Efficacy and safety of oral ritlecitinib for the treatment of active nonsegmental vitiligo: A randomized phase 2b clinical trial

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Background: Vitiligo is a chronic autoimmune disorder characterized by depigmented patches of the skin.

Objective: To evaluate the efficacy and safety of ritlecitinib, an oral JAK3 (Janus kinase)/TEC (tyrosine kinase expressed in hepatocelluar carcinoma) inhibitor, in patients with active nonsegmental vitiligo in a phase 2b trial (NCT03715829).

Methods: Patients were randomized to once-daily oral ritlecitinib ± 4-week loading dose (200/50 mg, 100/50 mg, 30 mg, or 10 mg) or placebo for 24 weeks (dose-ranging period). Patients subsequently received ritlecitinib 200/50 mg daily in a 24-week extension period. The primary efficacy endpoint was percent change from baseline in Facial-Vitiligo Area Scoring Index at week 24.

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Data sharing statement: Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual anonymized participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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Results: A total of 364 patients were treated in the dose-ranging period. Significant differences from placebo in percent change from baseline in Facial-Vitiligo Area Scoring Index were observed for the ritlecitinib 50 mg groups with (−21.2 vs 2.1; $P < .001$) or without (−18.5 vs 2.1; $P < .001$) a loading dose and ritlecitinib 30 mg group (−14.6 vs 2.1; $P = .01$). Accelerated improvement was observed after treatment with ritlecitinib 200/50 mg in the extension period ($n = 187$). No dose-dependent trends in treatment-emergent or serious adverse events were observed across the 48-week treatment.

Limitations: Patients with stable vitiligo only were excluded.

Conclusions: Oral ritlecitinib was effective and well tolerated over 48 weeks in patients with active nonsegmental vitiligo. (J Am Acad Dermatol 2023;88:395-403.)

Key words: JAK inhibitor; JAK/STAT signaling; randomized clinical trial; ritlecitinib; skin depigmentation; TEC inhibitor; VASI; vitiligo.

INTRODUCTION

Vitiligo, an autoimmune depigmenting disorder has a worldwide prevalence of 0.5%-2.0% and impacts quality of life.[1-4] Nonsegmental vitiligo (NSV), characterized by symmetric body distribution, accounts for 85%-90% of cases.[1,5-7] Vitiligo has an unpredictable clinical course.[8] Spontaneous repigmentation may occur in approximately 10% of vitiligo patients.[9]

CAPSULE SUMMARY

- JAK3/TEC inhibition may decrease abnormal cytokine and T-cell signaling involved in vitiligo pathogenesis, leading to repigmentation.
- Treatment with ritlecitinib, an oral JAK3/TEC inhibitor, was well tolerated and efficacious over 48 weeks in patients with active nonsegmental vitiligo, supporting further investigation of ritlecitinib in phase 3 studies.

Treatment goals for vitiligo include arresting progression, repigmentation of existing lesions, and maintenance of repigmentation.[10] Treatment options for vitiligo are limited and often require lengthy treatment and/or have limited efficacy.[11-13] Current strategies for repigmentation include narrow-band ultraviolet B phototherapy, topical and systemic immunosuppressants, and surgical procedures.[1,11-13]

The current theory on vitiligo pathogenesis involves cytotoxic CD8+ T cells that target melanocytes and the cytokines IFN-γ (interferon gamma), IL-2 (interleukin 2), and IL-15.[6,12,14,15] Notably, IL-2 and IL-15 may activate and promote CD49a+/CD8+ tissue-resident memory T cells to induce melanocyte apoptosis and maintain disease activity.[14-16] IFN-γ, IL-2, and IL-15 signal through the JAK (Janus kinase)/STAT (signal transducer and activator of transcription) pathway.[17] The involvement of the T-cell receptor in recognition of autoantigens suggests a contribution of tyrosine kinases expressed in the hepatocellular carcinoma (TEC) kinase family, such as inducible tyrosine kinase, which has been evoked in T-cell-mediated autoimmune disorders.[18]

JAK inhibitors represent a novel class of targeted immunotherapy with demonstrated efficacy in immune-mediated diseases, including dermatologic conditions.[12,19-24] Ritlecitinib is an orally bioavailable small molecule that inhibits JAK3 and the TEC kinase family.[25] Ritlecitinib is highly selective for JAK3 over JAK1/JAK2/TYK2 and potently inhibits signaling of IL-2 and IL-15, and thus, may be beneficial for the treatment of vitiligo.[15,25] Additionally, ritlecitinib may modulate CD8+ T cell cytotoxic activity by inhibiting the TEC family kinase inducible tyrosine kinase.[25] Ritlecitinib is under investigation for treatment of rheumatoid arthritis, alopecia areata, ulcerative colitis, and Crohn's disease.[26-28] We evaluated the efficacy and safety of oral ritlecitinib in patients with active NSV in a phase 2b study.

METHODS

Study design

This phase 2b, randomized, double-blind, placebo-controlled, parallel-group, multicenter, and dose-ranging study (NCT03715829) was conducted at 80 sites in Australia, Belgium, Canada, Germany, Italy, Japan, South Korea, Spain, Taiwan, and the United States from November 2018 to February 2021. A 24-week dose-ranging period was followed by a 24-week extension period and 8-week follow-up. The final protocol, any amendments, and informed consent documentation were approved by the institutional review board/independent ethics committee at each study center. This study was conducted in compliance with the Declaration of Helsinki and all

Abbreviations used:

AE:	adverse event
BSA:	body surface area
CFB:	change from baseline
F-VASI:	Facial Vitiligo Area Scoring Index
F-VASI75:	75% improvement on the Facial Vitiligo Scoring Index
IFN:	interferon
IL:	interleukin
JAK:	Janus kinase
NSV:	nonsegmental vitiligo
PGIC-V:	Patient Global Impression of Change-Vitiligo
SAE:	serious adverse event
TEAE:	treatment-emergent adverse event
TEC:	tyrosine kinase expressed in hepatocellular carcinoma
T-VASI:	Total Vitiligo Area Scoring Index

International Conference on Harmonization Good Clinical Practice guidelines. All patients provided written informed consent.

Patients

Eligible patients were aged 18-65 years with a clinical diagnosis of NSV for ≥3 months, body surface area (BSA) involvement of 4%-50% excluding palms, soles, and feet, BSA facial involvement ≥0.25%, excluding vermillions, and ≥1 active lesion, defined as new/extending lesion(s) in the past 3 months confirmed by photographs/medical record, confetti-like lesion(s), trichrome lesion(s), or Koebner phenomenon/phenomena excluding history-based isomorphic reaction.

Patients were excluded if they had other types of vitiligo, including segmental vitiligo (mixed vitiligo permitted), or other disorders causing hypopigmentation. Additional exclusion criteria are described in Supplementary Methods, available via Mendeley at https://data.mendeley.com/datasets/ctb8brksnm/1.

Randomization and treatment

In the dose-ranging period, patients were randomized (Supplementary Methods, available via Mendeley at https://data.mendeley.com/datasets/ctb8brksnm/1) to 1 of 5 treatment groups or placebo as follows: 2 groups received a ritlecitinib loading dose of 100 or 200 mg daily for 4 weeks followed by maintenance dosing of 50 mg daily for 20 weeks (200/50 and 100/50 mg, respectively); 3 groups without a ritlecitinib loading dose received 50, 30, or 10 mg daily for 24 weeks; or matching placebo for 24 weeks.

Patients were allocated to treatment in the extension period based on response at week 16 of the dose-ranging period. Nonresponders (<50% change from baseline [%CFB] in Total-Vitiligo Area Scoring Index [T-VASI]) were allocated to an open-label brepocitinib group, an open-label ritlecitinib plus narrow-band ultraviolet B therapy group, or a blinded 200/50-mg ritlecitinib group. The blinded 200/50-mg ritlecitinib group is included in this analysis.

Outcomes

The centrally-read Facial Vitiligo Area Scoring Index (F-VASI) was assessed by 2 independent observers based on facial photographs taken at the study site (Supplementary Methods, available via Mendeley at https://data.mendeley.com/datasets/ctb8brksnm/1). The primary endpoint was the %CFB in the centrally-read F-VASI at week 24; the key secondary endpoint was the proportion of patients with ≥75% improvement on the centrally-read F-VASI (F-VASI75) at week 24. The %CFB in the centrally-read F-VASI at designated time points were secondary endpoints in the dose-ranging period (except week 24) and exploratory endpoints in the extension period.

The locally-read F-VASI and T-VASI were assessed by investigators at the site without the use of photographs (Supplementary Methods). The %CFB in locally-read F-VASI and T-VASI at designated time points were secondary endpoints in the dose-ranging period and exploratory endpoints in the extension period.

The Patient Global Impression of Change-Vitiligo (PGIC-V) is a 1-item questionnaire to assess a patient's impression of disease improvement relative to baseline on a 7-point Likert scale from "very much improved" to "very much worse". The proportion of patients achieving "very much improved" or "much improved" on the PGIC-V was an exploratory endpoint in the dose-ranging and extension periods.

Patients were monitored for adverse events (AEs) from the time of informed consent through a minimum 28 days after last study drug administration. The incidence of treatment-emergent AEs (TEAEs), serious AEs (SAEs), and specific clinical laboratory abnormalities were primary safety endpoints in the dose-ranging and extension periods.

Statistical analysis

The primary patient population for the efficacy endpoints during the dose-ranging period was the full analysis set, defined as all patients who received ≥1 dose of randomized study medication and had a baseline and ≥1 post-baseline measurement. The safety analysis set included all patients who received ≥1 dose of study medication. The primary population for the extension period efficacy endpoints included all patients assigned to ritlecitinib

200/50 mg in the extension period. The total sample size for the study was computed to be ~330 randomized with the expectation of ~260 completers, assuming 20% loss to follow-up within 6 months of study initiation.

The %CFB in the centrally- and locally-read F-VASI and locally-read T-VASI were analyzed using ANCOVA (analysis of covariance) models, with treatment, baseline score for the respective measure, and Fitzpatrick skin type as covariates. Missing data were handled using the observed case method. For binary data, 90% confidence intervals (CIs) were calculated using the Blyth-Still-Castella exact method for 1-sample proportions, and 90% CIs and *P* values of difference from placebo were calculated using the Chan and Zhang exact method. Missing data were handled using non-responder imputation or the observed case method.

Adjustment for multiple comparisons was made for the primary efficacy endpoint for the ritlecitinib 200/50-, 100/50-, and 50-mg groups with Hochberg's step-up procedure using observed *P* values. The familywise Type I error rate was controlled at 1-sided $\alpha = 0.05$. No adjustments for multiple comparisons were made for other analyses. Two-sided *P* values are reported.

RESULTS

Patients

Dose-ranging period. Of 578 patients screened, 366 were randomized and 364 received treatment (Supplementary Fig 1, available via Mendeley at https://data.mendeley.com/datasets/ctb8brksnm/1). Sixty-six patients (18.1%) discontinued treatment, most commonly due to patient withdrawal (*n* = 29 [8.0%]). Demographic and baseline characteristics were generally similar across groups (Table I).

Extension period. One hundred eighty-seven patients were assigned to ritlecitinib 200/50 mg in the extension period (Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/ctb8brksnm/1). Twenty-nine patients (15.5%) discontinued treatment, most commonly due to patient withdrawal (*n* = 12 [6.4%]).

Efficacy

Dose-ranging period. The mean (90% CI) % CFB in centrally-read F-VASI at week 24 (primary endpoint) was −21.2 (−28.0, −14.4), −21.2 (−28.0, −14.3), −18.5 (−25.8, −11.2), −14.6 (−23.6, −5.6), −3.0 (−10.7, 4.7), and 2.1 (−4.6, 8.8) for the ritlecitinib 200/50-, 100/50-, 50-, 30-, and 10-mg, and placebo groups, respectively (primary endpoint; Fig 1, *A*; Supplementary Table II, available via Mendeley at https://data.mendeley.com/datasets/ctb8brksnm/1). The difference versus placebo was significant for ritlecitinib 50 mg with or without a loading dose (200/50 mg, adjusted $P < .001$; 100/50 mg, adjusted $P < .001$; 50 mg, adjusted $P < .001$) and 30 mg (unadjusted $P = .01$). The difference versus placebo was evident as early as week 8 for ritlecitinib 50 mg with or without a loading dose (Fig 1, *A*).

In the ritlecitinib 200/50-, 100/50-, 50-, 30-, and 10-mg, and placebo groups, respectively, 12.1%, 8.5%, 7.7%, 2.7%, 2.3%, and 0% of patients achieved centrally-read F-VASI75 at week 24 (key secondary endpoint; Fig 1, *B*; Supplementary Table II). The difference from placebo was significant for ritlecitinib 50 mg with or without a loading dose (200/50 mg, unadjusted $P = .008$; 100/50 mg, unadjusted $P = .03$; 50 mg, unadjusted $P = .04$).

Mean (90% CI) %CFB in locally-read T-VASI at week 24 was −14.7 (−20.4, −8.9), −19.2 (−24.6, −13.8), −14.7 (−20.1, −9.0), −14.0 (−20.9, −7.2), −12.1 (−18.5, −5.7), and −11.0 (−16.5, −5.4) for the ritlecitinib 200/50-, 100/50-, 50-, 30-, and 10-mg, and placebo groups, respectively. The difference versus placebo trended towards significant for ritlecitinib 50 mg with a 100 mg 4-week loading dose (unadjusted $P = .07$, Supplementary Table II).

The proportion of patients (90% CI) who achieved "very much improved" or "much improved" on the PGIC-V at week 24 was 18.0% (10.5, 28.3), 21.4% (12.9, 31.6), 12.0% (5.4, 21.2), 21.2% (11.7, 36.1), 15.0% (6.7, 26.9), and 8.9% (4.4, 17.3) in the respective groups and was significantly greater with ritlecitinib 100/50 mg versus placebo.

Extension period. Patients treated with ritlecitinib 200/50 mg in the extension period demonstrated accelerated improvement on the centrally-read F-VASI after week 28, regardless of initial treatment allocation (Fig 1, *C*). Mean (90% CI) %CFB in centrally-read F-VASI at weeks 24 and 48, respectively, was −19.0 (−26.9, −11.0) and −63.4 (−72.5, −54.3) for the ritlecitinib 200/50 → 200/50-mg group; −17.0 (−25.4, −8.6) and −66.0 (−76.8, −55.3) for the ritlecitinib 100/50 → 200/50-mg group; −12.8 (−21.5, −4.1) and −60.2 (−69.9, −50.4) for the ritlecitinib 50 → 200/50-mg group; −11.5 (−21.4, −1.6) and −66.1 (−79.3, −52.9) for the ritlecitinib 30 → 200/50-mg group; −1.2 (−9.3, 6.8) and −42.1 (−51.6, −32.7) for the ritlecitinib 10 → 200/50-mg group; and 1.9 (−5.9, 9.6) and −51.1 (−60.4, −41.9) for the placebo → ritlecitinib 200/50-mg group. Continuous repigmentation with no plateau was observed up to week 48 (Supplementary Fig 2, available via Mendeley at https://data.mendeley.com/datasets/ctb8brksnm/1). The mean %CFB in the locally-read F-VASI,

Table I. Demographic and baseline characteristics of patients in the dose-ranging period

	Ritlecitinib 200/ 50 mg (*N* = 65)	Ritlecitinib 100/ 50 mg (*N* = 67)	Ritlecitinib 50 mg (*N* = 67)	Ritlecitinib 30 mg (*N* = 50)	Ritlecitinib 10 mg (*N* = 49)	Placebo (*N* = 66)	Total (*N* = 364)
Female, No. (%)	30 (46.2)	31 (46.3)	39 (58.2)	28 (56.0)	25 (51.0)	40 (60.6)	193 (53.0)
Age, mean (SD), y	45.4 (12.2)	44.2 (11.2)	43.3 (10.4)	44.7 (13.5)	46.6 (10.0)	46.1 (11.5)	45.0 (11.5)
Race, No. (%)							
White	44 (67.7)	47 (70.1)	45 (67.2)	39 (78.0)	33 (67.3)	38 (57.6)	246 (67.6)
Black/African American	3 (4.6)	0	0	4 (8.0)	1 (2.0)	2 (3.0)	10 (2.7)
Asian	15 (23.1)	17 (25.4)	17 (25.4)	5 (10.0)	11 (22.4)	21 (31.8)	86 (23.6)
American Indian or Alaska Native	0	0	0	1 (2.0)	0	0	1 (0.3)
Multiracial	0	1 (1.5)	1 (1.5)	0	2 (4.1)	1 (1.5)	5 (1.4)
Not reported	3 (4.6)	2 (3.0)	4 (6.0)	1 (2.0)	2 (4.1)	4 (6.1)	16 (4.4)
Disease duration, mean (SD), y	19.0 (12.4)	17.3 (12.8)	19.8 (12.8)	18.3 (13.3)	17.6 (12.5)	18.0 (13.1)	18.4 (12.8)
Received prior medication, No. (%)	40 (61.5)	44 (65.7)	48 (71.6)	38 (76.0)	30 (61.2)	46 (69.7)	246 (67.6)
Full analysis set, No.	64	67	67	50	49	66	363
Total VASI score, mean (SD), %	17.0 (10.2)	16.9 (11.4)	16.7 (10.5)	19.8 (12.0)	15.7 (10.1)	17.7 (10.6)	17.3 (10.8)
Locally read F-VASI, mean (SD), %	1.1 (1.0)	1.2 (1.0)	0.9 (0.7)	1.1 (0.8)	1.1 (1.0)	1.0 (0.8)	1.0 (0.9)
Centrally read F-VASI, mean (SD), %	0.8 (0.9)	0.9 (0.8)	0.7 (0.6)	0.8 (0.8)	0.8 (0.8)	0.7 (0.7)	0.8 (0.8)
Total BSA, mean (SD), %	21.4 (12.3)	19.6 (12.7)	20.9 (11.7)	23.5 (12.8)	18.6 (10.8)	21.5 (12.7)	20.9 (12.2)
Fitzpatrick skin type, No. (%)							
I-II	16 (25.0)	15 (22.4)	20 (29.9)	12 (24.0)	11 (22.4)	17 (25.8)	91 (25.1)
III-VI	48 (75.0)	52 (77.6)	47 (70.1)	38 (76.0)	38 (77.6)	49 (74.2)	272 (74.9)

Daily dosing.
BSA, Body surface area; *F-VASI*, Facial Vitiligo Area Scoring Index; *VASI*, Vitiligo Area Scoring Index.

excluding patients with <0.5% baseline centrally-read BSA (post hoc analysis; Supplementary Fig 3, available via Mendeley at https://data.mendeley.com/datasets/ctb8brksnm/1), and locally-read T-VASI (Supplementary Fig 4, available via Mendeley at https://data.mendeley.com/datasets/ctb8brksnm/1) showed similar trends of accelerated improvement in the extension period when all patients received ritlecitinib 200/50 mg.

The proportion of patients (90% CI) who were "very much improved" or "much improved" on the PGIC-V increased from week 24 to week 48 in all treatment sequences, ranging from 2.9% (0.3, 11.9) to 19.4% (8.8, 32.7) at week 24 and 10.7% (4.0, 23.8) to 57.9% (38.6, 76.2) at week 48 (Supplementary Fig 5, available via Mendeley at https://data.mendeley.com/datasets/ctb8brksnm/1).

Safety

Dose-ranging period. There were 277 (76.1%) patients with 756 TEAEs in the dose-ranging period (Table II); most were mild (40.1%) or moderate (33.0%) in severity. The 3 most common TEAEs were nasopharyngitis (15.9%), upper respiratory tract infection (11.5%), and headache (8.8%) (Supplementary Table III, available via Mendeley at https://data.mendeley.com/datasets/ctb8brksnm/1). Similar rates of infections and infestations were observed across all groups. Nineteen (5.2%) patients discontinued treatment due to AEs during the dose-ranging period. There were no dose-dependent trends in TEAEs, SAEs, severe AEs, AEs leading to discontinuation, herpes zoster AEs, or most common AEs up to week 24. There were no deaths in the study. No clinically meaningful trends for hematology or chemistry laboratory parameters were observed. Four (1.1%) patients had SAEs, all considered unrelated to treatment by investigators (Supplementary-Additional Safety Information, available via Mendeley at https://data.mendeley.com/datasets/ctb8brksnm/1). Four patients had confirmed cases of herpes zoster (all non-serious),

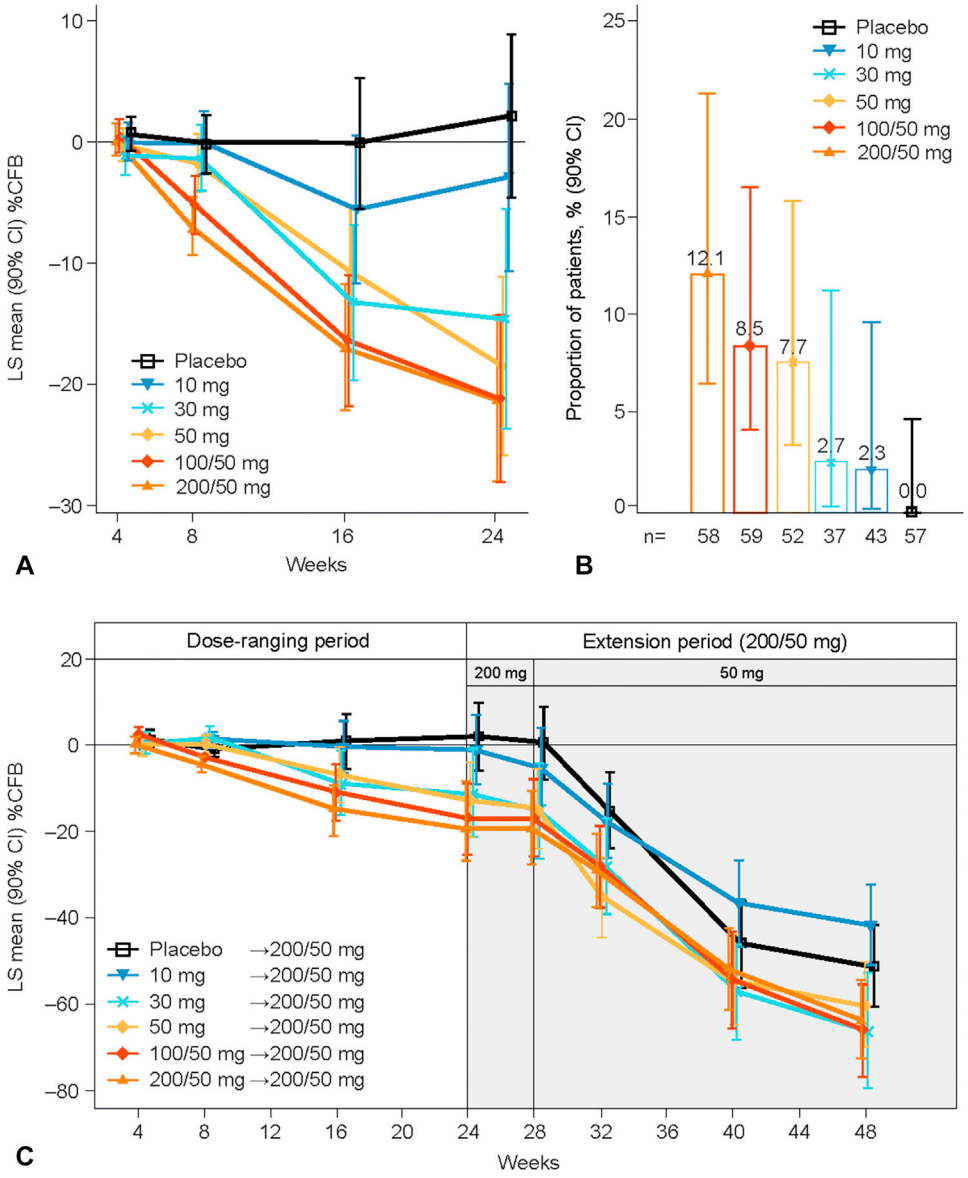

Fig 1. Centrally read F-VASI for patients with vitiligo. (**A**) Percent change from baseline (CFB) up to week 24 in the dose-ranging period, (**B**) proportion of patients achieving centrally read 75% improvement on the Facial Vitiligo Scoring Index at week 24 in the dose-ranging period, and (**C**) percent CFB up to week 48 in patients treated with ritlecitinib 200/50 mg daily in the extension period. Daily dosing. *%CFB*, Percent change from baseline; *CI*, confidence interval; *F-VASI*, Facial Vitiligo Area Scoring Index; *LS*, least square.

2 patients had malignancies (nonmelanoma skin cancers), and there were no thromboembolic events (Supplementary-Additional Safety Information).

Extension period. One hundred sixty-two of 187 patients (86.6%) had 647 TEAEs across the dose-ranging and extension periods (Supplementary Table IV, available via Mendeley at https://data.mendeley.com/datasets/ctb8brksnm/1). The most common TEAEs during the 48-week study period were nasopharyngitis (20.3%), upper respiratory tract infection (17.1%), and headache (13.4%) (Supplementary Table V, available via Mendeley at https://data.mendeley.com/datasets/ctb8brksnm/1). No clinically meaningful trends for hematologic or chemistry laboratory parameters were observed across the 48 weeks in patients receiving ritlecitinib 200/50 mg in the extension period (Supplementary Figs 6-10, available via Mendeley at https://data.mendeley.com/datasets/ctb8brksnm/1).

Table II. Summary of treatment-emergent adverse events during the dose-ranging period

	Ritlecitinib 200/ 50 mg (*N* = 65)	Ritlecitinib 100/ 50 mg (*N* = 67)	Ritlecitinib 50 mg (*N* = 67)	Ritlecitinib 30 mg (*N* = 50)	Ritlecitinib 10 mg (*N* = 49)	Placebo (*N* = 66)	Total (*N* = 364)
AEs, No.	166	131	132	88	95	144	756
Patients with AEs, No. (%)	56 (86.2)	45 (67.2)	54 (80.6)	30 (60.0)	40 (81.6)	52 (78.8)	277 (76.1)
Patients with SAEs, No. (%)	0	0	1 (1.5)	1 (2.0)	1 (2.0)	1 (1.5)	4 (1.1)
Patients with severe AEs, No. (%)	2 (3.1)	0	5 (7.5)	1 (2.0)	1 (2.0)	2 (3.0)	11 (3.0)
Patients who discontinued study due to AEs, No. (%)	2 (3.1)	4 (6.0)	5 (7.5)	2 (4.0)	3 (6.1)	3 (4.5)	19 (5.2)

Daily dosing.
AE, Adverse event; *SAE*, serious adverse event.

DISCUSSION

This is a randomized, placebo-controlled study of an oral, targeted immunomodulatory agent for active NSV. Ritlecitinib 50 mg (with or without loading dose)/30 mg showed significantly greater %CFB in the centrally-read F-VASI than placebo at week 24 (primary endpoint). The proportion of patients who achieved centrally-read F-VASI75 at week 24 was also significantly greater with ritlecitinib 50 mg (with or without loading dose) than placebo (key secondary endpoint). Accelerated improvement was observed after week 28 during the extension period across Fitzpatrick skin types (data not shown), and ritlecitinib up to 48 weeks was well tolerated.

This study employed a patient-centric approach[29] by examining patient-reported changes. During the extension period, 7.7%-19.4% of patients achieved clinically meaningful changes of "much improved" or "very much improved" in the ritlecitinib arms at week 24, and this proportion more than doubled at week 48 for most groups (24.0%-57.9%), suggesting continuous patient-reported improvement with longer treatment duration. This finding was directionally aligned with the F-VASI and T-VASI results at weeks 24 and 48. Future clinical studies may investigate additional vitiligo-specific health-related quality of life outcomes that are of priority to patients with vitiligo, using vitiligo-specific measures and the PGIC-V.

Based on in vitro studies and cellular assays, ritlecitinib has no effect on JAK1/JAK2/TYK2, suggesting no direct inhibitory effect on IFN-γ/type 1 IFN signaling.[25] However, ritlecitinib may decrease production of IFN-γ by activated CD8+ T cells and natural killer cells via an indirect mechanism, related to TEC kinase inhibition.[25] Furthermore, ritlecitinib inhibits γ-chain cytokines that may suppress pathogenic tissue-resident memory T cells.[14,30-32] This framework may explain the modest efficacy observed at a relatively early time point (week 24) that increases considerably at a later time point (week 48).

Ritlecitinib is the first oral JAK3/TEC inhibitor evaluated for vitiligo in a randomized phase 2 clinical trial; however, previous case reports and series have suggested efficacy of oral and topical JAK inhibitors for vitiligo treatment. Reports of oral tofacitinib (JAK1/JAK3 > JAK2 inhibitor) in 1,[33] 2,[34] and 10[35] patients showed efficacy with vitiligo, respectively. An additional case report on 1 patient with vitiligo reported skin repigmentation after treatment with oral ruxolitinib (JAK1/JAK2 inhibitor).[36] Treatment with ruxolitinib cream showed efficacy in a phase 2 study.[37]

As a systemic therapy, ritlecitinib may have advantages over topical treatments and phototherapy in inducing repigmentation and preventing disease spread. The former is especially important for areas that may be more difficult to repigment.[38] Treatment of large vitiligo lesions would also be an advantage of oral agents like ritlecitinib. Combination treatment with JAK inhibitors and phototherapy could be considered,[34] and future studies will analyze combination therapy efficacy.

Limitations of this study included the exclusion of patients with stable vitiligo only, although data suggest ritlecitinib promotes repigmentation in stable lesions.[39] The majority of patients were White, with less than 5% of patients reporting as Black or African-American. Higher baseline pigmentation could impact self-reported assessments and physician scoring. This is important to consider for future studies, as patients with darker baseline skin tones

may have a more pronounced psychosocial burden and can face greater social stigma.[40,41] The COVID-19 pandemic meant some virtual consultations, which may have impacted the data. Low baseline facial involvement in some patients may have made assessment more challenging.

In conclusion, this phase 2 trial suggests that ritlecitinib is an effective and well-tolerated treatment for patients with active NSV. As indicated by the data during the extension period, longer treatment duration may be required for optimal repigmentation.

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Conflicts of interest

KE declares acting as a consultant for Incyte, La Roche Posay, Pfizer, Pierre Fabre, Sanofi, and Viela Bio. EP, YY, LAC, AB, AS, DY, and MSV are employees of Pfizer and hold stock and/or stock options with Pfizer. KG was an employee of Pfizer at the time of the study and held stock and/or stock options with Pfizer. GH declares being an investigator for Amgen, Athenex, Boehringer Ingelheim, Bond Avillion, Bristol Myers Squibb, Celgene, Eli Lilly, Novartis, Janssen, MC2, PellePharm, Pfizer, and UCB; and a consultant, advisor, or speaker for AbbVie, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Castle Biosciences, Dermavant, Dermtech, Eli Lilly, Janssen, LEO Pharma, Novartis, Ortho Dermatologics, Pfizer, Regeneron, Sanofi Genzyme, SUN Pharmaceuticals, and UCB. IH declares being a consultant for Galderma Laboratories and UCB; an investigator for Arcutis, Avita, Bayer, Lenicura, L'Oréal, and Unigen; and a consultant and investigator for Incyte and Pfizer; serving on scientific advisory boards for AbbVie; and being co-chair of Global Vitiligo Foundation in a non-funded capacity. AKG declares being a consultant for AbbVie, Allergan Aesthetics, and Viela Bio. MP declares being a consultant, advisor, or speaker for Incyte, Pfizer, Pierre Fabre, and PPM. DT declares being a consultant, investigator, speaker, and participating in scientific advisory boards for AbbVie, Almirall, Amgen, Biogen Idec, BMS, Janssen-Cilag, LEO Pharma, Eli Lilly, Novartis, Pfizer, Regeneron, Samsung, Sanofi, and UCB; and research/educational grants from AbbVie, LEO Pharma, and Novartis. JEH declares acting as a consultant and investigator for Pfizer, Genzyme/Sanofi, Incyte, Rheos Medicines, Sun Pharmaceuticals, Leo Pharma, Villaris Therapeutics, Dermavant, and TeVido BioDevices; and a consultant for Temprian Therapeutics, AbbVie, Inc, Janssen, Almirall, Methuselah Health, Pandion, AnaptysBio, Avita, NIRA Biosciences, Admirx, Granular Therapeutics, Platelet BioGenesis, Inc; he has equity in TeVido Biodevices, Rheos, Villaris Therapeutics, Inc, and NIRA Biosciences; and is a founder of Villaris Therapeutics, Inc, and NIRA Biosciences. JMB declares acting as a consultant for Pfizer, AbbVie, LaserOptek, and Ilooda. KT declares being a speaker for AbbVie, Eli Lilly, Janssen, Novartis, Pfizer, Sanofi, and UCB. RS declares providing professional services to Amgen, Bayer, Boehringer Ingelheim, Celgene, Coherus Biosciences, Cutanea, Eli Lilly, GlaxoSmithKline, Janssen, LEO Pharma, MedImmune, Merck & Co, MSD, Novartis, Oncobiologics, Pfizer, Regeneron, Roche, Samson Clinical, and Sun Pharma. AGP declares acting as a consultant for AbbVie, Arcutis, Avita, Chromaderm, Immune Tolerance Network, Incyte, Pfizer, TWi, Viela Bio, and Villaris, and holds stock options with Tara Medical and Zerigo Health. BK declares receiving honoraria and/or consultation fees from Aclaris Therapeutics, Arena Therapeutics, Bristol-Myers Squibb, Concert Pharmaceuticals, Dermavant Sciences, Eli Lilly, Pfizer, Regeneron, and Viela Bio, and serving on a speakers bureau for Pfizer. The other authors have no conflicts of interest to declare.

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