Efficacy and safety of the oral Janus kinase 1 inhibitor povorcitinib in patients with extensive vitiligo in a phase 2, randomized, double-blinded, dose-ranging, placebo-controlled study

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Background: No repigmentation treatments are approved for vitiligo affecting > 10% body surface area.

Objective: To assess efficacy and safety of povorcitinib (oral, selective Janus kinase 1 inhibitor) in extensive nonsegmental vitiligo.

Methods: This double-blinded, placebo-controlled, dose-ranging phase 2 study (NCT04818346) randomized adult patients 1:1:1:1 to once-daily povorcitinib 15, 45, or 75 mg or placebo for 24 weeks. Subsequently, patients received povorcitinib 45 mg (initially randomized to 45 mg) or 75 mg (initially randomized to placebo, 15, or 75 mg) until week 52, followed by 24-week post-treatment follow-up. Primary endpoint was percentage change from baseline in total Vitiligo Area Scoring Index (T-VASI) at week 24.

Results: Of 171 patients (mean total body surface area/T-VASI, 28.2%/25.5) randomized, 82.5% completed the 24-week treatment. At week 24, povorcitinib significantly improved T-VASI from baseline (15 mg,

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Patient consent: All patients provided written informed consent.

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Data sharing statement: Incyte Corporation (Wilmington, DE, USA) is committed to data sharing that advances science and medicine while protecting patient privacy. Qualified external scientific researchers may request anonymized data sets 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 (eg, US, EU, JPN). Data will be available for request after the primary publication or 2 years after the study has ended. Information on Incyte's clinical trial data sharing policy and instructions for submitting clinical trial data requests are available at: https://www.incyte.com/Portals/0/Assets/Compliance%20and%20Transparency/clinical-trial-data-sharing.pdf?ver=2020-05-21-132838-960.

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19.1%; 45 mg, 17.8%; 75 mg, 15.7%) versus placebo (−2.3%; least squares mean povorcitinib vs placebo, $P < .01$). Continuous improvement was observed through week 52. Incidence of grade ≥ 3 treatment-emergent adverse events was similar across treatment groups, with no new safety signals.

Limitations: Limited demographic diversity.

Conclusion: Povorcitinib demonstrated substantial total body and facial repigmentation in adult patients with extensive nonsegmental vitiligo and was generally well tolerated through 52 weeks of treatment. (J Am Acad Dermatol 2025;93:946-55.)

Key words: clinical trial; double-blind; efficacy; F-VASI; INCB054707; JAK1 inhibitor; JAK/STAT signaling; oral administration; placebo-controlled; povorcitinib; randomized; safety; skin repigmentation; T-VASI; vitiligo.

INTRODUCTION

Vitiligo is a chronic autoimmune disease characterized by depigmented patches of skin due to progressive loss of melanocytes.[1] The estimated worldwide prevalence of vitiligo (0.2% to 0.5%) varies geographically.[2] Nonsegmental vitiligo (NSV) can have an unpredictable disease course and negative psychosocial impact on many patients, causing feelings of stigmatization[3] and affecting quality of life (QoL).[4,5]

CAPSULE SUMMARY

- Orally administered systemic Janus kinase 1 inhibitors may represent promising treatment options for patients with extensive vitiligo.
- Povorcitinib (oral, selective Janus kinase 1 inhibitor) was generally well tolerated and produced substantial facial and total body repigmentation over 52 weeks of treatment, supporting continued investigation in phase 3 trials.

Vitiligo pathogenesis is largely regulated by interferon gamma−chemokine axis activation of the Janus kinase (JAK)/signal transducer and activator of transcription pathway.[1,6-8] Because interferon gamma signaling requires the JAK−signal transducer and activator of transcription pathway, targeted JAK inhibition was proposed as an effective strategy for vitiligo treatment. Ruxolitinib (JAK1/JAK2 inhibitor) cream is currently the only approved repigmentation therapy for vitiligo, indicated for treatment of lesions covering ≤10% body surface area in patients aged ≥12 years.[9] Povorcitinib, an oral, selective JAK1 inhibitor, may represent a promising therapy for patients with more extensive NSV. Here, efficacy and safety of povorcitinib were evaluated over 52 weeks of treatment in a phase 2 study of adult patients with extensive NSV (NCT04818346).

METHODS

Study design and patients

This multicenter, parallel-group, randomized, double-blinded, placebo-controlled, dose-ranging phase 2 study of povorcitinib in vitiligo was conducted in the United States and Canada. Eligible patients were aged 18-75 years with a clinical diagnosis of NSV and depigmented areas that included ≥0.5% facial body surface area (F-BSA), ≥8% total body surface area (T-BSA), and scores ≥0.5 on facial Vitiligo Area Scoring Index (F-VASI) and ≥8 on total Vitiligo Area Scoring Index (T-VASI; all body regions, including the face). Patients could enroll regardless of vitiligo disease status (recorded signs of disease activity within anatomical regions) or stage (not captured). Full eligibility criteria are provided in Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/52jtsjjd24/1.

An interactive response technology system was used to assign patient identification numbers, track visits, randomize patients per prespecified parameters, and mask treatment group assignments. For the double-blinded, placebo-controlled period, patients were stratified by T-BSA involvement (8% to 20% and >20%) and randomized equally (1:1:1:1) to povorcitinib 15, 45, or 75 mg or matched placebo control once daily for 24 weeks (Supplementary Fig 1, available via Mendeley at https://data.mendeley.com/datasets/52jtsjjd24/1). In the double-blinded treatment extension, patients initially randomized to placebo or povorcitinib 15 mg were allocated to povorcitinib 75 mg, and patients initially randomized to povorcitinib 45 or 75 mg maintained the same treatment until week 52. Safety follow-up visits were scheduled 4 weeks after the last dose of study drug, with additional post-treatment follow-up visits at 12 and 24 weeks after the last dose of study drug.

The protocol and amendments were reviewed and approved by the independent ethics committee

Abbreviations used:

CPK:	creatine phosphokinase
F-BSA:	facial body surface area
F-VASI:	facial Vitiligo Area Scoring Index
F-VASI50:	≥50% reduction from baseline in F-VASI
F-VASI75:	≥75% reduction from baseline in F-VASI
ITT:	intent-to-treat
JAK:	Janus kinase
LSM:	least squares mean
NSV:	nonsegmental vitiligo
PaGIC-V:	Patient Global Impression of Change—Vitiligo
PRO:	patient-reported outcome
QoL:	quality of life
SAE:	serious adverse event
T-BSA:	total body surface area
TEAE:	treatment-emergent adverse event
T-VASI:	total Vitiligo Area Scoring Index
T-VASI50:	≥50% reduction from baseline in T-VASI
VNS:	Vitiligo Noticeability Scale

or institutional review board at each study center. This study was conducted in compliance with the Declaration of Helsinki, study protocol, applicable Good Clinical Practice, and all applicable laws and regulations. All patients provided written informed consent. Patients and investigators remained blinded to treatment assignments during the placebo-controlled and extension periods of the study. The study sponsor remained blinded through completion of the placebo-controlled period and was unblinded after primary database lock.

Endpoints and assessments

The primary endpoint was the percentage change from baseline in T-VASI at week 24. The key secondary endpoint was the percentage of patients achieving ≥50% reduction from baseline in T-VASI (T-VASI50) at week 24. Safety and tolerability were assessed as the secondary endpoint, including evaluation of the incidence and severity of treatment-emergent adverse events (TEAEs) and monitoring of laboratory data.

Additional endpoints included percentage change from baseline in T-VASI and F-VASI through week 52 and the percentage of patients achieving T-VASI and F-VASI milestones of ≥50%/≥75%/≥90% reduction from baseline (T-VASI50/T-VASI75 T-VASI90 and ≥50% reduction from baseline in F-VASI [F-VASI50]/≥75% reduction from baseline in F-VASI [F-VASI75]/≥90% reduction from baseline in F-VASI, respectively) through week 52. Evaluation of post-treatment maintenance of response included the percentage change from baseline in T-VASI and F-VASI through week 76.

Patient-reported outcomes (PROs) and QoL were evaluated at selected study visits through week 52 (Supplementary Methods, available via Mendeley at https://data.mendeley.com/datasets/52jtsjjd24/1). PROs included color-matching, Vitiligo Noticeability Scale (VNS), Patient Global Impression of Change—Vitiligo (PaGIC-V) questionnaires, and the 9-item Treatment Satisfaction Questionnaire for Medication.[10] QoL questionnaires included the Vitiligo-specific QoL,[11] Dermatology Life Quality Index,[12] World Health Organization-Five Well-Being Index,[13] EuroQoL 5-Dimension 5-Level Questionnaire,[14] and Hospital Anxiety and Depression Scale.[15]

Statistical analysis

The planned sample size was 160 patients, based on a 2-sample *t*-test for statistical comparison of the primary efficacy endpoint. Based on results from a previous phase 2 study,[16] mean percentage change from baseline in T-VASI at week 24 was assumed to be −20 for the 45-mg or 75-mg groups and 0 for the placebo group, with a common standard deviation (SD) of 25. Using a 0.05 2-sided alpha, 40 patients/group would have >90% power to detect a difference between either of the highest povorcitinib dose groups and placebo. The planned sample size would also have >80% power to detect a significant difference in T-VASI50 at week 24 with a 0.05 2-sided alpha, assuming response rates of 20% for the 45-mg or 75-mg groups and 1% for the placebo group using a chi-square test.

All randomized patients were included in the intent-to-treat (ITT) population used for summarizing demographics, baseline characteristics, patient disposition, and efficacy analyses. The safety population included all patients who received ≥1 dose of povorcitinib or placebo during the placebo-controlled period. Analyses were conducted with SAS software v9.4. Mean percentage change from baseline in T-VASI at week 24 (primary endpoint; ITT population) was assessed via mixed-effect model for repeated measures with the fixed effect of treatment group, stratification factor (T-BSA, 8% to 20% and >20%), visit (weeks 4, 8, 12, 16, 20, and 24), treatment by visit interaction, and the covariates of baseline measurement and baseline measurement by visit interaction. The variance-covariance matrix of the within-participant errors was modeled as unstructured. A superiority test between each povorcitinib group and placebo was based on least squares

mean (LSM). For T-VASI50 at week 24 (key secondary endpoint; ITT population), exact logistic regression with treatment and stratification factor was used to compare each povorcitinib group versus placebo. Patients with missing postbaseline values up to week 24 were imputed as nonresponders for the dichotomous T-VASI50, F-VASI50, and F-VASI75 endpoints. Analyses of other endpoints and time points were based on observed values without imputation, and no statistical analysis was conducted.

RESULTS

Patients

Between May 6, 2021 and May 24, 2023, 285 patients were screened, 171 randomized (placebo, n = 43; povorcitinib 15 mg, n = 43; 45 mg, n = 43; 75 mg, n = 42), and 168 (98.2%) treated; 141 (82.5%) completed the 24-week placebo-controlled period (Supplementary Fig 2, available via Mendeley at https://data.mendeley.com/datasets/52jtsjjd24/1). Thirty patients (17.5%) discontinued treatment, mostly due to adverse events and lost to follow-up (each n = 8; 4.7%). Of 138 patients entering the extension period, 119 (86.2%) completed through week 52; primary reasons for treatment discontinuation were patient withdrawal (n = 8; 5.8%) and lost to follow-up (n = 4; 2.9%). After treatment completion, 34 patients entered the post-treatment period, with 32 completing the final visit at week 76.

Patients' median (range) age was 50 (23-74) years, and 54.4% (93/171) were female (Table I). Fifty (29.2%) patients had Fitzpatrick skin type II, 55 (32.2%) type III, and 35 (20.5%) type IV, with 114 (66.7%) having fairer skin (types I-III) and 57 (33.3%) having darker skin (types IV-VI). Mean (SD) disease duration was 19.4 (14.0) years, and 49 (28.7%) patients reported a family history of vitiligo. Baseline mean (SD) T-VASI and F-VASI were 25.5 (19.1) and 1.31 (0.77), respectively. F-BSA >1.5% was observed in 64 (37.4%) patients, and T-BSA >20% and >50% in 90 (52.6%) and 25 (14.6%) patients, respectively. Nearly half (48.0%) of patients had ≥1 active lesion in ≥1 anatomic area. Forty-seven patients (27.5%) reported thyroid disorders, and many reported using previous treatments for NSV, including topical corticosteroids (51.5%), topical calcineurin inhibitors (37.4%), and narrowband ultraviolet B phototherapy (34.5%; Supplementary Table II, available via Mendeley at https://data.mendeley.com/datasets/52jtsjjd24/1).

Efficacy

At week 24, percentage improvement from baseline in T-VASI (primary endpoint) was statistically superior in patients receiving any dose of povorcitinib versus placebo (15 mg, 19.1%; 45 mg, 17.8%; 75 mg, 15.7%; placebo, −2.3%; all LSM povorcitinib vs placebo, $P < .01$; Fig 1). Following protocol-defined dose change after week 24 for the extension period, continued improvements in T-VASI were seen through week 52 of treatment. Patients who crossed over from placebo to povorcitinib 75 mg showed improvements in T-VASI during the extension period. Percentage improvement from baseline in F-VASI was statistically superior in patients treated with any dose of povorcitinib versus placebo at week 24 (15 mg, 27.7%; 45 mg, 36.4%; 75 mg, 29.4%; placebo, 5.1%; all LSM povorcitinib vs placebo, $P < .01$) and continued to improve through week 52 (Fig 2). Patients who crossed over from placebo to povorcitinib 75 mg after week 24 showed improvements in F-VASI during the extension period. After completion of study treatment at week 52, T-VASI and F-VASI improvements were maintained through week 76 in the post-treatment period in a subset of patients (Figs 1 and 2).

The key secondary endpoint, T-VASI50 at week 24, was achieved by more patients who received povorcitinib (15 mg, 9.3%; 45 mg, 11.6%; 75 mg, 4.8%) versus placebo (2.3%), but this did not reach statistical significance (odds ratio [95% confidence interval]: 15 mg, 4.3 [0.4-221.0]; 45 mg, 5.5 [0.6-273.5]; 75 mg, 2.1 [0.1-126.4]; all $P > .05$). T-VASI50 responses continued to improve through week 52 of treatment (Table II). Similar trends were observed for T-VASI75 and T-VASI90. Additionally, more patients who received povorcitinib achieved F-VASI50, F-VASI75, and F-VASI90 (Table II) versus placebo at week 24 and continued to improve through week 52. Representative clinical images of facial and body repigmentation are shown in Supplementary Fig 3, available via Mendeley at https://data.mendeley.com/datasets/52jtsjjd24/1.

Improvements in PROs were observed with povorcitinib administration through week 52 (Supplementary Results, available via Mendeley at https://data.mendeley.com/datasets/52jtsjjd24/1), including color matching, VNS, facial and total PaGIC-V (Supplementary Figs 4 to 6, available via Mendeley at https://data.mendeley.com/datasets/52jtsjjd24/1), and Treatment Satisfaction Questionnaire for Medication (Supplementary Table III, available via Mendeley at https://data.mendeley.com/datasets/52jtsjjd24/1). However, no meaningful improvements were observed in QoL measures, including the Vitiligo-specific QoL, Dermatology Life Quality Index, and Hospital Anxiety and Depression Scale measures (Supplementary Table III, available via Mendeley at https://data.mendeley.com/datasets/52jtsjjd24/1).

Table I. Patient demographics and clinical characteristics at baseline

Characteristic	Placebo (*n* = 43)	Povorcitinib 15 mg (*n* = 43)	Povorcitinib 45 mg (*n* = 43)	Povorcitinib 75 mg (*n* = 42)	Total (*N* = 171)
Age, median (range), y	51.0 (24-72)	45.0 (23-67)	51.0 (25-72)	52.5 (24-74)	50.0 (23-74)
Female, *n* (%)	24 (55.8)	29 (67.4)	21 (48.8)	19 (45.2)	93 (54.4)
Race, *n* (%)					
White	34 (79.1)	32 (74.4)	38 (88.4)	28 (66.7)	132 (77.2)
Black	2 (4.7)	3 (7.0)	1 (2.3)	3 (7.1)	9 (5.3)
Asian	2 (4.7)	4 (9.3)	0	7 (16.7)	13 (7.6)
Other	5 (11.6)	4 (9.3)	4 (9.3)	4 (9.5)	17 (9.9)
Hispanic, *n* (%)	8 (18.6)	6 (14.0)	11 (25.6)	7 (16.7)	32 (18.7)
Fitzpatrick skin type, *n* (%)					
I	2 (4.7)	2 (4.7)	4 (9.3)	1 (2.4)	9 (5.3)
II	13 (30.2)	10 (23.3)	13 (30.2)	14 (33.3)	50 (29.2)
III	13 (30.2)	14 (32.6)	18 (41.9)	10 (23.8)	55 (32.2)
IV	11 (25.6)	11 (25.6)	4 (9.3)	9 (21.4)	35 (20.5)
V	4 (9.3)	6 (14.0)	3 (7.0)	8 (19.0)	21 (12.3)
VI	0	0	1 (2.3)	0	1 (0.6)
F-VASI, mean (SD)	1.49 (0.77)	1.30 (0.75)	1.33 (0.80)	1.13 (0.74)	1.31 (0.77)
F-VASI >1.5, *n* (%)	17 (39.5)	14 (32.6)	15 (34.9)	9 (21.4)	55 (32.2)
T-VASI, mean (SD)	28.3 (21.5)	27.1 (20.1)	23.6 (19.8)	22.7 (14.2)	25.5 (19.1)
T-VASI >20, *n* (%)	22 (51.2)	22 (51.2)	16 (37.2)	20 (47.6)	80 (46.8)
T-VASI >50, *n* (%)	8 (18.6)	5 (11.6)	4 (9.3)	2 (4.8)	19 (11.1)
F-BSA,* mean (SD), %	1.62 (0.84)	1.41 (0.81)	1.45 (0.81)	1.20 (0.75)	1.42 (0.81)
F-BSA >1.5%, *n* (%)	20 (46.5)	16 (37.2)	18 (41.9)	10 (23.8)	64 (37.4)
T-BSA, mean (SD), %	30.6 (23.2)	30.8 (20.9)	25.5 (20.2)	25.8 (15.9)	28.2 (20.2)
T-BSA >20%, *n* (%)	22 (51.2)	25 (58.1)	21 (48.8)	22 (52.4)	90 (52.6)
T-BSA >50%, *n* (%)	9 (20.9)	9 (20.9)	5 (11.6)	2 (4.8)	25 (14.6)
Duration of disease, mean (SD), y	19.5 (14.0)	17.6 (13.0)	19.9 (15.5)	20.5 (13.7)	19.4 (14.0)
Disease activity,† *n* (%)					
≥1 active lesion in ≥1 anatomic area	22 (51.2)	23 (53.5)	21 (48.8)	16 (38.1)	82 (48.0)
≥1 active lesion in ≥2 anatomic areas	18 (41.9)	18 (41.9)	17 (39.5)	11 (26.2)	64 (37.4)
≥1 active lesion on face	11 (25.6)	10 (23.3)	13 (30.2)	5 (11.9)	39 (22.8)
Vitiligo family history, *n* (%)	15 (34.9)	9 (20.9)	11 (25.6)	14 (33.3)	49 (28.7)

F-BSA, Facial body surface area; *F-VASI*, facial Vitiligo Area Scoring Index; *SD*, standard deviation; *T-BSA*, total body surface area; *T-VASI*, total Vitiligo Area Scoring Index.

*Percentage of total BSA.

†Each VASI anatomic area was assessed for the presence of confetti-like depigmentation (yes/no), Koebner phenomenon (yes/no), and/or hypochromic areas/borders (trichrome lesions; yes/no).

Safety

During the placebo-controlled period, 74.6% of all povorcitinib-treated patients and 57.1% of placebo-treated patients reported any TEAE (Table III). The most common TEAEs with povorcitinib were COVID-19, headache, fatigue, increased blood creatine phosphokinase (CPK), and acne. No cases of increased blood CPK were associated with clinical symptoms (Supplementary Table IV, available via Mendeley at https://data.mendeley.com/datasets/52jtsjjd24/1), and all acne cases were grade 1 or 2. No cases of herpes zoster, malignancies, or thromboembolic events were reported during placebo control. A total of 13 grade ≥3 TEAEs and 2 serious adverse events (SAEs) (COVID-19 infection [*n* = 1] and substance-induced psychotic disorder [*n* = 1]) were reported by povorcitinib-treated patients, but none were deemed by investigators to be related to treatment (Supplementary Results, available via Mendeley at https://data.mendeley.com/datasets/52jtsjjd24/1).

The safety profile of povorcitinib remained consistent during treatment extension through week 52 (Table III and Supplementary Table IV, available via Mendeley at https://data.mendeley.com/datasets/52jtsjjd24/1), and no fatal TEAEs occurred. The most common TEAEs were COVID-19, increased blood CPK, acne, and nasopharyngitis. Three patients developed localized herpes zoster of grades 1 (*n* = 1) or 2 (*n* = 2) during treatment

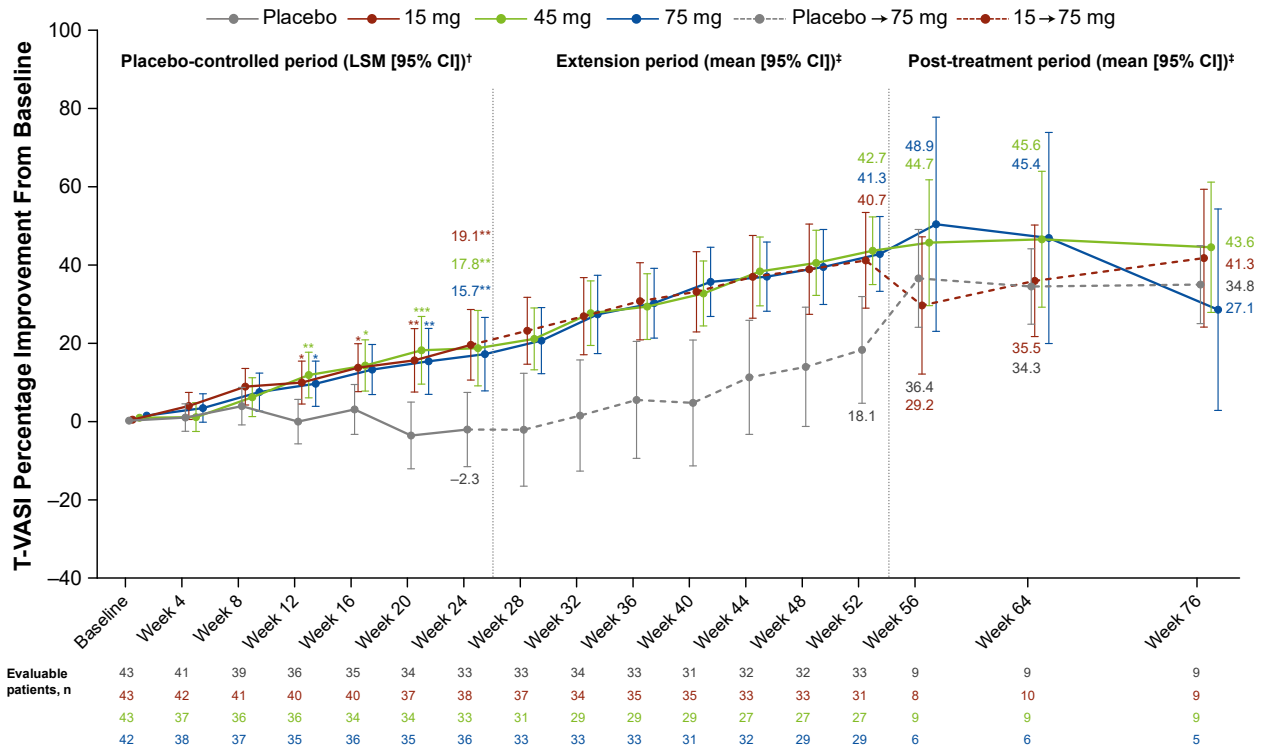

Fig 1. Povorcitinib efficacy assessed by T-VASI in patients with vitiligo. Efficacy of povorcitinib in T-VASI percentage improvement from baseline to week 52 in the treatment period (primary endpoint) and from baseline to week 76 in the post-treatment period (exploratory endpoint). *CI*, Confidence interval; *LSM*, least squares mean; *T-VASI*, total Vitiligo Area Scoring Index. *$P < .05$, **$P < .01$, ***$P < .001$, LSM difference for povorcitinib versus placebo. †LSM was calculated with mixed model repeated measures without imputation for missing values. ‡Data were reported as observed with no imputation, and no statistical analysis was conducted. Data points are offset to avoid overlap.

extension; none were considered serious and all resolved (Supplementary Results, available via Mendeley at https://data.mendeley.com/datasets/52jtsjjd24/1). No other new safety signals or SAEs were observed after week 24.

There were no clinically relevant changes in laboratory values throughout 52 weeks of treatment, and most patients had normal hematology parameters; observed laboratory abnormalities in CPK were asymptomatic. There were no clinically meaningful trends in hemoglobin or platelet levels over time.

DISCUSSION

This randomized, controlled phase 2 study evaluated povorcitinib, an oral, selective JAK1 inhibitor, in patients with extensive vitiligo with no upper limit on the percentage of affected body surface area. This is the first study to use percentage change in T-VASI as the primary outcome measure and to collect follow-up data for 24 weeks post-treatment. This trial included a large percentage of patients with more extensive disease (F-BSA >1.5% in 37.4% of patients; T-BSA >20% in 52.6%) and is thus inherently challenging to treat. In patients with extensive NSV, povorcitinib demonstrated substantial total body and facial repigmentation, showing similar efficacy across doses without dose effect. Povorcitinib treatment at all doses produced superior improvements in T-VASI and F-VASI at week 24 compared with placebo control, which is a positive milestone for patients with extensive NSV following only 6 months of treatment.

Larger percentages of patients who received any dose of povorcitinib versus placebo achieved T-VASI50, F-VASI50, and F-VASI75 at week 24. Although there were no statistically significant changes in T-VASI50 responses with povorcitinib versus placebo at week 24, longer duration of therapy is generally required for nonfacial repigmentation,[16] and 6 months may not be sufficient to achieve this endpoint. After 52 weeks of continuous therapy, patients originally randomized to povorcitinib showed continued improvement in repigmentation without reaching a treatment plateau. The high

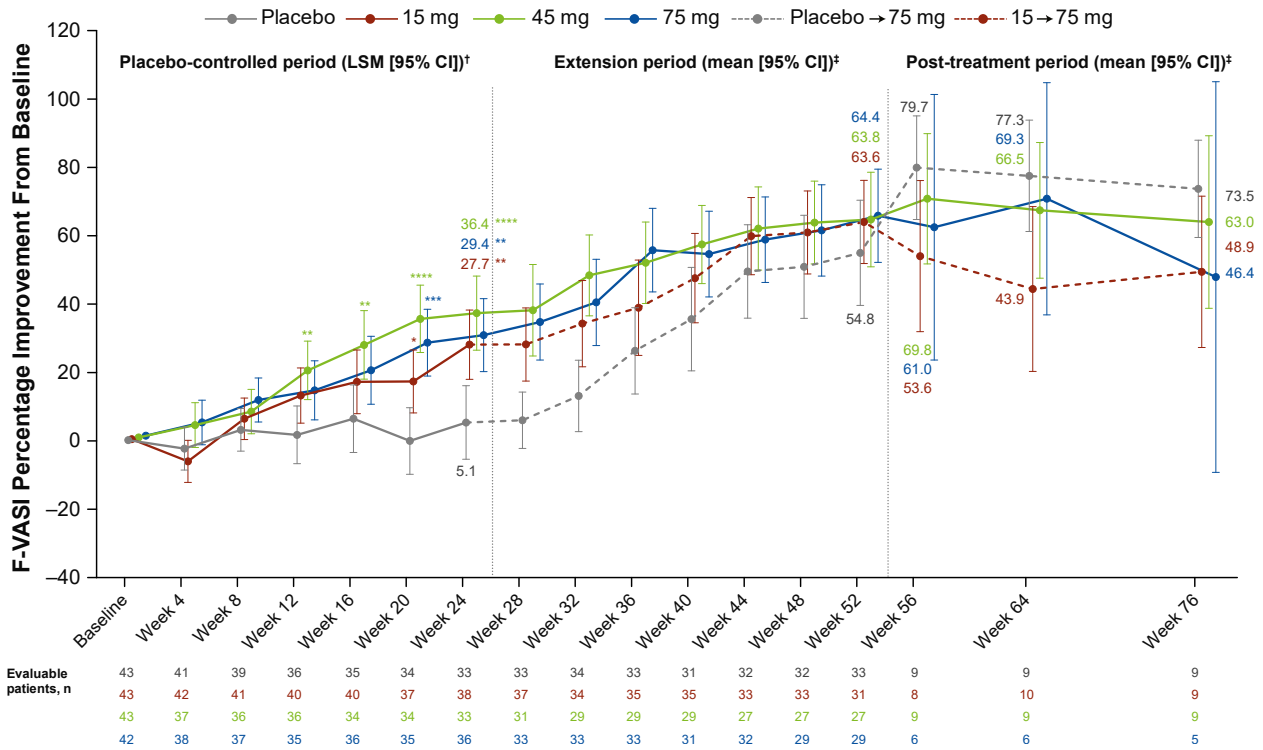

Fig 2. Povorcitinib efficacy assessed by F-VASI in patients with vitiligo. Efficacy of povorcitinib in F-VASI percentage improvement from baseline to week 52 in the treatment period and from baseline to week 76 in the post-treatment period (exploratory endpoints). *CI*, Confidence interval; *F-VASI*, Facial Vitiligo Area Scoring Index; *LSM*, least squares mean. $^{**}P < .01$, $^{***}P < .001$, $^{****}P < .0001$, LSM difference for povorcitinib versus placebo. †LSM was calculated with mixed model repeated measures without imputation for missing values. ‡Data were reported as observed with no imputation, and no statistical analysis was conducted. Data points are offset to avoid overlap.

rates of T-VASI50 and F-VASI75 at week 52 in particular are encouraging, as these response thresholds are considered treatment successes by patients and clinicians.[17] Among patients randomized to placebo, those who crossed over to povorcitinib after week 24 also showed improvement at week 52. Additionally, improvements in total body and facial repigmentation were maintained in a subset of patients for 24 weeks (week 52 to 76) after stopping povorcitinib treatment, although sample sizes during post-treatment follow-up were small, and findings need to be confirmed in larger populations. PROs of color matching, VNS, and PaGIC-V responses suggest povorcitinib efficacy was meaningful to patients, although QoL improvements were minimal. Given the continuous clinical improvement without plateau, longer-term treatment may be required for substantive QoL improvements, although current tools may lack sensitivity to detect small vitiligo changes.[18]

Povorcitinib was generally well tolerated at all doses. No treatment-related SAEs were reported, and grade ≥3 TEAEs occurred at similar incidences across treatment groups. Although blood CPK level was increased in 7.9% of patients during placebo control and 15.2% during treatment extension, it was not associated with any clinical symptoms. Acne, a common adverse event of JAK inhibitors,[19] was observed in 7.1% of patients during placebo control and 13.8% of patients during treatment extension; however, acne did not result in any treatment interruptions or discontinuation. The 3 cases of herpes zoster that occurred during treatment extension were all grade 1 or 2, and none were considered serious. No new safety signals were observed after 24 weeks of treatment.

Limitations include that the study was conducted during the COVID-19 pandemic, which may have contributed to patients being lost to follow-up. Additionally, most enrolled patients were older (median, 50 years), White, and had vitiligo for more than 10 years (mean, 19.4 years). Although randomization was stratified by T-BSA thresholds (8% to 20% and >20%), there were some imbalances across treatment groups for patients. Overall, sample

Table II. Summary of T-VASI and F-VASI responses

Endpoint,* *n* (%)	Placebo → Povorcitinib 75 mg† (*n* = 43)	Povorcitinib 15 mg → 75 mg† (*n* = 43)	Povorcitinib 45 mg (*n* = 43)	Povorcitinib 75 mg (*n* = 42)
T-VASI responses				
T-VASI50				
Week 12	0	1 (2.3)	2 (4.7)	1 (2.4)
Week 24‡	1 (2.3)	4 (9.3)	5 (11.6)	2 (4.8)
Week 36§	1 (3.0)	10 (28.6)	5 (17.2)	5 (15.2)
Week 52‖	5 (15.2)	14 (45.2)	10 (37.0)	11 (37.9)
T-VASI75				
Week 12	0	0	0	0
Week 24‡	0	2 (4.7)	1 (2.3)	1 (2.4)
Week 36§	0	3 (8.6)	1 (3.4)	4 (12.1)
Week 52‖	1 (3.0)	5 (16.1)	2 (7.4)	3 (10.3)
T-VASI90				
Week 12	0	0	0	0
Week 24‡	0	0	0	0
Week 36§	0	0	0	0
Week 52‖	0	2 (6.5)	1 (3.7)	1 (3.4)
F-VASI responses				
F-VASI50				
Week 12	1 (2.3)	4 (9.3)	9 (20.9)	6 (14.3)
Week 24‡	3 (7.0)	7 (16.3)	15 (34.9)¶	10 (23.8)
Week 36§	10 (30.3)	13 (37.1)	17 (58.6)	21 (63.6)
Week 52‖	21 (63.6)	22 (71.0)	21 (77.8)	20 (69.0)
F-VASI75				
Week 12	1 (2.3)	1 (2.3)	2 (4.7)	1 (2.4)
Week 24‡	1 (2.3)	5 (11.6)	6 (14.0)	5 (11.9)
Week 36§	2 (6.1)	8 (22.9)	9 (31.0)	12 (36.4)
Week 52‖	15 (45.5)	15 (48.4)	15 (55.6)	17 (58.6)
F-VASI90				
Week 12	0	1 (2.3)	1 (2.3)	0
Week 24‡	1 (2.3)	2 (4.7)	2 (4.7)	2 (4.8)
Week 36§	0	3 (8.6)	3 (10.3)	5 (15.2)
Week 52‖	6 (18.2)	9 (29.0)	7 (25.9)	10 (34.5)

F-VASI, Facial Vitiligo Area Scoring Index; *F-VASI50*, ≥50% reduction from baseline in F-VASI; *F-VASI75*, ≥75% reduction from baseline in F-VASI; *F-VASI90*, ≥90% reduction from baseline in F-VASI; *T-VASI*, total Vitiligo Area Scoring Index; *T-VASI50*, ≥50% reduction from baseline in T-VASI; *T-VASI75*, ≥75% reduction from baseline in T-VASI; *T-VASI90*, ≥90% reduction from baseline in T-VASI.

*During the placebo-controlled period (up to week 24), missing postbaseline values were imputed as nonresponders; during the extension period (after week 24), responses were reported as observed, and no statistical analyses were conducted.

†Patients receiving placebo and povorcitinib 15 mg crossed over to povorcitinib 75 mg after week 24.

‡At week 24, logistic regression with treatment and stratification factor was used to compare each povorcitinib group versus placebo.

§Evaluable patients at week 36: placebo → 75 mg, *n* = 33; 15 mg → 75 mg, *n* = 35; 45 mg, *n* = 29; 75 mg, *n* = 33.

‖Evaluable patients at week 52: placebo → 75 mg, *n* = 33; 15 mg → 75 mg, *n* = 31; 45 mg, *n* = 27; 75 mg, *n* = 29.

¶$P < .01$ for response rate difference for povorcitinib versus placebo.

sizes in each treatment group ($n \sim 40$ per group) and during post-treatment follow-up ($n \leq 10$ per group) were small, and findings need to be confirmed in larger patient populations.

In conclusion, oral povorcitinib was associated with substantial total body and facial repigmentation in patients with extensive NSV, with confirmed superiority to placebo at 24 weeks, and continued improvement without plateau through 52 weeks of treatment in this phase 2 study. All doses of povorcitinib were generally well tolerated, and no treatment-related SAEs were reported. These data support further evaluation of the efficacy and safety of povorcitinib in the ongoing global phase 3 registrational studies of patients with extensive NSV (STOP-V1, NCT06113445; STOP-V2, NCT06113471).

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Table III. Summary of TEAEs

Placebo-controlled (up to week 24) event, *n* (%)	Placebo (*n* = 42)	Povorcitinib 15 mg (*n* = 43)	Povorcitinib 45 mg (*n* = 41)	Povorcitinib 75 mg (*n* = 42)	Total povorcitinib (*N* = 126)
Any TEAE	24 (57.1)	29 (67.4)	30 (73.2)	35 (83.3)	94 (74.6)
Grade ≥3	4 (9.5)	3 (7.0)	5 (12.2)	5 (11.9)	13 (10.3)
SAE*	1 (2.4)	0	1 (2.4)	1 (2.4)	2 (1.6)
Discontinued due to TEAEs	2 (4.8)	2 (4.7)	2 (4.9)	3 (7.1)	7 (5.6)
Fatal TEAE	0	0	0	0	0
Most common TEAEs†					
COVID-19	5 (11.9)	8 (18.6)	8 (19.5)	6 (14.3)	22 (17.5)
Headache	5 (11.9)	7 (16.3)	1 (2.4)	5 (11.9)	13 (10.3)
Fatigue	2 (4.8)	3 (7.0)	3 (7.3)	6 (14.3)	12 (9.5)
Blood CPK increased‡	3 (7.1)	3 (7.0)	3 (7.3)	4 (9.5)	10 (7.9)
Acne	0	0	3 (7.3)	6 (14.3)	9 (7.1)
Nausea	1 (2.4)	2 (4.7)	2 (4.9)	3 (7.1)	7 (5.6)
Upper respiratory tract infection	1 (2.4)	3 (7.0)	4 (9.8)	0	7 (5.6)
Infections					
Grade ≥3	0	0	1 (2.4)§	0	1 (0.8)
Herpes zoster	0	0	0	0	0

Treatment extension (weeks 24 to 52) event, *n* (%)	Placebo → 75 mg (*n* = 35)	15 mg → 75 mg (*n* = 37)	45 mg (*n* = 32)	75 mg (*n* = 34)	Total povorcitinib (*N* = 138)
Any TEAE	27 (77.1)	28 (75.7)	21 (65.6)	31 (91.2)	107 (77.5)
Grade ≥3	6 (17.1)	3 (8.1)	2 (6.3)	3 (8.8)	14 (10.1)
SAE	0	0	0	0	0
Discontinued due to TEAEs	1 (2.9)	1 (2.7)	1 (3.1)	1 (2.9)	4 (2.9)
Fatal TEAE	0	0	0	0	0
Most common TEAEs†					
COVID-19	9 (25.7)	6 (16.2)	7 (21.9)	10 (29.4)	32 (23.2)
Blood CPK increased‡	9 (25.7)	5 (13.5)	2 (6.3)	5 (14.7)	21 (15.2)
Acne	8 (22.9)	7 (18.9)	0	4 (11.8)	19 (13.8)
Nasopharyngitis	2 (5.7)	3 (8.1)	2 (6.3)	2 (5.9)	9 (6.5)
Upper respiratory tract infection	1 (2.9)	4 (10.8)	2 (6.3)	1 (2.9)	8 (5.8)
ALT increased	2 (5.7)	2 (5.4)	2 (6.3)	1 (2.9)	7 (5.1)
Urinary tract infection	0	3 (8.1)	2 (6.3)	2 (5.9)	7 (5.1)
Infections					
Grade ≥3	0	1 (2.7)	0	0	1 (0.7)
Herpes zoster	1 (2.9)	0	1 (3.1)§	1 (2.9)	3 (2.2)

ALT, Alanine aminotransferase; *CPK*, creatine phosphokinase; *SAE*, serious adverse event; *TEAE*, treatment-emergent adverse event.
*All SAEs occurred during the placebo-controlled period but were not deemed by investigators to be related to study drug (Supplementary Results, available via Mendeley at https://data.mendeley.com/datasets/52jtsjjd24/1).
†Events occurring in ≥5% of all patients treated with povorcitinib.
‡Blood CPK increase was not associated with any clinical symptoms (Supplementary Results, available via Mendeley at https://data.mendeley.com/datasets/52jtsjjd24/1).
§Infection leading to treatment discontinuation; grade 3 COVID-19 during the placebo-controlled period and grade 2 herpes zoster (not serious) during treatment extension.

employee of ICON (Blue Bell, PA, USA), based on the authors' input and direction, and was funded by Incyte.

Conflicts of interest

Dr Pandya has served as an investigator for Avita, Clinuvel, and Incyte; a consultant for AbbVie, Avita, Boehringer Ingelheim, Incyte, Lilly, Pfizer, Sun Pharma, Thalocan, Villaris, Vimela, Vyne, and WCG; and has partial ownership of Tara Medical. Dr Ezzedine is a consultant for AbbVie, Almirall, Bristol Myers Squibb, Incyte Corporation, La Roche-Posay, Lilly, Pfizer, Pierre Fabre, and Sanofi. Dr Passeron has received grants and/or honoraria from AbbVie, ACM Pharma, Almirall, Amgen, Astellas, Bristol Myers Squibb, Calypso, Celgene, Galderma, Genzyme/Sanofi, GlaxoSmithKline, Incyte, Janssen, LEO Pharma, Eli Lilly, Novartis, Pfizer, Sun Pharmaceuticals, Takeda, UCB, and Vyne Therapeutics; is the cofounder of NIKAIA Pharmaceuticals; and has patents on WNT agonists or

GSK3b antagonist for repigmentation of vitiligo and on the use of CXCR3B blockers in vitiligo. Dr van Geel is a consultant and/or investigator for AbbVie, Bristol Myers Squibb, Idorsia Pharmaceuticals, Incyte, Merck/MSD, Pfizer, and Sun Pharma and is chair of the Vitiligo Task Force for the European Academy of Dermatology and Venereology (EADV). Drs Brown, Erskine, and Wagya are employees and shareholders of Incyte. Dr Santos is an employee and shareholder of Incyte and an accredited inventor for patent titled JAK1 pathway inhibitors for the treatment of vitiligo. Dr Blauvelt has served as a speaker (received honoraria) for Eli Lilly and Company and UCB; has served as a scientific advisor (received honoraria) for AbbVie, Almirall, Alumis, Amgen, AnaptysBio, Apogee, Arcutis, Boehringer Ingelheim, Bristol Myers Squibb, Celltrion, Corvus, Dermavant, Eli Lilly and Company, Galderma, GlaxoSmithKline, Immunovant, Incyte, IQVIA, Janssen, LEO, Lipidio, Merck, Novartis, Oruka, Paragon, Pfizer, Regeneron, Sanofi, Spherix Global Insights, Sun Pharma, Syncona, Takeda, UCB, and Union; has acted as a clinical study investigator (institution has received clinical study funds) for AbbVie, Acelyrin, Almirall, Alumis, Amgen, Arcutis, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant, Eli Lilly and Company, Galderma, Incyte, Janssen, LEO, Merck, Novartis, Pfizer, Regeneron, Sanofi, Sun Pharma, Takeda, and UCB; and owns stock in Lipidio and Oruka.

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