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ORIGINAL RESEARCH

Long-Term Integrated Safety Summary of Ruxolitinib Cream in Phase 3 Clinical Trials of Patients with Vitiligo

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ABSTRACT

Introduction: Ruxolitinib cream demonstrated superior repigmentation versus vehicle at week 24 with continued improvement through week 104 in phase 3 studies of patients (aged ≥ 12 years) with nonsegmental vitiligo. Here, we evaluated long-term safety of ruxolitinib cream in an integrated analysis of phase 3 vitiligo studies.

Methods: Reported incidence and exposure-adjusted incidence rates (EAIRs) of treatment-emergent adverse events (TEAEs) were determined.

Results: Over 104 weeks, 673 patients with vitiligo applied either ruxolitinib cream ($n = 637$; 867.9 person-years [PY]) or vehicle ($n = 270$; 131.1 PY). TEAEs (EAIR, patients/100 PY) with

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ruxolitinib cream versus vehicle occurred in 62.6% (46.0) versus 37.0% (76.3) of patients, most commonly nasopharyngitis (7.2% [5.3] vs 2.6% [5.3]) and application site acne (6.0% [4.4] vs 1.1% [2.3]). No serious treatment-related TEAEs were reported with ruxolitinib cream. EAIRs (patients/100 PY) were low for acne-related TEAEs (7.1), skin and subcutaneous tissue infections (4.0), cytopenias (2.4), and liver enzyme elevations (2.2). Malignancies, serious infections, and thromboembolic events were rare (0.7, 0.5, and 0.2 patients/100 PY, respectively), and none were considered related to treatment. No major adverse cardiovascular events or deaths occurred.

***Conclusion*:** Ruxolitinib cream demonstrated tolerability, with no unexpected safety findings through 2 years in patients with vitiligo. Graphical Plain Language Summary available for this article.

***Trial Registration*:** Clinicaltrials.gov identifiers, NCT04052425 (registered on August 8, 2019), NCT04057573 (registered on August 14, 2019), and NCT04530344 (registered on August 25, 2020).

Keywords: Janus kinase inhibitor; Ruxolitinib cream; Vitiligo

Key Summary Points

Why carry out this study?

Ruxolitinib cream has previously demonstrated significant repigmentation compared with vehicle cream in phase 3 studies of patients (aged ≥ 12 years) with nonsegmental vitiligo.

Because repigmentation of lesional skin is a gradual process that likely requires continuous treatment, this analysis aimed to evaluate the long-term safety of ruxolitinib cream through an integrated analysis of phase 3 vitiligo studies.

What was learned from the study?

In this integrated analysis of phase 3 clinical trials, long-term application of ruxolitinib cream did not result in any unexpected safety findings in adults and adolescents with nonsegmental vitiligo.

Ruxolitinib cream demonstrated tolerability through 2 years of treatment in patients with nonsegmental vitiligo; no serious treatment-related adverse events were reported.

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DIGITAL FEATURES

This article is published with supplementary digital features, including a Graphical Plain Language Summary, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.30146218 and the Supplementary Materials for this article.

INTRODUCTION

Vitiligo is a chronic autoimmune disorder resulting in skin depigmentation and reduced quality of life [1–3]. Although vitiligo is typically considered a difficult disease to manage [4], Janus kinase (JAK) inhibitors have shown considerable promise as treatment for lesion repigmentation [5, 6]. JAK inhibitors have been extensively studied in other dermatologic diseases, including atopic dermatitis (AD) and alopecia areata [7].

Ruxolitinib cream is a topical formulation of ruxolitinib, a JAK1/JAK2 selective inhibitor [8]. The long-term safety analysis of ruxolitinib cream for the treatment of AD in phase 3 clinical trials demonstrated tolerability over 52 weeks

in > 1000 patients [9]. Malignancies and serious infections, which included sepsis and pneumonia, were infrequent (< 1% of patients with AD) and none were considered related to treatment. Major adverse cardiovascular events (MACE) and thrombotic events occurred in five patients with AD (< 1%), all of whom had known risk factors [9]. In a postmarketing, 1-year safety analysis, ruxolitinib cream was well tolerated with no reports of serious infections, MACE, or thromboses [10].

In patients with vitiligo, twice-daily (BID) application of 1.5% ruxolitinib cream resulted in significant repigmentation versus vehicle cream in a phase 2, randomized, dose-ranging study and two phase 3 randomized, vehicle-controlled studies [11, 12]. In these studies, all application site reactions and all treatment-related adverse events (AEs) were mild or moderate in severity (grades 1 or 2). Additionally, no accumulation of AEs was observed over 3 years of treatment in the phase 2 study [13].

Because repigmentation of lesional skin is a slow process [14] that may require several years of treatment, it is important to establish the long-term safety and tolerability of continuous ruxolitinib cream use in patients with vitiligo. Thus, this analysis aims to report long-term safety data with ruxolitinib cream monotherapy in adults and adolescents with vitiligo using integrated phase 3 clinical trial data.

METHODS

Study Designs and Patients

Pooled data were included from two multinational phase 3 studies (TRuE-V1, NCT04052425; TRuE-V2, NCT04057573; both 52 weeks) and a rollover, phase 3, long-term extension study (TRuE-V LTE, NCT04530344; additional 52 weeks [total 104 weeks]). The study design and eligibility criteria for the TRuE-V phase 3 studies have been described previously [12].

Briefly, TRuE-V1 and TRuE-V2 were identically designed, randomized, phase 3 studies that evaluated the efficacy and safety of 1.5% ruxolitinib cream BID in adolescent and adult patients (≥ 12 years) with nonsegmental vitiligo who had depigmented areas ≤ 10% of total body surface area (BSA), including ≥ 0.5% facial BSA and ≥ 3% BSA on nonfacial areas [12]. Patients were randomized 2:1 to apply 1.5% ruxolitinib cream BID or vehicle cream BID for 24 weeks. Following completion of the double-blind period, all patients applied open-label 1.5% ruxolitinib cream BID for 28 weeks.

In TRuE-V LTE, patients who completed TRuE-V1/TRuE-V2 were eligible to enroll. Patients who achieved ≥ 90% improvement from baseline in facial Vitiligo Area Scoring Index (F-VASI90) at week 52 in TRuE-V1/TRuE-V2 were randomized 1:1 to vehicle cream BID or 1.5% ruxolitinib cream BID (double-blind) until the end of treatment (week 104); if patients relapsed (< 75% improvement from baseline in facial Vitiligo Area Scoring Index [< F-VASI75]), they applied open-label 1.5% ruxolitinib cream BID rescue treatment. Patients who did not achieve F-VASI90 at week 52 continued to apply open-label 1.5% ruxolitinib cream BID until week 104.

These studies were conducted in accordance with Good Clinical Practice guidelines, provisions of the Declaration of Helsinki, and applicable regulations. Study protocols were approved by each site's institutional review board. All patients in this article have given written consent to participate and for publication of their case details.

Assessments

Safety was assessed in all studies through monitoring of AEs, vital signs, and laboratory data. AEs were tabulated using Medical Dictionary for Regulatory Activities version 23.1 preferred terms. The severity of AEs was graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. AEs of interest included acne-related AEs,

skin and subcutaneous tissue infections, serious infections, malignancies, thromboembolic AEs, MACE, cytopenias, thrombocytosis, and liver enzyme elevations. AEs of interest were further assessed using pharmacokinetic and/or clinical laboratory data (including hemoglobin and platelet levels), as appropriate.

Statistical Analysis

This integrated safety analysis included pooled data for patients in phase 3 studies with ≥ 1 application of 1.5% ruxolitinib cream or vehicle at any time. Safety data are reported as observed events according to the treatment (i.e., ruxolitinib cream or vehicle) patients were applying at AE onset. Exposure-adjusted incidence rates (EAIRs), calculated as the number of patients reporting the event per 100 person-years (PY) of exposure with 95% CI, are also reported.

RESULTS

Patients and Ruxolitinib Cream Exposure

A total of 673 patients were enrolled in the phase 3 studies and applied ≥ 1 dose of 1.5% ruxolitinib cream or vehicle cream (Supplementary Material Fig. 1). Baseline demographics and disease characteristics for the pooled patient population are summarized in Supplementary Material Table 1. The mean (SD) age was 39.5 (15.1) years; 72 patients (10.7%) were aged 12 to 17 years. Slightly more patients were female (n = 358 [53.2%]), and 485 patients (72.1%) had Fitzpatrick skin types I–III. Most patients in the study had long-standing disease; the median (range) disease duration was 12.0 (0–60.5) years.

The mean (SD) durations of ruxolitinib cream and vehicle application were 497.7 (231.0) and 177.3 (85.8) days, respectively, and the median (range) were 561.0 (1–817) and 168.0 (1–552) days. Across studies, patients had a total of 867.9 PY of ruxolitinib cream exposure and 131.1 PY of vehicle exposure.

Safety Profile

Treatment-emergent AEs (TEAEs) occurred in 399 patients (62.6%) while applying ruxolitinib cream in the three studies over a period of up to 104 weeks (Table 1). TEAEs occurred in 100 patients (37.0%) while applying vehicle. The EAIRs (95% CI) of any TEAE with ruxolitinib cream and vehicle were 46.0 (41.6–50.7) and 76.3 (62.1–92.8) patients/100 PY, respectively.

Overall, the most common TEAEs with application of ruxolitinib cream and vehicle were COVID-19 (14.0% and 4.8%, respectively), nasopharyngitis (7.2% and 2.6%), application site acne (6.0% and 1.1%), and upper respiratory tract infection (5.2% and 1.9%). Rates of common TEAEs were generally similar between ruxolitinib cream and vehicle when adjusted for exposure (Table 1). Among the 70 adolescents (aged 12–17 years) who applied ruxolitinib cream, the safety profile (Supplementary Material Table 2) was generally similar to the overall study population. Enrollment in TRuE-V1/TRuE-V2 began shortly before the COVID-19 pandemic. As such, COVID-19 was not considered to be relevant to ruxolitinib cream application on the basis of its prevalence at the time of the studies [12].

Of the 637 patients who applied ruxolitinib cream, 100 patients (15.7%) had AEs considered by investigators to be related to treatment, most of which were mild or moderate application site reactions. The only non-application site reactions that were considered treatment related and occurred in > 1 patient were fatigue, headache, oral herpes, and upper respiratory tract infection (n = 2 each), all which were mild or moderate in severity. Serious AEs were infrequent, occurring in 4.1% of patients who applied ruxolitinib cream, and were considered by investigators to be unrelated to treatment. Discontinuations of ruxolitinib cream due to TEAEs were low (0.6%; application site eczema, application site rash, fatigue, road traffic accident [n = 1 each]), with only application site eczema and fatigue considered to be treatment related. All of these events resolved.

Across studies, 108 patients (17.0%) and 16 patients (5.9%) reported an application site

Table 1 Safety summary

	Vehicle ($n = 270$; PY = 131.1)		1.5% RUX cream ($n = 637$; PY = 867.9)	
	n (%)	EAIR (95% CI), patients/100 PY	*n* (%)	EAIR (95% CI), patients/100 PY
Patients with TEAEs	100 (37.0)	76.3 (62.1–92.8)	399 (62.6)	46.0 (41.6–50.7)
Most frequent TEAEs[a]				
COVID-19	13 (4.8)	9.9 (5.3–17.0)	89 (14.0)	10.3 (8.2–12.6)
Nasopharyngitis	7 (2.6)	5.3 (2.2–11.0)	46 (7.2)	5.3 (3.9–7.1)
Application site acne	3 (1.1)	2.3 (0.5–6.7)	38 (6.0)	4.4 (3.1–6.0)
Upper respiratory tract infection	5 (1.9)	3.8 (1.2–8.9)	33 (5.2)	3.8 (2.6–5.3)
Headache	7 (2.6)	5.3 (2.2–11.0)	30 (4.7)	3.5 (2.3–4.9)
Application site pruritus	7 (2.6)	5.3 (2.2–11.0)	29 (4.6)	3.3 (2.2–4.8)
Sinusitis	6 (2.2)	4.6 (1.7–10.0)	19 (3.0)	2.2 (1.3–3.4)
Urinary tract infection	1 (0.4)	0.8 (0.02–4.3)	18 (2.8)	2.1 (1.2–3.3)
Application site dermatitis	0	0	17 (2.7)	2.0 (1.1–3.1)
ALT increased	1 (0.4)	0.8 (0.02–4.3)	13 (2.0)	1.5 (0.8–2.6)
Discontinuations due to TEAEs	1 (0.4)	0.8 (0.02–4.3)	4 (0.6)	0.5 (0.1–1.2)
Patients with TRAEs	19 (7.0)	14.5 (8.7–22.6)	100 (15.7)	11.5 (9.4–14.0)
Most frequent TRAEs[a]				
Application site acne	2 (0.7)	1.5 (0.2–5.5)	29 (4.6)	3.3 (2.2–4.8)
Application site pruritus	7 (2.6)	5.3 (2.2–11.0)	26 (4.1)	3.0 (2.0–4.4)
Discontinuations due to TRAEs	1 (0.4)	0.8 (0.02–4.3)	2 (0.3)	0.2 (0.03–0.8)
Patients with SAEs	1 (0.4)[b]	0.8 (0.02–4.3)	26 (4.1)[c]	3.0 (2.0–4.4)
Patients with TRSAEs	0	0	0	0
Patients with fatal TEAEs	0	0	0	0

ALT alanine aminotransferase, *EAIR* exposure-adjusted incidence rate, *PY* person-years, *RUX* ruxolitinib, *SAE* serious adverse event, *TEAE* treatment-emergent adverse event, *TRAE* treatment-related adverse event, *TRSAE* treatment-related serious adverse event

[a]Occurred in ≥ 2% of patients in either treatment group

[b]SAE was tibia fracture ($n = 1$)

[c]SAEs included acute respiratory failure ($n = 1$), anal fistula ($n = 1$), angina pectoris ($n = 1$), appendiceal abscess ($n = 1$), appendicitis ($n = 1$), bipolar I disorder ($n = 1$), COVID-19 pneumonia ($n = 1$), cholelithiasis ($n = 1$), concussion ($n = 1$), coronary artery stenosis ($n = 1$), cystocele ($n = 1$), hepatitis infectious mononucleosis ($n = 1$), hip fracture ($n = 1$), hypersensitivity ($n = 1$), intervertebral disc disorder ($n = 1$), joint dislocation ($n = 1$), kidney contusion ($n = 1$), mental status changes ($n = 1$), myocarditis ($n = 1$), otosclerosis ($n = 1$), papillary thyroid cancer ($n = 1$), pelvic prolapse ($n = 1$), prostate cancer ($n = 1$), rectocele ($n = 1$), rhabdomyolysis ($n = 1$), spinal fracture ($n = 1$), spinal osteoarthritis ($n = 1$), subacute combined cord degeneration ($n = 1$), ureterolithiasis ($n = 1$), uterine leiomyoma ($n = 1$), and uterine prolapse ($n = 1$)

Table 2 Application site reactions

	Vehicle ($n = 270$; PY = 131.1)		1.5% RUX cream ($n = 637$; PY = 867.9)	
	n (%)	EAIR (95% CI), patients/100 PY	*n* (%)	EAIR (95% CI), patients/100 PY
Patients with any ASR	16 (5.9)	12.2 (7.0–19.8)	108 (17.0)	12.4 (10.2–15.0)
Acne	3 (1.1)	2.3 (0.5–6.7)	38 (6.0)	4.4 (3.1–6.0)
Pruritus	7 (2.6)	5.3 (2.2–11.0)	29 (4.6)	3.3 (2.2–4.8)
Dermatitis	0	0	17 (2.7)	2.0 (1.1–3.1)
Rash	2 (0.7)	1.5 (0.2–5.5)	12 (1.9)	1.4 (0.7–2.4)
Erythema	1 (0.4)	0.8 (0–4.3)	9 (1.4)	1.0 (0.5–2.0)
Folliculitis	0	0	7 (1.1)	0.8 (0.3–1.7)
Exfoliation	1 (0.4)	0.8 (0.02–4.3)	6 (0.9)	0.7 (0.3–1.5)
Discoloration	1 (0.4)	0.8 (0.02–4.3)	5 (0.8)	0.6 (0.2–1.3)
Dryness	1 (0.4)	0.8 (0.02–4.3)	5 (0.8)	0.6 (0.2–1.3)
Pain	0	0	5 (0.8)	0.6 (0.2–1.3)
Eczema	1 (0.4)	0.8 (0.02–4.3)	4 (0.6)	0.5 (0.1–1.2)
Irritation	1 (0.4)	0.8 (0.02–4.3)	2 (0.3)	0.2 (0.03–0.8)
Papules	1 (0.4)	0.8 (0.02–4.3)	2 (0.3)	0.2 (0.03–0.8)
Urticaria	0	0	2 (0.3)	0.2 (0.03–0.8)
Bruise	0	0	1 (0.2)	0.1 (0–0.6)
Cyst	0	0	1 (0.2)	0.1 (0–0.6)
Paresthesia	1 (0.4)	0.8 (0.02–4.3)	1 (0.2)	0.1 (0–0.6)
Not specified[a]	0	0	1 (0.2)	0.1 (0–0.6)
Vesicles	0	0	1 (0.2)	0.1 (0–0.6)

ASR application site reaction, *EAIR* exposure-adjusted incidence rate, *MedDRA* Medical Dictionary for Regulatory Activities, *PY* person-years, *RUX* ruxolitinib

[a]Reported as the MedDRA term "application site reaction"

reaction while applying ruxolitinib cream and vehicle, respectively (Table 2); the EAIR (95% CI) of application site reactions was 12.4 (10.2–15.0) and 12.2 (7.0–19.8) patients/100 PY, respectively. The most common application site reactions among patients who applied ruxolitinib cream were application site acne ($n = 38$ [6.0%]) and application site pruritus ($n = 29$ [4.6%]).

AEs of Interest

Serious infections, malignancies or unspecified neoplasms, and thromboembolic events were rare among patients who applied ruxolitinib cream (Table 3). Most patients (72.7% [8/11]) had low trough ruxolitinib plasma concentrations (< 55 nM), well below the 281-nM threshold for JAK-related myelosuppression [8]) at assessments prior to AE onset.

Table 3 TEAEs of interest

	Vehicle (*n* = 270; PY = 131.1)		1.5% RUX cream (*n* = 637; PY = 867.9)	
	n **(%)**	**EAIR (95% CI), patients/100 PY**	***n*** **(%)**	**EAIR (95% CI), patients/100 PY**
Serious infections[a]	0	0	4 (0.6)	0.5 (0.1–1.2)
Appendiceal abscess	0	0	1 (0.2)	0.1 (0–0.6)
Appendicitis	0	0	1 (0.2)	0.1 (0–0.6)
COVID-19 pneumonia	0	0	1 (0.2)	0.1 (0–0.6)
Hepatitis infectious mononucleosis	0	0	1 (0.2)	0.1 (0–0.6)
Malignancies or unspecified tumors[a]	1 (0.4)	0.8 (0.02–4.3)	6 (0.9)	0.7 (0.3–1.5)
Basal cell carcinoma[b]	0	0	1 (0.2)	0.1 (0–0.6)
Colon adenoma[b]	0	0	1 (0.2)	0.1 (0–0.6)
Ovarian cancer[b]	0	0	1 (0.2)	0.1 (0–0.6)
Ovarian neoplasm[b]	0	0	1 (0.2)	0.1 (0–0.6)
Papillary thyroid cancer	0	0	1 (0.2)	0.1 (0–0.6)
Prostate cancer	0	0	1 (0.2)	0.1 (0–0.6)
Squamous cell carcinoma of skin[b]	1 (0.4)	0.8 (0.02–4.3)	0	0
Thromboembolic TEAEs[a,b]	0	0	2 (0.3)	0.2 (0.03–0.8)
Cardiac ventricular thrombosis	0	0	1 (0.2)	0.1 (0–0.6)
Transient ischemic attack	0	0	1 (0.2)	0.1 (0–0.6)
MACE	0	0	0	0
Acne-related TEAEs[b]	6 (2.2)	4.6 (1.7–10.0)	62 (9.7)	7.1 (5.5–9.2)
Application site acne	3 (1.1)	2.3 (0.5–6.7)	38 (6.0)	4.4 (3.1–6.0)
Acne	1 (0.4)	0.8 (0.02–4.3)	11 (1.7)	1.3 (0.6–2.3)
Application site folliculitis	0	0	7 (1.1)	0.8 (0.3–1.7)
Folliculitis[a]	1 (0.4)	0.8 (0.02–4.3)	5 (0.8)	0.6 (0.2–1.3)
Acneiform dermatitis	1 (0.4)	0.8 (0.02–4.3)	2 (0.3)	0.2 (0.03–0.8)
Acne pustular[a]	0	0	1 (0.2)	0.1 (0–0.6)
Thrombocytosis[a,b,c]	0	0	2 (0.3)	0.2 (0.03–0.8)
Cytopenias[b,d]	2 (0.7)	1.5 (0.2–5.5)	21 (3.3)	2.4 (1.5–3.7)
Erythropenia[a]	1 (0.4)	0.8 (0.02–4.3)	10 (1.6)	1.2 (0.6–2.1)
Leukopenia	1 (0.4)	0.8 (0.02–4.3)	10 (1.6)	1.2 (0.6–2.1)
Thrombocytopenia[a]	0	0	2 (0.3)	0.2 (0.03–0.8)
Liver enzyme elevations[b,e]	2 (0.7)	1.5 (0.2–5.5)	19 (3.0)	2.2 (1.3–3.4)

EAIR exposure-adjusted incidence rate, *MACE* major adverse cardiovascular events, *PY* person-years, *RUX* ruxolitinib, *TEAE* treatment-emergent adverse event

Table 3 continued

[a]None were considered by the investigator to be related to treatment

[b]None were considered serious

[c]Includes AEs reported as thrombocytosis and platelet count increased ($n = 1$ each)

[d]Cytopenias included erythropenia (anemia, decreased hematocrit, decreased hemoglobin, and microcytic anemia), leukopenia (leukopenia, lymphopenia, neutropenia, neutrophil count decreased, and white blood cell count decreased), and thrombocytopenia (platelet count decreased)

[e]Includes AEs reported as alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, transaminases increased, blood bilirubin increased, and hepatomegaly

Serious infections occurred in four patients who applied ruxolitinib cream (0.6%; 0.5 [95% CI, 0.1–1.2] patients/100 PY), with each event occurring in one patient (appendiceal abscess, appendicitis, COVID-19 pneumonia, hepatitis infectious mononucleosis). No cases of tuberculosis, hepatitis B, or hepatitis C were reported.

Malignancies or unspecified neoplasms occurred in six patients who applied ruxolitinib cream (0.9%; 0.7 [95% CI, 0.3–1.5] patients/100 PY). Two of these events were serious (papillary thyroid cancer and prostate cancer [$n = 1$ each]) and each event occurred in patients with risk factors for these malignancies (i.e., an asymptomatic thyroid nodule for many years and a history of prostatomegaly, respectively). The 66-year-old man with a prior history of prostatomegaly was diagnosed with prostate cancer during the LTE period (day 323) and had a ruxolitinib plasma concentration of 267 nM at the prior pharmacokinetic assessment prior to diagnosis (day 281); ruxolitinib cream application continued after diagnosis. Among patients who applied ruxolitinib cream, two patients (0.3%; 0.2 [95% CI, 0.03–0.8] patients/100 PY) had thromboembolic events (transient ischemic attack, cardiac ventricular thrombosis). Both patients had risk factors for thromboembolic events; notably, the patient who had a cardiac ventricular thrombosis had an extensive medical history of cardiac events. Importantly, no MACE were reported through 2 years of ruxolitinib cream application. All events of serious infections, malignancies or unspecified neoplasms, and thromboembolic events were considered by the investigators to be unrelated to treatment and did not result in treatment discontinuation (Supplementary Material Table 3).

Acne-related AEs (e.g., application site acne, folliculitis) were slightly more frequent among patients who applied ruxolitinib cream versus vehicle when adjusted for exposure (7.1 [95% CI, 5.5–9.2] vs 4.6 [1.7–10.0] patients/100 PY, respectively; Table 3). A total of 35 patients (5.5%) who applied ruxolitinib cream experienced acne-related AEs that were considered by the investigators to be possibly related to treatment. All of these events were mild or moderate, and most were ongoing at the end of the study. No acne-related events resulted in discontinuation, although one patient had a 36-day treatment interruption due to worsening acne. Among patients who applied ruxolitinib cream, the frequency of application site acne was consistent among adolescents (aged 12–17 years, 5.7%) and adults (aged 18–64 years, 5.9%; aged ≥ 65 years, 7.1%).

The incidence of skin and subcutaneous tissue infections was slightly higher among patients who applied ruxolitinib cream versus vehicle (4.0 [95% CI, 2.8–5.6] vs 2.3 [0.5–6.7] patients/100 PY), although the overall incidence was low (Table 4). Herpes zoster was reported in two patients who applied ruxolitinib cream; although one event was located on a treated area, neither event was considered related to treatment and both resolved with concomitant medication. Postherpetic neuralgia was reported in one patient who applied ruxolitinib cream but was not considered related to treatment.

Overall, the incidence of cytopenias was low but numerically higher among patients who applied ruxolitinib cream versus vehicle

(2.4 [95% CI, 1.5–3.7] vs 1.5 [0.2–5.5] patients/100 PY); all cytopenias were mild or moderate. One patient (0.1%) who applied ruxolitinib cream had recurrent episodes of moderate leukopenia, moderate lymphopenia, and mild neutropenia throughout the study that were considered by the investigator as possibly related to treatment. Plasma concentrations of ruxolitinib for this patient ranged from 13.3 nM (week 40) to 84.5 nM (week 24). This patient also had mild neutropenia and leukopenia at screening, which resolved by the baseline visit. No dose changes to ruxolitinib cream were made during the study. Thrombocytosis occurred in two patients (0.3%) who applied ruxolitinib cream; events were mild or moderate and considered not related to treatment. Mean levels of laboratory-assessed hemoglobin and platelets were generally consistent throughout the study period (Supplementary Material Fig. 2).

The incidence of liver enzyme elevations was slightly higher among patients who applied ruxolitinib cream versus vehicle (2.2 [95% CI, 1.3–3.4] vs 1.5 [0.2–5.5] patients/100 PY), although the overall incidence was low. Liver enzyme elevations that occurred during ruxolitinib cream application were mild or moderate, considered unrelated to treatment, and most resolved or were resolving.

DISCUSSION

In this analysis, we evaluated the long-term safety of ruxolitinib cream versus vehicle among 673 patients with vitiligo in a clinical trial setting. Pooled data from the phase 3 TRuE-V studies support the longer-term safety and tolerability profile of ruxolitinib cream in patients with vitiligo. Nasopharyngitis, application site acne, and upper respiratory tract infections were the most common AEs observed with ruxolitinib cream. EAIRs for these AEs were similar with ruxolitinib cream and vehicle. Furthermore, the safety profile in adolescents (aged 12–17 years) was consistent with the profile observed in the overall population.

Application site reactions were mild or moderate in severity, and application site pain was infrequent. No serious AEs were considered by investigators to be related to ruxolitinib cream. Serious infections, malignancies, and thromboembolic events were rare and not considered by investigators to be related to treatment. In some cases, patients' medical history likely contributed to these AEs. In a prior analysis of phase 2 and phase 3 studies, nonmelanoma skin cancer events were infrequent, occurring in 5 of 789 patients who applied ruxolitinib cream (1141.7 PY) and were not associated with elevated ruxolitinib plasma concentrations [15].

Among patients with AEs of interest and available plasma ruxolitinib concentrations prior to AE occurrence, most had trough plasma ruxolitinib concentrations below the mean steady-state concentration observed in TRuE-V1/TRuE-V2 studies (approximately 60 nM) [12] and well below the half-maximal inhibitory concentration for JAK-related myelosuppression in bone marrow (281 nM) [8].

Acne, skin and subcutaneous tissue infections, thrombocytosis, cytopenias, and liver enzyme elevations were all mild or moderate and did not result in treatment discontinuation. Acne has been observed with other JAK inhibitors [16, 17] and may include worsening of existing acne, acneiform eruptions, or de novo acne [17–19]. In a recent meta-analysis, an increased risk of acne was associated with JAK inhibitor use; however, the risk of acne was lower with ruxolitinib cream compared with systemic JAK inhibitors [20]. Traditional topical therapies have been effective in treating comedonal acne and mild to moderate papulopustular acne without discontinuation of JAK inhibitor therapy [21]. In this analysis, the prevalence of application site acne was similar in adolescents and adults, suggesting that these events were driven by JAK inhibition rather than age-related susceptibility. Notably, no acne-related AEs resulted in discontinuation of ruxolitinib cream and only one event resulted in a treatment interruption of short duration.

To date, limited long-term safety data are available from clinical studies in patients with

Table 4 Skin and subcutaneous tissue infections

	Vehicle (*n* = 270; PY = 131.1)		1.5% RUX cream (*n* = 637; PY = 867.9)	
	n (%)	EAIR (95% CI), patients/100 PY	*n* (%)	EAIR (95% CI), patients/100 PY
Skin and subcutaneous tissue infections[a]	3 (1.1)	2.3 (0.5–6.7)	35 (5.5)	4.0 (2.8–5.6)
Any bacterial infection	1 (0.4)	0.8 (0.02–4.3)	18 (2.8)	2.1 (1.2–3.3)
Application site folliculitis	0	0	7 (1.1)	0.8 (0.3–1.7)
Folliculitis[b]	1 (0.4)	0.8 (0.02–4.3)	5 (0.8)	0.6 (0.2–1.3)
Cellulitis[b]	0	0	3 (0.5)	0.3 (0.1–1.0)
Paronychia[b]	0	0	2 (0.3)	0.2 (0.03–0.8)
Skin bacterial infection[b]	0	0	1 (0.2)	0.1 (0–0.6)
Any viral infection[b]	0	0	8 (1.3)	0.9 (0.4–1.8)
Herpes simplex	0	0	4 (0.6)	0.5 (0.1–1.2)
Herpes zoster	0	0	2 (0.3)	0.2 (0.03–0.8)
Hand-foot-and-mouth disease	0	0	1 (0.2)	0.1 (0–0.6)
Varicella	0	0	1 (0.2)	0.1 (0–0.6)
Any fungal infection[b]	1 (0.4)	0.8 (0.02–4.3)	6 (0.9)	0.7 (0.3–1.5)
Body tinea	0	0	2 (0.3)	0.2 (0.03–0.8)
Fungal skin infection	0	0	1 (0.2)	0.1 (0–0.6)
Onychomycosis	0	0	1 (0.2)	0.1 (0–0.6)
Tinea pedis	0	0	1 (0.2)	0.1 (0–0.6)
Tinea versicolor	1 (0.4)	0.8 (0.02–4.3)	1 (0.2)	0.1 (0–0.6)
Any parasitic infection[b]	0	0	3 (0.5)	0.3 (0.1–1.0)
Acarodermatitis	0	0	2 (0.3)	0.2 (0.03–0.8)
Demodicidosis	0	0	1 (0.2)	0.1 (0–0.6)
Any other infection[b]	1 (0.4)	0.8 (0.02–4.3)	2 (0.3)	0.2 (0.03–0.8)
Skin infection	0	0	1 (0.2)	0.1 (0–0.6)
Subcutaneous abscess	1 (0.4)	0.8 (0.02–4.3)	1 (0.2)	0.1 (0–0.6)

EAIR exposure-adjusted incidence rate, *RUX* ruxolitinib, *PY* person-years

[a]None were considered serious

[b]None were considered by the investigator to be related to treatment

vitiligo. Based on the pooled phase 3 safety analysis presented here and earlier phase 2 study results through 3 years of treatment [13], there is no evidence to date of accumulation of AEs among patients with vitiligo. However, more long-term analyses and real-world studies

evaluating the safety of ruxolitinib cream are needed to better understand its safety profile in diverse populations and clinical settings.

A limitation of this study was that patient follow-up was limited to 2 years, which may not capture late-onset or cumulative AEs. Additionally, despite the adolescent population being representative of worldwide prevalence (11% in these studies vs approximately 20% of world population) [22], the adolescent sample size was small, limiting the generalizability of the results.

CONCLUSION

This analysis of ruxolitinib cream safety data from the vitiligo phase 3 studies demonstrates the tolerability of ruxolitinib cream among adults and adolescents through 2 years of treatment, with few serious AEs, none of which were considered related to treatment. The safety profile of ruxolitinib cream was generally stable throughout long-term treatment; no new safety signals were observed compared with prior analyses.

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Data Availability. Incyte Corporation (Wilmington, Delaware, USA) is committed to data sharing that advances science and medicine while protecting patient privacy. Qualified external scientific researchers may request anonymized datasets owned by Incyte for the purpose of conducting legitimate scientific research. Researchers may request anonymized datasets from any interventional study (except phase 1 studies) for which the product and indication have been approved on or after 1 January 2020 in at least 1 major market (e.g., US, EU, JPN). Data will be available for request after the primary publication or 2 years after the study has ended. Information on Incyte's clinical trial data sharing policy and instructions for submitting clinical trial data requests are available at: https://www.incyte.com/Portals/0/Assets/Compliance%20and%20Transparency/clinical-trial-data-sharing.pdf?ver=2020-05-21-132838-960.

Declarations

Conflict of Interest. David Rosmarin is an Editorial Board member of *Dermatology and Therapy* and was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions; has served as a consultant, speaker, or investigator for AbbVie, Abcuro, Almirall, AltruBio, Amgen, Arena, Astria, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Concert, CSL Behring,

Dermavant Sciences, Dermira, Dualitas, EMD Serono, Galderma, Incyte Corporation, Janssen, Kymera, Kyowa Kirin, Lilly, Merck, Nektar, Novartis, Pfizer, RAPT Therapeutics, Recludix, Regeneron Pharmaceuticals, Revolo Biotherapeutics, Sanofi, Sun Pharmaceuticals, UCB, Viela Bio, and Zura Bio. Amit G. Pandya has served as an investigator for Aclaris Therapeutics, Immune Tolerance Network, Incyte Corporation, and Pfizer; a consultant for AbbVie, Arcutis, Avita Medical, Chromaderm, Immune Tolerance Network, Incyte Corporation, Pfizer, TWi, Viela Bio, and Villaris; and holds stock options for Tara Medical and Zerigo Health. Thierry Passeron has received grants and/or honoraria from AbbVie, ACM Pharma, Almirall, Amgen, Astellas, Bristol Myers Squibb, Calypso, Celgene, Eli Lilly, Galderma, Genzyme/Sanofi, GlaxoSmithKline, Incyte Corporation, Janssen, LEO Pharma, Novartis, Pfizer, Sun Pharmaceuticals, Takeda, UCB, and Vyne Therapeutics; is the cofounder of NIKAIA Pharmaceuticals; and has patents on WNT agonists and GSK3b antagonists for repigmentation of vitiligo and on the use of CXCR3B blockers in vitiligo. Seth B. Forman has received honoraria, clinical research grants, or fees as a consultant, speaker, advisory board member, and/or investigator for AbbVie, Aclaris Therapeutics, Asana BioSciences, AstraZeneca, Athenex, Celgene Corporation, Cutanea Life Sciences, Eli Lilly, Incyte Corporation, Innovaderm Research, Novartis, Pfizer, Promius Pharma, Regeneron, UCB, Valeant Pharmaceuticals North America, and Xbiotech. Jacek Zdybski has served as an investigator for Almirall, Amgen, Bristol Myers Squibb, Celgene, Eli Lilly, Galderma, Incyte Corporation, Innovaderm, Pfizer, Regeneron, Sun Pharmaceuticals, and Syneos Health. Mark Amster has been a primary investigator and received revenue from Acrotech Biopharma, Amgen, Arcutis Biotherapeutics, Bausch Health, Biopharmex, Boehringer Ingelheim, Botanix Pharmaceuticals, Cara Therapeutics, Concert Pharmaceuticals, Dermavant, Dermira, DermTech, Dr. Reddys Laboratories, Eli Lilly, Foamix, Highlight Pharmaceuticals, Incyte Corporation, Janssen, Kademis Ltd, LEO Pharma, Mayne Pharma, Mitsubishi Tanabe Pharma, Novartis, Novella, Pfizer, RAPT Therapeutics, Trevi Therapeutics, UCB Biopharma, Ventyx Biosciences, Vitae Pharmaceuticals, and Xbiotech USA and has received honoraria as a consultant for AbbVie, Cara Pharmaceuticals, Incyte Corporation, and Janssen. Christina Feser has served as a speaker, consultant, advisory board member, and/or investigator for AbbVie, Aclaris, Acrotech Biopharma, Almirall, Amgen, Arcutis, Bristol Myers Squibb, Castle Biosciences, Cutanea, Eli Lilly and Company, Incyte Corporation, Kymab, LEO Pharma, Merck, MoonLake, Nektar Therapeutics, Novan, Novartis, Paradigm Medical, ParaPro, Pfizer, Skin Life Science, SkinTech, Takeda, Technoderma, and Ventyx. Kim A. Papp has received honoraria and/or research grants from AbbVie, Acelyrin, Akros, Alumis, Amgen, Arcutis, Bausch Health/Valeant, Boehringer Ingelheim, Bristol Myers Squibb, Can-Fite Biopharma, Celltrion, Concert Pharmaceuticals, Dermavant, Dermira, DiCE Pharmaceuticals, DiCE Therapeutics, Eli Lilly, Evelo Biosciences, Forbion, Galderma, Horizon Therapeutics, Incyte Corporation, Janssen, Kymab, Kyowa Hakko Kirin, LEO Pharma, Meiji Seika Pharma, Mitsubishi Pharma, Nimbus Therapeutics, Novartis, Pfizer, Reistone, Sandoz, Sanofi-Aventis/Genzyme, Sun Pharmaceuticals, Takeda, Tarsus Pharmaceuticals, UCB Pharma, and Zai Lab. Anthony Nuara has received research funding from AbbVie, Aclaris Therapeutics, AOBiome, AstraZeneca, Boehringer Ingelheim, Galderma, Incyte Corporation, Novartis, and Pfizer and has served as a paid speaker and/or consultant for AbbVie, Amgen, Castle Biosciences, Bristol Myers Squibb, Dermavant, Galderma, Incyte Corporation, Janssen, and Novartis. Deanna Kornacki, Shaoceng Wei, and Haobo Ren are employees and shareholders of Incyte Corporation. John E. Harris has served as a consultant for AbbVie, Aclaris Therapeutics, BiologicsMD, EMD Serono, Genzyme/Sanofi, Janssen, Pfizer, Rheos Medicines, Sun Pharmaceuticals, TeVido BioDevices, The Expert Institute, 3rd Rock Ventures, and Villaris Therapeutics; has served as an investigator for Aclaris Therapeutics, Celgene, Dermira, EMD Serono, Genzyme/Sanofi, Incyte Corporation, LEO Pharma, Pfizer, Rheos Medicines, Stiefel/GlaxoSmithKline, Sun Pharmaceuticals, TeVido BioDevices, and Villaris Therapeutics; holds equity in Aldena Therapeutics, NIRA Biosciences,

Rheos Medicines, TeVido BioDevices, and Villaris Therapeutics; is a scientific founder of Aldena Therapeutics, NIRA Biosciences, and Villaris Therapeutics; and has patents pending for IL-15 blockade for treatment of vitiligo, JAK inhibition with light therapy for vitiligo, and CXCR3 antibody depletion for treatment of vitiligo. Khaled Ezzedine has served as a consultant for AbbVie, Almirall, Bristol Myers Squibb, Incyte Corporation, La Roche-Posay, Lilly, Pfizer, Pierre Fabre Pharmaceuticals, and Sanofi.

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