27568

Maintenance of Repigmentation After Discontinuation of Ruxolitinib Cream in Patients With Vitiligo

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Background

- Vitiligo is a chronic autoimmune disease resulting in skin depigmentation[1,2]
- Disease pathogenesis is mediated by interferon-γ through the chemokines C-X-C motif chemokine ligand (CXCL) 9 and CXCL10, a signaling pathway regulated by Janus kinase (JAK) 1 and JAK2[3,4]
- Treatment with ruxolitinib cream (JAK1/JAK2 inhibitor) in adult patients with vitiligo resulted in substantial repigmentation over 52 weeks in a phase 2, randomized, dose-ranging study[5]

Objective

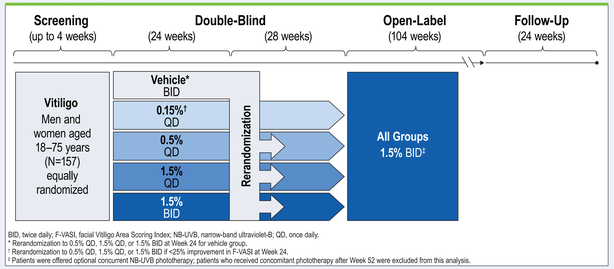
- To describe maintenance of repigmentation among responders following ruxolitinib cream discontinuation in a phase 2 study and explore baseline differences in biomarkers between patients who maintained or lost repigmentation

Methods

Patients and Study Design

- This phase 2 study (NCT03099304) enrolled adult patients (aged 18–75 years) with vitiligo that included depigmentation ≥0.5% of body surface area (BSA) on the face and ≥3% of BSA on nonfacial areas
- Key exclusion criteria included dermatologic disease confounding vitiligo assessment, previous use of JAK inhibitor therapy, and use of the following therapies for vitiligo: any biological or experimental therapy within 12 weeks (or 5 half-lives) of screening, phototherapy within 8 weeks of screening, or immunomodulating treatments within 4 weeks of screening
- Patients were equally randomized to receive ruxolitinib cream (1.5% twice daily [BID], 1.5% once daily [QD], 0.5% QD, or 0.15% QD) or vehicle BID for 24 weeks (**Figure 1**)
  - Patients were instructed to treat lesions constituting ≤20% of baseline total BSA for the duration of the study
- After 24 weeks, patients either were rerandomized (patients who initially received vehicle and those treated with 0.15% ruxolitinib cream QD who did not achieve ≥25% improvement from baseline in facial Vitiligo Area Scoring Index [F-VASI] at Week 24) to 1 of the 3 higher ruxolitinib cream doses or maintained their original dose until Week 52
- After Week 52, patients who completed baseline, Week 24, and Week 52 assessments could continue to receive open-label treatment with 1.5% ruxolitinib cream BID for an additional 104 weeks (total treatment duration of up to 156 weeks)
  - Patients were offered optional concomitant narrow-band ultraviolet-B (NB-UVB) phototherapy while continuing open-label treatment with 1.5% ruxolitinib cream BID (refer to poster 27636 for analyses of concomitant ruxolitinib cream and NB-UVB phototherapy); patients who received concomitant phototherapy after Week 52 were excluded from this analysis

Figure 1. Study Design



BID, twice daily; F-VASI, facial Vitiligo Area Scoring Index; NB-UVB, narrow-band ultraviolet-B; QD, once daily.
* Rerandomization to 0.5% QD, 1.5% QD, or 1.5% BID at Week 24 for vehicle group.
† Rerandomization to 0.5% QD, 1.5% QD, or 1.5% BID if <25% improvement in F-VASI at Week 24.
‡ Patients were offered optional concurrent NB-UVB phototherapy; patients who received concomitant phototherapy after Week 52 were excluded from this analysis.

Assessments

- Maintenance of repigmentation was assessed among responders from the phase 2 study who discontinued ruxolitinib cream after 104 weeks of treatment
- Patients initially randomized to any dose of ruxolitinib cream with evidence of facial repigmentation at Week 24 (ie, F-VASI improvements of >0%) who completed ≥1 follow-up visit 1, 3, or 6 months after 52 weeks of 1.5% ruxolitinib cream BID (Weeks 52–104) were analyzed
- Loss of repigmentation was defined as an increase in Vitiligo Area Scoring Index (VASI) score during the last follow-up visit vs Week 104 on ruxolitinib cream

Statistical Analyses

- Data were summarized using descriptive statistics

Results

Patients

- Of 157 randomized patients, 123 continued treatment during the open-label period, and 22 completed treatment; the open-label treatment period is ongoing
- Sixteen patients who completed treatment at Week 104 and ≥1 follow-up visit at data cutoff were included in the analysis (1.5% BID, n=3; 1.5% QD, n=5; 0.5% QD, n=3; 0.15% QD, n=5 [including 2 patients rerandomized to 1.5% BID or 0.5% QD after Week 24])
  - Mean (SD) age among patients was 48.6 (11.4) years; 56.3% were male and 93.8% were White (**Table 1**)
- Most patients (15 of 16) had 3-month follow-up visits, 1 of whom also completed a 6-month follow-up visit; 1 patient initially randomized to 1.5% ruxolitinib cream QD was lost to follow-up after the 1-month follow-up visit

Table 1. Patient Demographics and Baseline Characteristics

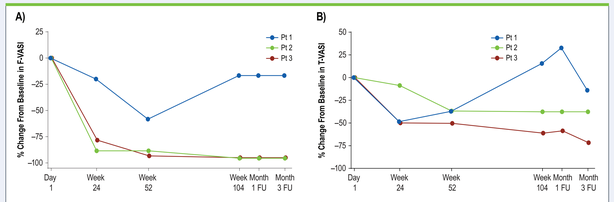
Parameter	Patients n=16
Age, mean (SD), y	48.6 (11.4)
Male, n (%)	9 (56.3)
White, n (%)	15 (93.8)
Skin type, n (%)	
I	1 (6.3)
II	4 (25.0)
III	6 (37.5)
IV	4 (25.0)
V	1 (6.3)
VI	0
Baseline F-VASI, mean (SD)	1.54 (0.99)
Baseline T-VASI, mean (SD)	15.4 (11.6)
Facial BSA,* mean (SD), %	1.78 (0.96)
Total BSA, mean (SD), %	19.1 (12.6)
Disease duration, median (range), y	14.5 (2.6–40.8)
Diagnosed in childhood, n (%)	4 (25.0)
Other autoimmune disorders, n (%)	5 (31.3)
Thyroid disorders	4 (25.0)
Juvenile diabetes mellitus	1 (6.3)
Prior therapy, n (%)	
Topical corticosteroids	9 (56.3)
Calcineurin inhibitors	5 (31.3)
Phototherapy†	5 (31.3)

BSA, body surface area; F-VASI, facial Vitiligo Area Scoring Index; NB-UVB, narrow-band ultraviolet-B; PUVA, psoralen ultraviolet-A; T-VASI, total Vitiligo Area Scoring Index.
* Percentage of total BSA.
† Phototherapy includes NB-UVB phototherapy, excimer laser, and PUVA photochemotherapy.

Maintenance of Repigmentation

- After the last visit on treatment (Week 104), 4 patients (25.0%) experienced loss of total body repigmentation and 3 patients (18.8%) experienced loss of facial repigmentation at the last follow-up visit; 1 of these patients had both facial and total body repigmentation loss
  - Total body repigmentation loss per total VASI (T-VASI) ranged from 1.2% to 9.8%; first occurrence of repigmentation loss ranged from 1 to 6 months
  - Facial repigmentation loss per F-VASI ranged from 4.0% to 98.9%, with first occurrence of repigmentation loss at 3 months; 1 patient did not have a 1-month follow-up visit
- No patients from the 1.5% ruxolitinib cream BID treatment group (with 2 years' exposure) experienced loss of repigmentation at Week 104 vs last follow-up (**Figure 2**)

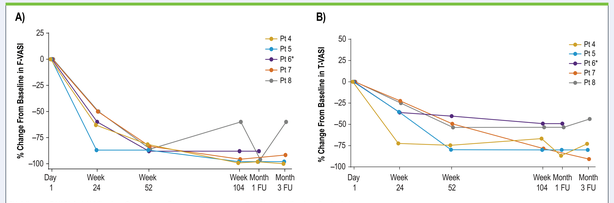
Figure 2. Percentage Change From Baseline in (A) F-VASI and (B) T-VASI Scores Among Patients Initially Randomized to 1.5% Ruxolitinib Cream BID



BID, twice daily; FU, follow-up; F-VASI, facial Vitiligo Area Scoring Index; Pt, patient; T-VASI, total Vitiligo Area Scoring Index.
Data points are staggered on x-axes for visibility of patient-level data.

- Two patients from the 1.5% ruxolitinib cream QD group lost facial or total body repigmentation during follow-up (**Figure 3**)
  - Patient 7 showed minor facial repigmentation loss per F-VASI at the 3-month follow-up vs Week 104 (–91.7% vs –95.7%) but showed improvement in total body repigmentation per T-VASI (–90.8% vs –78.5%)
  - Patient 8 showed some total body repigmentation loss per T-VASI at 3-month follow-up vs Week 104 (–43.7% vs –53.5%) but no facial repigmentation loss per F-VASI (–60.0% vs –60.0%)

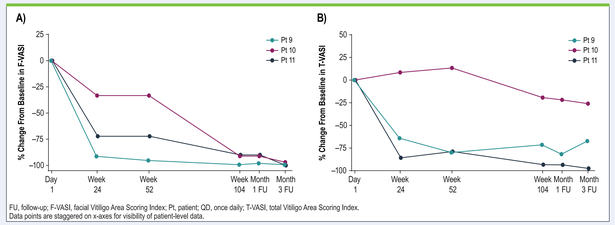
Figure 3. Percentage Change From Baseline in (A) F-VASI and (B) T-VASI Scores Among Patients Initially Randomized to 1.5% Ruxolitinib Cream QD



FU, follow-up; F-VASI, facial Vitiligo Area Scoring Index; Pt, patient; QD, once daily; T-VASI, total Vitiligo Area Scoring Index.
Data points are staggered on x-axes for visibility of patient-level data.
* Patient 6 was lost to follow-up after the 1-month follow-up visit.

- One patient from the 0.5% ruxolitinib cream QD group (patient 9) lost some total body repigmentation per T-VASI at 3-month follow-up vs Week 104 (–67.3% vs –71.5%) but had no facial repigmentation loss per F-VASI (–99.3% vs –99.3%; **Figure 4**)

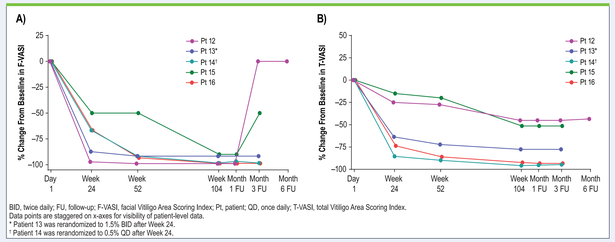
Figure 4. Percentage Change From Baseline in (A) F-VASI and (B) T-VASI Scores Among Patients Initially Randomized to 0.5% Ruxolitinib Cream QD



FU, follow-up; F-VASI, facial Vitiligo Area Scoring Index; Pt, patient; QD, once daily; T-VASI, total Vitiligo Area Scoring Index.
Data points are staggered on x-axes for visibility of patient-level data.

- Three patients from the 0.15% ruxolitinib cream QD group lost facial and/or total body repigmentation during follow-up (**Figure 5**)
  - Patient 12 had complete loss of facial repigmentation per F-VASI at 3- and 6-month follow-ups vs Week 104 (0% vs –98.9%) but only minor total body repigmentation loss per T-VASI at 6-month follow-up (–43.6% vs –45.2%)
  - Patient 14 (rerandomized to 0.5% QD after Week 24) experienced no facial repigmentation loss per F-VASI at 3-month follow-up vs Week 104 (–98.3% vs –98.3%) and only minor total body repigmentation loss per T-VASI (–94.7% vs –95.9%), with repigmentation loss first occurring at 1-month follow-up (–95.3%)
  - Patient 15 showed facial repigmentation loss per F-VASI at 3-month follow-up vs Week 104 (–50.0% vs –90.0%) but no total body repigmentation loss per T-VASI (–51.4% vs –51.4%)
  - Interestingly, patient 13 (rerandomized to 1.5% BID after Week 24) did not experience any loss of facial or total body repigmentation at 3-month follow-up vs Week 104

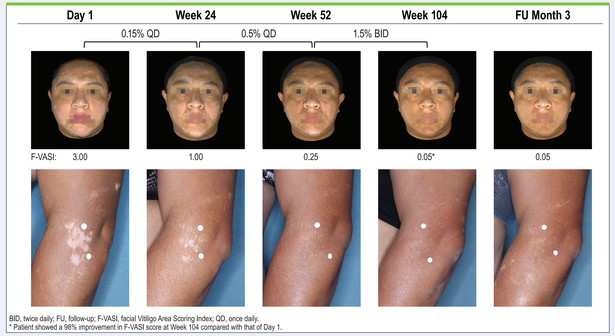
Figure 5. Percentage Change From Baseline in (A) F-VASI and (B) T-VASI Scores Among Patients Initially Randomized to 0.15% Ruxolitinib Cream QD



BID, twice daily; FU, follow-up; F-VASI, facial Vitiligo Area Scoring Index; Pt, patient; QD, once daily; T-VASI, total Vitiligo Area Scoring Index.
Data points are staggered on x-axes for visibility of patient-level data.
* Patient 13 was rerandomized to 1.5% BID after Week 24.
† Patient 14 was rerandomized to 0.5% QD after Week 24.

- Representative clinical images show maintenance of facial repigmentation and minor loss of total body repigmentation in a patient initially randomized to 0.15% ruxolitinib cream QD (**Figure 6**)
  - At the end of treatment (Week 104), the patient had a 98% improvement in F-VASI score compared with baseline

Figure 6. Representative Clinical Images of Patient 14 Initially Randomized to 0.15% Ruxolitinib Cream QD

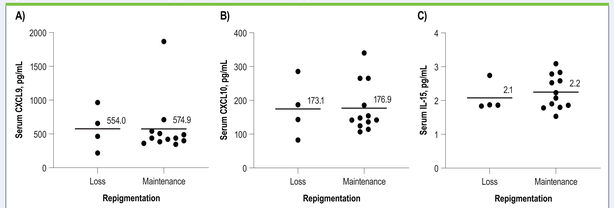


BID, twice daily; FU, follow-up; F-VASI, facial Vitiligo Area Scoring Index; QD, once daily.
* Patient showed a 98% improvement in F-VASI score at Week 104 compared with that of Day 1.

Baseline Differences in Biomarkers

- There were no significant differences in baseline serum levels of CXCL9, CXCL10, or interleukin-15 (IL-15) in patients who experienced loss vs maintenance of repigmentation after ruxolitinib cream discontinuation (**Figure 7**)
  - CXCL9 and CXCL10 are biomarkers of vitiligo activity; both are increased in the serum of patients with vitiligo vs healthy controls and in patients with active vs stable vitiligo[6]
  - IL-15 may be a biomarker of vitiligo severity, with elevated serum levels in patients with vitiligo vs healthy controls[7]

Figure 7. Baseline Serum Levels of (A) CXCL9, (B) CXCL10, and (C) IL-15



CXCL9/10, C-X-C motif chemokine ligand 9/10; IL-15, interleukin-15.
Horizontal lines indicate mean serum values.

Safety

- Three patients experienced grade 1 or 2 adverse events during follow-up, none of which were related to treatment
  - Reported adverse events were seasonal allergy (0.5% QD initially, n=1), lip swelling (1.5% QD initially, n=1), and influenza (0.15% QD initially, n=1)

Conclusions

- **This exploratory analysis suggests that repigmentation with ruxolitinib cream may be maintained after treatment discontinuation**
  - **Twelve of 16 patients (75.0%) maintained total body repigmentation and 13 (81.3%) maintained facial repigmentation during follow-up of 1 to 6 months**
  - **No patients initially randomized to 1.5% ruxolitinib cream BID (n=3; with 2 years' exposure) experienced loss of repigmentation at the last follow-up**
- **Baseline serum levels of CXCL9, CXCL10, or IL-15 may not be predictive of maintenance of response to ruxolitinib cream**
- **Larger follow-up studies are needed to confirm these findings**

Disclosures

DR has received honoraria as a consultant for AbbVie, Celgene, Dermavant Sciences, Dermira, Eli Lilly and Company, Janssen, Kyowa Kirin, Novartis, Pfizer, Regeneron Pharmaceuticals, Sanofi, Sun Pharmaceuticals, UCB, and VielaBio; research support from AbbVie, Amgen, Bristol Myers Squibb, Celgene, Dermira, Eli Lilly and Company, Incyte Corporation, Janssen, Merck, Novartis, Pfizer, and Regeneron Pharmaceuticals; and has served as a paid speaker for AbbVie, Celgene, Eli Lilly and Company, Janssen, Novartis, Pfizer, Regeneron Pharmaceuticals, and Sanofi. AGP has served as an investigator for Aclaris Therapeutics, Immune Tolerance Network, Incyte Corporation, and Pfizer; a consultant for Arcutis, Avita, Chromaderm, Immune Tolerance Network, Incyte Corporation, Pfizer, Viela Bio, and Villaris; and a board member who also holds stock options for Clarify Medical and Tara Medical. PG has served as a consultant for Aclaris Therapeutics, Clarify Medical, DermaForce, Incyte Corporation, Proctor & Gamble, and Versicolor Technologies and a principal investigator for Aclaris Therapeutics, Allergan/SkinMedica, Clinuvel Pharmaceuticals, Incyte Corporation, Johnson & Johnson, L'Oreal, Merz Pharma, Pfizer, Thync Global Inc., and VT Cosmetics. ML is an employee of Mount Sinai Hospital, which receives research funds from AbbVie, Amgen, Arcutis, Avotres, Boehringer Ingelheim, Dermavant, Eli Lilly, Incyte Corporation, Janssen Research & Development, LLC, Ortho Dermatologics, Regeneron, and UCB, Inc; 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. ABG has received honoraria as an advisory board member and consultant for AnaptysBio, Avotres Therapeutics, Beiersdorf, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Incyte Corporation, Janssen, LEO Pharma, Novartis, Sun Pharmaceuticals, and UCB; has stock options in Xbiotech; and has received institutional research/educational grants from Boehringer Ingelheim, Incyte Corporation, Janssen, Novartis, UCB, Xbiotech, and Sun Pharmaceuticals to Mount Sinai School of Medicine. IH has served as an advisory board member for AbbVie; a consultant for Incyte Corporation, Pfizer, and UCB; a principal investigator for AbbVie, Allergan, Bayer, Clinuvel Pharmaceuticals, Estée Lauder, Ferndale Laboratories, Galderma Laboratories LP, GE Healthcare, Incyte Corporation, Janssen, Janssen Biotech, Johnson & Johnson, Lenicura, LEO Pharma, Pfizer, and Unigen; a subinvestigator for Amgen, Bristol Myers Squibb, Foamix Pharmaceuticals, and Janssen; president of the HS Foundation; and co-chair of the Global Vitiligo Foundation. KB, FIK, SW, and BR are employees and shareholders of Incyte Corporation. 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 Corporation, LEO Pharma, Pfizer, Rheos Medicines, Stiefel/GlaxoSmithKline, Sun Pharmaceuticals, TeVido BioDevices, and Villaris Therapeutics; holds equity in Rheos Medicines, TeVido BioDevices, and Villaris Therapeutics; is a scientific founder of 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.

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