JAMA Dermatology | Original Investigation

Combination of Baricitinib and Phototherapy in Adults With Active Vitiligo
A Randomized Clinical Trial

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IMPORTANCE Vitiligo is a chronic autoimmune disorder leading to skin depigmentation and reduced quality of life (QOL). Patients with extensive and very active disease are the most difficult to treat.

OBJECTIVE To assess the efficacy and adverse events of baricitinib combined with narrowband UV-B in adults with severe, active, nonsegmental vitiligo.

DESIGN, SETTING, AND PARTICIPANTS This academic, multicenter, double-blind, noncomparative randomized clinical trial was conducted at 4 dermatology departments between July 2021 and April 2023 and included adult patients with extensive and active nonsegmental vitiligo. The study was designed to evaluate the effect of baricitinib plus narrowband UV-B based solely on the results from this experimental group. The placebo group was used as a calibration group. Data were analyzed from August to November 2023.

INTERVENTIONS Participants were randomized 3:1 to baricitinib, 4 mg per day, or placebo for 36 weeks alone for the first 12 weeks and then in combination with narrowband UV-B twice a week from weeks 12 to 36.

MAIN OUTCOMES AND MEASURES The primary outcome was mean percentage change in total Vitiligo Area Scoring Index (VASI) score from baseline to week 36 (baricitinib group). The prespecified aim of the study was to show that the reduction in the baricitinib plus narrowband UV-B was significantly greater than 42.9%, a repigmented surface threshold previously observed in patients treated with narrowband UV-B alone. Adverse events and secondary outcomes of change in disease activity and QOL were assessed. Post hoc analyses were additionally performed.

RESULTS Of 49 included patients, 35 (71%) were female, and the median (IQR) age was 49.9 (38.4-59.8) years. A total of 37 patients were randomized to the baricitinib group and 12 to the placebo group. The mean change in total VASI at week 36 was −44.8% (95% CI, −58.4% to −31.3%) for the baricitinib group and −9.2% (95% CI, −27.7% to 24.7%) for the placebo group. This was not significantly greater than the sufficient repigmented surface threshold of 42.9%. Post hoc analyses showed a significant difference at week 36 for total VASI score in the baricitinib plus narrowband UV-B group compared with placebo plus narrowband UV-B (−44.8% vs −9.2%, respectively; $P = .02$). There was a greater improvement in disease activity and QOL in the baricitinib group vs placebo group and no significant difference in the number of adverse events.

CONCLUSIONS AND RELEVANCE This proof-of-concept randomized clinical trial confirmed the efficacy of baricitinib combined with narrowband UV-B in the treatment of patients with extensive and active vitiligo.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT04822584

Visual Abstract

Supplemental content

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JAMA Dermatol. doi:10.1001/jamadermatol.2024.5737
Published online January 22, 2025.

Vitiligo is a chronic autoimmune skin depigmenting disorder, with a worldwide prevalence of 0.5% to 2.0%.[1,2] While vitiligo does not affect life expectancy, it has an impact on quality of life (QOL) and mental well-being.[3-6] Patients with severe active disease are at high risk of developing new lesions rapidly without effective treatment, and systemic immunomodulating agents should be considered to stabilize the disease.

Vitiligo skin is consistently associated with infiltration of immune cells, characterized by the presence of plasmacytoid dendritic cells producing elevated levels of type I interferon (IFN) alfa[7], important for the initiation of the disease, and resident memory CD8 T cells producing elevated levels of the type 1 immune-related cytokines IFN gamma and tumor necrosis factor α.[8-11] This proinflammatory environment impacts the proliferation, function, and survival of melanocytes,[12] leading to their disappearance. Recent studies suggest that the immune response in vitiligo is not restricted to IFN gamma but could be associated with a type 2 immune response, as evidenced by increased IL-13 production.[13-16] Moreover, Janus kinase (JAK) inhibitors target the pathway in which resident memory T cells become dependent on IL-15 for their survival as they establish residence in the epidermis.[17-19]

In response to inflammatory cytokines, the JAK-signal transducers and activators of transcription signaling pathway plays a role in the inflammatory cellular processes of immune and epithelial cells.[13,15,16,20] Therefore, JAK inhibitors may present a promising treatment strategy in vitiligo. The topical JAK1/JAK2 inhibitor ruxolitinib is now approved for the management of vitiligo, although the treatment is only recommended for patients with vitiligo involving the face and less than 10% of the body surface area.[21]

As a systemic therapy, baricitinib may have advantages over topical treatments to rapidly stabilize the disease in patients with very active disease and where larger areas are involved. Previous reports described the clinical benefit of JAK1 inhibitors (upadacitinib)[22] and JAK3/TEC inhibitors (ritlecitinib)[23,24] alone in the management of vitiligo.

Narrowband UV-B is the standard treatment for widespread or active vitiligo.[25] Narrowband UV-B therapy regulates the inflammatory component of vitiligo[26] and reduces the known impact of inflammation on the proliferation of melanocytes. In addition to its immunosuppressive actions, narrowband UV-B promotes the differentiation and proliferation of melanocytes and thus stimulates repigmentation of the skin.

The use of phototherapy alongside JAK inhibitors has been associated with possibly potentiating the response to vitiligo treatment in case series using oral JAK inhibitors[27,28] and a phase 2 trial with a topical JAK inhibitor.[29] Thus far, however, systemic, oral JAK inhibitors have not been evaluated with concomitant phototherapy, to our knowledge.

The aim of this study was to assess the efficacy and adverse events of the combination of baricitinib and narrowband UV-B in adults with severe, active, nonsegmental vitiligo in a double-blind, proof-of-concept phase 2 randomized clinical trial.

Key Points

Question What are the efficacy and tolerance of oral baricitinib combined with narrowband UV-B in patients with active and extensive vitiligo disease, the most severe form of vitiligo?

Findings In this double-blind, randomized clinical trial that included 49 patients, the mean change in total Vitiligo Area Scoring Index score at week 36 was −44.8% for the baricitinib group and −9.2% for the placebo group,

Meanings This randomized clinical trial showed that baricitinib, a small molecule inhibiting Janus kinases 1 and 2, combined with phototherapy reduced the activity of the disease and provided rapid and clinically meaningful repigmentation in adults with severe, active vitiligo.

Methods

Study Design

This was a multicenter, double-blind, noncomparative, proof-of-concept phase 2 randomized clinical trial. It was conducted in the dermatology departments at 4 hospitals in France between July 2021 and April 2023. The study was designed to evaluate the effect of the combination of baricitinib plus narrowband UV-B based solely on the results from this experimental group. The placebo group was used as a calibration group, as previously proposed for the design of a phase 2 study.[30,31] The trial protocol (NCT04822584) can be found in Supplement 1.

The research was designed and conducted and the report was prepared in accordance with the French Code of Public Health, the Declaration of Helsinki, Good Clinical Practice, and the General Data Protection Regulation. This research received an approval from the French ethics committee CPP Tours Région Centre-Ouest 1 and authorization from the French National Agency for the Safety of Medicines and Health Products. All participants provided written informed consent. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline. The study's data and harms monitoring committee included an independent clinician, a methodologist, and a pharmacologist.

Participants

The study participants were aged 18 to 75 years, with a diagnosis of active nonsegmental vitiligo involving more than 5% of body surface area (excluding hands and feet). Participants had new patches or extensions of old lesions during the previous 6 months in addition to the presence of hypochromic aspect and/or perifollicular hypopigmentation under Wood lamp examination.

Participants were recruited over an 18-month period. Before any clinical or paraclinical examination was conducted for the research, informed consent was signed by the participant and the investigator. Personal and familial medical history was taken, including past therapies for vitiligo, and dermatological, physical, and biological examinations were performed to

ensure eligibility for participation. Vitiligo Area Scoring Index (VASI),[32] Vitiligo Extent Score (VES),[33] and Vitiligo Signs of Activity Score (VSAS)[34] outcomes were completed.

Reasons for exclusion from the study included individuals with segmental or mixed vitiligo, existing or a history of concomitant skin conditions that would interfere with study evaluations, or a history (or signs or symptoms suggestive) of lymphoproliferative disease. Those who received prior treatment with monoclonal antibody less than 5 half-lives prior to randomization, any oral JAK inhibitor, or more than 250 sessions of UV light therapies; those with hypersensitivity to baricitinib (or any of its excipients); or who had previously been randomized in this or any or other study investigating baricitinib were also excluded.

Randomization and Masking

Participants were randomized in a 3:1 ratio to receive baricitinib, 4 mg per day, orally for 36 weeks (the experimental group) or placebo once per day orally for 36 weeks (the placebo group). Following 12 weeks of baricitinib or placebo, both groups received narrowband UV-B (Philips TL-01 lamp) phototherapy twice per week for 24 weeks in compliance with the French Society of Photo-Dermatology protocol.

Randomization was performed in 2 blocks using the electronic application QUANTA View (Voisin Consulting Life Sciences). The first block involved generating a list of investigational product numbers. Following confirmation of inclusion criteria by the electronic case report form system, a randomized investigation product number was allocated to the participant by the interactive web response system and emailed to the investigator; the groups to which participants were randomized were unknown to the participants and investigators.

During the follow-up visits, dermatological, physical, and biological examinations were repeated, and female participants of childbearing potential had urinary pregnancy tests monthly. The end-of-treatment visit was at week 36.

Outcomes

The primary outcome was the mean percentage change in the total VASI score, as a measure of affected body surface area and the degree of depigmentation,[32,35] from baseline to week 36 of treatment with a combination of baricitinib and narrowband UV-B (twice a week). The secondary outcomes, based on recommendations of international consensus,[36,37] were a change in vitiligo extent and stage and disease activity assessed by the mean percentage change in total VASI score from baseline to weeks 12 and 24, facial VASI score, VES, Vitiligo European Task Force assessment-extent, and VSAS scores from baseline to weeks 12, 24, and 36.

The impact of vitiligo on QOL, based on mean percentage changes from baseline to weeks 12, 24, and 36, was measured using standardized dermatology-specific health-related QOL questionnaires: the SkinDex-29, the Dermatology Life Quality Index (DLQI),[38,39] and the Vitiligo Impact Patient Scale (VIPs).[40] A decrease in these primary and secondary outcome scores indicates an improvement in the participant's condition.

A 50% or greater, 75% or greater, and 90% or greater improvement in total VASI score and a 75% or greater and 90% or greater improvement in facial VASI score from baseline to weeks 12, 24, and 36 were calculated for the baricitinib and placebo groups. To monitor adverse events of the treatment, adverse events were identified at each study visit and recorded in the electronic case report form by the investigator.

Sample Size Calculation

The primary end point is the mean variation in percentage of the total VASI score between baseline and week 36. The number of patients required in the experimental arm was calculated to be able to detect a 62% change in the total VASI score after treatment. Including 36 patients in the experimental group, the mean minimum repigmented area to be reached with treatment is 62.0% to be able to conclude that it is greater than 42.9% (threshold above which efficacy is considered sufficient). This calculation is based on the formula of the *t* test comparing an average observed at a theoretical average (nQuery Advisor version 7.0 software; Statsols), for a unilateral 5% α risk, a 90% power, considering an SD of 0.365 for the mean repigmented surface. The sufficient repigmented surface threshold and its SD were calculated from the 95% CI associated with the estimate made in a study involving 22 participants with vitiligo treated with narrowband UV-B alone.[32] Three-fold more patients were included in the experimental arm compared with the control arm.[31,32]

Statistical Analysis

The primary efficacy analyses were done on the intention-to-treat (ITT) population (which included all patients who had undergone randomization). There was no patient withdrawal from the ITT analysis. Per-protocol data are available from the investigators. In case of missing data, no imputation was performed. If some data were missing for a given variable and a given patient, the data remained missing and were not included in the analysis. Data were analyzed from August 2023 to November 2023.

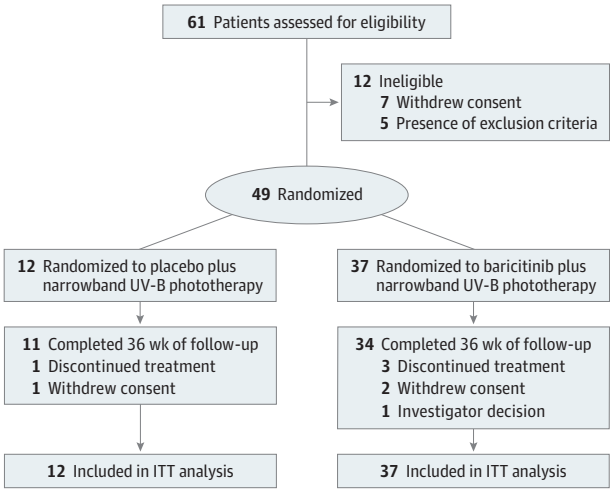
Prespecified Analysis

The mean percentage of repigmented surface area observed at 36 weeks (VASI) as well as its unilateral 95% CI were calculated in patients in the experimental group (baricitinib plus narrowband UV-B). The hypothesis that this percentage is higher than 42.9%, below which the treatment would be considered not efficacious enough, was tested by a 1-sample *t* test of an observed vs a theoretical mean, at the 5% unilateral type I error. No test of statistical comparison was first specified between the experimental group and the control group in this proof-of-concept phase 2 study.

Post Hoc Analyses

The significance of the difference in percentage change in total VASI, facial VASI, VES, VSAS, DLQI, SkinDex-29, and VIPs scores between the 2 groups was calculated using the nonparametric Wilcoxon test. Where the data were not normally distributed (Shapiro-Wilk test greater than 1%), the parametric Student *t* test was used. Statistical testing performed in the post

Figure 1. Study Flowchart



The total number of patients that experienced a premature withdrawal is 4: 1 in the placebo group and 3 in the baricitinib group. Reasons for discontinuation included withdrawal by the patients (n = 2) and discontinuation on investigator decision (1 patient who experienced a serious adverse event [pulmonary embolism]). ITT indicates intention-to-treat.

hoc analysis was 2-sided, and the significance threshold was $P < .05$. Analyses were performed with SAS software version 9.4 (SAS Institute). Post hoc analyses were justified by the results obtained in the calibrator group (placebo plus narrowband UV-B), which were lower than expected (a hypothetical repigmented surface threshold of 42.9%).

Results

Of 61 patients who were screened, 49 were deemed eligible to participate and randomly allocated to a study group. The median (IQR) age of participants was 49.9 (38.4-59.8) years; 35 (71%) were female, and 43 (88%) had Fitzpatrick skin types II to III. The 37 participants in the baricitinib group and the 12 participants in the placebo group were included in the ITT population (**Figure 1**); baseline characteristics of the ITT population are presented in **Table 1**. Of the 37 participants in the baricitinib group, 34 had assessments both at baseline and at week 36. A mean (SD) change of −44.8% (38.8%) was observed in the primary end point of total VASI score from baseline to 36 weeks (**Figure 2**; eFigure 1A in Supplement 2). This was not significantly greater that the sufficient repigmented surface threshold of 42.9%, as previously observed in patients treated with narrowband UV-B alone.[32] For most of the secondary efficacy end points, there was a mean percentage decrease from baseline in the baricitinib group, indicating an improvement in the participant's condition. In most cases, the mean percentage decrease was greater for the baricitinib compared with the placebo group. The percentage of participants who achieved a total VASI score improvement of 50% or more, 75% or more, and 90% or more as well as a facial VASI score improvement of 75% or more and 90% or more was greater in the baricitinib group compared with the placebo group at weeks 12, 24, and 36. From baseline to week 36, there was a 50%, 75%, and 90% improvement in total VASI score in 18 (53%), 9 (27%), and 2 (6%) participants in the baricitinib group, respectively, compared with 1 (9%), 0, and 0 participants in the placebo group, respectively. Moreover, there was a 75% and 90% improvement in facial VASI score in 19 (56%) and 17 (50%) participants in the baricitinib group, respectively, compared with 1 (9%) and 1 (9%) participants in the placebo group, respectively, from baseline to week 36 (**Figure 3**; eFigures 3 and 4 in Supplement 2).

Post hoc analyses showed a significant difference seen at week 36 for the primary end point of total VASI score in the baricitinib group compared with the placebo group (mean change in total VASI at week 36 for the baricitinib vs placebo group, −44.8% [95% CI, −58.4% to −31.3%] vs −9.2% [95% CI, −27.7% to 24.7%], respectively; $P = .02$). In addition, the mean percentage decrease was significantly greater for the baricitinib group compared with the placebo group for facial VASI score at week 24 and week 36, VES at week 36, Vitiligo European Task Force assessment-extent at week 36, and DLQI at week 24. No significant difference was observed for the VSAS and SkinDex-29 and the VIPs (Figure 3; eFigures 1 to 3 in Supplement 2).

Regarding harms, an adverse event was experienced by 24 participants (65%) in the baricitinib group and 7 participants (58%) in the placebo group (**Table 2**), with no significant difference between the 2 groups ($P = .58$). Serious adverse events were reported in both groups; 1 participant in the placebo group (8%) experienced a viral infection, while 1 participant (5%) experienced back pain and 1 (5%) experienced a pulmonary embolism in the baricitinib group. The difference between the 2 groups was not significant (eFigure 5 in Supplement 2). A total of 4 patients experienced a premature withdrawal, including 1 in the placebo group and 3 in the baricitinib group. Reasons for discontinuation included withdrawal by the patients (3 patients) and discontinuation on investigator decision (1 patient who experienced a serious adverse event [pulmonary embolism]).

Discussion

To our knowledge, this was the first phase 2 proof-of-concept randomized clinical trial to test the hypothesis that a JAK1/JAK2 inhibitor, in combination with phototherapy, would induce a better and faster repigmentation than phototherapy alone in the treatment of adults with severe, active, nonsegmental vitiligo. This study evaluated a novel therapeutic approach, where the experimental group received baricitinib alone for 12 weeks, with the goal of stopping the spread of the disease, alongside narrowband UV-B phototherapy for 24 weeks to promote melanocyte differentiation and proliferation, thereby stimulating repigmentation.

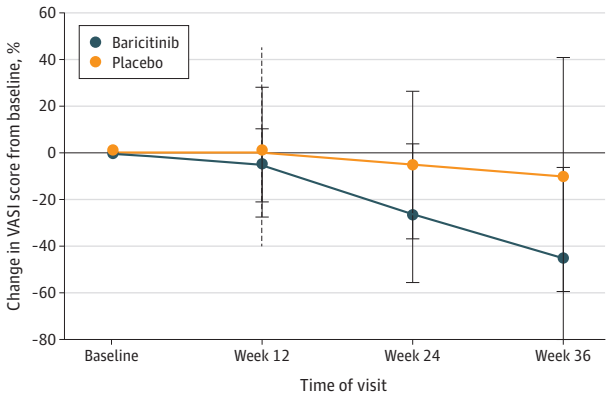
The inclusion of difficult-to-treat patients with extensive and very active disease could explain why the level of repigmentation in the baricitinib group was not significantly greater that the threshold of repigmented surface of 42.9%, as previ-

Table 1. Characteristics of the Intention-to-Treat Population at the Randomization Visit

Characteristic	Median (IQR)		
	Placebo plus narrowband UV-B (n = 12)	Baricitinib plus narrowband UV-B (n = 37)	All participants (N = 49)
Age, y	47.1 (36.9-52.6)	52.3 (42-60.8)	49.9 (38.4-59.8)
Sex, No. (%)			
Female	7 (58)	28 (76)	35 (71)
Male	5 (42)	9 (24)	14 (29)
Fitzpatrick skin type, No. (%)			
I to III	10 (83)	33 (89)	43 (88)
IV to VI	2 (17)	4 (11)	6 (12)
Duration of disease, y	13.5 (6.5-21)	16 (8-24)	16 (8-23)
Total VASI score	22.5 (9.8-30)	15 (9.8-23)	16 (9.8-26)
Facial VASI score	0.4 (0.2-0.9)	0.5 (0.1-1)	0.4 (0.1-1)
VES score	13.5 (6.9-21)	16 (7.7-21)	15 (7.6-21)
VETFa-extent score	22 (10.1-33.5)	17 (10.8-24)	17(10.8-29)
VSAS score	4 (3-7.5)	4 (3-9)	4 (3-8)
Quality of life			
DLQI score	4.5 (2-9)	4 (2-7)	4 (2.8)
SkinDex-29	65.5 (30-130)	64 (57-82)	64 (57-80)
VIPs score	30.5 (25-36.5)	27 (16-37)	27 (18-37)
Thyroid disorders, No. (%)	4 (33)	8 (22)	12 (25)

Abbreviations: DLQI, Dermatology Life Quality Index; VASI, Vitiligo Area Scoring Index; VES, Vitiligo Extent Score; VETFa, Vitiligo European Task Force assessment; VIPs, Vitiligo Impact Scale; VSAS, Vitiligo Signs of Activity Score.

Figure 2. Efficacy of the Combination of Baricitinib and Narrowband UV-B



Percentage change from baseline to week 36 for the primary end point of total Vitiligo Area Scoring Index (VASI) score. In the intention-to-treat analysis, at baseline, week 12, week 24, and week 36, a total of 37, 36, 33, and 34 patients in the baricitinib group, respectively, and 12, 12, 10, and 11 patients in the placebo group were analyzed. The dotted vertical line indicates the start of narrowband UV-B. Error bars indicate 95% CIs.

ously observed in the study by Hamzavi et al.[32] Indeed, in this study, mainly patients with stable disease were included, explaining the efficacy of narrowband UV-B alone. Here, the extent of repigmentation in the baricitinib group and the low level of repigmentation in the placebo group led us to perform post hoc analyses, which showed significant changes between the 2 group for total VASI score at week 36

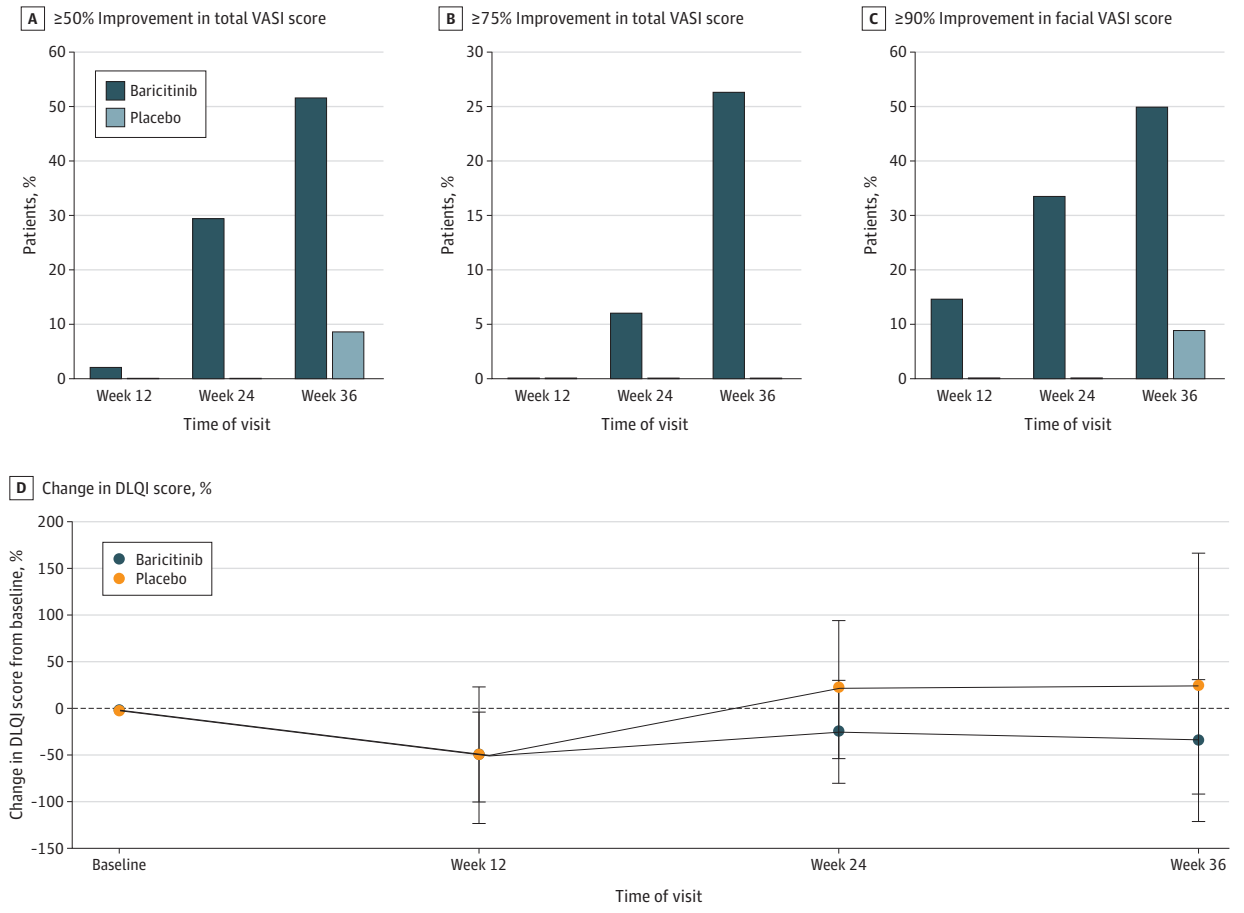
Repigmentation is an outcome of priority for individuals living with vitiligo.[36] A case report previously described almost complete vitiligo repigmentation in an adult man after taking oral baricitinib, 4 mg, daily, prescribed for their concurrent rheumatoid arthritis, for 8 months.[41] In addition, achievement of satisfactory repigmentation with oral baricitinib combined with narrowband UV-B phototherapy has been reported in 2 cases of generalized vitiligo.[42]

There was a decrease in the VSAS score from weeks 12 to 36 in the baricitinib group, indicating a reduction in visible clinical signs and an improvement in symptoms. An increase in VSAS score at week 12 in the placebo group indicated an increase in these signs and a worsening of symptoms compared with baseline. This supports one of the study hypotheses, that baricitinib could stop the spread of the disease in patients with active disease by dampening the inflammatory response.

Individuals with vitiligo may find lesions over the face and exposed sites of the hands and feet to be especially embarrassing, and finding a treatment to improve facial vitiligo is important to them.[21,35] An improvement from baseline of 75% in facial VASI score and 50% in total VASI score were previously identified as clinically meaningful thresholds by individuals living with vitiligo.[23,35] A study on the effect of the oral JAK inhibitor ritlecitinib as monotherapy to treat vitiligo reported that a significantly greater proportion of participants achieved centrally read facial VASI score improvement of 75% or more in the treatment group compared with the placebo group. The percentage of participants who achieved total VASI score improvement of 50% or more, 75% or more, and 90% or more and facial VASI score improvement of 75% or more and 90% or more was greater in the baricitinib group compared with the placebo group at weeks 12, 24, and 36. No plateau of efficacy was reached, and it could be assumed that continuing this strategy for a longer period of time may result in further increase in repigmentation.

Several studies have identified that improvements in QOL should be explored in future analyses.[21,23,43] There was a mean

Figure 3. Improvement in Total Vitiligo Area Scoring Index (VASI) Score, Facial VASI Score, and Dermatology Life Quality Index (DLQI) Score



In the intention-to-treat analysis, at baseline, week 12, week 24, and week 36, a total of 37, 36, 33, and 34 patients in the baricitinib group, respectively, and 12, 12, 10, and 11 patients in the placebo group were analyzed. Lower scores indicate less impact on quality of life. Error bars indicate 95% CIs.

Table 2. Adverse Events in Intention-to-Treat Population Up to 36 Weeks of Treatment

Measure	No. (%)		
	Placebo plus narrowband UV-B (n = 12)	Baricitinib plus narrowband UV-B (n = 37)	All participants (N = 49)
Any TEAE	7 (58)	24 (65)	31 (63)
TEAE by severity			
Serious AE	1 (8)	2 (5)	3 (6)
AE leading to discontinuation from study drug	3 (25)	1 (3)	4 (8)
Death	0	0	0
Most frequently reported TEAEs			
Infections	5 (42)	13 (35)	18 (37)
Headache	1 (8)	3 (8)	7 (14)
TEAE of special interest			
Pulmonary embolism	0	1 (3)	1 (2)
Participants with ≥1 treatment-emergent infection	5 (42)	13 (35)	18 (37)
COVID-19	3 (25)	5 (14)	8 (16)
Oral herpes	0	1 (3)	1 (2)
Varicella zoster	0	1 (3)	1 (2)

Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event.

percentage decrease in the DLQI score from baseline for the baricitinib group; the post hoc analysis indicated that this decrease was significantly greater than that seen in the placebo group at week 24. A greater decrease in the participant self-reported SkinDex-29 and VIPs scores in the baricitinib group compared with the placebo group was observed, except for the VIPs score at week 12. This indicated an improvement in perceived severity of the disease and QOL in those participants treated with baricitinib. However, we could not assess the cosmetic acceptability of the results obtained for each patient because the Vitiligo Noticeability Scale was not included in our analysis.

There was no significant difference in the number of adverse events or time to first adverse event between the 2 groups, suggesting that treatment with baricitinib in combination with narrowband-UV-B is well tolerated.[24] The harm profile of baricitinib in combination with narrowband UV-B does not appear different to that reported for baricitinib alone in the management of atopic dermatitis[44,45] and alopecia areata.[46,47]

Limitations

This study has limitations. There was a low number of participants included in our study, and the impact of JAK inhibitors alone on repigmentation was not well characterized. Furthermore, post hoc analyses involving multiple comparison could introduce some biases and must be taken into consideration. Further efficacy and adverse events analyses in a phase 3, comparative study is warranted.

Conclusions

This proof-of-concept randomized clinical trial highlighted the efficacy of combining the JAK1/JAK2 inhibitor baricitinib with narrowband UV-B in the treatment of adults with active vitiligo. It is a valuable contribution to the growing interest in the use of JAK inhibitors to treat autoimmune conditions and justifies the completion of a larger confirmatory phase 3 trial in the future.

ARTICLE INFORMATION

Accepted for Publication: October 30, 2024.

Published Online: January 22, 2025. doi:10.1001/jamadermatol.2024.5737

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Author Contributions: Dr Seneschal had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Statistical analysis: Seneschal, Guyon.
Obtained funding: Seneschal, Guyon, Boniface.
Administrative, technical, or material support: Seneschal, Mazereeuw-Hautier, Andreu.
Supervision: Seneschal, Mazereeuw-Hautier.

Conflict of Interest Disclosures: Dr Seneschal reported grants from Eli Lilly during the conduct of the study; grants from Calypso Biotech, Eli Lilly, Leo Pharma, Pfizer, Pierre Fabre, Sanofi, and Sun Pharmaceuticals; and personal fees from AbbVie, Bristol Myers Squibb, Novartis, and Viela Bio outside the submitted work; and has a patent for MMP9 inhibitors and uses thereof in the prevention or treatment of a depigmenting disorder issued and a patent for 3-dimensional model of depigmenting disorder licensed. Dr Passeron reported personal fees from Almirall, Abbvie, Amgen, Bristol Myers Squibb, Celgene, Galderma, GlaxoSmithKline, Incyte, Janssen, Leo Pharma, Eli Lilly, Merck Sharpe & Dohme, Novartis, Pfizer, Sanofi–Genzyme, Sun Pharmaceuticals, and UCB outside the submitted work. Dr Boniface reported grants from Eli Lilly during the conduct of the study; grants from Calypso, Leo Pharma, Pfizer, Pierre Fabre, Sanofi, and Almirall; and nonfinancial support from AnaptysBio outside the submitted work; and has a patent for WO2018109222A1 issued. No other disclosures were reported.

Funding/Support: This study was funded by Eli Lilly.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Meeting Presentation: These data have been previously presented in part at the European Academy of Dermatology and Venereology Congress; October 13, 2023; Berlin, Germany; and at the Global Vitiligo Foundation meeting; March 7, 2024; San Diego, California.

Data Sharing Statement: See Supplement 3.

Additional Contributions: We thank the patients for granting permission to publish this information. We thank Ali Hutton, MSc, and Duncan Marriott, PhD (Rx Communications, Mold, UK), for providing writing and editorial assistance, for which they were compensated.

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