BioSciences, AstraZeneca, Athenex, Celgene Corporation, Cutanea Life Sciences, Eli Lilly, Incyte Corporation, Innovaderm Research, Novartis, Pfizer, Promius Pharma, Regeneron, UCB, Valeant Pharmaceuticals North America, and XBiotech. 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. 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.

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