Open-label treatment extension of ruxolitinib cream in vitiligo: findings from the Topical Ruxolitinib Evaluation in Vitiligo (TRuE-V) long-term extension phase III study

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Dear Editor, Ruxolitinib cream, a topical Janus kinase (JAK) 1/JAK2 inhibitor, is the first approved repigmentation treatment for nonsegmental vitiligo in patients ≥ 12 years old.[1] The phase III Topical Ruxolitinib Evaluation in Vitiligo (TRuE-V1/TRuE-V2) studies demonstrated the superiority of 1.5% ruxolitinib cream to vehicle in clinical measures of repigmentation, including the Vitiligo Area Scoring Index (VASI).[2] We evaluated repigmentation outcomes and safety with continued ruxolitinib cream treatment for an additional year in the rollover TRuE-V long-term extension (LTE) study (clinicaltrials.gov/study/NCT04530344).

The TRuE-V trials adhered to the Declaration of Helsinki, Good Clinical Practice guidelines, and country-specific laws and regulations, including patient-provided written informed consent or assent. Patients who completed TRuE-V1/TRuE-V2[2] could enter TRuE-V LTE and were assigned to cohorts based on whether they achieved ≥ 90% improvement from baseline in facial VASI (F-VASI 90) at week 52. All patients with < F-VASI 90 continued applying open-label 1.5% ruxolitinib cream twice daily for an additional 52 weeks in TRuE-V LTE (Figure 1a).

Endpoints (all secondary) were the percentage of patients achieving ≥ 75% improvement from baseline in facial VASI (F-VASI 75), F-VASI 90, ≥ 50% improvement from baseline in total VASI (T-VASI 50), achievement of self-reported Vitiligo Noticeability Scale (VNS) score of 4/5 (a lot less/no longer noticeable) at week 104, and Dermatology Life Quality Index (DLQI) change through week 104. Data were reported as observed. Safety was assessed in all patients who applied at least one dose of the study drug.

TRuE-V LTE enrolled 342 patients in the open-label treatment extension, including 224 who applied ruxolitinib cream from TRuE-V1/TRuE-V2 day 1 (RUX–RUX group) and 118 who crossed over from vehicle-control to ruxolitinib cream after TRuE-V1/TRuE-V2 at week 24 (VEH–RUX group). Seventy-two (of 342; 21%) patients discontinued open-label treatment [RUX–RUX, 47 of 224 (21.0%); VEH–RUX, 25 of 118 (21.2%)], primarily due to voluntary patient withdrawal [31 of 224 (13.8%); 17 of 118 (14.4%)]. Few patients discontinued for lack of efficacy [2 of 224 (0.9%); 0 of 118] or following adverse events [1 of 224 (0.4%); 1 of 118 (0.8%)].

Among patients who applied ruxolitinib cream in the open-label treatment extension, observed response rates for achieving repigmentation outcomes increased steadily through 2 years of treatment, regardless of when ruxolitinib cream was first applied in TRuE-V1/TRuE-V2 (from day 1 or after week 24). Among patients in the RUX–RUX group, 117 of 177 (66.1%) achieved F-VASI 75 at week 104, increasing from 40 of 222 (18.0%) at week 24 and 68 of 221 (30.8%) at week 52 (Figure 1b). F-VASI 90 was achieved by 60 of 177 (33.9%) at week 104, increasing from 2.3% (5 of 221; incorrectly assigned to open-label treatment extension) at week 52 (Figure 1c). T-VASI 50 was achieved by 113 of 177 (63.8%) at week 104, increasing from 94 of 221 (42.5%) at week 52 (Figure 1d). The percentage of patients in the

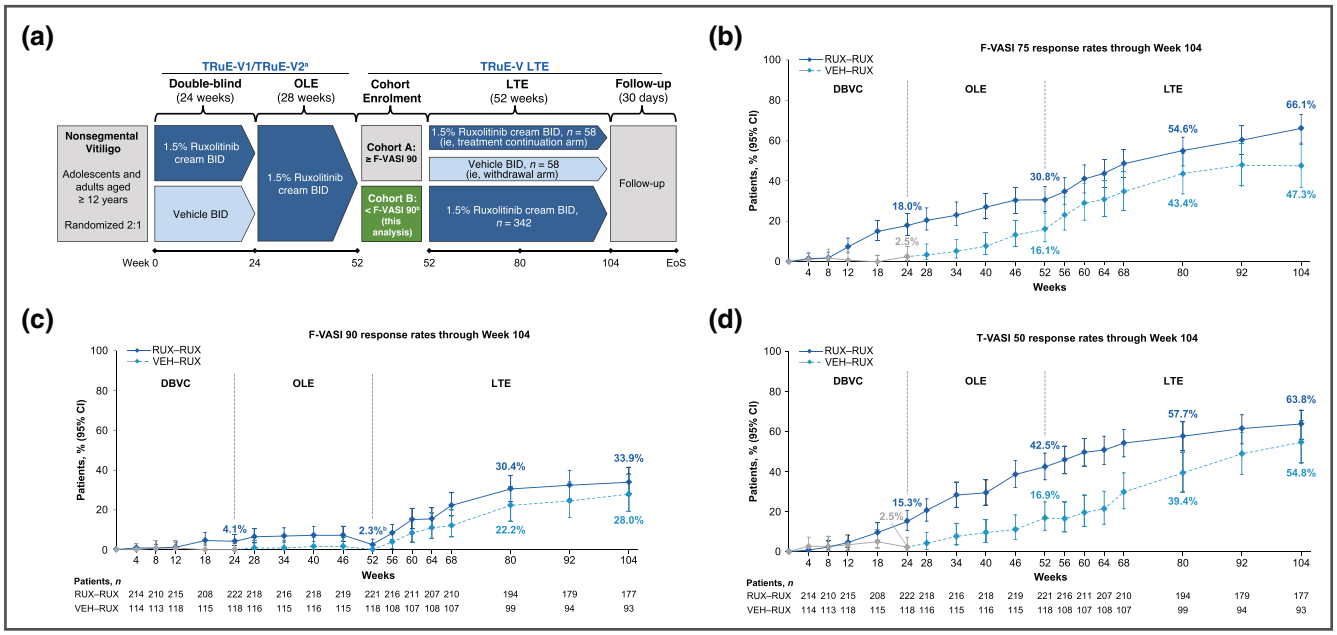

Figure 1 TRuE-V study design and clinical efficacy with OLE. (a) TRuE-V study design. VASI response rates through 2 years of treatment among patients achieving (b) F-VASI 75, (c) F-VASI 90 and (d) T-VASI 50. BID, twice daily; CI, confidence interval; DBVC, double-blind vehicle-controlled; EoS, end of study; F-VASI 75 or F-VASI 90, ≥ 75% or ≥ 90% improvement from baseline in facial VASI; LTE, long-term extension; OLE, open-label extension; RUX–RUX, 1.5% ruxolitinib cream from day 1 in TRuE-V1/TRuE-V2; TRuE-V, Topical Ruxolitinib Evaluation in Vitiligo; T-VASI 50, ≥ 50% improvement from baseline in total VASI; VASI, Vitiligo Area Scoring Index; VEH–RUX, crossed over from vehicle to 1.5% ruxolitinib cream after week 24 in TRuE-V1/TRuE-V2. [a]See Rosmarin *et al.*[2] [b]Five patients who applied 1.5% ruxolitinib cream from day 1 in TRuE-V1/TRuE-V2 and achieved F-VASI 90 at week 52 were incorrectly assigned to cohort B at TRuE-V LTE baseline and included in outcomes analyses; data were reported as observed.

RUX–RUX group who achieved VNS 4/5 was similar at Weeks 52 (78 of 221, 35.3%) and 104 (77 of 178, 43.3%). Repigmentation outcomes in the VEH–RUX group (Figure 1b–d) were consistent with RUX–RUX outcomes over time, although overall VASI response rates were lower given the shorter duration of ruxolitinib cream treatment. VNS 4/5 rates increased among patients in the VEH–RUX group with an additional year of active treatment [week 52, 14 of 118 (11.9%); week 104, 28 of 93 (30.1%)]. DLQI scores were consistent through week 104 in RUX–RUX and VEH–RUX groups (mean change from Week 52, −0.06 and −0.48, respectively).

Treatment-emergent adverse events (TEAEs) occurred in 173 of 342 (50.6%) patients in the open-label treatment extension [RUX–RUX, 114 of 224 (50.9%); VEH–RUX, 59 of 118 (50.0%)]. The most common TEAEs (occurring in ≥2% of 342 patients) were COVID-19 (13.2%), nasopharyngitis (4.7%), upper respiratory tract infection (2.9%) and urinary tract infection (2.3%). Application-site acne [6 of 342 (1.8%); 1 treatment-related] and application-site pruritus [4 of 342 (1.2%); all treatment-related] occurred infrequently; all events were mild/moderate (grade 1/2), and none was serious. Only one patient (0.3%) had a TEAE leading to discontinuation [VEH–RUX: road traffic accident (grade 3, nonserious)]. Serious TEAEs occurred in 11 of 342 (3.2%) patients [RUX–RUX, 7 of 224 (3.1%); VEH–RUX, 4 of 118 (3.4%); none treatment-related].

Study limitations include the rollover design with lack of power calculations for sample size and inclusion of five patients with F-VASI 90 at TRuE-V1/TRuE-V2 week 52 in TRuE-V LTE outcomes analysis because they were incorrectly assigned to the open-label treatment extension. As-observed VASI response rates may also be overstated due to potential discontinuation of slower responders. Additionally, inaccurate patient recall of baseline locations of repigmented lesions and fluctuations in treatment adherence may have occurred over 2 years of twice-daily treatment, although likely to be reflective of real-world usage.

These findings indicate that continued ruxolitinib cream application may allow further repigmentation in many patients and that lack of meaningful response (i.e. F-VASI 75 and/or T-VASI 50)[3] at 52 weeks does not preclude meaningful repigmentation with ongoing treatment. F-VASI 75, F-VASI 90 and T-VASI 50 response rates increased with ruxolitinib cream treatment through 2 years without plateau, regardless of when ruxolitinib cream was first applied in TRuE-V1/TRuE-V2. These results support previous findings that complete or near-complete repigmentation often requires at least 12 months of treatment[4] and highlight the importance of further assessment of prolonged ruxolitinib cream treatment in real-world settings. Long-term ruxolitinib cream application in TRuE-V LTE was well tolerated, consistent with previous clinical trial and real-world findings.

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These data have previously been presented in part at: American Academy of Dermatology Annual Meeting (New Orleans, LA, USA; 17–21 March 2023), with encores at SIDeMaST – 97th Congresso Nazionale (Naples, Italy; 13–16 June 2023) and Journées Dermatologiques de Paris (JDP) 2023 (Paris, France; 5–9 December 2023).

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Conflicts of interest: The full Conflicts of Interest list is provided in Appendix S2 (see Supporting Information).

Data availability: Incyte Corporation (Wilmington, DE, 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 I studies) for which the product

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Ethics statement: Trial protocols were approved by an institutional review board or ethics committee at participating centres. The trials were conducted in accordance with the Declaration of Helsinki and adhered to Good Clinical Practice guidelines and applicable country-specific laws and regulations.

Patient consent: Written informed consent or assent was provided by all patients.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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These data are from different clinical trials and cannot be directly compared.

Co-primary endpoints PASI 90 and IGA 0/1 at Week 16 were met.**Secondary endpoints. †N= mNRI, missing data were imputed with mNRI (patients with missing data following treatment discontinuation due to lack of efficacy or a TRAE were counted as non-responders; multiple imputation methodology was used for other missing data). ‡43.9% (n=189/431), and 43.4% (n=116/267) of biologic-naïve and TNFi-IR PsA patients achieved the primary endpoint of ACR 50 at Week 16 in BE OPTIMAL and BE COMPLETE, respectively (vs 10.0% [n=28/281] and 6.8% [n=9/133] placebo, p<0.0001); 54.5% (n=235/431) and 51.7% (n=138/267) maintained it at Week 52 (NRI).[4–6]

ACR 50, ≥50% response in the American College of Rheumatology criteria; **AS**, ankylosing spondylitis; **CRP**, C-reactive protein; **DMARD**, disease-modifying antirheumatic drug; **HS**, hidradenitis suppurativa; **IGA**, Investigator's Global Assessment; **(m)NRI**, (modified) non-responder imputation; **MRI**, magnetic resonance imaging; **nr-axSpA**, non-radiographic axial spondyloarthritis; **NSAID**, non-steroidal anti-inflammatory drug; **PASI 75/90/100**, ≥75/90/100% improvement from baseline in Psoriasis Area and Severity Index; **PsA**, psoriatic arthritis; **PsD**, psoriatic disease; **PsO**, psoriasis; **TNFi-IR**, tumour necrosis factor-α inhibitor – inadequate responder; **TRAE**, treatment-related adverse event.

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