Efficacy and Safety of Ruxolitinib Cream for the Treatment of Atopic Dermatitis: Results From Two Phase 3, Randomized, Double-Blind Studies

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Background

- Atopic dermatitis (AD) is a chronic, inflammatory skin disease that greatly impacts patients' quality of life[1,2]
- Janus kinases (JAKs) modulate inflammatory cytokines involved in the pathogenesis of AD[3] and may also directly modulate itch[4]
- Ruxolitinib (RUX) is a potent, selective inhibitor of JAK1 and JAK2[5]
- In a phase 2 study (NCT03011892), RUX cream provided strength-dependent efficacy in patients with AD and a safety profile similar to vehicle[6]

Objectives

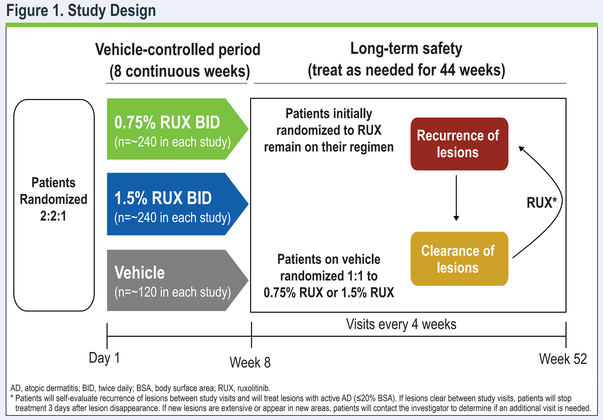
- To report efficacy and safety of RUX cream in patients with AD in two phase 3 studies (TRuE-AD1 [NCT03745638] and TRuE-AD2 [NCT03745651])

Methods

Patients and Study Design

- Eligible patients were aged ≥12 years with AD for ≥2 years, an Investigator's Global Assessment (IGA) score of 2 or 3, and 3% to 20% affected body surface area
- 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/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 either of 2 RUX cream strength regimens (0.75% twice daily [BID], 1.5% BID) or vehicle cream for 8 weeks of double-blind treatment
  - Patients on RUX cream could subsequently continue treatment for 44 weeks; patients initially randomized to vehicle were re-randomized 1:1 to either RUX cream regimen

Figure 1. Study Design



AD, atopic dermatitis; BID, twice daily; BSA, body surface area; RUX, ruxolitinib.
* Patients will self-evaluate recurrence of lesions between study visits and will treat lesions with active AD (≤20% BSA). If lesions clear between study visits, patients will stop treatment 3 days after lesion disappearance. If new lesions are extensive or appear in new areas, patients will contact the investigator to determine if an additional visit is needed.

Assessments

- The primary endpoint was the proportion of patients achieving IGA-treatment success (IGA-TS; score of 0/1 with ≥2-grade improvement from baseline) at Week 8
- The main secondary endpoints were the proportion of patients achieving ≥75% improvement in Eczema Area and Severity Index score vs baseline (EASI-75) and the proportion of patients with a ≥4-point improvement in itch numerical rating scale (NRS) score from baseline to Week 8

Statistical Analyses

- The primary and main secondary endpoints were analyzed by logistic regression using the intent-to-treat population
- All other secondary endpoints were analyzed using descriptive statistics
- The efficacy population consisted of 631 patients for TRuE-AD1 (all randomized patients) and 577 patients for TRuE-AD2 (vehicle, n=118; 0.75% RUX, n=231; 1.5% RUX, n=228)
- All patients who applied the study cream at least once (same as all randomized patients) were included in the safety population in both studies

Results

Patients

- In TRuE-AD1, 631 patients were randomized, and 558 (88.4%) completed treatment in the 8-week vehicle-controlled period
- In TRuE-AD2, 618 patients were randomized, and 561 (90.8%) completed treatment in the 8-week vehicle-controlled period
- Distribution of baseline demographics and clinical characteristics was similar across treatment groups **(Table 1)**

Table 1. Patient Demographics and Baseline Clinical Characteristics

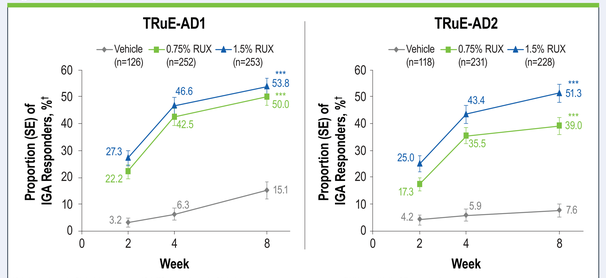
	TRuE-AD1			TRuE-AD2		
	Vehicle (n=126)	0.75% RUX (n=252)	1.5% RUX (n=253)	Vehicle (n=124)	0.75% RUX (n=248)	1.5% RUX (n=246)
Age, median (range), y	31.5 (12–82)	34.0 (12–85)	30.0 (12–77)	37.5 (12–82)	33.0 (12–81)	32.0 (12–85)
12–17, n (%)	23 (18.3)	53 (21.0)	47 (18.6)	22 (17.7)	55 (22.2)	45 (18.3)
≥18, n (%)	103 (81.7)	199 (79.0)	206 (81.4)	102 (82.3)	193 (77.8)	201 (81.7)
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)	175 (69.2)	84 (67.7)	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)
Other	12 (9.5)	26 (10.3)	21 (8.3)	8 (6.5)	11 (4.4)	11 (4.5)
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
Baseline 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
Baseline 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
Itch NRS score ≥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)

BSA, body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; NRS, numerical rating scale; RUX, ruxolitinib.
* Data missing from 1 patient in the 1.5% RUX group in TRuE-AD1.

Efficacy

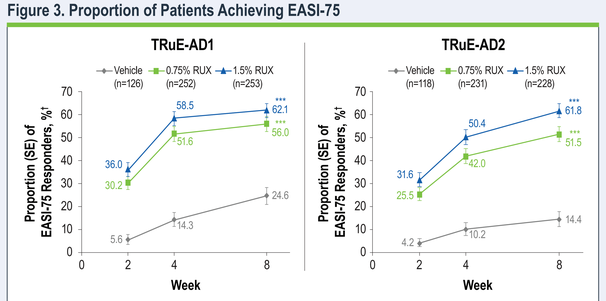
- Significantly more patients treated with RUX cream regimens vs vehicle demonstrated IGA-TS (primary endpoint); responses were time and strength dependent **(Figure 2)**
- Significantly more patients treated with RUX cream achieved EASI-75 vs vehicle; responses were time and strength dependent **(Figure 3)**
- Both strengths of RUX cream showed greater improvement in mean percentage change in EASI scores vs vehicle; statistical significance was observed at Week 2 and later **(Figure 4)**
- Significantly greater reductions in itch NRS scores were observed within 12 hours of the first application of RUX cream (1.5%; $P<0.05$; **Figure 5**) vs vehicle
- Significantly more patients treated with RUX cream demonstrated clinically meaningful reduction in itch (≥4-point improvement in itch NRS) vs vehicle **(Figure 6)**

Figure 2. Proportion of Patients With IGA-TS



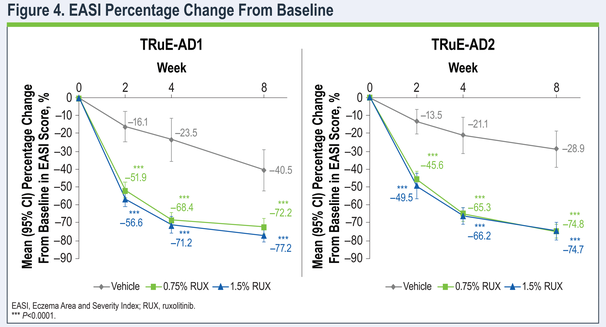
IGA, Investigator's Global Assessment; IGA-TS, Investigator's Global Assessment-treatment success; RUX, ruxolitinib; SE, standard error.
*** $P<0.0001$.
† Defined as patients achieving an IGA score of 0 or 1 with an improvement of ≥2 points from baseline. Patients with missing post-baseline values were imputed as nonresponders at Weeks 2, 4, and 8.

Figure 3. Proportion of Patients Achieving EASI-75



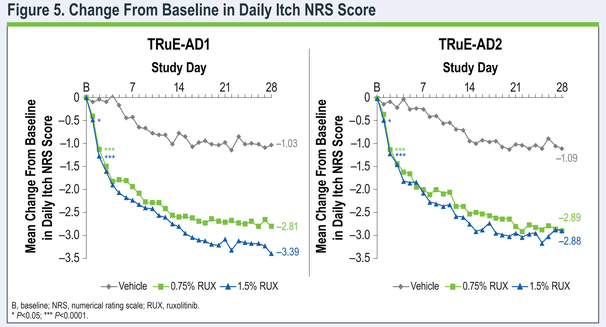
EASI-75, ≥75% improvement in Eczema Area and Severity Index score from baseline; RUX, ruxolitinib; SE, standard error.
*** $P<0.0001$.
† Patients with missing post-baseline values were imputed as nonresponders at Weeks 2, 4, and 8.

Figure 4. EASI Percentage Change From Baseline



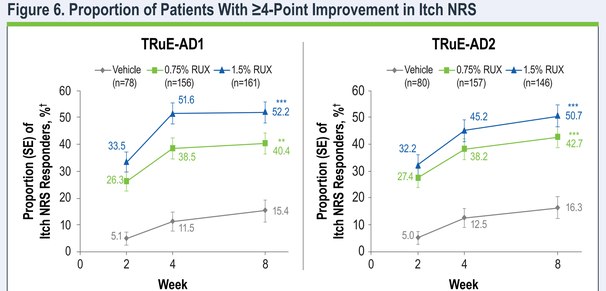
EASI, Eczema Area and Severity Index; RUX, ruxolitinib.
*** $P<0.0001$.

Figure 5. Change From Baseline in Daily Itch NRS Score



B, baseline; NRS, numerical rating scale; RUX, ruxolitinib.
* $P<0.05$; *** $P<0.0001$.

Figure 6. Proportion of Patients With ≥4-Point Improvement in Itch NRS



NRS, numerical rating scale; RUX, ruxolitinib; SE, standard error.
** $P<0.001$; *** $P<0.0001$.
† Patients in the analysis had an NRS score ≥4 at baseline. Patients with missing post-baseline values were imputed as nonresponders at Weeks 2, 4, and 8.

Safety

- RUX cream was well tolerated and not associated with clinically significant application site reactions **(Table 2)**
- All treatment-related treatment-emergent adverse events (TEAEs) were mild or moderate in severity
- No TEAEs suggestive of a relationship to bioavailability were observed

Table 2. Treatment-Emergent Adverse Events

	TRuE-AD1			TRuE-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)
Patients with TEAE, n (%)	44 (34.9)	74 (29.4)	73 (28.9)	40 (32.3)	73 (29.4)	58 (23.6)
Patients with treatment-related TEAE, n (%)	16 (12.7)	15 (6.0)	14 (5.5)	12 (9.7)	8 (3.2)	11 (4.5)
Most common treatment-related TEAEs, n (%)						
Application site burning	2 (1.6)	0	2 (0.8)	8 (6.5)	2 (0.8)	2 (0.8)
Application site pruritus	2 (1.6)	2 (0.8)	0	4 (3.2)	2 (0.8)	0
Pruritus	2 (1.6)	2 (0.8)	1 (0.4)	0	0	0
Discontinuation due to a TEAE, n (%)	5 (4.0)	3 (1.2)	3 (1.2)	3 (2.4)	1 (0.4)	0
Serious TEAE, n (%)*	2 (1.6)	1 (0.4)	2 (0.8)	0	3 (1.2)	1 (0.4)

RUX, ruxolitinib; TEAE, treatment-emergent adverse event.
* No serious TEAEs were related to RUX treatment.

Conclusions

- **Ruxolitinib cream showed superior efficacy vs vehicle in IGA-TS, EASI-75, and ≥4-point reduction in itch NRS score in these two phase 3 studies**
- **Application of ruxolitinib cream brought about rapid (within 12 hours of initiation of therapy), substantial, and sustained reduction in itch**
- **Ruxolitinib cream demonstrated a dual mode of action: antipruritic and anti-inflammatory**
- **No notable safety findings (either local or systemic) were associated with treatment, including on sensitive skin areas**
- **The successful outcomes of TRuE-AD1 and TRuE-AD2 support the potential of ruxolitinib cream as an effective and well-tolerated topical treatment for patients with AD**

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, Genentech, Gilead, GlaxoSmithKline, InflaRx, Janssen, Kyowa Hakko Kirin, LEO Pharma, MedImmune, 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, Novartis, Pierre Fabre, Menlo Therapeutics, and Trevi; has received speaker honoraria from AbbVie, Janssen-Cilag, LEO Pharma, Novartis, Sanofi-Genzyme, Sun Pharma, and Eli Lilly; and has received clinical trial funding from AbbVie, Almirall, Amgen, Galapagos, Holm, Incyte, InflaRX, Janssen-Cilag, Menlo Therapeutica, 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, Kamedis, LEO Pharma, L'oreal, Menlo, Novartis, Ortho Dermatologics, Pfizer, Regeneron, Sanofi, Sun Pharma, and Taro. DT has served as an investigator for AbbVie, Avillion, Amgen, Arcutis, Astellas, Astion, Boehringer Ingelheim, Celgene, Dermira, DS BioPharma, Dow Pharmaceuticals, Eli Lilly, F. Hoffmann-La Roche Ltd, Galderma, GlaxoSmithKline, Incyte, Isotechnika, Janssen, LEO Pharma, Merck, Novartis, Pfizer, Regeneron, and UCB Biopharma. MEK, 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, LEO Pharma, Menlo Therapeutics, Novartis, Pfizer, Regeneron, Sanofi Genzyme, and Valeant.

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