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Ruxolitinib Cream Rapidly Decreases Skin Pain in Atopic Dermatitis

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Background

- Atopic dermatitis (AD) is an inflammatory skin disease associated with skin pain[1]
- Skin pain is the second most common symptom of AD (after itch)[2] and is frequently linked to scratching and fissures in the skin[3]
- Janus kinases (JAKs) play an important role in the pathogenesis of AD by mediating proinflammatory cytokines[4] and may be involved in the mechanisms of inflammatory pain[5]
- Ruxolitinib cream is a topical selective inhibitor of JAK1 and JAK2 in development for the treatment of AD[6]
- 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 compared with vehicle and was well tolerated[6]

Objective

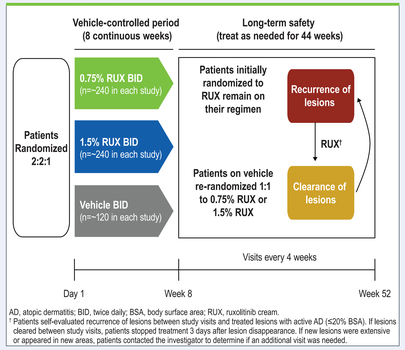
- To describe the effect of ruxolitinib cream on skin pain in adolescent and adult patients with AD using pooled data from two phase 3 trials

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 (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 regimen

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 of ruxolitinib cream was assessed by the proportion of patients achieving IGA-treatment success (IGA-TS; IGA score of 0 or 1 with a ≥2-grade improvement from baseline), ≥75% improvement in Eczema Area and Severity Index vs baseline (EASI-75), and daily itch scores per the numerical rating scale (NRS; worst level of itch over 24 hours, ranging from 0 [no itch] to 10 [worst imaginable itch])
- Skin pain was assessed with the following endpoints:
  - Worst skin pain scores per NRS (daily and Weeks 2, 4, and 8)
  - Proportion of patients achieving a skin pain NRS score of 0 or 1 (NRS 0/1)
  - Proportion of patients achieving "no pain/discomfort" per the EuroQol 5-Dimensions 5-Levels (EQ-5D-5L) questionnaire[7]
  - Change from baseline in EQ-5D visual analog scale (VAS)

Statistical Analyses

- All analyses were conducted using the pooled data from the vehicle-controlled portion of both studies
- The proportions of patients achieving IGA-TS or EASI-75 were assessed using logistic regression
- Daily skin pain and daily itch NRS scores were assessed using analysis of variance
- Skin pain NRS at Weeks 2, 4, 8 as well as EQ VAS scores were assessed using analysis of covariance
- The proportions of patients achieving skin pain NRS 0/1 were compared using the chi-square test
- Categorical EQ-5D-5L data 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)

Results

Patients

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

Table 1. Patient Demographics and Baseline Clinical Characteristics

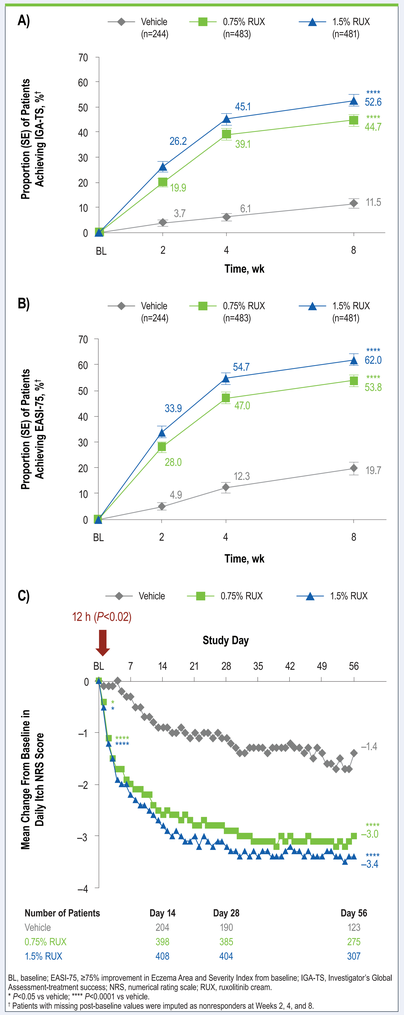
Characteristic	Vehicle (n=250)	0.75% RUX (n=500)	1.5% RUX (n=499)	Total (N=1249)
Age, median (range), y	34.0 (12–82)	33.0 (12–85)	31.0 (12–85)	32.0 (12–85)
Female, n (%)	159 (63.6)	304 (60.8)	308 (61.7)	771 (61.7)
Race, n (%)				
White	170 (68.0)	345 (69.0)	355 (71.1)	870 (69.7)
Black	61 (24.4)	118 (23.6)	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)
Skin pain NRS score, mean (SD)*	4.2 (2.8)	4.1 (2.8)	4.0 (2.8)	NA
EQ VAS score, mean (SD)*	77.4 (18.0)	76.1 (18.3)	77.6 (18.5)	NA
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; EQ, EuroQol; IGA, Investigator's Global Assessment; NA, not available; NRS, numerical rating scale; RUX, ruxolitinib cream; VAS, visual analog scale.
* Data from the efficacy-evaluable population (vehicle, n=244; 0.75% RUX, n=483; 1.5% RUX, n=481).
† Patient reported.

Efficacy

- Ruxolitinib cream significantly reduced inflammation (IGA-TS [**Figure 2A**] and EASI-75 [**Figure 2B**]) at Week 8 (P<0.0001), and started to reduce itch within 12 hours of first application (P<0.02; **Figure 2C**), compared with vehicle

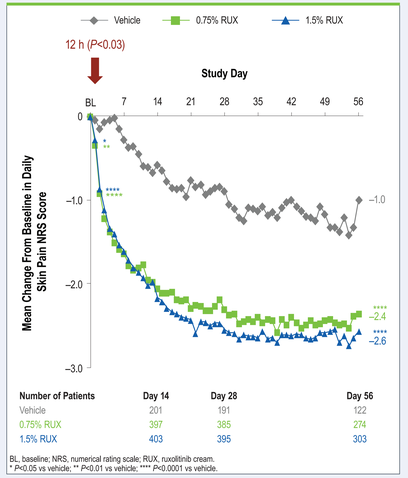
Figure 2. Proportion of Patients Achieving (A) IGA-TS and (B) EASI-75, and (C) Mean Change From Baseline in Daily Itch NRS Score



BL, baseline; EASI-75, ≥75% improvement in Eczema Area and Severity Index from baseline; IGA-TS, Investigator's Global Assessment-treatment success; NRS, numerical rating scale; RUX, ruxolitinib cream.
* P<0.05 vs vehicle; **** P<0.0001 vs vehicle.
† Patients with missing post-baseline values were imputed as nonresponders at Weeks 2, 4, and 8.

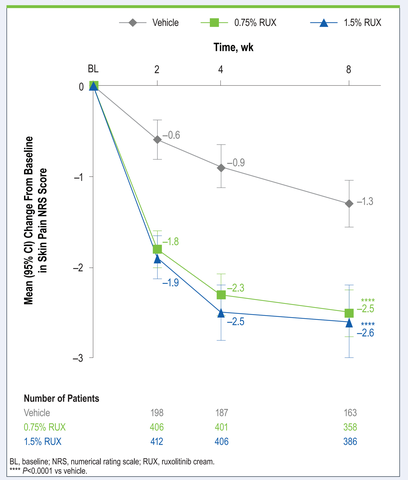
- Patients who applied ruxolitinib cream had significantly greater mean reductions from baseline in skin pain NRS score within 12 hours of the first application (–0.3 for both 0.75% and 1.5% ruxolitinib cream) vs vehicle (–0.04; both P<0.03; **Figure 3**); further reductions were observed over time (–2.5/–2.6 vs –1.3, respectively, at Week 8; both P<0.0001; **Figure 4**)

Figure 3. Mean Change From Baseline in Daily Skin Pain NRS Score



BL, baseline; NRS, numerical rating scale; RUX, ruxolitinib cream.
* P<0.05 vs vehicle; ** P<0.01 vs vehicle; **** P<0.0001 vs vehicle.

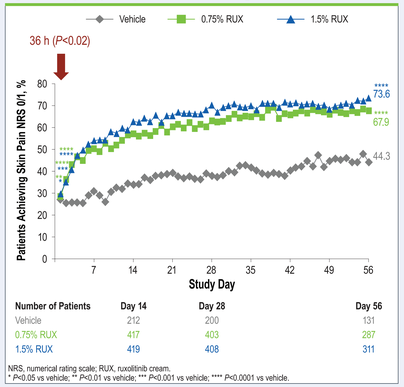
Figure 4. Mean Change From Baseline in Skin Pain NRS Score at Weeks 2, 4, and 8



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

- On Day 2 (approximately 36 hours after first application), a significantly larger proportion of patients who applied ruxolitinib cream 0.75%/1.5% achieved skin pain NRS 0/1 vs vehicle (36.3%/35.3% vs 25.7%; both P<0.02); further improvements were observed over time (Day 56, 67.9%/73.6% vs 44.3%; both P<0.0001; **Figure 5**)

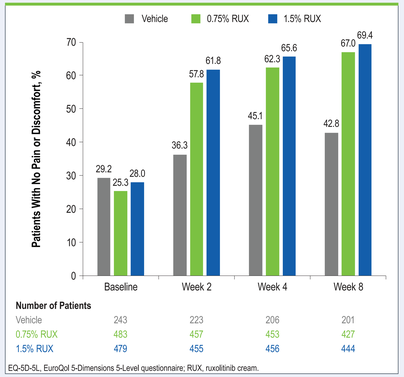
Figure 5. Daily Proportion of Patients Achieving Skin Pain NRS 0/1



NRS, numerical rating scale; RUX, ruxolitinib cream.
* P<0.05 vs vehicle; ** P<0.01 vs vehicle; *** P<0.001 vs vehicle; **** P<0.0001 vs vehicle.

- At Week 8, there was a significantly greater change from baseline in EQ VAS score (indicating improved quality of life) for patients receiving ruxolitinib cream (0.75%/1.5%) compared with vehicle (8.1/8.2 vs 2.4; both P<0.0001)
- The majority of patients receiving ruxolitinib cream (0.75%/1.5%) reported no pain or discomfort per EQ-5D-5L (4th dimension) at Week 8 (67.0%/69.4%) compared with vehicle (42.8%; **Figure 6**)

Figure 6. Proportion of Patients With No Pain or Discomfort per EQ-5D-5L (4th Dimension)



EQ-5D-5L, EuroQol 5-Dimensions 5-Level questionnaire; RUX, ruxolitinib cream.

Safety

- Ruxolitinib cream was well tolerated with an adverse event (AE) profile similar to vehicle[6]; no serious AEs were related to ruxolitinib cream
  - Application site reactions, such as stinging/burning, were infrequent (<1%) with ruxolitinib cream; none were clinically significant

Conclusions

- **Ruxolitinib cream significantly decreased inflammation, itch, and skin pain in adolescents and adults with AD during the 8-week treatment period**
- **Significant reductions in skin pain vs vehicle were observed within 12 hours of the first application of ruxolitinib cream**
- **More patients who applied ruxolitinib cream vs vehicle reported no pain or discomfort**

Disclosures

AB has served as a scientific advisor 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. JCS has served as an advisor for AbbVie, LEO Pharma, Novartis, Pierre Fabre, Menlo Therapeutics, 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. 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, Incyte Corporation, 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. 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. JIS received honoraria for advisory board, speaker, and consultant services from AbbVie, Asana, Bluefin, Boehringer Ingelheim, Celgene, Dermavant, Dermira, Eli Lilly, Galderma, GlaxoSmithKline, Glenmark, Incyte Corporation, Kiniksa, LEO Pharma, Menlo, Novartis, Pfizer, Realm, Regeneron, and Sanofi and research grants for investigator services from Galderma and GlaxoSmithKline. BSK has served as a consultant to AbbVie, Almirall, Amagma, Cara Therapeutics, Daewoong, Incyte Corporation, OM Pharma, and Pfizer; has served on advisory boards for AstraZeneca, Boehringer Ingelheim, Cara Therapeutics, Celgene Corporation, Regeneron Pharmaceuticals, Sanofi Genzyme, and Trevi Therapeutics; is a shareholder in Locus Biosciences; and has a pending patent for JAK inhibitors in chronic itch. SGK has served as an advisory board member or consultant for AbbVie, Galderma, Incyte Corporation, Kiniksa Pharmaceuticals, Regeneron Pharmaceuticals, and Pfizer Inc; and has received grant funding from Pfizer Inc, Galderma, and Kiniksa Pharmaceuticals. MEK, MEV, and KS are employees and shareholders of Incyte Corporation. 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.

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