313

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Itch-Free State in Patients With Atopic Dermatitis Treated With Ruxolitinib Cream

Andrew Blauvelt, MD, MBA,[1]* Jacek C. Szepietowski, MD, PhD, FRCP (Edin),[2] Kim Papp, MD, PhD,[3] Eric L. Simpson, MD, MCR,[4] Jonathan I. Silverberg, MD, PhD, MPH,[5] Brian S. Kim, MD, MTR,[6] Shawn G. Kwatra, MD,[7] Michael E. Kuligowski, MD, PhD, MBA,[8] May E. Venturanza, MD,[8] Kang Sun, PhD,[8] Leon Kircik, MD[9]

[1]Oregon Medical Research Center, Portland, OR, USA; [2]Wroclaw Medical University, Wroclaw, Poland; [3]K. Papp Clinical Research and Probity Medical Research, Waterloo, ON, Canada; [4]Oregon Health & Science University, Portland, OR, USA; [5]George Washington University, Washington, DC, USA; [6]Washington University School of Medicine, St. Louis, MO, USA; [7]Johns Hopkins University School of Medicine, Baltimore, MD, USA; [8]Incyte Corporation, Wilmington, DE, USA; [9]Icahn School of Medicine at Mount Sinai, New York, NY, USA

*Presenting author

Background

- Atopic dermatitis (AD) is a highly pruritic, chronic, inflammatory skin disease[1]
- Itch is reported to be the most burdensome symptom of AD[2]; some patients with AD report itch every day[3]
  - Inadequate control of AD is associated with greater itch interference with daily living[4]
  - The negative impact of itch in patients with AD highlights the need for achievement of an itch-free state
- Janus kinases (JAKs) play an important role in the pathogenesis of AD and the development of itch by mediating proinflammatory cytokines in skin and sensory neurons[5,6]
- Ruxolitinib cream is a topical 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[7]

Objective

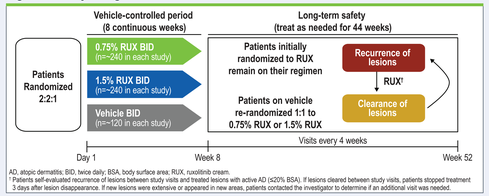
- To describe the effect of ruxolitinib cream on achievement of an itch-free state in adolescent and adult patients with AD using pooled data from two phase 3 trials

Methods

Study Design and Patients

- Eligible patients were aged ≥12 years with AD for ≥2 years and had an Investigator's Global Assessment 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

- The effects of ruxolitinib cream on itch were assessed by the proportion of patients achieving an itch numerical rating scale score of 0 or 1 (NRS 0/1)
  - Patients were given an electronic diary to be completed each evening and were instructed to report their worst level of itch during the past 24-hour period from 0 (no itch) to 10 (worst imaginable itch)
  - The by-visit itch NRS score for post-baseline visits (Weeks 2, 4, 8) was determined by averaging the 7 daily itch NRS scores before the study visit; if ≥4 daily scores were missing, the itch NRS score for the study visit was classified as missing
- The effects on eczema-related itch were also assessed using the proportion of patients reporting no days of itch per item 1 (frequency of itch; Q1) of the Patient-Oriented Eczema Measure (POEM)[8] at baseline and Weeks 2, 4, and 8
- Itch-free state was also assessed stratified by baseline itch NRS score (<6 or ≥6)

Statistical Analyses

- All analyses were conducted using the pooled data from the vehicle-controlled portion of both studies
- The proportion of patients achieving itch NRS 0/1 and the number of days with no itch per POEM Q1 were assessed using logistic regression
- Cumulative incidence plots were created for time to itch NRS 0/1
  - A log-rank test was used for between-group comparisons
- 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
- The mean (SD) itch NRS score at baseline was 5.1 (2.4)
- Distribution of baseline demographics and clinical characteristics was similar across treatment groups (**Table 1**)

Table 1. Patient Demographics and Baseline Clinical Characteristics

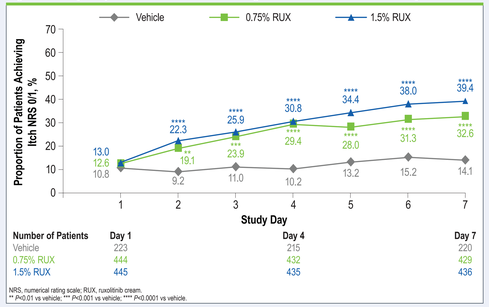
Characteristic	Vehicle (n=250)	0.75% RUX (n=500)	1.5% RUX (n=499)	Total (N=1249)
Age, median (range), y	34.0 (12–82)	33.0 (12–85)	31.0 (12–85)	32.0 (12–85)
Female, n (%)	159 (63.6)	304 (60.8)	308 (61.7)	771 (61.7)
Race, n (%)				
White	170 (68.0)	345 (69.0)	355 (71.1)	870 (69.7)
Black	61 (24.4)	118 (23.6)	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)
Baseline POEM Q1 (itch frequency) response, n (%)*				
No days	5 (2.1)	9 (1.9)	13 (2.8)	27 (2.3)
1–2 days	18 (7.5)	30 (6.3)	35 (7.4)	83 (7.0)
3–4 days	33 (13.8)	75 (15.8)	63 (13.3)	171 (14.4)
5–6 days	29 (12.1)	44 (9.3)	50 (10.6)	123 (10.4)
Every day	155 (64.6)	317 (66.7)	311 (65.9)	783 (66.0)
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; IGA, Investigator's Global Assessment; NRS, numerical rating scale; POEM Q1, Patient-Oriented Eczema Measure–Question 1; RUX, ruxolitinib cream.
* Data available for 1187 patients (vehicle, n=240; 0.75% RUX, n=475; 1.5% RUX, n=472).
† Patient reported.

Efficacy

- A significantly higher proportion of patients who applied 0.75% and 1.5% ruxolitinib cream achieved itch NRS 0/1 vs vehicle as early as Day 2 (approximately 36 hours after first application; 19.1% and 22.3% for 0.75% and 1.5% ruxolitinib cream, respectively, vs 9.2%; both $P<0.01$; **Figure 2**)

Figure 2. Daily Proportion of Patients Achieving Itch NRS 0/1 in the First 7 Days

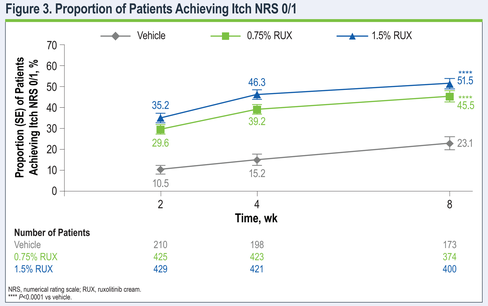


Number of Patients	Day 1	Day 4	Day 7
Vehicle	223	215	220
0.75% RUX	444	432	429
1.5% RUX	445	435	436

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

- At Week 8, the proportion of patients achieving itch NRS 0/1 (average of daily NRS measurements over the 7 days before the Week 8 visit) was significantly higher for patients who applied ruxolitinib cream (0.75%/1.5%) compared with vehicle (45.5%/51.5% vs 23.1%; both $P<0.0001$; **Figure 3**)

Figure 3. Proportion of Patients Achieving Itch NRS 0/1

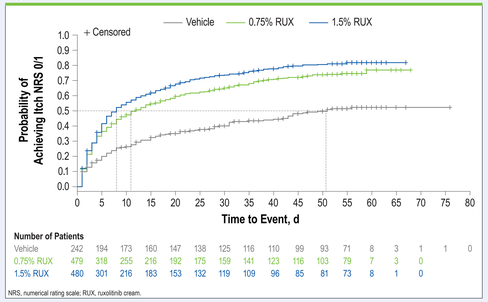


Number of Patients			
Vehicle	210	198	173
0.75% RUX	425	423	374
1.5% RUX	429	421	400

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

- Median time to achieve the first observed day with itch NRS 0/1 was shorter for ruxolitinib cream (12.0 and 8.0 days for 0.75% and 1.5% ruxolitinib cream, respectively) vs vehicle (51.0 days; **Figure 4**); cumulative incidence rates for achieving ≥1 day with itch NRS 0/1 were significantly higher for ruxolitinib cream (log-rank $P<0.0001$ [both])

Figure 4. Kaplan-Meier Curve of Time to Achieve Itch NRS 0/1

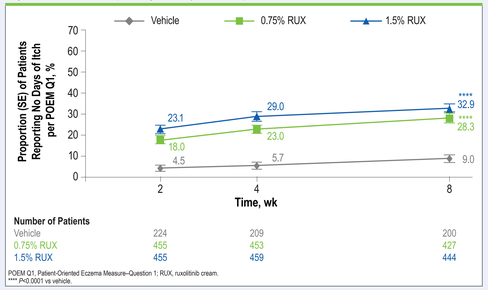


Number of Patients																		
Vehicle	242	194	173	160	147	138	125	116	110	99	93	71	8	3	1	1	0	
0.75% RUX	479	318	255	216	192	175	159	141	123	116	103	79	7	3	0			
1.5% RUX	480	301	216	183	153	132	119	109	96	85	81	73	8	1	0			

NRS, numerical rating scale; RUX, ruxolitinib cream.

- Significantly more patients reported no days of itch with ruxolitinib cream per POEM Q1 at Week 8 (28.3% and 32.9% for 0.75% and 1.5% ruxolitinib cream, respectively) vs vehicle (9.0%; both $P<0.0001$; **Figure 5**)

Figure 5. Patients Reporting No Days of Itch per POEM Q1

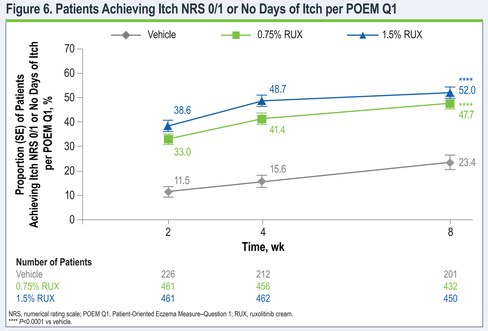


Number of Patients			
Vehicle	224	209	200
0.75% RUX	455	453	427
1.5% RUX	455	459	444

POEM Q1, Patient-Oriented Eczema Measure–Question 1; RUX, ruxolitinib cream.
**** $P<0.0001$ vs vehicle.

- As assessed by itch NRS 0/1 or POEM, more patients achieved itch-free status at Week 8 with ruxolitinib cream vs vehicle (47.7% and 52.0% for 0.75% and 1.5% ruxolitinib cream, respectively, vs 23.4%; both $P<0.0001$; **Figure 6**) regardless of baseline itch score (**Figure 7**)

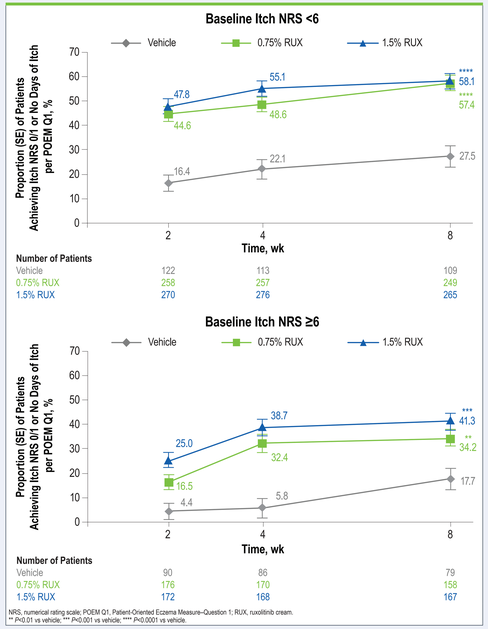
Figure 6. Patients Achieving Itch NRS 0/1 or No Days of Itch per POEM Q1



Number of Patients			
Vehicle	226	212	201
0.75% RUX	461	456	432
1.5% RUX	461	462	450

NRS, numerical rating scale; POEM Q1, Patient-Oriented Eczema Measure–Question 1; RUX, ruxolitinib cream.
**** $P<0.0001$ vs vehicle.

Figure 7. Patients Achieving Itch NRS 0/1 or No Days of Itch per POEM Q1 by Baseline Itch NRS Score



Number of Patients			
Vehicle	122	113	109
0.75% RUX	258	257	249
1.5% RUX	270	276	265

Number of Patients			
Vehicle	90	86	79
0.75% RUX	176	170	158
1.5% RUX	172	168	167

NRS, numerical rating scale; POEM Q1, Patient-Oriented Eczema Measure–Question 1; RUX, ruxolitinib cream.
** $P<0.01$ vs vehicle; *** $P<0.001$ vs vehicle; **** $P<0.0001$ vs vehicle.

Safety

- Ruxolitinib cream was well tolerated with an adverse event (AE) profile similar to vehicle[7]; no serious AEs were related to ruxolitinib cream

Conclusions

- **A significantly greater number of patients treated with ruxolitinib cream achieved and sustained an itch-free state vs vehicle during the 8-week treatment period**
- **Patients who applied ruxolitinib cream had a substantially shorter median time to itch NRS 0/1 vs vehicle**

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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