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

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Background

- Atopic dermatitis (AD) is a chronic, intensely pruritic, inflammatory skin dermatosis that greatly impacts patients' quality of life[1,2]
- Janus kinases (JAKs) act downstream of proinflammatory cytokines and itch mediators involved in the pathogenesis of AD[3,4]
- Ruxolitinib cream is a topical selective inhibitor of JAK1 and JAK2 in development for the treatment of AD[5]
- In a phase 2 study (NCT03011892), ruxolitinib cream provided high rates of strength-dependent efficacy in patients with AD and a safety profile similar to vehicle[6]

Objective

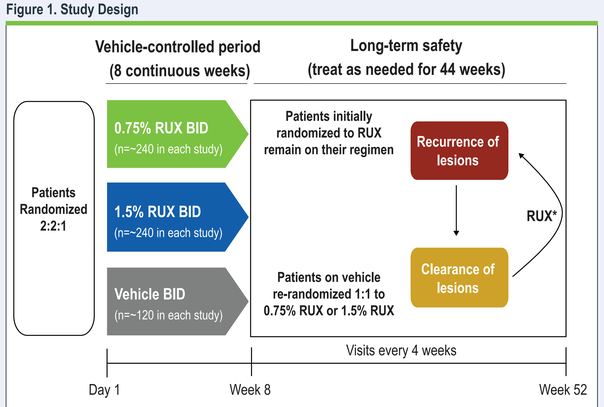
- To evaluate the efficacy and safety of ruxolitinib cream using pooled data from two phase 3 studies (TRuE-AD1 [NCT03745638] and TRuE-AD2 [NCT037456511]) in adolescent and adult patients with AD

Methods

Study Design and Patients

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

Figure 1. Study Design



AD, atopic dermatitis; BID, twice daily; BSA, body surface area; RUX, ruxolitinib cream.
* 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 or 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), the proportion of patients with a ≥4-point improvement in itch numerical rating scale (NRS4) score from baseline to Week 8, and the proportion of patients with a ≥6-point improvement in the Patient-Reported Outcomes Measurement Information System (PROMIS) Short Form–Sleep Disturbance (8b) 24-hour recall score at Week 8
- An additional secondary endpoint was mean percentage change from baseline in Scoring Atopic Dermatitis (SCORAD) score

Statistical Analyses

- All analyses were conducted using the pooled data from both studies
- The primary and main secondary endpoints were analyzed by logistic regression
- All other secondary endpoints were analyzed using descriptive statistics
- The efficacy population consisted of 1208 patients (vehicle, n=244; 0.75% ruxolitinib cream, n=483; 1.5% ruxolitinib cream, n=481)
- The safety population consisted of all randomized patients (vehicle, n=250; 0.75% ruxolitinib cream, n=500; 1.5% ruxolitinib cream, n=499)

Results

Patients

- Of 1249 patients randomized, 130 (10.4%) discontinued treatment during 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

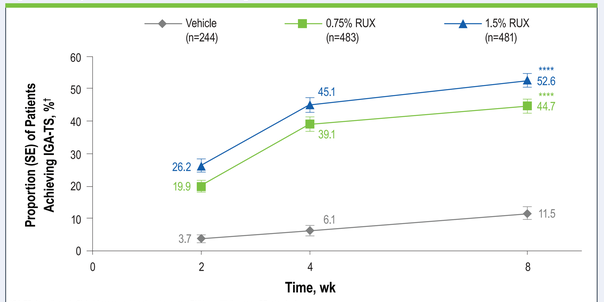
Characteristic	Vehicle (n=250)	0.75% RUX (n=500)	1.5% RUX (n=499)	Total (N=1249)
Age, median (range), y	34.0 (12–82)	33.0 (12–85)	31.0 (12–85)	32.0 (12–85)
12–17, n (%)	45 (18.0)	108 (21.6)	92 (18.4)	245 (19.6)
≥18, n (%)	205 (82.0)	392 (78.4)	407 (81.6)	1004 (80.4)
Female, n (%)	159 (63.6)	304 (60.8)	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)
Other	19 (7.6)	37 (7.4)	31 (6.2)	87 (7.0)
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
Baseline EASI, mean ± SD	7.8±4.8	8.1±4.9	7.8±4.8	8.0±4.8
≤7, n (%)	127 (50.8)	249 (49.8)	244 (48.9)	620 (49.6)
>7, n (%)	123 (49.2)	251 (50.2)	255 (51.1)	629 (50.4)
Baseline 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
Itch NRS score ≥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±6.5

BSA, body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; NRS, numerical rating scale; RUX, ruxolitinib cream.
* Data missing from 69 patients (vehicle, n=15; 0.75% RUX, n=33; 1.5% RUX, n=21).
† Patient-reported facial involvement.

Efficacy

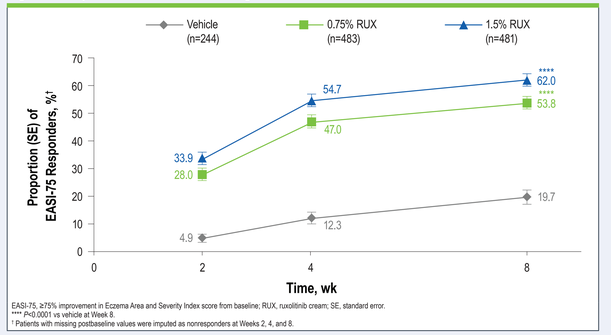
- Significantly more patients achieved IGA-TS at Week 8 with 0.75% and 1.5% ruxolitinib cream vs vehicle (44.7% and 52.6% vs 11.5%, respectively; both *P*<0.0001; **Figure 2**)
- Significantly more patients achieved EASI-75 at Week 8 with 0.75% and 1.5% ruxolitinib cream vs vehicle (53.8% and 62.0% vs 19.7%, respectively; both *P*<0.0001; **Figure 3**)
- Significantly greater itch reduction was observed within 12 hours of first 0.75% and 1.5% ruxolitinib cream application vs vehicle (mean change from baseline, –0.4 and –0.5 vs –0.1, respectively; both *P*<0.02; **Figure 4**)
- Significantly more patients demonstrated clinically meaningful improvement in itch (NRS4) and sleep disturbance (≥6-point improvement in PROMIS sleep disturbance [8b]) with ruxolitinib cream vs vehicle (**Figure 5**)
  - Significantly more patients achieved NRS4 at Week 8 with 0.75% and 1.5% ruxolitinib cream vs vehicle (41.5% and 51.5% vs 15.8%, respectively; both *P*<0.0001)
  - Considerable improvement in PROMIS 8b (≥6-point reduction) was achieved at Week 8 with 0.75% and 1.5% ruxolitinib cream vs vehicle (20.9% and 23.8% vs 14.2%, respectively; both *P*<0.05)
- Significant change from baseline in SCORAD score was achieved at Week 8 with 0.75% and 1.5% ruxolitinib cream regimens vs vehicle (–62.9% and –67.3% vs –30.4%, respectively; both *P*<0.0001; **Figure 6**)

Figure 2. Proportion of Patients Achieving IGA-TS



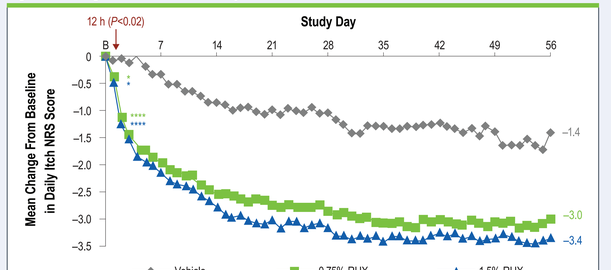
IGA-TS, Investigator's Global Assessment-treatment success; RUX, ruxolitinib cream; SE, standard error.
**** *P*<0.0001 vs vehicle at Week 8.
† Defined as patients achieving an IGA score of 0 or 1 with an improvement of ≥2 points from baseline. Patients with missing postbaseline values were imputed as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

Figure 3. Proportion of Patients Achieving EASI-75



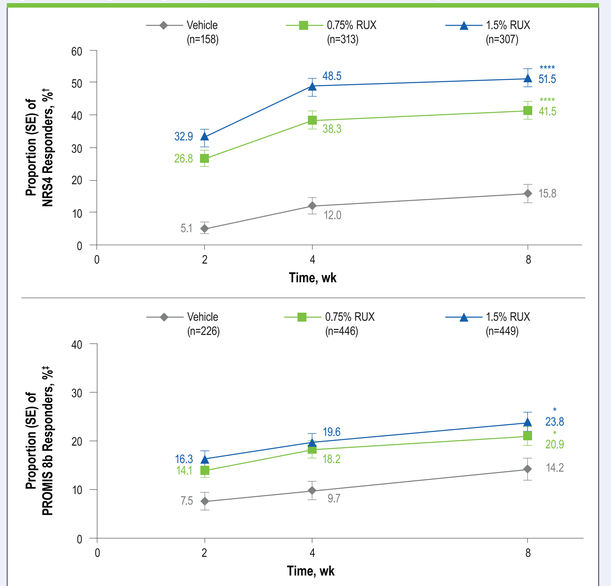
EASI-75, ≥75% improvement in Eczema Area and Severity Index score from baseline; RUX, ruxolitinib cream; SE, standard error.
**** *P*<0.0001 vs vehicle at Week 8.
† Patients with missing postbaseline values were imputed as nonresponders at Weeks 2, 4, and 8.

Figure 4. Change From Baseline in Daily Itch NRS Score



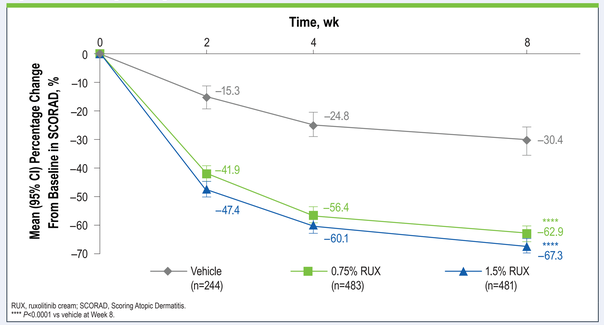
B, baseline; NRS, numerical rating scale; RUX, ruxolitinib cream.
* *P*<0.02 vs vehicle. **** *P*<0.0001 vs vehicle.

Figure 5. Clinically Meaningful Improvement in Itch NRS and PROMIS Sleep Disturbance Score (8b)



NRS, numerical rating scale; PROMIS, Patient-Reported Outcomes Measurement Information System; RUX, ruxolitinib cream; SE, standard error.
* *P*<0.05 vs vehicle at Week 8. **** *P*<0.0001 vs vehicle at Week 8.
† Patients in the analysis had an NRS score ≥4 at baseline. Patients with missing postbaseline values were imputed as nonresponders at Weeks 2, 4, and 8.
‡ Defined as a ≥6-point improvement from baseline in the PROMIS sleep disturbance score (8b). Patients with missing postbaseline values were imputed as nonresponders at Weeks 2, 4, and 8.

Figure 6. Percentage Change From Baseline in SCORAD Score



RUX, ruxolitinib cream; SCORAD, Scoring Atopic Dermatitis.
**** *P*<0.0001 vs vehicle at Week 8.

Safety

- Ruxolitinib cream was well tolerated and not associated with clinically significant application site reactions (**Table 2**)
- No serious adverse events (AEs) related to ruxolitinib cream were reported
- No treatment-emergent AEs suggestive of a relationship to bioavailability were observed
  - Ruxolitinib plasma levels were consistently low, with near-flat mean value curves throughout treatment

Table 2. Treatment-Emergent Adverse Events

AE, n (%)	Vehicle (n=250)	0.75% RUX (n=500)	1.5% RUX (n=499)
Patients with TEAE	83 (33.2)	145 (29.0)	132 (26.5)
Treatment-related AE	28 (11.2)	23 (4.6)	24 (4.8)
Most common treatment-related AEs*			
Application site burning†	11 (4.4)	3 (0.6)	4 (0.8)
Application site pruritus†	6 (2.4)	4 (0.8)	0
Discontinuation due to a TEAE	8 (3.2)	4 (0.8)	4 (0.8)
Serious TEAE‡	2 (0.8)	4 (0.8)	3 (0.6)

AE, adverse event; RUX, ruxolitinib cream; TEAE, treatment-emergent adverse event.
* Occurring in >0.5% of the total patient population.
† Patient-reported tolerability was not lesion specific and was reported for all treated areas.
‡ No serious TEAEs were considered related to RUX treatment.

Conclusions

- **Application of ruxolitinib cream brought about rapid (within 12 hours of initiation of therapy), substantial, and sustained reduction in itch**
- **Ruxolitinib cream demonstrated superior efficacy vs vehicle for achieving IGA-TS, EASI-75, NRS4, a ≥6-point improvement in PROMIS 8b, and change from baseline in SCORAD**
- **Ruxolitinib cream demonstrated a dual mode of action: antipruritic and anti-inflammatory**
- **The AE profile was similar to vehicle; the rate of application site reactions was low**
- **These results demonstrate the potential of ruxolitinib cream as an effective and well-tolerated topical treatment for 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, GSK, InflaRx, Janssen, Kyowa Hakko Kirin, LEO Pharma, MedImmune, Meiji Seika Pharma, Merck (MSD), Merck Serono, Mitsubishi Pharma, Moberg Pharma, Novartis, Pfizer, PRCI, 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 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, 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 Corporation, 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 Corporation, LEO Pharma, Menlo Therapeutics, Novartis, Pfizer, Regeneron, Sanofi Genzyme, and Valeant.

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