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Effect of Ruxolitinib Cream on Sleep Disturbance and Sleep Impairment: Pooled Analysis From Two Randomized Phase 3 Studies

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Background

- Atopic dermatitis (AD) is a chronic, highly pruritic, inflammatory skin disease
- Patients' quality of life (QoL) is significantly impacted by sleep disturbances[1,2]
  - Most patients with AD report poor sleep quality[3,4]
- Janus kinases (JAKs) act downstream of proinflammatory cytokines and itch mediators involved in the pathogenesis of AD[5,6]
- Ruxolitinib cream is a selective inhibitor of JAK1 and JAK2 in development for the treatment of AD[7]
- 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 vs vehicle and was well tolerated[8]
  - In a pooled analysis, significantly more patients who applied ruxolitinib cream vs vehicle achieved Investigator's Global Assessment-treatment success at Week 8 (score of 0 or 1 with ≥2-grade improvement from baseline), the primary endpoint of the study (44.7%/52.6% for 0.75%/1.5% ruxolitinib cream, respectively, vs 11.5% for vehicle; *P*<0.0001)

Objective

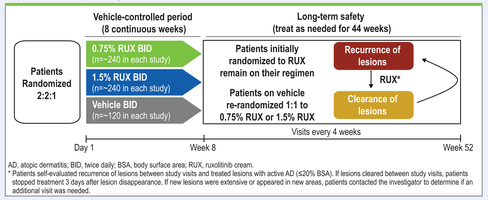
- To evaluate the effects of ruxolitinib cream on sleep disturbance and sleep-related impairment in adolescent and adult patients with AD

Methods

Patients

- Eligible patients were aged ≥12 years with AD for ≥2 years and had an Investigator's Global Assessment 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 0.75% ruxolitinib cream twice daily (BID), 1.5% ruxolitinib cream BID, or vehicle cream BID for 8 weeks of double-blind 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; data from this 44-week period are not reported here

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

- Sleep quality was assessed using the validated Patient-Reported Outcomes Measurement Information System (PROMIS) sleep-related impairment (8a) and sleep disturbance (8b) Short Form questionnaires,[9] which were modified to be completed daily with a 24-hour recall
  - The PROMIS Short Form sleep-related impairment and sleep disturbance are 8-item questionnaires with each item rated on a 5-point scale with a range in score from 8–40; higher scores indicate greater impairment or disturbance
  - Raw scores were not converted to T-scores for analysis
  - A 6-point improvement in score from baseline was determined to be clinically meaningful
    - The sleep-related impairment assessment is focused on self-reported perceptions of alertness, sleepiness, and tiredness during usual waking hours
    - The sleep disturbance assessment is focused on self-reported perceptions of sleep quality, sleep depth, and restoration associated with sleep
- Patient-Oriented Eczema Measure (POEM) item 2 (number of nights of disturbed sleep due to eczema over the past 7 days) responses by category were assessed at Weeks 2, 4, and 8
  - The POEM is a 7-item QoL assessment that evaluates how many days the patient has been bothered by various aspects of their disease during the past 7 days; higher scores indicate more severe skin symptoms[10]
- Mean change from baseline in the SCORing Atopic Dermatitis (SCORAD) sleeplessness score was assessed at Weeks 2, 4, and 8
  - The degree that AD interfered with sleep over the last 3 days was assessed using a visual analog scale from 0 ("no problem at all") to 10 ("unbearable problem")[11]

Statistical Analyses

- All analyses were conducted using the pooled data from both studies
- The efficacy population consisted of 1208 patients (vehicle, n=244; 0.75% ruxolitinib cream, n=483; 1.5% ruxolitinib cream, n=481)
- The proportion of patients who achieved a ≥6-point improvement in PROMIS sleep-related impairment and sleep disturbance scores was analyzed by logistic regression
  - Patients with missing post-baseline values were imputed as nonresponders
- Statistical significance for change from baseline in PROMIS sleep-related impairment and PROMIS sleep disturbance was assessed using analysis of variance (ANOVA)
- Data for POEM and SCORAD were analyzed using descriptive statistics

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

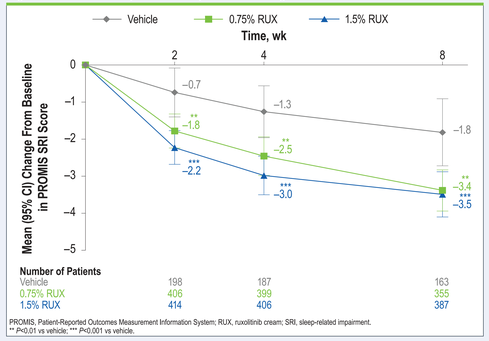
Characteristic	Vehicle (n=250)	0.75% RUX (n=500)	1.5% RUX (n=499)	Total (N=1249)
Age, median (range), y	34.0 (12–82)	33.0 (12–85)	31.0 (12–85)	32.0 (12–85)
Female, n (%)	159 (63.6)	304 (60.8)	308 (61.7)	771 (61.7)
Race, n (%)				
White	170 (68.0)	345 (69.0)	355 (71.1)	870 (69.7)
Black	61 (24.4)	118 (23.6)	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)
≥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)
PROMIS, mean (SD)†‡				
Sleep-related impairment	16.8 (6.1)	17.3 (6.2)	17.4 (6.2)	NA
Sleep disturbance	18.7 (5.8)	19.1 (6.1)	19.0 (6.1)	NA
SCORAD sleeplessness, mean (SD)†	3.6 (2.7)	3.5 (2.8)	3.4 (2.8)	NA

BSA, body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; NA, not available; NRS, numerical rating scale; PROMIS, Patient-Reported Outcomes Measurement Information System; SCORAD, SCORing Atopic Dermatitis; RUX, ruxolitinib cream.
* Patient reported.
† Data from the efficacy-evaluable population (vehicle, n=244; 0.75% RUX, n=483; 1.5% RUX, n=481).
‡ Raw scores.

Patient-Reported Outcomes

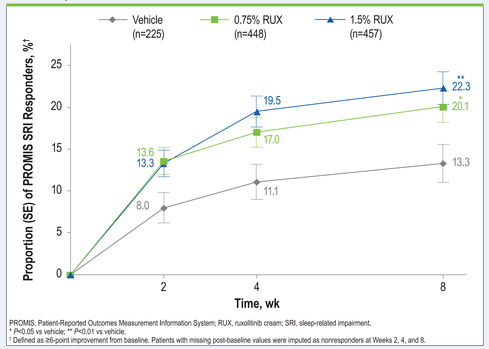
- At Week 2, a significantly greater reduction in mean change from baseline in PROMIS sleep-related impairment scores (indicating less impairment) was reported in patients who applied ruxolitinib cream (0.75%/1.5%) vs vehicle (–1.8/–2.2 vs –0.7; *P*<0.01); responses improved with time, indicating progressive sleep improvement (**Figure 2**)
- Significantly more patients who applied ruxolitinib cream achieved a ≥6-point improvement from baseline in sleep-related impairment score vs patients who applied vehicle at Week 8 (20.1%/22.3% vs 13.3%; *P*<0.05; **Figure 3**)
  - Among patients with PROMIS sleep-related impairment scores ≥14 at baseline, significantly more patients who received ruxolitinib cream achieved a ≥6-point improvement from baseline vs vehicle at Week 8 (30.3%/33.9% vs 20.3%; *P*<0.05/*P*<0.01)
- At Week 2, a significantly greater reduction in mean change from baseline in PROMIS sleep disturbance scores (indicating less disturbance) was reported in patients who applied ruxolitinib cream (0.75%/1.5%) vs vehicle (–1.8/–2.5 vs –0.8; *P*<0.01); responses improved with time, indicating progressive sleep improvement (**Figure 4**)
- Significantly more patients who applied ruxolitinib cream achieved a ≥6-point improvement from baseline in sleep disturbance score vs patients who applied vehicle at Week 8 (20.9%/23.8% vs 14.2%; *P*<0.05; **Figure 5**)
  - Among patients with PROMIS sleep disturbance scores ≥14 at baseline, significantly more patients who received ruxolitinib cream achieved a ≥6-point improvement from baseline vs vehicle at Week 8 (26.5%/30.5% vs 17.9%; *P*<0.05/*P*<0.01)
- More patients reported no nights of disturbed sleep with ruxolitinib cream (66.1%/71.6%) vs vehicle (44.3%) at Week 8 as assessed by POEM item 2 (**Figure 6**)
- A greater reduction in mean change from baseline in SCORAD sleeplessness scores (indicating improved sleep quality) was reported in patients who applied ruxolitinib cream vs vehicle at Weeks 2, 4, and 8 (**Figure 7**)

Figure 2. PROMIS Sleep-Related Impairment Change From Baseline



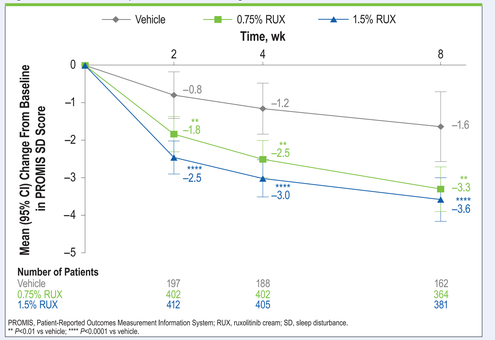
PROMIS, Patient-Reported Outcomes Measurement Information System; RUX, ruxolitinib cream; SRI, sleep-related impairment.
** *P*<0.01 vs vehicle; *** *P*<0.001 vs vehicle.

Figure 3. Proportion of Patients Achieving a ≥6-Point Improvement in PROMIS Sleep-Related Impairment Score



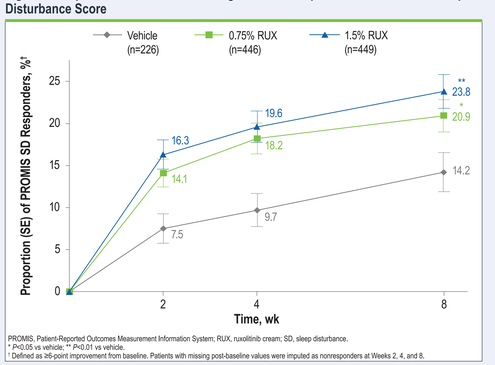
PROMIS, Patient-Reported Outcomes Measurement Information System; RUX, ruxolitinib cream; SRI, sleep-related impairment.
* *P*<0.05 vs vehicle; ** *P*<0.01 vs vehicle.
† Defined as ≥6-point improvement from baseline. Patients with missing post-baseline values were imputed as nonresponders at Weeks 2, 4, and 8.

Figure 4. PROMIS Sleep Disturbance Change From Baseline



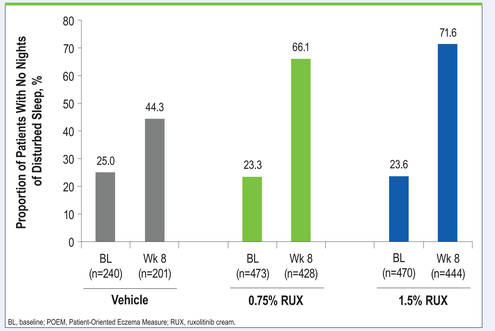
PROMIS, Patient-Reported Outcomes Measurement Information System; RUX, ruxolitinib cream; SD, sleep disturbance.
** *P*<0.01 vs vehicle; **** *P*<0.0001 vs vehicle.

Figure 5. Proportion of Patients Achieving a ≥6-Point Improvement in PROMIS Sleep Disturbance Score



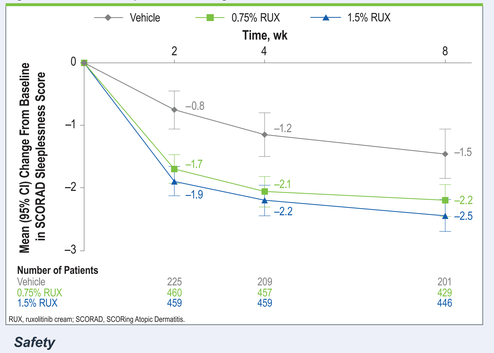
PROMIS, Patient-Reported Outcomes Measurement Information System; RUX, ruxolitinib cream; SD, sleep disturbance.
* *P*<0.05 vs vehicle; ** *P*<0.01 vs vehicle.
† Defined as ≥6-point improvement from baseline. Patients with missing post-baseline values were imputed as nonresponders at Weeks 2, 4, and 8.

Figure 6. Proportion of Patients With No Nights of Disturbed Sleep in the Last Week per POEM Item 2



BL, baseline; POEM, Patient-Oriented Eczema Measure; RUX, ruxolitinib cream.

Figure 7. SCORAD Sleeplessness Change From Baseline



RUX, ruxolitinib cream; SCORAD, SCORing Atopic Dermatitis.

Safety

- Ruxolitinib cream was well tolerated with an adverse event (AE) profile similar to vehicle[8]; no serious AEs were related to ruxolitinib cream

Conclusions

- **Ruxolitinib cream produced early and progressive improvements in sleep quality and related impact as demonstrated by mean change from baseline in PROMIS sleep-related impairment and sleep disturbance scores, as well as the SCORAD sleeplessness score, in patients with AD**
- **More patients who received ruxolitinib cream achieved a clinically meaningful ≥6-point improvement from baseline in PROMIS sleep-related impairment and sleep disturbance scores and no nights of disturbed sleep as assessed by POEM vs vehicle at Week 8**
- **The therapeutic anti-inflammatory and antipruritic effects of topical JAK inhibition observed with ruxolitinib cream provide clinically relevant improvement in sleep parameters in adolescents and adults with AD**

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. MB is an investigator for Incyte Corporation, DT has served as an investigator and/or consultant/advisor for AbbVie, Almirall, Amgen, Asana Biosciences, Biogen Idec, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Galapagos, Galderma, Janssen-Cilag, Kyowa Kirin, LEO Pharma, Novartis, Pfizer, Regeneron, Samsung, Sandoz, Sanofi, Target-Solution, and UCB; and has received grants from AbbVie, Celgene, LEO Pharma, and Novartis. LM is an investigator for AbbVie, Eli Lilly, Galderma, Incyte Corporation, LEO Pharma, Pfizer, and Sanofi; and is a consultant with honorarium for AbbVie, Eli Lilly, Galderma, LEO Pharma, Menlo Therapeutics, Novartis, Pfizer, and Sanofi. 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 GlaxoSmithKline and Galderma. LAB is a consultant for AbbVie, Allakos, AstraZeneca, BenevolentAI, Incyte Corporation, Janssen, LEO Pharma, Eli Lilly, NAOS Bioderma, Novartis, Pfizer, Principia Biopharma, Rapt Therapeutics, Regeneron, Sanofi Genzyme, Sanofi-Aventis, UCB, and Vimalan Biosciences Inc.; an investigator for AbbVie, AstraZeneca, Kiniksa, LEO Pharma, Pfizer, Regeneron, and Sanofi; and owns stock in Gilead, Medtronics, Moderna, and 3M. MEK, MEV, and KS are employees and shareholders of Incyte Corporation. 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.

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