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## Two Phase 3, Randomized, Controlled Trials of Ruxolitinib Cream for Vitiligo

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### ABSTRACT

#### BACKGROUND

Vitiligo is a chronic autoimmune disease that causes skin depigmentation. A cream formulation of ruxolitinib (an inhibitor of Janus kinase 1 and 2) resulted in repigmentation in a phase 2 trial involving adults with vitiligo.

#### METHODS

We conducted two phase 3, double-blind, vehicle-controlled trials (Topical Ruxolitinib Evaluation in Vitiligo Study 1 [TRuE-V1] and 2 [TRuE-V2]) in North America and Europe that involved patients 12 years of age or older who had nonsegmental vitiligo with depigmentation covering 10% or less of total body-surface area. Patients were randomly assigned in a 2:1 ratio to apply 1.5% ruxolitinib cream or vehicle control twice daily for 24 weeks to all vitiligo areas on the face and body, after which all patients could apply 1.5% ruxolitinib cream through week 52. The primary end point was a decrease (improvement) of at least 75% from baseline in the facial Vitiligo Area Scoring Index (F-VASI; range, 0 to 3, with higher scores indicating a greater area of facial depigmentation), or F-VASI75 response, at week 24. There were five key secondary end points, including improved responses on the Vitiligo Noticeability Scale.

#### RESULTS

A total of 674 patients were enrolled, 330 in TRuE-V1 and 344 in TRuE-V2. In TRuE-V1, the percentage of patients with an F-VASI75 response at week 24 was 29.8% in the ruxolitinib-cream group and 7.4% in the vehicle group (relative risk, 4.0; 95% confidence interval [CI], 1.9 to 8.4;  $P < 0.001$ ). In TRuE-V2, the percentages were 30.9% and 11.4%, respectively (relative risk, 2.7; 95% CI, 1.5 to 4.9;  $P < 0.001$ ). The results for key secondary end points showed superiority of ruxolitinib cream over vehicle control. Among patients who applied ruxolitinib cream throughout 52 weeks, adverse events occurred in 54.8% in TRuE-V1 and 62.3% in TRuE-V2; the most common adverse events were application-site acne (6.3% and 6.6%, respectively), nasopharyngitis (5.4% and 6.1%), and application-site pruritus (5.4% and 5.3%).

#### CONCLUSIONS

In two phase 3 trials, application of ruxolitinib cream resulted in greater repigmentation of vitiligo lesions than vehicle control through 52 weeks, but it was associated with acne and pruritus at the application site. Larger and longer trials are required to determine the effect and safety of ruxolitinib cream in patients with vitiligo. (Funded by Incyte; TRuE-V1 and TRuE-V2 ClinicalTrials.gov numbers, NCT04052425 and NCT04057573.)

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VITILIGO IS A CHRONIC AUTOIMMUNE disease that results in skin depigmentation<sup>1,2</sup> and reduced quality of life.<sup>3,4</sup> Quality-of-life burden is affected by a high prevalence of psychosocial coexisting conditions among patients with vitiligo and is further affected by factors including lesion visibility (e.g., face and hand involvement) and extensive body-area involvement.<sup>4</sup> Skin lesions are characterized by white patches corresponding with a loss of functioning melanocytes in the epidermis.<sup>1,2</sup> Interferon- $\gamma$  plays an important role in vitiligo pathogenesis and signals through the Janus kinase (JAK) signal transducer and activator of transcription (STAT) pathway,<sup>5,6</sup> leading to up-regulation of C-X-C motif chemokine ligand 10 (CXCL10) and promoting CD8<sup>+</sup> T-cell recruitment, which drives melanocyte destruction.<sup>5-12</sup> At the time we collected and analyzed the data reported here, there were no approved treatments for repigmentation of vitiligo lesions in the United States or Europe.<sup>13</sup>

Small studies have provided evidence for repigmentation in patients with vitiligo after treatment with JAK inhibitors.<sup>14-16</sup> A cream formulation of ruxolitinib, an inhibitor of Janus kinase 1 (JAK1) and 2 (JAK2), resulted in repigmentation over 52 weeks in a phase 2, dose-ranging, randomized trial involving adults with vitiligo.<sup>17</sup> Among patients who applied 1.5% ruxolitinib cream twice daily, 45% had at least a 50% decrease (improvement) from baseline in the facial Vitiligo Area Scoring Index (F-VASI) at week 24 (primary end point), and 30% had a decrease of at least 75%, with improvement through week 52.<sup>17</sup> We conducted two phase 3 trials of ruxolitinib cream (Topical Ruxolitinib Evaluation in Vitiligo Study 1 [TRuE-V1] and 2 [TRuE-V2]) in **adolescents and adults** with nonsegmental vitiligo.

## METHODS

### TRIAL OVERSIGHT

The trial protocols (available with the full text of this article at NEJM.org) were approved by an institutional review board or ethics committee at participating centers. 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. Written informed consent or assent was provided by all the patients. Incyte spon-

sored the trials; it provided the active trial drug and matching vehicle cream (without active ingredient), participated in trial design, and collaborated with the authors in analyzing and interpreting the data and writing and approving the manuscript. The authors prepared the manuscript, with medical writing assistance funded by the sponsor. All the authors vouch for the accuracy and completeness of the data and for the adherence of the trials to the protocols. Agreements that required investigators to maintain data confidentiality were in place between the sponsor and the authors. The sponsor could not delay or interdict publication of the results of the trials.

### PATIENTS

**Eligible patients, who were recruited at participating trial centers, were 12 years of age or older and had received a diagnosis of nonsegmental vitiligo with depigmented areas covering 10% or less of total body-surface area, including at least 0.5% of body-surface area on the face and at least 3% of body-surface area on non-facial areas.** Patients were also required to have scores of 0.5 or higher on the F-VASI (range, 0 to 3, with higher scores representing a greater area of facial depigmentation across the forehead to original hairline, cheeks to jawline vertically and laterally from corner of mouth to tragus, nose, and eyelids) and scores of 3 or higher on the total Vitiligo Area Scoring Index (T-VASI; range, 0 to 100, with higher scores indicating a greater area of total body depigmentation across the head or neck, including the scalp; trunk, including genitalia; upper limbs, including axillae; hands; lower limbs, including buttocks; and feet). The methods of calculating these measures are given below. Key exclusion criteria were the presence of complete leukotrichia within any facial lesions, dermatologic disease confounding vitiligo assessment, previous use of JAK inhibitor therapy, and use of the following therapies for vitiligo before baseline: any biologic or experimental therapy within 12 weeks (or 5 half-lives), phototherapy within 8 weeks, immunomodulating treatments within 4 weeks, or topical treatments within 1 week.

### TRIAL DESIGN

These were two multinational, phase 3, double-blind, vehicle-controlled trials of identical design

conducted across 101 centers (Fig. S1 in the Supplementary Appendix, available at NEJM.org) in North America (United States and Canada) and Europe (Bulgaria, France, Germany, Italy, the Netherlands, Poland, and Spain). An interactive response technology system was used to manage enrollment, including assignment of patient trial numbers, tracking of visits, randomization according to prespecified characteristics, masking of trial-group assignments, and management of trial-drug inventory. Patients, who were stratified according to geographic region (North America or Europe) and Fitzpatrick skin type (I [pale white] or II [white] vs. III [light brown] to VI [deeply pigmented dark brown to black]), were randomly assigned in a 2:1 ratio to apply 1.5% ruxolitinib cream or matching vehicle cream twice daily to all depigmented vitiligo lesions on the face and body identified at trial entry for 24 weeks (Fig. S2). Patients and investigators remained unaware of the trial-group assignments throughout the trials; the sponsor was aware of the trial-group assignments after database lock for the primary analysis. After completion of the week 24 visit, all the patients could apply 1.5% ruxolitinib cream twice daily for an additional 28 weeks in an open-label treatment extension phase of the trials.

#### END POINTS

The primary end point was a decrease (improvement) of at least 75% from baseline in the F-VASI (F-VASI75 response) at week 24. The Vitiligo Area Scoring Index integrates the body-surface area with a depigmentation score (i.e., taking into account lesion integrity as opposed to margins only). The F-VASI is a tool for calculating the surface area of vitiligo depigmentation on the face on the basis of the size of the patient's palmar surface (i.e., the palm plus five digits), with degree of depigmentation estimated to the nearest percentage (0% [no depigmentation present], 10%, 25%, 50%, 75%, 90%, or 100% [no pigment present]), as detailed in the protocols.

Key secondary end points (all assessed at week 24) were a decrease of at least 50% in the F-VASI (F-VASI50 response), a decrease of at least 90% in the F-VASI (F-VASI90 response), a decrease of at least 50% in the T-VASI (T-VASI50 response), a Vitiligo Noticeability Scale (VNS) rating of a lot less noticeable or no longer noticeable (VNS response), and the percentage

change from baseline in facial body-surface area affected by vitiligo. Other prespecified secondary end points included the safety and side-effect profile of ruxolitinib cream on the basis of monitoring of adverse events and laboratory data; the percentage change from baseline in the F-VASI, the T-VASI, facial body-surface area affected by vitiligo, and total body-surface area affected by vitiligo; the percentage of patients having F-VASI improvements (i.e., a decrease of  $\geq 25\%$  in the F-VASI [F-VASI25 response], F-VASI50 response, F-VASI75 response, and F-VASI90 response) or T-VASI improvements (i.e., a decrease of  $\geq 25\%$  in the T-VASI [T-VASI25 response], T-VASI50 response, T-VASI75 response, and T-VASI90 response); the percentage of patients in each VNS category; the change from baseline in the Dermatology Life Quality Index (DLQI [for adults])<sup>18</sup> or the Children's Dermatology Life Quality Index (CDLQI)<sup>19</sup> during treatment; and population-based trough plasma concentrations of ruxolitinib at weeks 4, 24, and 40.

Exploratory end points included the percentage of patients having a facial or total Physician's Global Vitiligo Assessment (F-PhGVA and T-PhGVA, respectively; ranges, 0 to 4 on a Likert scale) of clear or almost clear (scores of 0 or 1; PhGVA response), the percentage of patients having a facial or total Patient's Global Impression of Change–Vitiligo (F-PaGIC-V and T-PaGIC-V, respectively; ranges, 1 to 7 on a Likert scale) of very much or much improved (scores of 1 or 2; PaGIC-V response), and the percentage of patients in each category of PhGVA, PaGIC-V, and color-matching (excellent, very good, good, poor, or very poor) during treatment. (Details on end points are provided in the Supplementary Appendix.)

#### STATISTICAL ANALYSIS

For each trial, a sample size of 300 patients was determined to provide sufficient statistical power ( $>88\%$ ) to detect the difference between ruxolitinib cream and vehicle control in the primary and key secondary end points. The trials aimed to include a population comprising at least 10% adolescent patients (12 to 17 years of age) and at least 50% patients who were younger than 40 years of age to ensure fair representation of patients with vitiligo. Multiple imputation was applied to account for missing values in the analysis of primary and key secondary end points, as

detailed in the statistical analysis plan, available with the protocols. The primary and key secondary end points were tested in a prespecified fixed sequence (F-VASI75 response, F-VASI50 response, F-VASI90 response, T-VASI50 response, VNS response, and percentage change from baseline in facial body-surface area affected by vitiligo, all at week 24) to control the rate of overall type I error with a two-sided alpha level of 0.05. Ruxolitinib cream and vehicle were compared with the use of exact logistic regression for binary end points, presented with relative risk, and were compared with the use of an analysis of covariance model for facial body-surface area affected by vitiligo. The relative risk was derived as the average of relative risks estimated from individual data sets multiply imputed, and the 95% confidence intervals for the relative risks are based on the pooled standard errors obtained with the use of Rubin's method<sup>20</sup> and normal approximation. All other secondary and exploratory end points were reported as observed without adjustments for multiplicity, and analyses were summarized with the use of descriptive statistics.

The efficacy analysis used the modified intention-to-treat population: in TRuE-V1, all randomly assigned patients were included; in TRuE-V2, 13 patients from one trial site were excluded for nonadherence to the protocol, which resulted in data-quality concerns (sensitivity analyses were performed to determine the effect of site exclusion). All the patients who applied at least one dose of ruxolitinib cream or vehicle were included in the safety analyses (safety population). Adverse events during the double-blind period (up to week 24) are reported in the safety population (ruxolitinib-cream group and vehicle group); adverse events during the open-label treatment extension period (after week 24) are reported in the treatment-extension evaluable population (ruxolitinib-cream group and vehicle-to-ruxolitinib-cream group). The pharmacokinetic-evaluable population (up to week 24) included patients who applied at least one dose of ruxolitinib cream and provided at least one postdose blood sample.

## RESULTS

### PATIENT CHARACTERISTICS

TRuE-V1 was conducted from September 20, 2019, to October 21, 2021, and TRuE-V2 was conducted from October 3, 2019, to October 1, 2021.

TRuE-V1 enrolled 330 patients (221 patients in the ruxolitinib-cream group and 109 in the vehicle group) at 45 centers in North America (29 centers) and Europe (16). TRuE-V2 enrolled 344 patients (229 patients in the ruxolitinib-cream group and 115 in the vehicle group) at 49 centers in North America (32 centers) and Europe (17). TRuE-V1 included all 330 randomly assigned patients in the efficacy and safety analyses. TRuE-V2 included 331 patients in the efficacy analyses (13 patients were excluded for nonadherence to the protocol; sensitivity analyses including data from this site confirmed that removal of these data did not affect the interpretation of efficacy results) and 343 patients in the safety analyses (1 randomly assigned patient did not apply  $\geq 1$  dose of ruxolitinib cream and was excluded). In the safety populations, 286 patients (86.7%) in TRuE-V1 and 308 (89.8%) in TRuE-V2 completed the 24-week double-blind periods (Fig. S3). The primary reasons for discontinuation of the trial agent during the double-blind period were loss to follow-up (21 patients [6.4%] in TRuE-V1 and 16 [4.7%] in TRuE-V2) and withdrawal by the patient (17 patients [5.2%] and 11 [3.2%], respectively).

The mean ( $\pm$ SD) age of the patients in the safety populations was  $40.2 \pm 15.9$  years in TRuE-V1 and  $38.9 \pm 14.3$  years in TRuE-V2. A total of 10.9% of the patients in TRuE-V1 and 10.5% of those in TRuE-V2 were 12 to 17 years of age, and 54.5% and 57.1%, respectively, of the patients were 40 years of age or younger; 56.4% and 50.1%, respectively, of the patients were girls or women. The trials included patients of all Fitzpatrick skin types; 78.5% of the patients in TRuE-V1 and 65.9% of those in TRuE-V2 had skin types I, II, or III (pale white, white, or light brown skin), and 21.5% and 34.1%, respectively, had skin types IV, V, or VI (moderate brown, dark brown, or deeply pigmented dark brown to black skin). The distribution of baseline characteristics was similar across trial groups for both trials (Table 1) and was representative of a population of patients who would apply topical treatment for vitiligo; however, 5% or fewer of the patients identified themselves as Black (see Table S1 for the representativeness of the patient population).

### EFFICACY

*Primary End Point: F-VASI75 Response at Week 24*

In TRuE-V1, approximately 66 of 221 patients (29.8%; missing values were estimated through



multiple imputation for the primary end point) in the ruxolitinib-cream group and 8 of 109 patients (7.4%) in the vehicle group had an F-VASI75 response at week 24 (relative risk, 4.0; 95% confidence interval [CI], 1.9 to 8.4;  $P<0.001$ ). In TRuE-V2, approximately 69 of 222 patients (30.9%) in the ruxolitinib-cream group and 12 of 109 patients (11.4%) in the vehicle group had such a response (relative risk, 2.7; 95% CI, 1.5 to 4.9;  $P<0.001$ ) (Table 2 and Fig. S4A). An F-VASI75 response was observed in 91 of 173 patients (52.6%) in TRuE-V1 and 85 of 177 patients (48.0%) in TRuE-V2 who applied ruxolitinib cream for 52 weeks and in 22 of 82 patients (27%) and 24 of 81 patients (30%), respectively, who crossed over from vehicle cream to ruxolitinib cream for 28 weeks.

#### Key Secondary End Points

At week 24, an F-VASI50 response was observed in approximately 113 of 221 patients (51.2%; missing values were estimated through multiple imputation for key secondary end points) in TRuE-V1 and 114 of 222 patients (51.4%) in TRuE-V2 who applied ruxolitinib cream, as compared with approximately 18 of 109 patients (16.9%) and 23 of 109 patients (20.9%), respectively, who applied vehicle cream (relative risk, 3.0 [95% CI, 1.9 to 4.8] and 2.5 [95% CI, 1.6 to 3.7], respectively;  $P<0.001$  in both trials) (Table 2 and Fig. S4B). An F-VASI90 response at week 24 occurred in approximately 34 of 221 patients (15.3%) in TRuE-V1 and 36 of 222 patients (16.3%) in TRuE-V2 with ruxolitinib cream, as compared with approximately 2 of 109 patients (2.2%) and 1 of 109 patients (1.3%), respectively, with vehicle (relative risk, 7.3 [95% CI, 1.8 to 29.5] [ $P=0.004$ ] and 13.1 [95% CI, 1.9 to 90.2] [ $P=0.006$ ], respectively) (Table 2 and Fig. S4C). F-VASI50 and F-VASI90 responses were numerically greater at week 52 than at week 24 (Table S2). A T-VASI50 response at week 24 was observed in approximately 46 of 221 patients (20.6%) in TRuE-V1 and 53 of 222 patients (23.9%) in TRuE-V2 who applied ruxolitinib cream, as compared with approximately 6 of 109 patients (5.1%) and 7 of 109 patients (6.8%), respectively, who applied vehicle cream (relative risk, 4.1 [95% CI, 1.6 to 10.5] [ $P=0.002$ ] and 3.5 [95% CI, 1.7 to 7.5] [ $P<0.001$ ], respectively) (Table 2 and Fig. S4D). A T-VASI50 response occurred in 92 of 173 patients (53.2%) in TRuE-V1 and 87 of 177 patients (49.2%) in TRuE-V2 who

applied ruxolitinib cream for 52 weeks and in 26 of 82 patients (32%) and 18 of 81 patients (22%), respectively, who crossed over from vehicle cream to ruxolitinib cream for 28 weeks. A VNS response at week 24 occurred in approximately 54 of 221 patients (24.5%) in TRuE-V1 and 46 of 222 patients (20.5%) in TRuE-V2 with ruxolitinib cream, as compared with approximately 4 of 109 patients (3.3%) and 5 of 109 patients (4.9%), respectively, with vehicle (relative risk, 7.5 [95% CI, 2.4 to 23.5] [ $P<0.001$ ] and 4.2 [95% CI, 1.7 to 10.2] [ $P=0.001$ ], respectively) (Table 2 and Figs. S5A and S6); a numerically greater percentage of patients had VNS responses at week 52 than at week 24. The least-squares mean percentage change from baseline in facial body-surface area affected by vitiligo was -28.9% in TRuE-V1 and -26.4% in TRuE-V2 with ruxolitinib cream, as compared with -9.5% and -7.0%, respectively, with vehicle ( $P<0.001$  in both trials) (Table 2 and Fig. S5B).

#### Other Secondary and Exploratory End Points

Patients who applied ruxolitinib cream rather than vehicle cream had numerically greater improvements from baseline, with separation between trial groups at approximately week 12 in the F-VASI and T-VASI on the basis of visual inspection of values over time (Fig. S7) as well as facial body-surface area and total body-surface area affected by vitiligo (Fig. S8), with continued separation through week 52 on the basis of visual inspection; however, no definite conclusions can be drawn from these data because there was no adjustment of the widths of confidence intervals for multiple comparisons. Patients who applied ruxolitinib cream showed visible improvement in repigmentation of facial and nonfacial lesions (Fig. S9). However, there were no meaningful improvements from baseline in DLQI and CDLQI scores through week 52. Data on these end points are also provided in Table S2.

At week 24, a numerically larger percentage of patients who applied ruxolitinib cream rather than vehicle cream had F-PhGVA and T-PhGVA responses (Fig. S10) as well as F-PaGIC-V and T-PaGIC-V responses (Fig. S11), with further improvement at week 52 on the basis of visual inspection of results over time; however, no conclusions can be drawn from these data because there was no adjustment for multiplicity. The percentage of patients who reported good-to-

**Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Safety Population).\***

| Characteristic                               | TRuE-V1            |                                         |                  | TRuE-V2            |                                         |                  |
|----------------------------------------------|--------------------|-----------------------------------------|------------------|--------------------|-----------------------------------------|------------------|
|                                              | Vehicle<br>(N=109) | 1.5%<br>Ruxolitinib<br>Cream<br>(N=221) | Total<br>(N=330) | Vehicle<br>(N=115) | 1.5%<br>Ruxolitinib<br>Cream<br>(N=228) | Total<br>(N=343) |
| Age — yr                                     | 39.7±16.7          | 40.5±15.4                               | 40.2±15.9        | 39.8±12.1          | 38.4±15.2                               | 38.9±14.3        |
| Age group — no. (%)                          |                    |                                         |                  |                    |                                         |                  |
| 12–17 yr                                     | 11 (10.1)          | 25 (11.3)                               | 36 (10.9)        | 6 (5.2)            | 30 (13.2)                               | 36 (10.5)        |
| 18–64 yr                                     | 85 (78.0)          | 180 (81.4)                              | 265 (80.3)       | 106 (92.2)         | 186 (81.6)                              | 292 (85.1)       |
| ≥65 yr                                       | 13 (11.9)          | 16 (7.2)                                | 29 (8.8)         | 3 (2.6)            | 12 (5.3)                                | 15 (4.4)         |
| Female sex — no. (%)                         | 50 (45.9)          | 136 (61.5)                              | 186 (56.4)       | 60 (52.2)          | 112 (49.1)                              | 172 (50.1)       |
| Race or ethnic group — no. (%)†              |                    |                                         |                  |                    |                                         |                  |
| White                                        | 96 (88.1)          | 180 (81.4)                              | 276 (83.6)       | 93 (80.9)          | 182 (79.8)                              | 275 (80.2)       |
| Black                                        | 4 (3.7)            | 11 (5.0)                                | 15 (4.5)         | 5 (4.3)            | 12 (5.3)                                | 17 (5.0)         |
| Asian                                        | 4 (3.7)            | 5 (2.3)                                 | 9 (2.7)          | 7 (6.1)            | 12 (5.3)                                | 19 (5.5)         |
| Other                                        | 2 (1.8)            | 9 (4.1)                                 | 11 (3.3)         | 7 (6.1)            | 19 (8.3)                                | 26 (7.6)         |
| Not reported                                 | 3 (2.8)            | 16 (7.2)                                | 19 (5.8)         | 3 (2.6)            | 3 (1.3)                                 | 6 (1.7)          |
| Fitzpatrick skin type — no. (%)‡             |                    |                                         |                  |                    |                                         |                  |
| I                                            | 3 (2.8)            | 10 (4.5)                                | 13 (3.9)         | 1 (0.9)            | 2 (0.9)                                 | 3 (0.9)          |
| II                                           | 40 (36.7)          | 74 (33.5)                               | 114 (34.5)       | 32 (27.8)          | 57 (25.0)                               | 89 (25.9)        |
| III                                          | 43 (39.4)          | 89 (40.3)                               | 132 (40.0)       | 45 (39.1)          | 89 (39.0)                               | 134 (39.1)       |
| IV                                           | 15 (13.8)          | 34 (15.4)                               | 49 (14.8)        | 25 (21.7)          | 55 (24.1)                               | 80 (23.3)        |
| V                                            | 7 (6.4)            | 11 (5.0)                                | 18 (5.5)         | 10 (8.7)           | 17 (7.5)                                | 27 (7.9)         |
| VI                                           | 1 (0.9)            | 3 (1.4)                                 | 4 (1.2)          | 2 (1.7)            | 8 (3.5)                                 | 10 (2.9)         |
| Geographic region — no. (%)                  |                    |                                         |                  |                    |                                         |                  |
| North America                                | 73 (67.0)          | 147 (66.5)                              | 220 (66.7)       | 83 (72.2)          | 160 (70.2)                              | 243 (70.8)       |
| Europe                                       | 36 (33.0)          | 74 (33.5)                               | 110 (33.3)       | 32 (27.8)          | 68 (29.8)                               | 100 (29.2)       |
| F-VASI§                                      | 1.00±0.59          | 0.93±0.58                               | 0.95±0.59        | 0.83±0.52          | 0.90±0.52                               | 0.88±0.52        |
| T-VASI¶                                      | 6.42±1.92          | 6.49±2.02                               | 6.47±1.99        | 7.02±2.20          | 6.84±2.06                               | 6.90±2.10        |
| Facial BSA affected by vitiligo — %          | 1.15±0.71          | 1.05±0.69                               | 1.09±0.70        | 0.92±0.57          | 0.98±0.57                               | 0.96±0.57        |
| Total BSA affected by vitiligo — %           | 7.22±2.01          | 7.28±2.03                               | 7.26±2.02        | 7.68±2.04          | 7.44±2.01                               | 7.52±2.02        |
| Duration of disease — yr                     | 13.2±10.0          | 13.9±11.7                               | 13.6±11.1        | 16.0±11.6          | 15.9±12.1                               | 15.9±11.9        |
| Received diagnosis in childhood<br>— no. (%) | 34 (31.2)          | 72 (32.6)                               | 106 (32.1)       | 43 (37.4)          | 96 (42.1)                               | 139 (40.5)       |
| Disease stability — no. (%)**                |                    |                                         |                  |                    |                                         |                  |
| Stable                                       | 80 (73.4)          | 165 (74.7)                              | 245 (74.2)       | 88 (76.5)          | 166 (72.8)                              | 254 (74.1)       |
| Progressive                                  | 29 (26.6)          | 56 (25.3)                               | 85 (25.8)        | 27 (23.5)          | 62 (27.2)                               | 89 (25.9)        |
| Other autoimmune disorders<br>— no. (%)††    | 18 (16.5)          | 53 (24.0)                               | 71 (21.5)        | 18 (15.7)          | 37 (16.2)                               | 55 (16.0)        |
| Thyroid disorders                            | 17 (15.6)          | 50 (22.6)                               | 67 (20.3)        | 15 (13.0)          | 35 (15.4)                               | 50 (14.6)        |
| Juvenile diabetes mellitus                   | 1 (0.9)            | 0                                       | 1 (0.3)          | 0                  | 0                                       | 0                |
| Pernicious anemia                            | 0                  | 1 (0.5)                                 | 1 (0.3)          | 0                  | 0                                       | 0                |
| Other                                        | 1 (0.9)            | 5 (2.3)                                 | 6 (1.8)          | 6 (5.2)            | 5 (2.2)                                 | 11 (3.2)         |

**Table 1. (Continued.)**

| Characteristic                 | TRuE-V1            |                                         |                  | TRuE-V2            |                                         |                  |
|--------------------------------|--------------------|-----------------------------------------|------------------|--------------------|-----------------------------------------|------------------|
|                                | Vehicle<br>(N=109) | 1.5%<br>Ruxolitinib<br>Cream<br>(N=221) | Total<br>(N=330) | Vehicle<br>(N=115) | 1.5%<br>Ruxolitinib<br>Cream<br>(N=228) | Total<br>(N=343) |
| Previous therapy — no. (%)†‡   | 61 (56.0)          | 131 (59.3)                              | 192 (58.2)       | 76 (66.1)          | 143 (62.7)                              | 219 (63.8)       |
| Topical calcineurin inhibitors | 31 (28.4)          | 72 (32.6)                               | 103 (31.2)       | 37 (32.2)          | 74 (32.5)                               | 111 (32.4)       |
| Topical glucocorticoids        | 28 (25.7)          | 67 (30.3)                               | 95 (28.8)        | 28 (24.3)          | 66 (28.9)                               | 94 (27.4)        |
| NB-UVB phototherapy            | 20 (18.3)          | 41 (18.6)                               | 61 (18.5)        | 27 (23.5)          | 52 (22.8)                               | 79 (23.0)        |
| Excimer laser therapy          | 8 (7.3)            | 18 (8.1)                                | 26 (7.9)         | 14 (12.2)          | 16 (7.0)                                | 30 (8.7)         |
| PUVA photochemotherapy         | 4 (3.7)            | 8 (3.6)                                 | 12 (3.6)         | 8 (7.0)            | 15 (6.6)                                | 23 (6.7)         |
| Vitamin D derivatives          | 2 (1.8)            | 4 (1.8)                                 | 6 (1.8)          | 1 (0.9)            | 0                                       | 1 (0.3)          |
| Other                          | 11 (10.1)          | 24 (10.9)                               | 35 (10.6)        | 14 (12.2)          | 34 (14.9)                               | 48 (14.0)        |

\* Plus-minus values are means  $\pm$ SD. Percentages may not total 100 because of rounding. BSA denotes body-surface area, NB-UVB narrow-band ultraviolet B, PUVA psoralen and ultraviolet A, TRuE-V1 Topical Ruxolitinib Evaluation in Vitiligo Study 1, and TRuE-V2 Topical Ruxolitinib Evaluation in Vitiligo Study 2.

† Race and ethnic group were reported by the patient. "Other" includes American Indian or Alaska Native, Native Hawaiian or Pacific Islander, and other.

‡ Fitzpatrick skin types range from I to VI: type I indicates pale white; type II, white; type III, light brown; type IV, moderate brown; type V, dark brown; and type VI, deeply pigmented dark brown to black.

§ Scores on the facial Vitiligo Area Scoring Index (F-VASI) range from 0 to 3, with higher scores indicating a greater area of facial depigmentation.

¶ Scores on the total Vitiligo Area Scoring Index (T-VASI) range from 0 to 100, with higher scores indicating a greater area of total body depigmentation.

|| Shown is the percentage of total BSA.

\*\* The determination of disease stability was based on investigator judgment.

†† Patients could report multiple autoimmune disorders.

‡‡ Patients could have used multiple previous lines of therapy. "Other" includes other types of phototherapy, oral glucocorticoids, surgical techniques, and other.

excellent color-matching was higher in the ruxolitinib-cream group than in the vehicle group at week 24 (Fig. S12).

#### SAFETY AND PHARMACOKINETICS

The incidences and types of adverse events that emerged or worsened after the first dose of a trial agent were similar in both trials (Table 3). In the double-blind period, adverse events were mainly mild or moderate and occurred in 45.7% (TRuE-V1) and 50.0% (TRuE-V2) of the patients in the ruxolitinib-cream group and in 38.5% and 33.9%, respectively, of the patients in the vehicle group. The most common adverse events were application-site acne (ruxolitinib-cream group, 5.9% in TRuE-V1 and 5.7% in TRuE-V2; vehicle group, none and 2.6%, respectively) and application-site pruritus (ruxolitinib-cream group, 5.0% in TRuE-V1 and 5.3% in TRuE-V2; vehicle group, 3.7% and 1.7%, respectively). All acne and pruri-

tus events were mild or moderate; patients continued treatment with ruxolitinib cream, with the exception of one patient with acne who had a 3-day dose change to once-daily application before resuming twice-daily application. Safety findings were generally consistent in the open-label treatment extension (Table 3).

Among patients who applied ruxolitinib cream throughout 52 weeks, adverse events occurred in 54.8% of the patients in TRuE-V1 and in 62.3% of those in TRuE-V2. The most common adverse events (other than coronavirus disease 2019 [Covid-19], which, on the basis of its prevalence at the time the trials were conducted, was not considered to be relevant to ruxolitinib-cream application) were application-site acne (6.3% in TRuE-V1 and 6.6% in TRuE-V2), nasopharyngitis (5.4% and 6.1%, respectively), and application-site pruritus (5.4% and 5.3%) (Table S3). It is notable that only 5 patients

**Table 2. Primary and Key Secondary Efficacy End Points (Double-Blind Period; Modified Intention-to-Treat Population).\***

| End Point                                                                                 | TRuE-V1                 |                                        |                           |            | TRuE-V2                |                                        |                           |            |
|-------------------------------------------------------------------------------------------|-------------------------|----------------------------------------|---------------------------|------------|------------------------|----------------------------------------|---------------------------|------------|
|                                                                                           | Vehicle<br>(N = 109)    | 1.5% Ruxolitinib<br>Cream<br>(N = 221) | Relative Risk<br>(95% CI) | P<br>Value | Vehicle<br>(N = 109)   | 1.5% Ruxolitinib<br>Cream<br>(N = 222) | Relative Risk<br>(95% CI) | P<br>Value |
| <b>Primary end point</b>                                                                  |                         |                                        |                           |            |                        |                                        |                           |            |
| F-VASI75 response at wk 24 — % (95% CI)†                                                  | 7.4 (2.2 to 12.6)       | 29.8 (23.5 to 36.1)                    | 4.0 (1.9 to 8.4)          | <0.001     | 11.4 (5.2 to 17.7)     | 30.9 (24.5 to 37.3)                    | 2.7 (1.5 to 4.9)          | <0.001     |
| <b>Key secondary end points</b>                                                           |                         |                                        |                           |            |                        |                                        |                           |            |
| F-VASI50 response at wk 24 — % (95% CI)†                                                  | 16.9 (9.3 to 24.6)      | 51.2 (44.4 to 58.0)                    | 3.0 (1.9 to 4.8)          | <0.001     | 20.9 (12.9 to 28.9)    | 51.4 (44.6 to 58.3)                    | 2.5 (1.6 to 3.7)          | <0.001     |
| F-VASI90 response at wk 24 — % (95% CI)†                                                  | 2.2 (0 to 5.1)          | 15.3 (10.4 to 20.2)                    | 7.3 (1.8 to 29.5)         | 0.004      | 1.3 (0 to 3.8)         | 16.3 (11.2 to 21.5)                    | 13.1 (1.9 to 90.2)        | 0.006      |
| T-VASI50 response at wk 24 — % (95% CI)†                                                  | 5.1 (0.6 to 9.7)        | 20.6 (15.2 to 26.0)                    | 4.1 (1.6 to 10.5)         | 0.002      | 6.8 (1.9 to 11.7)      | 23.9 (18.1 to 29.8)                    | 3.5 (1.7 to 7.5)          | <0.001     |
| VNS response at wk 24 — % (95% CI)†‡                                                      | 3.3 (0 to 6.9)          | 24.5 (18.5 to 30.4)                    | 7.5 (2.4 to 23.5)         | <0.001     | 4.9 (0.7 to 9.2)       | 20.5 (14.9 to 26.1)                    | 4.2 (1.7 to 10.2)         | 0.001      |
| LSM percentage change from baseline in facial BSA affected by vitiligo at wk 24 (95% CI)§ | −9.5<br>(−15.9 to −3.2) | −28.9<br>(−33.2 to −24.5)              | NA                        | <0.001     | −7.0<br>(−14.5 to 0.5) | −26.4<br>(−31.5 to −21.4)              | NA                        | <0.001     |

\* F-VASI50 denotes a decrease (improvement) of at least 50% in the F-VASI from baseline, F-VASI75 a decrease of at least 75% in the F-VASI from baseline, F-VASI90 a decrease of at least 90% in the F-VASI from baseline, NA not applicable, and T-VASI50 a decrease of at least 50% in the T-VASI from baseline.

† Multiple imputation was applied to account for missing values.

‡ A Vitiligo Noticeability Scale (VNS) response was defined as a rating of a lot less noticeable or no longer noticeable.

§ An analysis of covariance model was applied to determine least-squares mean (LSM) and P value.

who applied ruxolitinib cream at any time during the 52-week trials reported application-site pain that was considered to be related to treatment. A total of 14 patients who applied ruxolitinib cream at any time during the trials had serious adverse events (Table S4). Three patients discontinued double-blind treatment because of an adverse event (fatigue and application-site rash in 1 patient each in the ruxolitinib-cream group and nausea and headache in the same patient in the vehicle group), and 1 patient discontinued the open-label treatment extension (application-site eczema in 1 patient).

The incidence of hematopoietic adverse events was less than 1% (Table S5); such events were mild or moderate in severity, and none were considered to be related to the trial agent. The majority of patients had normal hemoglobin and platelet levels throughout the treatment period (Fig. S13). Plasma concentrations of ruxolitinib were similar in the two trials (mean [±SD] steady-state concentration average of weeks 4 and 24, 55.8±56.7 nM in TRuE-V1 and 58.0±68.1 nM in TRuE-V2) (Fig. S14 and Table S6).

## DISCUSSION

These two phase 3, double-blind, randomized, vehicle-controlled trials of repigmentation therapy in patients with vitiligo yielded similar results, showing statistical superiority of 1.5% ruxolitinib cream twice daily over vehicle cream for the primary and all key secondary end points at week 24, with approximately one third of patients having an F-VASI75 response for facial repigmentation (primary end point). The results for secondary end points were generally in the same direction as the results of the primary analysis. **There was a numerical increase in the percentage of patients who met the criteria for the primary and key secondary end points through week 52**, including among patients who crossed over from vehicle to ruxolitinib cream for 28 weeks; however, no definite conclusions can be drawn from these results because of the lack of multiplicity correction. Efficacy at week 52 in patients who crossed over to active treatment, after 28 weeks of ruxolitinib cream, was consistent with week 24 data in patients who applied ruxolitinib cream from day 1.

These trials examined facial repigmentation as the primary end point and total body repig-



**Table 3. Adverse Events during the Double-Blind Period and Open-Label Treatment Extension Period.**

| Adverse Event                                           | TRuE-V1                             |                                         |                                                      |                                         | TRuE-V2              |                                         |                                                      |                                         |
|---------------------------------------------------------|-------------------------------------|-----------------------------------------|------------------------------------------------------|-----------------------------------------|----------------------|-----------------------------------------|------------------------------------------------------|-----------------------------------------|
|                                                         | Double-Blind Period*                |                                         | Extension Period†                                    |                                         | Double-Blind Period* |                                         | Extension Period†                                    |                                         |
|                                                         | Vehicle<br>(N=109)                  | 1.5%<br>Ruxolitinib<br>Cream<br>(N=221) | Vehicle<br>to 1.5%<br>Ruxolitinib<br>Cream<br>(N=90) | 1.5%<br>Ruxolitinib<br>Cream<br>(N=193) | Vehicle<br>(N=115)   | 1.5%<br>Ruxolitinib<br>Cream<br>(N=228) | Vehicle<br>to 1.5%<br>Ruxolitinib<br>Cream<br>(N=98) | 1.5%<br>Ruxolitinib<br>Cream<br>(N=199) |
|                                                         | <i>number of patients (percent)</i> |                                         |                                                      |                                         |                      |                                         |                                                      |                                         |
| Any adverse event                                       | 42 (38.5)                           | 101 (45.7)                              | 31 (34.4)                                            | 65 (33.7)                               | 39 (33.9)            | 114 (50.0)                              | 38 (38.8)                                            | 82 (41.2)                               |
| Most common adverse events‡                             |                                     |                                         |                                                      |                                         |                      |                                         |                                                      |                                         |
| Covid-19§                                               | 5 (4.6)                             | 3 (1.4)                                 | 1 (1.1)                                              | 11 (5.7)                                | 2 (1.7)              | 10 (4.4)                                | 5 (5.1)                                              | 9 (4.5)                                 |
| Application-site acne                                   | 0                                   | 13 (5.9)                                | 0                                                    | 1 (0.5)                                 | 3 (2.6)              | 13 (5.7)                                | 5 (5.1)                                              | 3 (1.5)                                 |
| Nasopharyngitis                                         | 4 (3.7)                             | 9 (4.1)                                 | 2 (2.2)                                              | 3 (1.6)                                 | 1 (0.9)              | 10 (4.4)                                | 3 (3.1)                                              | 4 (2.0)                                 |
| Headache                                                | 2 (1.8)                             | 6 (2.7)                                 | 2 (2.2)                                              | 3 (1.6)                                 | 4 (3.5)              | 11 (4.8)                                | 1 (1.0)                                              | 6 (3.0)                                 |
| Application-site pruritus                               | 4 (3.7)                             | 11 (5.0)                                | 1 (1.1)                                              | 1 (0.5)                                 | 2 (1.7)              | 12 (5.3)                                | 0                                                    | 0                                       |
| Upper respiratory tract infection                       | 5 (4.6)                             | 6 (2.7)                                 | 3 (3.3)                                              | 2 (1.0)                                 | 0                    | 7 (3.1)                                 | 2 (2.0)                                              | 0                                       |
| Sinusitis                                               | 3 (2.8)                             | 4 (1.8)                                 | 1 (1.1)                                              | 3 (1.6)                                 | 2 (1.7)              | 6 (2.6)                                 | 0                                                    | 0                                       |
| Application-site dermatitis                             | 0                                   | 3 (1.4)                                 | 0                                                    | 1 (0.5)                                 | 0                    | 1 (0.4)                                 | 0                                                    | 5 (2.5)                                 |
| Application-site rash                                   | 1 (0.9)                             | 5 (2.3)                                 | 1 (1.1)                                              | 1 (0.5)                                 | 1 (0.9)              | 2 (0.9)                                 | 0                                                    | 1 (0.5)                                 |
| Oral herpes                                             | 2 (1.8)                             | 2 (0.9)                                 | 2 (2.2)                                              | 2 (1.0)                                 | 1 (0.9)              | 3 (1.3)                                 | 1 (1.0)                                              | 0                                       |
| Urinary tract infection                                 | 1 (0.9)                             | 5 (2.3)                                 | 0                                                    | 1 (0.5)                                 | 0                    | 1 (0.4)                                 | 1 (1.0)                                              | 2 (1.0)                                 |
| Acne                                                    | 1 (0.9)                             | 2 (0.9)                                 | 3 (3.3)                                              | 0                                       | 0                    | 1 (0.4)                                 | 1 (1.0)                                              | 2 (1.0)                                 |
| Pyrexia                                                 | 0                                   | 1 (0.5)                                 | 0                                                    | 0                                       | 0                    | 5 (2.2)                                 | 0                                                    | 1 (0.5)                                 |
| Application-site exfoliation                            | 0                                   | 0                                       | 0                                                    | 0                                       | 1 (0.9)              | 5 (2.2)                                 | 1 (1.0)                                              | 0                                       |
| Hypothyroidism                                          | 0                                   | 0                                       | 2 (2.2)                                              | 1 (0.5)                                 | 0                    | 2 (0.9)                                 | 0                                                    | 0                                       |
| Adverse event related to trial agent¶                   | 10 (9.2)                            | 38 (17.2)                               | 5 (5.6)                                              | 7 (3.6)                                 | 6 (5.2)              | 28 (12.3)                               | 6 (6.1)                                              | 12 (6.0)                                |
| Most common adverse events related to trial agent‡¶     |                                     |                                         |                                                      |                                         |                      |                                         |                                                      |                                         |
| Application-site acne                                   | 0                                   | 12 (5.4)                                | 0                                                    | 1 (0.5)                                 | 2 (1.7)              | 10 (4.4)                                | 3 (3.1)                                              | 3 (1.5)                                 |
| Application-site pruritus                               | 4 (3.7)                             | 11 (5.0)                                | 1 (1.1)                                              | 0                                       | 2 (1.7)              | 10 (4.4)                                | 0                                                    | 0                                       |
| Application-site exfoliation                            | 0                                   | 0                                       | 0                                                    | 0                                       | 1 (0.9)              | 5 (2.2)                                 | 0                                                    | 0                                       |
| Serious adverse event  **                               | 1 (0.9)                             | 6 (2.7)                                 | 1 (1.1)                                              | 1 (0.5)                                 | 0                    | 2 (0.9)                                 | 2 (2.0)                                              | 2 (1.0)                                 |
| Adverse event leading to discontinuation of trial agent | 1 (0.9)                             | 1 (0.5)                                 | 0                                                    | 0                                       | 0                    | 1 (0.4)                                 | 0                                                    | 1 (0.5)                                 |

\* Adverse events during the double-blind period (up to week 24) are reported in the safety population (ruxolitinib-cream group and vehicle group).

† Adverse events during the open-label treatment extension period (after week 24) are reported in the treatment-extension evaluable population (ruxolitinib-cream group and vehicle-to-ruxolitinib-cream group).

‡ Shown are events that occurred in more than 2% of the patients in any group.

§ On the basis of the prevalence of coronavirus disease 2019 (Covid-19) at the time the trials were conducted, the incidence of Covid-19 was not considered to be relevant to ruxolitinib-cream application.

¶ The relatedness of the adverse event to the trial agent was determined by the investigator.

|| No serious adverse events were considered by investigators to be related to the trial agent according to criteria prespecified in the protocol.

\*\* In TRuE-V1, serious adverse events with application of ruxolitinib cream were anal fistula, appendicitis, concussion, hepatitis due to infectious mononucleosis, hypersensitivity, kidney contusion, myocarditis, prostate cancer, and subacute combined cord degeneration (in one patient each); hypersensitivity and subacute combined cord degeneration occurred in the same patient. In TRuE-V2, serious adverse events with ruxolitinib cream were appendiceal abscess, coronary-artery stenosis, joint dislocation, papillary thyroid cancer, rhabdomyolysis, and ureterolithiasis (in one patient each).

mentation as one of five key secondary end points. The repigmentation process is lengthy.<sup>21</sup> JAK inhibition with ruxolitinib cream reduces skin-associated inflammatory mediators (e.g.,

CXCL10) in circulation,<sup>17</sup> disrupting vitiligo pathogenesis and allowing time for melanocyte recruitment and repigmentation.<sup>22</sup> The lower incidence of total body repigmentation than of

facial repigmentation after 6 months of treatment, with approximately 20% of patients having a T-VASI50 response and 50% of patients having an F-VASI50 response, is due to recognized differences in the nature of repigmentation of facial as compared with nonfacial body areas. The rate of nonfacial repigmentation is further affected by involvement of the hands and feet, which are typically resistant to repigmentation, partly because of a lower density of hair follicles.<sup>23</sup>

Phase 2 trial data with ruxolitinib cream showed that F-VASI75 and T-VASI50 responses indicate clinically meaningful repigmentation.<sup>17</sup> These findings were supported by another study that showed that most patients considered at least 75% facial repigmentation and at least 50% nonfacial repigmentation to be indicators of treatment success.<sup>24</sup> In TRuE-V1 and TRuE-V2, half the patients who applied ruxolitinib cream from day 1 had at least 75% facial repigmentation and at least 50% total body repigmentation at 1 year. No direct comparisons can be made with existing data for repigmentation with other monotherapies,<sup>25,26</sup> including phototherapy,<sup>27,28</sup> or with combination therapy.<sup>15,29-31</sup> A clinical trial investigating ruxolitinib cream in combination with narrow-band ultraviolet B phototherapy in patients with vitiligo is in progress (ClinicalTrials.gov number, NCT05247489).

The efficacy of ruxolitinib cream was supported by positive patient-reported outcomes, including rating vitiligo lesions as a lot less or no longer noticeable (VNS response), rating lesions as much or very much improved (PaGIC-V response), and reporting color-matching as good to excellent during 24 weeks of double-blind treatment. Although not comparable, a higher percentage of patients than of physicians reported a favorable response to treatment according to the PaGIC-V and the PhGVA, respectively, which indicates that patients may be more optimistic regarding changes in their lesions. Nonetheless, no meaningful quality-of-life improvements were evident in the two trials; however, the DLQI and CDLQI instruments include physical symptoms such as itch and pain<sup>18,19</sup> and may lack sensitivity in vitiligo.<sup>32</sup>

The incidences of adverse events with ruxolitinib cream were similar across both trials. Application-site acne and application-site pruritus were the most common treatment-related adverse events, each reported in approximately 5%

of the patients who applied ruxolitinib cream for 52 weeks; there were no resulting treatment discontinuations. Acne is a common adverse event with JAK inhibitors,<sup>33</sup> although the pathogenesis of acne in this context is not yet understood. Further analyses to better understand and characterize these acneiform lesions are warranted. It is notable that stinging or burning at the application site, which is often reported with topical calcineurin inhibitors,<sup>34</sup> was infrequent with ruxolitinib cream. In addition, mean plasma concentrations of ruxolitinib were well below the half-maximal concentration for thrombopoietin-stimulated STAT3 phosphorylation (281 nM),<sup>35</sup> a proxy for evaluating JAK-related myelosuppression in bone marrow. Hematopoietic adverse events were infrequent and were considered by the investigators to be unrelated to treatment.

Limitations to interpreting these trial results include that the trials were conducted during the Covid-19 pandemic, which may have contributed to patients being lost to follow-up. In addition, most enrolled patients were White and had skin types I, II, or III. Although generalization to patients with darker skin types is limited on the basis of patient enrollment, subgroup analyses of phase 2 data indicated that incidences of repigmentation response may be similar among patients with fairer skin and those with darker skin<sup>36</sup>; similar analysis of pooled phase 3 data from TRuE-V1 and TRuE-V2 is ongoing. Because skin pigmentation (coloring) is dependent on melanin production by melanocytes and is regulated by genetic and environmental factors, among others,<sup>37</sup> restoring melanocyte function (through JAK inhibition) may be sufficient to restore consistent skin coloring regardless of skin type. Long-term safety evaluations of ruxolitinib cream from the 156-week phase 2 trial are ongoing.

In these two phase 3 trials, ruxolitinib cream showed superiority to vehicle control in repigmentation of vitiligo. Patient-reported outcomes suggest that changes were meaningful to patients, although there were no substantial between-group differences in quality of life. Larger and longer trials are required to determine the effect and risks of ruxolitinib cream for the treatment of vitiligo.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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