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TO THE EDITOR

Vitiligo is a chronic autoimmune disease resulting in patches of skin depigmentation (Taïeb and Picardo, 2009) and reduced QOL (Morrison et al., 2017). Disease pathogenesis is driven by IFN-γ signaling through Jak1 and 2 (Rashighi and Harris, 2015). Combination phototherapy with topical corticosteroids or topical calcineurin inhibitors has been shown to significantly improve repigmentation versus monotherapy in patients with vitiligo (Batchelor et al., 2020; Dong et al., 2021). Previous reports with Jak inhibitors have suggested additional therapeutic benefits with concomitant phototherapy (Joshipura et al., 2018; Liu et al., 2017). In these patients, it has been proposed that Jak inhibition suppresses inflammatory signals that result in melanocyte destruction, leading to the potential recovery of melanocytes that may be enhanced during phototherapy-induced stimulation (Liu et al., 2017). Ruxolitinib is a Jak1/Jak2 inhibitor (Quintás-Cardama et al., 2010), and a topical formulation is in development for the treatment of vitiligo. In a phase 2, randomized, dose-ranging study in 157 adult patients with vitiligo (NCT03099304), ruxolitinib cream was associated with substantial repigmentation over 52 weeks and was well tolerated (Rosmarin et al., 2020). In this study, we report the safety and efficacy of ruxolitinib cream with concomitant narrow-band UVB (NB-UVB) phototherapy during the open-label phase after week 52 of the phase 2 study.

After the 52-week double-blind period of the study, patients received open-label treatment with 1.5% ruxolitinib cream twice daily (BID) up to week 156 (end of study); additional details of the patient population and study design were previously reported (Rosmarin et al., 2020). During the open-label treatment period, patients were offered optional concomitant NB-UVB phototherapy according to the standard phototherapy protocols of each investigator site. Phototherapy could be initiated at any time after the week 52 study visit. Efficacy assessments at week 104 included the change in facial Vitiligo Area Scoring Index (F-VASI) and total body Vitiligo Area Scoring Index (T-VASI) (total body including the face) from the last visit before addition of NB-UVB phototherapy; the proportion of patients achieving F-VASI improvements ≥50, ≥75, and ≥90% from baseline (F-VASI50, F-VASI75, and F-VASI90, respectively); and the proportion of patients achieving T-VASI improvements ≥25, ≥50, and ≥75% from baseline (T-VASI25, T-VASI50, and T-VASI75, respectively). The subpopulation of patients who had not achieved the primary endpoint of F-VASI50 at week 24 was also evaluated to determine whether the addition of phototherapy could improve responses in patients who did not initially show substantive improvement at week 24; with no substantial response after 6 months of monotherapy, patients may be motivated to try additional therapy, such as phototherapy. Safety and tolerability of 1.5% ruxolitinib cream BID and concomitant NB-UVB phototherapy were also assessed, including the frequency of reported adverse events. Data were summarized using descriptive statistics; no imputation was applied. The study protocol was approved by the institutional review board at each study site that enrolled patients in this analysis (Henry Ford Medical Center, Detroit, MI; Icahn School of Medicine at Mount Sinai, New York, NY; Tufts Medical Center, Boston, MA; University of Massachusetts Medical School, Worcester, MA; University of Texas Southwestern Medical Center, Dallas, TX), and all patients provided written informed consent.

A total of 19 patients (mean age = 47.2 years, 63.2% male) received add-on NB-UVB for ≥12 weeks during open-label treatment at various frequencies, most commonly thrice weekly (47.4%) (Supplementary Table S1). Of these 19 patients, 12 (mean age = 45.4 years, 66.7% male) had not achieved F-VASI50 at week 24 (initial randomization group: 0.15% once daily, n = 4; 0.5% once daily, n = 4; 1.5% once daily, n = 2; 1.5% BID, n = 2) (Supplementary Table S2). After the addition of NB-UVB phototherapy, F-VASI and T-VASI scores improved in 15 of 19 patients (78.9%) and 18 of 19 patients (94.7%), respectively. In these 19 patients, the mean percentage improvement at week 104 was 50.2% for F-VASI and 29.5% for T-VASI versus the improvement at the last visit before the addition of NB-UVB phototherapy. Among the 12 patients who had not achieved F-VASI50 at week 24, F-VASI scores improved in 10 patients (83.3%), and T-VASI scores improved in 11 patients (91.7%), with mean percentage improvements of 47.8 and 31.1%, respectively. Representative images of three patients who used a combination of 1.5% ruxolitinib cream BID and NB-UVB phototherapy during open-label treatment are shown in Figure 1. All F-VASI and T-VASI threshold response parameters at week 104 were increased after the addition of NB-UVB compared with those from the last visit before combination therapy (Figure 2a), including F-VASI75, F-VASI90, T-VASI50, and T-VASI75. Post-combination therapy response parameters were similar to data at week 104 from 70 patients who remained on ruxolitinib cream alone from day 1;

Abbreviations: BID, twice daily; F-VASI, facial Vitiligo Area Scoring Index; NB-UVB, narrow-band UVB; T-VASI, total body Vitiligo Area Scoring Index

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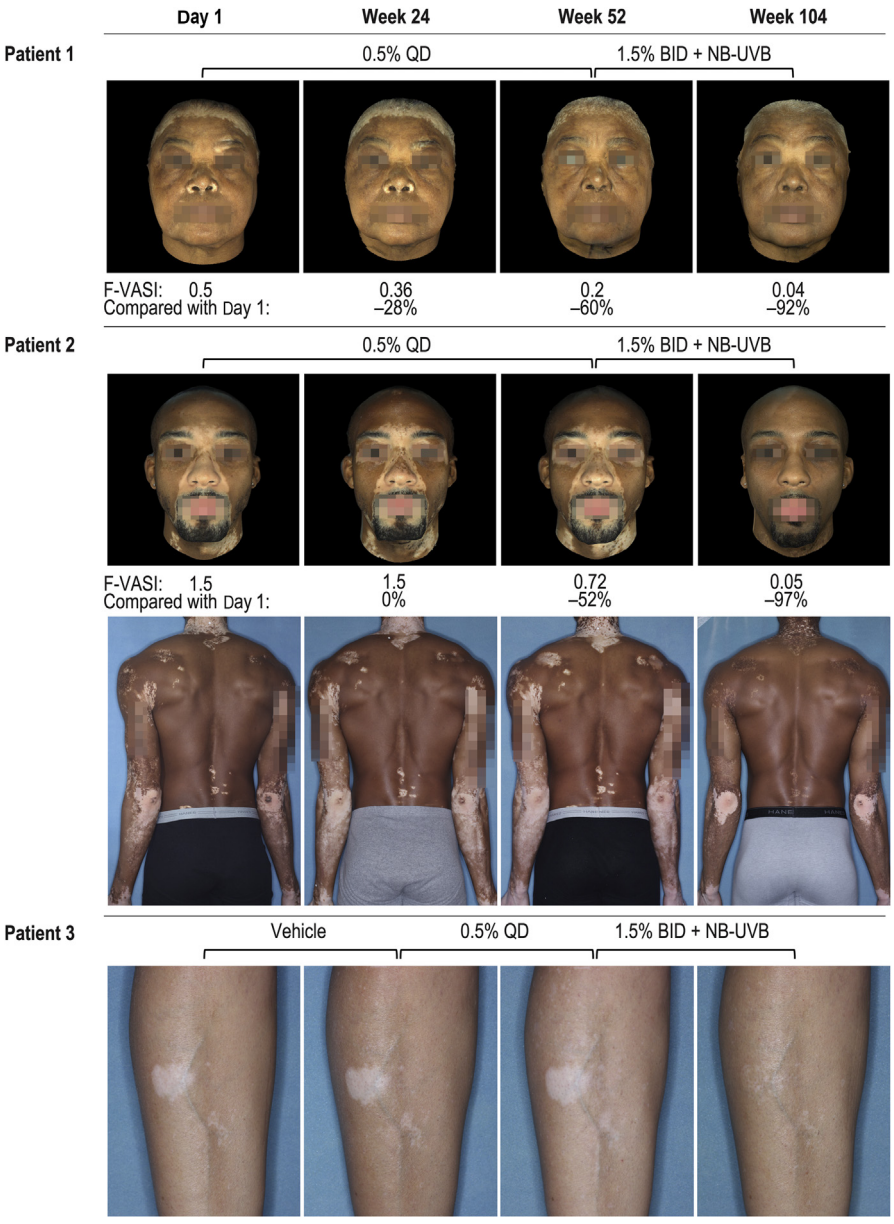

Figure 1. Representative clinical images showing facial and total body vitiligo lesions of patients treated with a combination of 1.5% ruxolitinib cream BID and NB-UVB phototherapy during the open-label period. Patients provided consent for the publication of photographs. BID, twice daily; F-VASI, facial Vitiligo Area Scoring Index; NB-UVB, narrow-band UVB; QD, once daily.

responses were higher at week 104 versus week 52 among patients who received ruxolitinib cream alone (Figure 2b and Supplementary Table S3). In patients who had not achieved F-VASI50 at week 24, the combination of ruxolitinib cream and NB-UVB phototherapy increased all F-VASI and T-VASI threshold parameters at week 104 compared with those from the visit before combination therapy (Supplementary Figure S1).

Combination therapy with 1.5% ruxolitinib cream BID and NB-UVB phototherapy was well tolerated, with only four patients experiencing adverse events (all grade 1 or 2), none of which were considered to be related to the treatment (Supplementary Table S4). No phototherapy burns were observed, and no adverse events related to skin malignancies or laboratory abnormalities were reported.

In summary, the addition of NB-UVB phototherapy to ruxolitinib cream resulted in improvement in facial and total body repigmentation and was well tolerated. The frequency of adverse events was low, and none were considered to be related to the treatment. Study limitations include the open-label design and that a relatively small number of patients received concomitant ruxolitinib cream and NB-UVB, most of whom had fairer skin types (i.e., skin types II—III). In addition, phototherapy regimens were heterogeneous, and variations in sun exposure may have confounded the contribution of NB-UVB phototherapy in this analysis. Additional studies with ruxolitinib cream in combination with NB-UVB phototherapy are planned.

Data availability statement

Incyte (Wilmington, DE) 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 January 1, 2020 in at least one major market (e.g., United States, European Union, Japan). 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

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CONFLICTS OF INTEREST

AGP has served as an investigator for Aclaris Therapeutics, Immune Tolerance Network, Incyte, and Pfizer and as a consultant for AbbVie, Arcutis, Avita

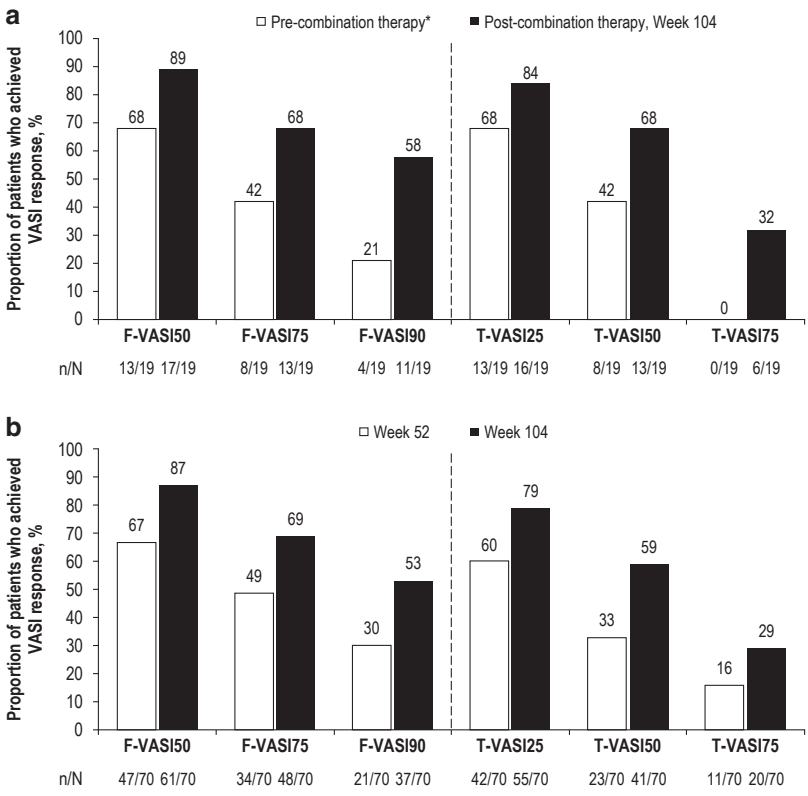

Figure 2. The proportion of patients who achieved VASI response. Response (**a**) before and after a combination of 1.5% ruxolitinib cream BID and NB-UVB phototherapy* (n = 19)† and (**b**) among patients receiving ruxolitinib cream alone (n = 70) at weeks 52 and 104. F-VASI50/75/90 indicates ≥50/≥75/≥90% improvement in facial VASI. T-VASI25/50/75 indicates ≥25/≥50/≥75% improvement in total body VASI. Asterisk (*) indicates that patients could start combination phototherapy at any time after the week 52 study visit. The dagger symbol (†) includes all treatment groups, including patients who received vehicle and 0.15% ruxolitinib cream QD through week 24. BID, twice daily; F-VASI, facial Vitiligo Area Scoring Index; NB-UVB, narrow-band UVB; QD, once daily; T-VASI, total body Vitiligo Area Scoring Index; VASI, Vitiligo Area Scoring Index.

Medical, Chromaderm, Immune Tolerance Network, Incyte, Pfizer, TWi, Viela Bio, and Villaris and also holds stock options for Tara Medical and Zerigo Health. JEH 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, 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 the treatment of vitiligo, Jak inhibition with light therapy for vitiligo, and CXCR3 antibody depletion for treatment of vitiligo. ML is an employee of Mount Sinai Hospital (New York, NY), which receives research funds from AbbVie, Amgen, Arcutis, Avotres, Boehringer Ingelheim, Dermavant Sciences, Eli Lilly, Incyte, Janssen Research & Development, LLC, Ortho Dermatologics, Regeneron, and UCB, and is a consultant for Aditum Bio, Almirall, AnaptysBio, Arcutis, Aristea, Arrive Technology, Avotres Therapeutics, BioMX, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Castle Biosciences, Corrona, Dermavant Sciences, Dr. Reddy's Laboratories, Evelo, Evommune, Facilitate International Dermatologic Education, Forte, Foundation for Research and Education in Dermatology, Helsinn, LEO Pharma, Meiji Seika Pharma, Mindera, Pfizer, and Verrica. IHH has served as an advisory board member for AbbVie; a consultant for Boehringer Ingelheim, Clarify Medical, Galderma Laboratories LP, Incyte, Pfizer, and UCB; a principal investigator for Avita, Bayer, Estée Lauder, Ferndale Laboratories, Incyte, Lenicura, L'Oréal, Pfizer, and Unigen; a subinvestigator for Arcutis; a president of the HS Foundation; and a cochair of the Global Vitiligo Foundation. KB and SW are employees and shareholders of Incyte. FIK was an employee and shareholder of Incyte at the time this study was conducted. DR has received honoraria as a consultant for AbbVie, Abcuro, AltruBio, Boehringer Ingelheim, Bristol MyersSquibb, Celgene, Concert, Dermavant Sciences, Dermira, Incyte, Janssen, Kyowa Kirin, Lilly, Novartis, Pfizer, Regeneron, Sanofi, Sun Pharmaceuticals, UCB, and VielaBio; has received research support from AbbVie, Amgen, Bristol Meyers Squibb, Celgene, Dermira, Galderma, Incyte, Janssen, Lilly, Merck, Novartis, Pfizer, and Regeneron; and has served as a paid speaker for AbbVie, Amgen, Celgene, Janssen, Lilly, Novartis, Pfizer, Regeneron, and Sanofi.

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AUTHOR CONTRIBUTIONS

Conceptualization: AGP, IHH, KB, FIK; Data Curation: FIK; Formal Analysis: FIK; Investigation: JEH, ML, DR; Project Administration: JEH, ML, KB; Supervision: JEH, ML, KB; Validation: IHH, KB, FIK, SW; Writing - Original Draft Preparation: AGP, JEH, ML, IHH, KB, FIK, SW, DR; Writing - Reviewing and Editing: AGP, JEH, ML, IHH, KB, FIK, SW, DR

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2022.05.1093

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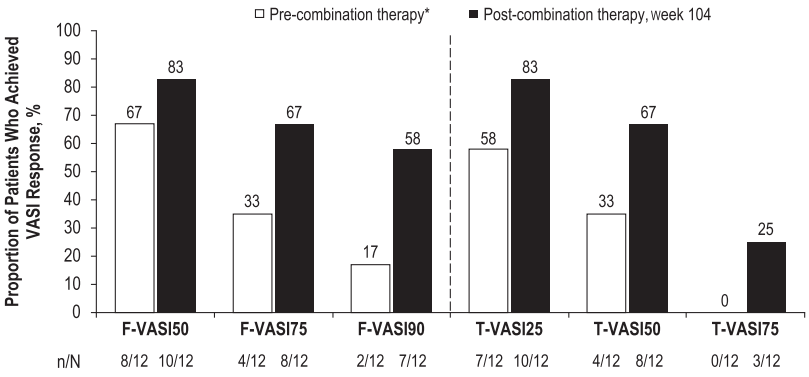
SUPPLEMENTARY MATERIALS



Supplementary Figure S1. The proportion of patients who achieved VASI response before and after a combination of 1.5% ruxolitinib cream BID and NB-UVB phototherapy* among patients who had not achieved F-VASI50 at week 24 (n = 12)†. F-VASI50/75/90 indicates ≥50/≥75/≥90% improvement in facial VASI. T-VASI25/50/75 indicates ≥25/≥50/≥75% improvement in total body VASI. Asterisk (*) indicates that patients could start combination phototherapy at any time after the week 52 study visit. The dagger symbol (†) indicates patients who received any dose of ruxolitinib cream since day 1. BID, twice daily; F-VASI, facial Vitiligo Area Scoring Index; NB-UVB, narrow-band UVB; T-VASI, total body Vitiligo Area Scoring Index; VASI, Vitiligo Area Scoring Index.

Supplementary Table S1. Patient Demographics and Baseline Disease Characteristics among Patients Who Received a Combination of 1.5% Ruxolitinib Cream BID and NB-UVB Phototherapy after Week 52

Parameter	All Patients (N = 19)	Patients Who Had Not Achieved F-VASI50 at Week 24 (n = 12)
Age, mean (SD), y	47.2 (10.8)	45.4 (11.9)
Male, n (%)	12 (63.2)	8 (66.7)
White, n (%)	15 (78.9)	10 (83.3)
Skin type, n (%)		
I	0	0
II	5 (26.3)	5 (41.7)
III	8 (42.1)	4 (33.3)
IV	3 (15.8)	1 (8.3)
V	0	0
VI	3 (15.8)	2 (16.7)
Baseline F-VASI, mean (SD)	1.39 (0.91)	1.51 (0.98)
Baseline T-VASI, mean (SD)	17.0 (11.9)	19.0 (13.8)
Facial BSA,[1] mean (SD), %	1.43 (0.9)	1.54 (1.0)
Total BSA, mean (SD), %	19.5 (12.9)	22.2 (14.8)
Disease duration, median (range), y	23.0 (3.0–56.8)	25.5 (3.0–56.8)
Diagnosed in childhood, n (%)	4 (21.1)	3 (25.0)
Other autoimmune disorders,[2] n (%)	4 (21.1)	3 (25.0)
Previous therapy, n (%)		
Topical corticosteroids	11 (57.9)	6 (50.0)
Topical calcineurin inhibitors	11 (57.9)	5 (41.7)
Phototherapy[3]	15 (78.9)	8 (66.7)
Duration of concomitant ruxolitinib cream and NB-UVB phototherapy, mean (range), wk	40 (15–51)	39 (15–47)
Frequency of NB-UVB during concomitant ruxolitinib cream therapy, n (%)		
Once weekly	1 (5.3)	0
Twice weekly	7 (36.8)	4 (33.3)
Thrice weekly	9 (47.4)	6 (50.0)
Every other day	2 (10.5)	2 (16.7)

Abbreviations: BID, twice daily; BSA, body surface area; F-VASI, facial Vitiligo Area Scoring Index; NB-UVB, narrow-band UVB; PUVA, psoralen UVA; T-VASI, total body Vitiligo Area Scoring Index.
F-VASI50 indicates ≥50% improvement in F-VASI.
[1]Percentage of total BSA.
[2]Thyroid disorders for all patients.
[3]Phototherapy includes NB-UVB phototherapy, excimer laser, and PUVA photochemotherapy.

Supplementary Table S2. Initial Treatment Groups among Patients Who Received a Combination of 1.5% Ruxolitinib Cream BID and NB-UVB Phototherapy after Week 52

Treatment Group, n (%)[1]	All Patients (N = 19)	Patients Who Had Not Achieved F-VASI50 at Week 24 (n = 12)[2]
Day 1—week 24		
Vehicle	3 (15.8)	N/A
0.15% QD	4 (21.1)	4 (33.3)
0.5% QD	6 (31.6)	4 (33.3)
1.5% QD	3 (15.8)	2 (16.7)
1.5% BID	3 (15.8)	2 (16.7)
Weeks 24—52		
0.15% QD	2 (10.5)	2 (16.7)
0.5% QD	7 (36.8)	4 (33.3)
1.5% QD	5 (26.3)	3 (25.0)
1.5% BID	5 (26.3)	3 (25.0)

Abbreviations: BID, twice daily; BSA, body surface area; F-VASI, facial Vitiligo Area Scoring Index; N/A, not applicable; NB-UVB, narrow-band UVB; QD, once daily.

F-VASI50 indicates ≥50% improvement in F-VASI.

[1]At week 24, patients in the vehicle group as well as patients in the 0.15% ruxolitinib cream QD group who did not achieve ≥25% improvement from baseline in F-VASI were rerandomized to one of the three higher ruxolitinib cream dose groups to week 52. Patients initially randomized to one of the three higher ruxolitinib cream groups remained in their group to week 52. After week 52, all patients applied 1.5% ruxolitinib cream BID.

[2]Patients who received any dose of ruxolitinib cream since day 1.

Supplementary Table S3. The Proportion of Patients Treated with Ruxolitinib Cream Alone Who Achieved VASI Response at Weeks 52 and 104

Patients, %	Visit	F-VASI50	F-VASI75	F-VASI90	T-VASI25	T-VASI50	T-VASI75
All patients (N = 70)[1]	Week 52	67	49	30	60	33	16
	Week 104	87	69	53	79	59	29
Received 1.5% ruxolitinib cream BID (n = 16)[2]	Week 52	69	63	31	75	31	13
	Week 104	94	75	56	88	69	31
Had not achieved F-VASI50 at week 24 (n = 29)[3]	Week 52	41	28	14	34	14	3
	Week 104	76	48	38	52	38	17

Abbreviations: BID, twice daily; F-VASI, facial Vitiligo Area Scoring Index; NB-UVB, narrow-band UVB; QD, once daily; T-VASI, total body Vitiligo Area Scoring Index; VASI, Vitiligo Area Scoring Index.

F-VASI50/75/90 indicates ≥50/≥75/≥90% improvement in F-VASI, and T-VASI25/50/75 indicates ≥25/≥50/≥75% improvement in T-VASI.

[1]Includes all treatment groups, including patients who received vehicle and 0.15% ruxolitinib cream QD through week 24.

[2]Patients who received 1.5% ruxolitinib cream BID since day 1.

[3]Patients who received any dose of ruxolitinib cream since day 1.

Supplementary Table S4. Patient-Level AEs Reported after Receiving Concomitant NB-UVB Phototherapy

Patient	NB-UVB Frequency	AE[1]
1	Twice weekly	Anxiety, blurred vision, abnormal coordinating, insomnia, migraine, muscular weakness, muscle twitching, myalgia, sleep disorder, upper respiratory infection
2	Thrice weekly	Abdominal wall abscess, hyperglycemia, tooth infection
3	Twice weekly	Sinus congestion
4	Every other day	Application site dermatitis, salpingectomy

Abbreviations: AE, adverse event; NB-UVB, narrow-band UVB.
[1]No AEs were considered to be related to treatment.