Once-daily upadacitinib versus placebo in adults with extensive non-segmental vitiligo: a phase 2, multicentre, randomised, double-blind, placebo-controlled, dose-ranging study

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eClinicalMedicine 2024;73: 102655
Published Online xxx
https://doi.org/10.1016/j.eclinm.2024.102655

Summary

Background Janus kinase (JAK) inhibition is a promising approach for treating vitiligo. We aimed to assess the efficacy and safety of upadacitinib, an oral selective JAK inhibitor, in adults with non-segmental vitiligo.

Methods This was a phase 2, multicentre, randomised, double-blind, placebo-controlled, dose-ranging study completed at 33 clinical centres in the United States, Canada, France, and Japan. Eligible patients were aged 18–65 years with non-segmental vitiligo and had a Facial Vitiligo Area Scoring Index (F-VASI) ≥0.5 and a Total Vitiligo Area Scoring Index (T-VASI) ≥5. Patients were randomly assigned (2:2:2:1:1) using an interactive response technology to receive upadacitinib 6 mg (UPA6), upadacitinib 11 mg (UPA11), upadacitinib 22 mg (UPA22), or placebo (PBO; preassigned to switch to either UPA11 or UPA22 in period 2) once daily for 24 weeks (period 1). For weeks 24–52 (period 2), patients randomly assigned to upadacitinib continued their treatment, and patients receiving PBO switched to their preassigned upadacitinib dose in a blinded fashion. The primary endpoint was the percent change from baseline in F-VASI at week 24. Efficacy was analysed in the intention-to-treat population, and safety was examined in all randomly assigned patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT04927975.

Findings Between June 16, 2021, and June 27, 2022, 185 patients (including 115 [62%] who were female and 70 [38%] who were male) were randomly assigned to UPA6 (n = 49), UPA11 (n = 47), UPA22 (n = 43), or PBO (n = 46). At week 24, the LS mean difference versus PBO in the percent change from baseline in F-VASI was −7.60 (95% CI −22.18 to 6.97; p = 0.3037) for UPA6, −21.27 (95% CI −36.02 to −6.52; p = 0.0051) for UPA11, and −19.60 (95% CI −35.04 to −4.16; p = 0.0132) for UPA22. The LS mean difference versus PBO in the percent change from baseline in T-VASI was −7.45 (95% CI −16.86 to 1.96; p = 0.1198) for UPA6, −10.84 (95% CI −20.37 to −1.32; p = 0.0259) for UPA11 and −14.27 (95% CI −24.24 to −4.30; p = 0.0053) for UPA22. Ongoing treatment with upadacitinib induced continuous skin repigmentation over time without reaching a plateau through week 52. The rates for study drug discontinuation and serious treatment-emergent adverse events (TEAEs) were higher in the UPA22 group than in the UPA11 and UPA6 groups. Eight serious TEAEs, including one death of unknown cause and one case of infiltrating lobular breast carcinoma, were reported through 52 weeks; only two serious TEAEs (coronary artery arteriosclerosis [UPA6 (n = 1)] and non-fatal ischemic stroke [UPA11 (n = 1)]) were deemed by the investigator to have a reasonable possibility of being related to study drug. The one case of breast cancer in the UPA11 group was deemed unrelated to study drug, and the one death of unknown cause in the UPA22 group was reviewed and adjudicated and was deemed to be unrelated to study drug. The most common TEAEs were COVID-19, headache, acne, and fatigue. No new safety signals were observed.

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Interpretation Upadacitinib monotherapy led to substantial repigmentation of both facial and total body vitiligo lesions and may offer an effective treatment option for adults with extensive non-segmental vitiligo. Based on these findings, upadacitinib 15 mg is being investigated in adults and adolescents with non-segmental vitiligo in an ongoing phase 3 randomised controlled trial.

Funding AbbVie Inc.

Keywords: Clinical trial; Phase 3; Janus kinase inhibitors; Randomised controlled trial; Upadacitinib; Vitiligo

Research in context

Evidence before this study

Vitiligo remains challenging to treat and currently there are no approved systemic biologic or targeted therapies. The interferon gamma/Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway plays a central role in vitiligo pathogenesis, and JAK inhibition has been proposed as a promising therapeutic approach to treat vitiligo. A PubMed search for articles published in English between database inception and November 28, 2023, using the terms "vitiligo" AND "Janus kinase" was performed. Our search yielded 114 results. By using "clinical trial" as the MeSH term or article type, we identified four relevant studies. We conducted a separate search focusing on clinical trials evaluating oral or systemic treatments for vitiligo, but this search yielded few results. Topical ruxolitinib is currently approved for the treatment of non-segmental vitiligo in patients aged 12 years or older as reported in two randomised phase 3 studies; ruxolitinib, however, can only be applied to less than 10% of body surface area and does not prevent new lesions in untreated areas. Systemic agents are needed to treat patients with widespread and/or actively progressing disease. Oral ruxolitinib (a selective JAK1 and JAK2 inhibitor) and tofacitinib (an oral pan-JAK inhibitor) have shown efficacy in treating vitiligo in multiple case reports; however, these inhibitors have not yet been evaluated in clinical trials. A recent phase 2b study of ritlecitinib, an oral JAK3/tyrosine kinase expressed in hepatocellular carcinoma (TEC) inhibitor, demonstrated efficacy over placebo on the Facial Vitiligo Area Scoring Index (F-VASI) at week 24, but did not demonstrate superiority over placebo on the Total Vitiligo Area Scoring Index (T-VASI) in adults with active non-segmental vitiligo based on body involvement at the end of the double-blind, placebo-controlled period. At the initiation of the current study, no findings from other double-blind phase 2 or 3 studies have demonstrated the superiority of an oral JAK inhibitor over placebo based on T-VASI. Whether oral JAK inhibitors are effective as monotherapy for the repigmentation of larger body areas as assessed by T-VASI remains to be established. Upadacitinib is an oral selective JAK1 inhibitor that has demonstrated superior efficacy and acceptable safety in several immune-mediated conditions and is approved in multiple countries for the treatment of atopic dermatitis, rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease, ankylosing spondylitis, and non-radiographic axial spondyloarthritis.

Added value of this study

To the best of our knowledge, this is the first report of a phase 2 clinical trial evaluating an oral selective JAK1 inhibitor for the treatment of extensive non-segmental vitiligo. The primary endpoint was achieved with upadacitinib 11 mg and upadacitinib 22 mg. Upadacitinib continued to induce progressive repigmentation over time through 52 weeks of treatment. No new safety signals were identified beyond the upadacitinib safety profile previously reported in other disease states.

Implications of all the available evidence

Results from this study demonstrate that upadacitinib may represent a new treatment option for vitiligo, a condition with no approved systemic treatments and substantiate the clinical advancement of upadacitinib into phase 3 studies for vitiligo. Our findings support previous reports hypothesizing that JAK inhibition is a promising new treatment option for vitiligo and suggest upadacitinib monotherapy provides safe and effective facial and total body repigmentation in patients with extensive non-segmental vitiligo.

Introduction

Vitiligo is a chronic, immune-mediated disease[1–3] with a global prevalence ranging from 0.5% to 2%.[1] Vitiligo is characterized by patchy areas of depigmentation due to melanocyte loss in the epidermis or mucosa.[1–3] Areas of depigmentation may be localized to one side of the body in segmental vitiligo, or present with a bilateral distribution in non-segmental vitiligo.[2] Non-segmental vitiligo is more common and characterized by progressive onset with multiple flareups.[2]

Impairments in quality of life and negative effects on well-being,[2,4,5] as well as substantial increases in

healthcare costs and resource utilization, have been well established for vitiligo.[6] Patients with vitiligo often experience coexisting psychological conditions of anxiety, depression, sleep disturbance, and difficulties with relationships.[7] Globally, patients continue to be stigmatized, with vitiligo being considered a disqualifying condition for government or military positions in some countries.[8] Higher psychosocial disease burden and poorer well-being is generally experienced by females; individuals younger than 30 years; those with darker skin; and those with visibly affected areas, especially facial; and those with extensive body area involvement.[7,9] While therapeutic interventions provide improvements in quality of life,[5] many patients are not satisfied with their current treatment regimen and express a need for improved therapeutic options.[10]

Before the approval of topical ruxolitinib,[11] there were no approved repigmenting therapies for vitiligo; conventional treatment generally includes topical corticosteroids, topical calcineurin inhibitors, phototherapy, oral corticosteroids, and systemic immunosuppressants.[12] However, all available treatments have limitations.[13] Topical ruxolitinib can only be applied to less than 10% of the body surface area.[11] Patients with extensive, active, and/or rapidly progressing vitiligo depigmentation may require systemic treatment.[14,15]

Skin depigmentation associated with vitiligo is thought to involve melanocyte-specific CD8+ T cells infiltrating the affected skin, leading to loss of melanocytes.[3,16,17] When melanocyte-reactive CD8+ T cells encounter a melanocyte antigen, they produce interferon gamma,[3,16,18] which stimulates keratinocytes to express CXCL9 and CXCL10.[16] These chemokines bind to the CXCR3 receptor of melanocyte-reactive CD8+ T cells and recruit these cytotoxic T cells to the skin. The melanocyte-reactive CD8+ T cells produce more interferon gamma, which causes melanocyte destruction through the production of cytotoxic enzymes.[3,16,18] Vitiligo disease progression occurs via this positive-feedback loop of T-cell recruitment leading to continual loss of melanocytes.[18] Janus kinases (JAKs) are a family of cytoplasmic tyrosine kinases that assist with cytokine-mediated signal transduction through the JAK/signal transducer and activator of transcription (STAT) pathway.[3] This pathway is activated by interferon gamma and is involved in many immune-related disorders, including vitiligo.[3] JAK inhibition is a promising approach for the treatment of vitiligo as it disrupts the process of immune-mediated melanocyte apoptosis.[3]

Upadacitinib (RINVOQ; AbbVie Inc., North Chicago, IL, USA) is an oral, small-molecule, reversible JAK inhibitor that has greater inhibitory potency for JAK1 than for JAK2, JAK3, or tyrosine kinase 2.[19] Upadacitinib is approved for the treatment of several immune-mediated diseases including atopic dermatitis, Crohn's disease, ulcerative colitis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis.[20]

Here, we report the primary results through week 52 from a phase 2 dose-ranging study of upadacitinib monotherapy, which aimed to assess the efficacy and safety of upadacitinib for the treatment of adults with extensive non-segmental vitiligo.

Methods

Study design and participants

This was a phase 2, multicentre, randomised, double-blind, parallel-group, placebo-controlled, dose-ranging study performed at 33 clinical sites in the United States, Canada, France, and Japan. This 52-week study had a 35-day screening period, a 24-week double-blind treatment period (period 1), a 28-week blinded long-term extension period (period 2), and a 30-day follow-up period (Appendix Supplementary Figure S1).

Eligible patients were aged 18–65 years with non-segmental vitiligo and baseline scores of Facial Vitiligo Area Scoring Index (F-VASI) ≥0.5 and Total Vitiligo Area Scoring Index (T-VASI) ≥5. Patients with skin conditions that may interfere with the evaluation of vitiligo, those with uncontrolled thyroid disease, and patients with >33% leukotrichia on the face or >33% leukotrichia on the body (including face) were not eligible. Exclusionary prior therapies included any topical or systemic JAK inhibitor and permanent skin bleaching agents. A complete list of eligibility criteria is provided in the appendix (Supplementary Table S1).

Ethics

Independent ethics committees or institutional review boards at each site approved the study protocol, informed consent forms, and recruitment materials before patient enrolment. This study was conducted in accordance with the International Conference for Harmonisation guidelines, applicable regulations, and the Declaration of Helsinki. To protect patients' confidentiality, all patients and their associated samples were assigned a numerical code; no identifiable information was provided to the sponsor. All patients provided written informed consent before screening.

Randomisation and masking

Patients were randomly assigned (2:2:2:1:1) to one of five treatment groups using an interactive response technology system according to a schedule generated and distributed by randomisation specialists at AbbVie using WebRando. Block randomisation with a block size of 16 was used. Patient randomisation was stratified by age (≤50 versus > 50 years), baseline disease severity (T-VASI <15 versus T-VASI ≥15), and status of active vitiligo (Yes versus No). Patients received upadacitinib 6 mg (UPA6), upadacitinib 11 mg (UPA11), upadacitinib 22 mg (UPA22), or placebo (PBO; prespecified to

switch to either UPA11 or UPA22 in period 2) once daily for 24 weeks (period 1). For weeks 24–52 (period 2), patients randomised to UPA continued their treatment and patients receiving PBO switched to either UPA11 or UPA22 in a blinded fashion per prespecified randomised assignments. Upadacitinib and PBO tablets were identical in appearance. The AbbVie study team was blinded until the week 24 primary analysis. Patients, study investigators, and study site personnel were blinded to treatment throughout the study.

Procedures

Patients received a single daily, orally administered 6 mg, 11 mg, or 22 mg tablet of upadacitinib or PBO. Patients were encouraged to swallow the tablet at approximately the same time each day, with or without food. Patients were required to discontinue systemic vitiligo therapy (eg, corticosteroids, methotrexate) or supplemental vitiligo therapy (eg, antioxidants, herbal medicine) and any topical vitiligo therapy at least 30 days before the first dose of study drug. Patients could not have received any phototherapy for a minimum of 12 weeks before the first dose of study drug. Patients were allowed to receive natural daily light following a normal routine, but for a prolonged exposure to sunlight, sunscreen was recommended. Efficacy was assessed at baseline and study visits at weeks 2, 4, 8, 12, 18, 24, 28, 36, 44, and 52. Safety was monitored throughout the study and through 30 days following the last dose of study drug.

Outcomes

The primary efficacy endpoint was the percent change from baseline in F-VASI at week 24. Secondary endpoints at week 24 included the percent change from baseline in T-VASI, achievement of at least a 75% improvement (decrease) in F-VASI from baseline (F-VASI 75), achievement of at least a 50% improvement (decrease) in F-VASI from baseline (F-VASI 50), achievement of at least a 50% improvement (decrease) from baseline (T-VASI 50), and the change from baseline in the vitiligo quality-of-life (VitiQoL) instrument total score.

Additional efficacy endpoints assessed at week 24 included the percent change from baseline in the vitiligo extent score (VES), achievement of vitiligo noticeability scale (VNS) score of "a lot less noticeable (4)" or "no longer noticeable (5)," achievement of Physician's Global Impression of Change-Vitiligo (Physician's GIC-V) of "much better (1)" or "a little better (2)," and achievement of Patient's Global Impression of Change-Vitiligo (Patient's GIC-V) of "much better (1)" or "a little better (2)," and the change in VitiQoL Skin condition severity. All efficacy measures mentioned above were assessed at all other study visits up to week 52 as prespecified additional endpoints.

Safety was evaluated by the number and proportion of patients experiencing adverse events (AEs). Vital signs were measured, laboratory tests were performed, and physical examinations were completed throughout the study. The following AEs were assessed: treatment-emergent adverse events (TEAEs), serious AEs, TEAEs leading to death, TEAEs considered to be related to study drug, TEAEs leading to discontinuation of study drug, any severe TEAEs (grade 3 or above according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5), and TEAEs of special interest prespecified based on previous observations in patients receiving upadacitinib.

For period 1, TEAEs were defined as any AE that began or worsened after initiation of study drug through 30 days following the last dose of study drug in period 1 and before the first dose in period 2. For period 2, TEAEs were defined as any AE that began or worsened after initiation of study drug in period 2 through 30 days following the last dose of study drug in period 2. Exposure-adjusted number of events per 100 patient-years (PYs) for TEAEs occurring during the study were calculated for patients receiving any upadacitinib dose to adjust for differences in duration of upadacitinib treatment and potentially differences in duration of follow-up.

Statistical analysis

The primary analyses for all efficacy endpoints were conducted after all patients completed week 24 (period 1) or had prematurely discontinued from the study before week 24. This was the only and final analysis of efficacy for these endpoints in period 1. Assuming a week 24 percent change from baseline in F-VASI of 0% in the PBO arm, the planned sample size of 160 adults (40 patients per treatment group) in period 1 of the study would provide >90% power to detect the treatment difference of 40% reduction (assuming a standard deviation of 54.8%) in at least one upadacitinib group versus PBO. All statistical tests were two-sided at an alpha level of 0.1. There was no control for overall type 1 error or multiplicity; all p values are nominal. Efficacy analyses were conducted on the intention-to-treat population for each period of the study and were defined for period 1 as all patients who were randomised at baseline and for period 2 as all patients who entered period 2. Safety analyses were performed for period 1 on the safety population defined as all randomised patients who received at least one dose of study drug and on the "any upadacitinib treatment" population defined as all randomised patients who received at least one dose of upadacitinib during the study.

In period 1, continuous and categorical endpoints were analysed using the mixed-effect model repeat measurement (MMRM) and the Cochran-Mantel-Haenszel test, respectively. The MMRM included treatment, visit, and treatment-by-visit interaction, and stratification factors (age group [≤50 and > 50 years], baseline disease severity [T-VASI <15 and ≥ 15], and

status of active vitiligo [Yes/No]) as fixed factors and baseline value as a covariate. The Cochran-Mantel-Haenszel tests were adjusted for strata (age group [≤50 and > 50 years], baseline disease severity [T-VASI <15 and ≥ 15], and status of active vitiligo [Yes/No]) for comparison of two treatment groups. Treatment policy was used for handling the intercurrent events (ie, no intercurrent events were considered in this study). The primary approach to handling missing data for continuous endpoints was MMRM and for categorical endpoints was non-responder imputation incorporating multiple imputation (NRI-MI) for handling missing data due to COVID-19. In period 2, continuous endpoints were analysed using analysis of covariance model, and categorical endpoints were summarized descriptively. To summarize long-term efficacy up to week 52, all values collected in the study were used as observed (AO); missing evaluations were not imputed, and, thus, patients without an evaluation at a scheduled visit were not included in the AO analysis for that visit. Additional long-term analyses up to week 52 were performed using MMRM for selective continuous endpoints and NRI-MI for selective categorical variables. Baseline demographics (eg, self-reported sex, race) and safety data were summarized descriptively; missing safety data were not imputed. All statistical analyses were performed using SAS version 9.4 or later (SAS Institute, Cary, NC, USA) using the UNIX operating system. The study is registered with ClinicalTrials.gov, NCT04927975.

Role of the funding source

The design, study conduct, and financial support for this study was provided by AbbVie. AbbVie designed the study and performed data analyses and interpretation. The funders participated in writing, review, and approval of the manuscript. All authors had full access to the data, reviewed and approved the final version, and were responsible for the decision to submit the manuscript for publication. Medical writers, funded by AbbVie, assisted with manuscript preparation under the authors' direction.

Results

Between June 16, 2021, and June 27, 2022, 243 patients were screened and 185 were randomly assigned to receive either UPA6 (n = 49), UPA11 (n = 47), UPA22 (n = 43), or PBO (n = 46); 129 (92.8%) of the 139 patients in the upadacitinib groups and 44 (95.7%) of the 46 in the PBO group completed period 1. Of the 43 patients who received PBO in period 1 and entered period 2, 21 (48.8%) switched to UPA11 and 22 (51.2%) switched to UPA22 (Fig. 1). Nineteen (10.3%) of 185 patients discontinued study drug during period 1, and the rate of discontinuation of study drug in period 1 was higher in the UPA22 group than in the other treatment groups. An additional 21 patients discontinued study drug during period 2. All randomly assigned patients were included in the efficacy analyses.

Demographics and baseline disease characteristics were generally balanced among treatment groups (Table 1). Of 185 patients, 115 (62.2%) were female, 138 (74.6%) were White, and the mean age was 46.3 (SD 11.3) years. Overall, at baseline, the mean T-VASI was 21.53 (SD 16.66) and the mean F-VASI was 1.09 (SD 0.66). Of 185 patients, 126 (68.1%) had a baseline T-VASI above 10, and the mean duration since vitiligo diagnosis was 16.8 years (SD 13.2). Overall, 131 (70.8%) of 185 patients were designated by the investigators at baseline as having active vitiligo.

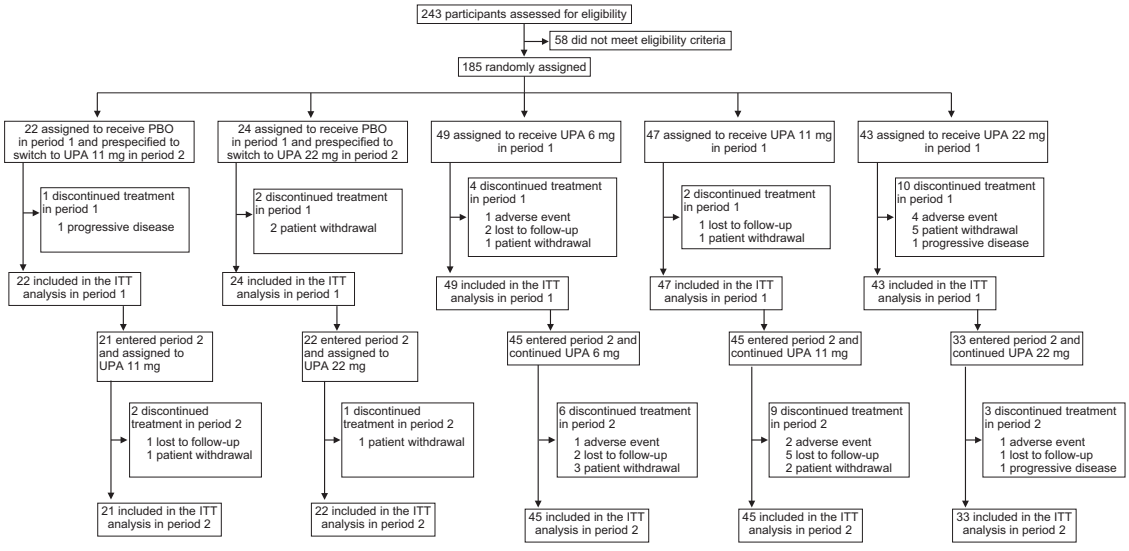

***Fig. 1:* Trial participants flow diagram**. ITT, intention to treat; PBO, placebo; UPA, upadacitinib.

	PBO (n = 46)	UPA 6 mg (n = 49)	UPA 11 mg (n = 47)	UPA 22 mg (n = 43)
Sex, n (%)				
Female	29 (63.0%)	26 (53.1%)	34 (72.3%)	26 (60.5%)
Male	17 (37.0%)	23 (46.9%)	13 (27.7%)	17 (39.5%)
Age, years				
Mean (SD)	46.8 (10.48)	45.1 (11.68)	45.5 (11.90)	48.2 (11.13)
Median (range)	47.5 (18–64)	45.0 (19–66)	45.0 (22–65)	49.0 (19–65)
Age group, n (%)				
≤50 years	26 (56.5%)	28 (57.1%)	28 (59.6%)	25 (58.1%)
>50 years	20 (43.5%)	21 (42.9%)	19 (40.4%)	18 (41.9%)
BMI, kg/m^2, mean (SD)	27.3 (8.1)	27.6 (5.7)	27.5 (6.6)	27.9 (5.8)
Race, n (%)[a]				
White	34 (77.3%)	35 (72.9%)	36 (76.6%)	33 (78.6%)
Black or African American	4 (9.1%)	3 (6.3%)	3 (6.4%)	1 (2.4%)
Asian	6 (13.6%)	6 (12.5%)	7 (14.9%)	6 (14.3%)
American Indian/Alaska Native	0	0	0	1 (2.4%)
Native Hawaiian/Pacific Islander	0	1 (2.1%)	0	0
Multiple	0	3 (6.4%)	1 (2.1%)	1 (2.4%)
Ethnicity, n (%)				
Hispanic or Latino	5 (10.9%)	6 (12.2%)	4 (8.5%)	5 (11.6%)
Fitzpatrick skin types, n (%)				
I	3 (6.5%)	1 (2.0%)	1 (2.1%)	1 (2.3%)
II	11 (23.9%)	13 (26.5%)	15 (31.9%)	14 (32.6%)
III	17 (37.0%)	17 (34.7%)	19 (40.4%)	17 (39.5%)
IV	9 (19.6%)	11 (22.4%)	9 (19.1%)	9 (20.9%)
V	4 (8.7%)	5 (10.2%)	2 (4.3%)	2 (4.7%)
VI	2 (4.3%)	2 (4.1%)	1 (2.1%)	0
Country, n (%)				
United States	23 (50.0%)	26 (53.1%)	24 (51.1%)	21 (48.8%)
Canada	6 (13.0%)	11 (22.4%)	8 (17.0%)	7 (16.3%)
France	12 (26.1%)	10 (20.4%)	11 (23.4%)	11 (25.6%)
Japan	5 (10.9%)	2 (4.1%)	4 (8.5%)	4 (9.3%)
Duration since vitiligo diagnosis, years, mean (SD)	18.5 (13.8)	16.0 (11.4)	17.9 (13.9)	14.7 (13.7)
Active vitiligo, n (%)	34 (73.9%)	33 (67.3%)	32 (68.1%)	32 (74.4%)
Total-Physician Global Vitiligo Assessment of depigmentation, n (%)[a]				
None	1 (2.3%)	0	0	0
Limited	2 (4.7%)	1 (2.1%)	7 (15.6%)	1 (2.5%)
Moderate	17 (39.5%)	24 (50.0%)	19 (42.2%)	21 (52.5%)
Extensive	18 (41.9%)	17 (35.4%)	16 (35.6%)	17 (42.5%)
Very extensive	5 (11.6%)	6 (12.5%)	3 (6.7%)	1 (2.5%)
Total-Patient Global Vitiligo Assessment of depigmentation, n (%)[a]				
None	0	0	0	1 (2.3%)
Limited	3 (6.8%)	2 (4.1%)	6 (12.8%)	2 (4.7%)
Moderate	21 (47.7%)	21 (42.9%)	13 (27.7%)	12 (27.9%)
Extensive	16 (36.4%)	15 (30.6%)	18 (38.3%)	20 (46.5%)
Very extensive	4 (9.1%)	11 (22.4%)	10 (21.3%)	8 (18.6%)
F-VASI, mean (SD)	1.04 (0.61)	1.15 (0.77)	1.02 (0.58)	1.16 (0.66)
T-VASI, mean (SD)	21.01 (16.95)	20.99 (15.97)	22.32 (18.18)	21.84 (15.93)
T-VASI >10, n (%)	32 (69.6%)	33 (67.3%)	30 (63.8%)	31 (72.1%)
T-VASI ≥15, n (%)	26 (56.5%)	29 (59.2%)	27 (57.4%)	25 (58.1%)
VES, mean (SD)	16.87 (16.54)	18.77 (18.11)	17.70 (15.31)	20.16 (16.91)
Prior topical therapy, n (%)	23 (50.0%)	20 (40.8%)	20 (42.6%)	18 (41.9%)
Prior phototherapy, n (%)	12 (26.1%)	4 (8.2%)	9 (19.1%)	10 (23.3%)

[a]Values are based on non-missing values from randomised patients. BMI, body mass index; F-VASI, Facial Vitiligo Area Scoring Index; PBO, placebo; T-VASI, Total Vitiligo Area Scoring Index; UPA, upadacitinib; VES, Vitiligo extent score.

Table 1: **Demographics and baseline characteristics of the intention-to-treat population (N = 185).**

The primary endpoint was achieved at week 24 for UPA11 and UPA22, but not for UPA6. At week 24, the least squares (LS) mean difference versus PBO in the percent change from baseline in F-VASI was −7.60 (95% CI −22.18 to 6.97; p = 0.3037) for UPA6, −21.27 (95% CI −36.02 to −6.52; p = 0.0051) for UPA11, and −19.60 (95% CI −35.04 to −4.16; p = 0.0132) for UPA22 (Table 2, Fig. 2). The LS mean percent change from baseline in F-VASI with UPA6, UPA11, and UPA22 at week 24 was generally consistent across prespecified subgroups including age, disease severity, Fitzpatrick skin types, and status of active vitiligo (Appendix Supplementary Figure S2). At week 24, the LS mean difference versus PBO in the percent change from baseline in T-VASI was −7.45 (95% CI −16.86 to 1.96; p = 0.1198) for UPA6, −10.84 (95% CI −20.37 to −1.32; p = 0.0259) for UPA11, and −14.27 (95% CI −24.24 to −4.30; p = 0.0053) for UPA22 (Table 2, Fig. 2). A greater proportion of patients reached F-VASI 75 at week 24 with UPA6 (four [8.2%] of 49 patients; difference versus PBO was 6.9%; 95% CI −1.3 to 15.2; p = 0.1000), UPA11 (nine [19.1%] of 47 patients; difference versus PBO was 17.8%; 95% CI 6.5–29.0; p = 0.0020), and UPA22 (six [14.0%] of 43 patients; difference versus PBO was 11.7%; 95% CI 1.4–21.9; p = 0.0258) than with PBO (one [2.2%] of 46 patients). Additionally, a greater proportion of patients reached F-VASI 50 with UPA6 (eight [16.3%] of 49 patients; difference versus PBO was 6.6; 95% CI −6.6 to 19.7; p = 0.3266), UPA11 (18 [38.3%] of 47 patients; difference versus PBO was 29.3%; 95% CI 13.8%–44.9; p = 0.0002), and UPA22 (17 [39.5%] of 43 patients; difference versus PBO was 28.7%; 95% CI 12.6–44.7; p = 0.0005) than with PBO (five [10.9%] of 46 patients) (Table 2). T-VASI 50 was reached by five (11.6%) of 43 patients receiving UPA22 with an adjusted difference versus PBO of 9.1% (95% CI 1.0–17.2; p = 0.0269). The change from baseline in VitiQoL total score at week 24 with any upadacitinib dose was similar to that observed with PBO.

At 24 weeks, a greater proportion of physicians reported clinically meaningful improvements ("much better [1]" or "a little better [2]" based on the Physician's GIC-V) for 21 (42.9%) of 49 patients in the UPA6 group (difference versus PBO was 18.2%; 95% CI 0.6–35.9; p = 0.0428), 28 (59.6%) of 47 patients in the UPA11 group (difference versus PBO was 37.8%; 95% CI 20.6–55.0; p < 0.0001), and 24 (55.8%) of 43 patients in the UPA22 group (difference versus PBO was 32.0%; 95% CI 14.0–50.0; p = 0.0005) compared with 11 (23.9%) of 46 patients in the PBO group (Table 2). The change from baseline in VitiQoL skin condition severity at week 24 was greater with UPA6 compared with PBO (difference versus PBO −0.4; 95% CI −0.8 to 0.0; p = 0.0545) and similar to that observed with PBO for UPA11 and UPA22. Clinically meaningful improvements ("much better [1]" or "a little better [2]" based on the Patient's GIC-V) were reported by a greater proportion of patients in the UPA6 group (17 [34.7%] of 49 patients; difference versus PBO was 14.3%; 95% CI −1.8 to 30.4; p = 0.0810), UPA11 group (26 [55.3%] of 47 patients; difference versus PBO was 38.5%; 95% CI 22.7–54.2; p < 0.0001), and the UPA22 group (26 [60.5%] of 43 patients; difference versus PBO was 41.1%, 95% CI 23.6–58.5; p < 0.0001). Additionally, improvement from baseline in the vitiligo extent score was greater with UPA22 compared with PBO (difference versus PBO −15.05%; 95% CI −27.10 to −3.01; p = 0.0146). Patient-reported noticeability as measured by the VNS indicated five (11.6%) of 43 patients who received UPA22 experienced clinically meaningful improvements ("a lot less noticeable [4]" or "no longer noticeable [5]") compared with no patients who received UPA6, UPA11, or PBO (adjusted difference versus PBO was 11.7%; 95% CI 3.5–20.0; p = 0.0054).

Ongoing treatment with upadacitinib induced progressive skin repigmentation over time without reaching a plateau through week 52. Based on AO data, F-VASI 75 was achieved at week 52 by 14 (36.8%) of 38 patients continuing UPA6, 24 (63.2%) of 38 patients continuing UPA11, and 11 (37.9%) of 29 patients continuing UPA22 (Table 3, Fig. 3). Similarly, T-VASI 50 was achieved by 12 (31.6%) of 38 patients receiving UPA6, 15 (39.5%) of 38 patients receiving UPA11, and 12 (41.4%) of 29 patients receiving UPA22. Among patients receiving PBO during period 1, only one (2.3%) of 43 patients assigned to PBO had reached either F-VASI 75 or T-VASI 50 at week 24. Yet, seven (36.8%) and four (21.1%) of 19 patients who switched from PBO to UPA11 reached F-VASI 75 and T-VASI 50 at week 52, respectively (Fig. 3). Likewise, six (28.6%) and two (9.5%) of 21 patients who switched to UPA22 reached F-VASI 75 and T-VASI 50 at week 52, respectively. Based on the Patient's GIC-V, 30 (76.9%) of 39 patients receiving UPA6, 34 (89.5%) of 38 patients receiving UPA11, and 25 (83.3%) of 30 patients receiving UPA22 perceived their vitiligo to be "much better [1]" or "a little better [2]" at week 52 (Table 3).

In period 2, additional analyses conducted using MMRM/NRI-MI for missing data are presented in appendix Supplementary Table S2. The percentage of patients achieving F-VASI 75 and T-VASI 50 through week 52 based on NRI-MI data are presented in appendix Supplementary Figure S3. The LS mean percent change from baseline in F-VASI and T-VASI through week 52 using AO data are presented in appendix Supplementary Figure S4.

During period 1, the incidence of any TEAEs was similar between upadacitinib and PBO (Table 4). The most common TEAEs were COVID-19, headache, acne, and fatigue. Most TEAEs were mild or moderate (appendix Supplementary Table S3); no severe TEAEs occurred in more than one patient. TEAEs designated by investigators as related to study drug occurred in 15

	PBO (n = 46)	UPA 6 mg (n = 49)	UPA 11 mg (n = 47)	UPA 22 mg (n = 43)
Primary endpoint				
Percent change from BL in F-VASI at week 24, LS mean (95% CI)	(n = 43) −14.36 (−24.86 to −3.85)	(n = 45) −21.96 (−32.18 to −11.75)	(n = 43) −35.63 (−46.11 to −25.14)	(n = 33) −33.96 (−45.41 to −22.50)
Difference versus PBO, LS mean (95% CI)	–	−7.60 (−22.18 to 6.97) p = 0.3037	−21.27 (−36.02 to −6.52) p = 0.0051	−19.60 (−35.04 to −4.16) p = 0.0132
Secondary endpoints				
Percent change in T-VASI at week 24	(n = 43)	(n = 45)	(n = 43)	(n = 33)
Percent change from BL, LS mean (95% CI)	−6.42 (−13.17 to 0.34)	−13.87 (−20.45 to −7.29)	−17.26 (−24.00 to −10.52)	−20.69 (−28.05 to −13.32)
Differences versus PBO, LS mean (95% CI)	–	−7.45 (−16.86 to 1.96) p = 0.1198	−10.84 (−20.37 to −1.32) p = 0.0259	−14.27 (−24.24 to −4.30) p = 0.0053
F-VASI 75 at week 24				
Responder, n (%) (95% CI)	1 (2.2%) (0.0–6.4)	4 (8.2%) (0.5–15.8)	9 (19.1%) (7.9–30.4)	6 (14.0%) (3.6–24.3)
Adjusted difference versus PBO, % (95% CI)	–	6.9 (−1.3 to 15.2) p = 0.1000	17.8 (6.5–29.0) p = 0.0020	11.7 (1.4–21.9) p = 0.0258
F-VASI 50 at week 24				
Responder, n (%) (95% CI)	5 (10.9%) (1.9–19.9)	8 (16.3%) (6.0–26.7)	18 (38.3%) (24.4–52.2)	17 (39.5%) (24.9–54.1)
Adjusted difference versus PBO, % (95% CI)	–	6.6 (−6.6 to 19.7) p = 0.3266	29.3 (13.8–44.9) p = 0.0002	28.7 (12.6–44.7) p = 0.0005
T-VASI 50 at week 24				
Responder, n (%) (95% CI)	1 (2.2%) (0–6.4)	3 (6.1%) (0–12.8)	3 (6.4%) (0–13.4)	5 (11.6%) (2.0–21.2)
Adjusted difference versus PBO, % (95% CI)	–	3.7 (−3.9 to 11.2) p = 0.3396	3.8 (−4.3 to 11.8) p = 0.3579	9.1 (1.0–17.2) p = 0.0269
Change in VitiQoL total score at week 24	(n = 40)	(n = 44)	(n = 44)	(n = 34)
Change from BL, LS mean (95% CI)	−5.5 (−10.3 to −0.8)	−7.5 (−12.0 to −3.0)	−3.7 (−8.2 to 0.9)	−6.6 (−11.6 to −1.6)
Differences versus PBO, LS mean (95% CI)	–	−1.9 (−8.3 to 4.4) p = 0.5454	1.9 (−4.5 to 8.3) p = 0.5647	−1.1 (−7.8 to 5.6) p = 0.7535
Additional endpoints				
Percent change in VES at week 24	(n = 43)	(n = 45)	(n = 43)	(n = 33)
Percent change from BL, LS mean (95% CI)	−7.57 (−15.74 to 0.61)	−14.84 (−22.79 to −6.89)	−13.65 (−21.81 to −5.50)	−22.62 (−31.56 to −13.68)
Differences versus PBO, LS mean (95% CI)	–	−7.27 (−18.62 to 4.07) p = 0.2071	−6.09 (−17.57 to 5.39) p = 0.2966	−15.05 (−27.10 to −3.01) p = 0.0146
VNS score of 4 “a lot less noticeable” or 5 “no longer noticeable” at week 24				
VNS score of 4 or 5, n (%) (95% CI)	0	0	0	5 (11.6%) (2.0–21.2)
Adjusted difference versus PBO, % (95% CI)	–	–	–	11.7 (3.5–20.0) p = 0.0054
Physician’s GIC-V score of 1 “much better” or 2 “a little better” at week 24				
Responder, n (%) (95% CI)	11 (23.9%) (11.6–36.2)	21 (42.9%) (29.0–56.7)	28 (59.6%) (45.5–73.6)	24 (55.8%) (41.0–70.7)
Adjusted difference versus PBO, % (95% CI)	–	18.2 (0.6–35.9) p = 0.0428	37.8 (20.6–55.0) p < 0.0001	32.0 (14.0–50.0) p = 0.0005
Patient’s GIC-V score of 1 “much better” or 2 “a little better” at week 24				
Responder, n (%) (95% CI)	9 (19.6%) (8.1–31.0)	17 (34.7%) (21.4–48.0)	26 (55.3%) (41.1–69.5)	26 (60.5%) (45.9–75.1)
Adjusted difference versus PBO, % (95% CI)	–	14.3 (−1.8 to 30.4) p = 0.0810	38.5 (22.7–54.2) p < 0.0001	41.1 (23.6–58.5) p < 0.0001
Change in VitiQoL skin condition severity at week 24 (MMRM)	(n = 40)	(n = 44)	(n = 44)	(n = 34)
Change from BL, LS mean (95% CI)	−0.1 (−0.4 to 0.2)	−0.5 (−0.8 to −0.3)	0.0 (−0.3 to 0.2)	−0.1 (−0.4 to 0.2)
Differences versus PBO, LS mean (95% CI)	–	−0.4 (−0.8 to 0.0) p = 0.0545	0.1 (−0.3 to 0.5) p = 0.6700	0.1 (−0.4 to 0.5) p = 0.7764

Results for the binary endpoints are based on Cochran-Mantel-Haenszel test with non-responder imputation incorporating multiple imputation. Results for the continuous endpoints are based on MMRM. BL, baseline; F-VASI, Facial Vitiligo Area Scoring Index; F-VASI 50, at least a 50% improvement in F-VASI; F-VASI 75, at least a 75% improvement in F-VASI; GIC-V, Global Impression of Change-Vitiligo; LS, least squares; MMRM, mixed-effect model repeat measurement; PBO, placebo; T-VASI, Total Vitiligo Area Scoring Index; T-VASI 50, at least a 50% improvement in T-VASI; UPA, upadacitinib; VES, Vitiligo Extent Score; VitiQoL, vitiligo quality-of-life; VNS, Vitiligo Noticeability Scale.

Table 2: **Primary, secondary, and additional efficacy endpoints at week 24 in the intention-to-treat population.**

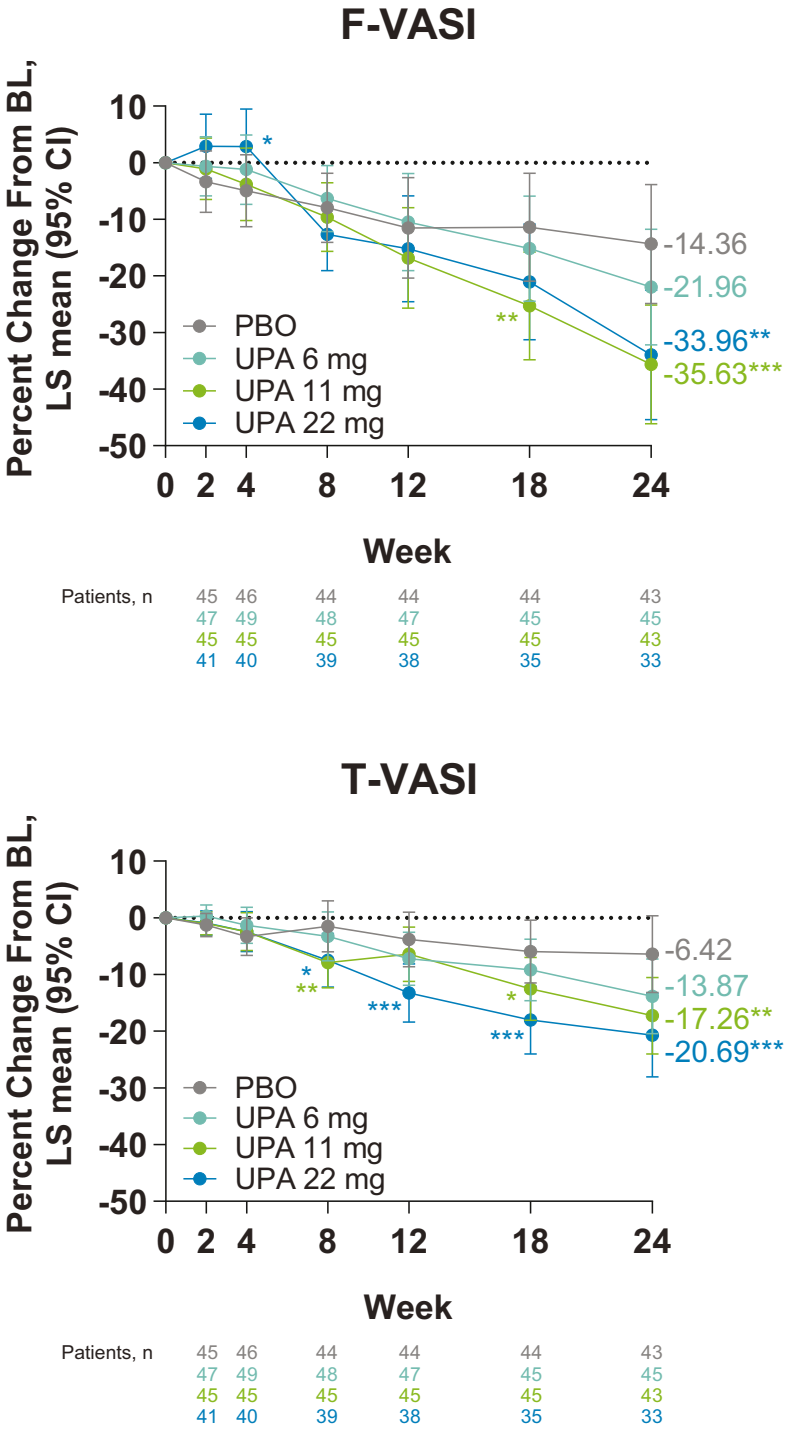

Fig. 2: **Percent change from baseline in F-VASI and T-VASI through week 24**. Data shown are based on mixed-effects model for repeated measures that included treatment, visit and treatment-by-visit interaction, and stratification factors (age group [≤50 and >50 years], baseline disease severity [T-VASI <15 and ≥ 15], and status of active vitiligo [Yes/No]) derived from actual values as fixed factors, and baseline value as a covariate. An unstructured variance covariance matrix was used. Parameter estimation was based on the assumption of data being missing at random and using the method of restrictive maximum likelihood. Values are LS mean (95% CI). BL, baseline; F-VASI, Facial Vitiligo Area Scoring Index; LS, least squares; PBO, placebo; T-VASI, Total Vitiligo Area Scoring Index; UPA, upadacitinib. *p ≤ 0.10; **p ≤ 0.05; ***p ≤ 0.01 versus PBO based on a two-sided test. There was no control for overall type I error or multiplicity; all p values for UPA versus PBO are nominal.

	PBO/UPA 11 mg	PBO/UPA 22 mg	UPA 6 mg	UPA 11 mg	UPA 22 mg
Percent change from BL in F-VASI, LS mean (95% CI)	(n = 19) −51.73 (−68.05 to −35.40)	(n = 21) −48.34 (−64.12 to −32.56)	(n = 38) −52.73 (−64.28 to −41.18)	(n = 38) −64.85 (−76.78 to −52.91)	(n = 29) −60.82 (−74.26 to −47.38)
F-VASI 75, n (%) (95% CI)	(n = 19) 7 (36.8%) (15.2–58.5)	(n = 21) 6 (28.6%) (9.2–47.9)	(n = 38) 14 (36.8%) (21.5–52.2)	(n = 38) 24 (63.2%) (47.8–78.5)	(n = 29) 11 (37.9%) (20.3–55.6)
F-VASI 50, n (%) (95% CI)	(n = 19) 10 (52.6%) (30.2–75.1)	(n = 21) 12 (57.1%) (36.0–78.3)	(n = 38) 19 (50.0%) (34.1–65.9)	(n = 38) 27 (71.1%) (56.6–85.5)	(n = 29) 20 (69.0%) (52.1–85.8)
Percent change from BL in T-VASI, LS mean (95% CI)	(n = 19) −33.80 (−45.67 to −21.93)	(n = 21) −26.95 (−38.54 to −15.37)	(n = 38) −35.13 (−43.50 to −26.75)	(n = 38) −44.71 (−53.39 to −36.02)	(n = 29) −44.39 (−54.09 to −34.68)
T-VASI 50, n (%) (95% CI)	(n = 19) 4 (21.1%) (2.7–39.4)	(n = 21) 2 (9.5%) (0.0–22.1)	(n = 38) 12 (31.6%) (16.8–46.4)	(n = 38) 15 (39.5%) (23.9–55.0)	(n = 29) 12 (41.4%) (23.5–59.3)
Change from BL in VitiQoL total score, LS mean (95% CI)	n = 17 −9.5 (−17.7 to −1.3)	n = 20 −7.9 (−15.7 to −0.2)	n = 39 −8.7 (−14.2 to −3.2)	n = 37 −5.3 (−11.1 to 0.5)	n = 30 −7.5 (−13.9 to −1.2)
Change from BL in VES, LS mean (95% CI)	(n = 19) −4.62 (−7.85 to −1.38)	(n = 21) −3.81 (−6.93 to −0.69)	(n = 38) −4.93 (−7.20 to −2.65)	(n = 37) −5.08 (−7.46 to −2.70)	(n = 29) −8.28 (−10.93 to −5.63)
VNS score of 4 "a lot less noticeable" or 5 "no longer noticeable", n (%) (95% CI)	(n = 19) 4 (21.1%) (2.7–39.4)	(n = 20) 2 (10.0%) (0.0–23.1)	(n = 39) 6 (15.4%) (4.1–26.7)	(n = 38) 6 (15.8%) (4.2–27.4)	(n = 30) 10 (33.3%) (16.5–50.2)
Physician's GIC-V score of 1 "much better" or 2 "a little better", n (%) (95% CI)	(n = 19) 14 (73.7%) (53.9–93.5)	(n = 21) 17 (81.0%) (64.2–97.7)	(n = 39) 32 (82.1%) (70.0–94.1)	(n = 39) 33 (84.6%) (73.3–95.9)	(n = 29) 24 (82.8%) (69.0–96.5)
Patient's GIC-V score of 1 "much better" or 2 "a little better", n (%) (95% CI)	(n = 19) 15 (78.9%) (60.6–97.3)	(n = 20) 13 (65.0%) (44.1–85.9)	(n = 39) 30 (76.9%) (63.7–90.1)	(n = 38) 34 (89.5%) (79.7–99.2)	(n = 30) 25 (83.3%) (70.0–96.7)

Results for the endpoints are based on as observed data. LS means and 95% CI are based on analysis of covariance for the continuous endpoints; 95% CI are based on normal approximation for the binary endpoints. BL, baseline; F-VASI, Facial Vitiligo Area Scoring Index; F-VASI 50, at least a 50% improvement in F-VASI; F-VASI 75, at least a 75% improvement in F-VASI; GIC-V, Global Impression of Change-Vitiligo; LS, least squares; PBO, placebo; T-VASI, Total Vitiligo Area Scoring Index; T-VASI 50, at least a 50% improvement in T-VASI; UPA, upadacitinib; VES, Vitiligo Extent Score; VitiQoL, vitiligo quality-of-life; VNS, Vitiligo Noticeability Scale.

Table 3: **Week 52 efficacy endpoints.**

(32.6%) of 46 patients receiving PBO, 14 of (28.6%) of 49 patients receiving UPA6, 17 (36.2%) of 47 patients receiving UPA11, and 14 (32.6%) of 43 patients receiving UPA22. Five patients had serious TEAEs (PBO, worsening nephrolithiasis unrelated to study drug [n = 1]; UPA6, coronary artery arteriosclerosis leading to study drug discontinuation that was considered by the investigator as reasonably possibly related to study drug [n = 1]; UPA22, COVID-19 pneumonia unrelated to study drug [n = 1], worsening uterus pain unrelated to study drug [n = 1], and death of unknown cause [n = 1]). The one reported death occurred in a 27-year-old male with attention deficit disorder, anxiety, alcohol use, as well as family history of cardiac death; the death was reviewed and adjudicated by an external cardiovascular adjudication committee and deemed as an undetermined/unknown cause of death; the investigator reported the death as having no reasonable possibility of being related to study drug. Five patients had any TEAE leading to discontinuation of study drug (PBO [n = 0], UPA6 [n = 1], UPA11 [n = 0], and UPA22 [n = 4]). TEAEs of special interest were reported for 18 (13.0%) of the 139 patients receiving upadacitinib. One patient in the UPA22 group had a serious infection of COVID-19 pneumonia leading to drug interruption, but this infection was not considered related to study drug. Six patients had hepatic disorders; all were due to laboratory abnormalities and were described as grade 1 or 2. Hematologic TEAEs of anaemia, neutropenia, and lymphopenia occurred infrequently, and none led to study drug discontinuation. Three patients had herpes zoster; all cases were localized, and none resulted in study drug discontinuation. In period 1, there were no reports of opportunistic infections, malignancy, non-melanoma skin cancer, lymphoma, adjudicated gastrointestinal perforation, renal dysfunction, cases of active tuberculosis, adjudicated major adverse cardiovascular events (MACE), or adjudicated venous thromboembolism (VTE).

Long-term safety of upadacitinib treatment was assessed through week 52. The exposure-adjusted number of AEs per 100 PYs was higher with UPA11 and UPA22 than with UPA6 (Table 4), and with any upadacitinib dose most TEAEs were mild or moderate (appendix Supplementary Table S4). Three additional serious TEAEs occurred during period 2 including ischaemic stroke (occurring in a 65-year-old female with hypertension, mild renal impairment, and family history of hypertension and myocardial infarction—this serious TEAE was adjudicated as non-fatal stroke with a reasonable possibility of being related to study drug [UPA11 (n = 1)]), invasive lobular breast carcinoma unrelated to study drug (UPA11 [n = 1]), and clavicle

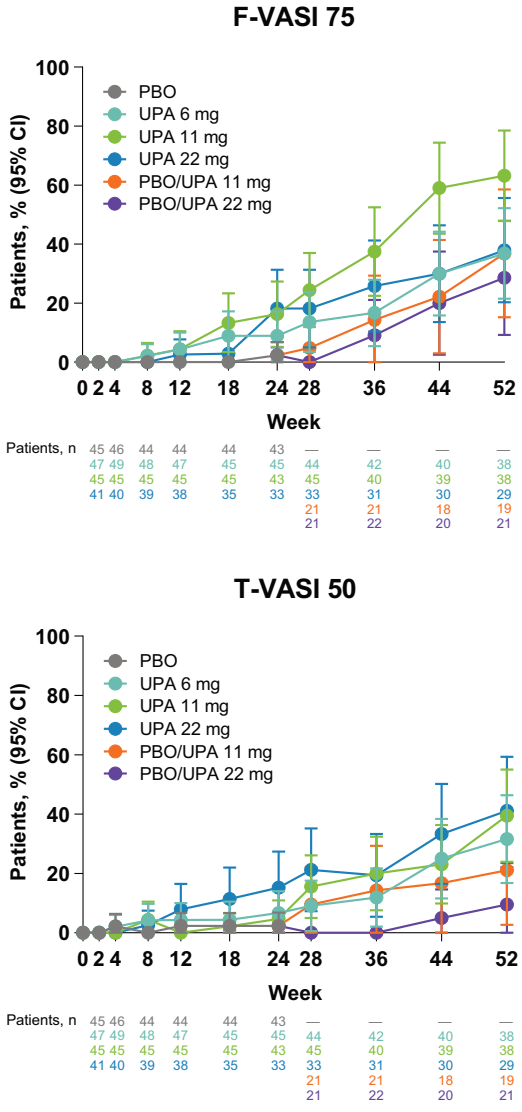

***Fig. 3:* Proportion of patients achieving F-VASI 75 and T-VASI 50 through week 52**. Data shown are as observed. Bars represent 95% CI based on the normal approximation to the binomial distribution. F-VASI 75, at least a 75% improvement in Facial Vitiligo Area Scoring Index; PBO, placebo; T-VASI 50, at least a 50% improvement in Total Vitiligo Area Scoring Index; UPA, upadacitinib.

fracture unrelated to study drug (UPA11 [n = 1]). During 52 weeks of upadacitinib treatment, there were no opportunistic infections, non-melanoma skin cancer, lymphoma, adjudicated gastrointestinal perforations, cases of active tuberculosis, or adjudicated VTE. Among all patients exposed to at least one dose of upadacitinib, only one serious infection (COVID-19 pneumonia) occurred. Four events of herpes zoster were reported with no notable difference in exposure-adjusted rates between upadacitinib doses; all events were localized and moderate, and none led to study drug discontinuation. Hematologic laboratory abnormalities occurred infrequently in all upadacitinib dose groups; all were grade 1 or 2 except for a single instance of grade 3 neutropenia (in the UPA6 group), and none resulted in study drug discontinuation. Hepatic disorders occurred in all upadacitinib dose groups with no notable difference in exposure-adjusted rates; all were due to laboratory abnormalities, were grade 1 or 2, and did not lead to study drug discontinuation.

Discussion

In this study of patients with extensive (mean T-VASI of 21.53) non-segmental vitiligo, the primary endpoint of change from baseline in F-VASI at week 24 was achieved by UPA11 and UPA22 dose levels, but not by UPA6. Substantial improvements and clinically meaningful differences with upadacitinib treatment compared with PBO were also observed for most secondary endpoints including the percent change from baseline in T-VASI at week 24. Vitiligo repigmentation is known to require considerable duration of treatment, particularly among patients with active and/or more extensive disease. Thus, improvement in F-VASI and T-VASI at week 24 is notable. The change from baseline in VitiQoL total score did not reveal clinically meaningful difference between groups at week 24. In general, response rates and clinical improvements were highest with UPA22. Treatment with upadacitinib continued to induce progressive improvement in skin repigmentation based on the percentage of patients achieving F-VASI 75 and T-VASI 50 at week 52. The observed improvement in skin repigmentation, as assessed using the continuous measures of LS mean percent change from baseline in F-VASI and T-VASI, as well as the categorical endpoints of F-VASI 75 and T-VASI 50, did not reach a plateau through week 52. Importantly, patient-centric findings showed that the improvement in the clinical scores translated into patient-reported improvement as well. Clinically meaningful improvements were reported at 24 weeks on the VNS by patients who received UPA22 and indicated their vitiligo as either "a lot less noticeable (4)" or "no longer noticeable (5)." A VNS score of 4 or 5 has been suggested to be a successful treatment response.[21] Furthermore, most patients indicated their vitiligo was "much better (1)" or "a little better (2)" based on the Patient's GIC-V, suggesting the improvement induced by upadacitinib was clinically meaningful. Taken together, these data demonstrate substantial differences with UPA11 and UPA22 dose levels compared with PBO in adults with extensive non-segmental vitiligo and provide insights to the utility of oral JAK inhibitors in the systemic treatment of vitiligo.

Recently, two phase 3 studies (TruE-V1 and TruE-V2) of the JAK1 and JAK2 inhibitor ruxolitinib topical cream demonstrated greater repigmentation of the skin

	Period 1 (Baseline to week 24), patients, n (%)				Any UPA treatment (Baseline to week 52), E (E/100 PYs)		
	PBO (n = 46)	UPA 6 mg (n = 49)	UPA 11 mg (n = 47)	UPA 22 mg (n = 43)	UPA 6 mg (n = 49)	UPA 11 mg (n = 68)	UPA 22 mg (n = 65)
Any TEAE	34 (73.9%)	33 (67.3%)	35 (74.5%)	35 (81.4%)	138 (314.9)	232 (435.4)	195 (431.2)
Any TEAE related to study drug according to the investigator	15 (32.6%)	14 (28.6%)	17 (36.2%)	14 (32.6%)	44 (100.4)	67 (125.8)	63 (139.3)
Any severe TEAE	1 (2.2%)	3 (6.1%)	2 (4.3%)	4 (9.3%)	6 (13.7)	6 (11.3)	5 (11.1)
Any serious TEAE	1 (2.2%)	1 (2.0%)	0	3 (7.0%)	1 (2.3)	3 (5.6)	3 (6.6)
Any TEAE leading to discontinuation of study drug	0	1 (2.0%)	0	4 (9.3%)	5 (11.4)	3 (5.6)	8 (17.7)
Deaths	0	0	0	1 (2.3%)[a]	0	0	1 (2.2)
TEAEs of special interest	3 (6.5%)	7 (14.3%)	3 (6.4%)	8 (18.6%)	16 (36.5)	13 (24.4)	16 (35.4)
Serious infections	0	0	0	1 (2.3%)	0	0	1 (2.2)
Opportunistic infection excluding tuberculosis and herpes zoster	0	0	0	0	0	0	0
Malignancy excluding NMSC	0	0	0	0	0	1 (1.9)	0
NMSC	0	0	0	0	0	0	0
Lymphoma	0	0	0	0	0	0	0
Hepatic disorder	1 (2.2%)	3 (6.1%)	1 (2.1%)	1 (2.3%)	6 (13.7)	4 (7.5)	6 (13.3)
Adjudicated gastrointestinal perforations	0	0	0	0	0	0	0
Anaemia	1 (2.2%)	0	0	0	0	1 (1.9)	1 (2.2)
Neutropenia	1 (2.2%)	1 (2.0%)	0	3 (7.0%)	2 (4.6)	1 (1.9)	4 (8.8)
Lymphopenia	0	1 (2.0%)	0	1 (2.3%)	2 (4.6)	0	2 (4.4)
Herpes zoster	0	1 (2.0%)	1 (2.1%)	1 (2.3%)	2 (4.6)	1 (1.9)	1 (2.2)
Renal dysfunction	0	0	0	0	0	1 (1.9)	0
Active tuberculosis	0	0	0	0	0	0	0
Adjudicated MACE	0	0	0	0	0	1 (1.9)	0
Adjudicated VTE	0	0	0	0	0	0	0
Most frequently reported TEAE (>5% in any UPA dose group during period 1)							
COVID-19	8 (17.4%)	7 (14.3%)	9 (19.1%)	9 (20.9%)	14 (31.9)	22 (41.3)	19 (42.0)
Headache	4 (8.7%)	0	9 (19.1%)	2 (4.7%)	2 (4.6)	18 (33.8)	6 (13.3)
Acne	1 (2.2%)	3 (6.1%)	4 (8.5%)	6 (14.0%)	5 (11.4)	7 (13.1)	13 (28.7)
Fatigue	1 (2.2%)	2 (4.1%)	2 (4.3%)	5 (11.6%)	4 (9.1)	3 (5.6)	5 (11.1)
Nasopharyngitis	3 (6.5%)	4 (8.2%)	2 (4.3%)	4 (9.3%)	5 (11.4)	8 (15.0)	9 (19.9)
Cough	1 (2.2%)	2 (4.1%)	4 (8.5%)	2 (4.7%)	2 (4.6)	5 (9.4)	4 (8.8)
Urinary tract infection	3 (6.5%)	1 (2.0%)	4 (8.5%)	2 (4.7%)	3 (6.8)	9 (16.9)	6 (13.3)
Anxiety	1 (2.2%)	1 (2.0%)	3 (6.4%)	0	1 (2.3)	3 (5.6)	0
Nausea	3 (6.5%)	0	2 (4.3%)	4 (9.3%)	0	3 (5.6)	4 (8.8)
Vomiting	0	1 (2.0%)	2 (4.3%)	3 (7.0%)	1 (2.3)	2 (3.8)	4 (8.8)
URTI	1 (2.2%)	3 (6.1%)	2 (4.3%)	0	5 (11.4)	9 (16.9)	3 (6.6)
Weight increased	1 (2.2%)	0	1 (2.1%)	3 (7.0%)	0	2 (3.8)	5 (11.1)
Insomnia	0	0	3 (6.4%)	0	0	3 (5.6)	0

[a]The one reported death was reviewed and adjudicated by an external cardiovascular adjudication committee and deemed as an undetermined/unknown cause of death; the investigator reported the death as having no reasonable possibility of being relate to study drug. E, events; MACE, major adverse cardiovascular event defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. NMSC, non-melanoma skin cancer; PBO, placebo; PYs, patient-years; TEAE, treatment-emergent adverse event; UPA, upadacitinib; URTI, upper respiratory tract infection; VTE, venous thromboembolism defined as deep vein thrombosis and pulmonary embolism.

Table 4: **Treatment-emergent adverse events.**

compared with a vehicle control.[22] At week 24, F-VASI 75 was reached by –29.8% (relative risk versus PBO was 4.0; 95% CI 1.9–8.4; p < 0.001) and 30.9% (relative risk versus PBO was 2.7; 95% CI 1.5–4.9; p < 0.001) and T-VASI 50 was reached by 20.6% (relative risk versus PBO was 4.1; 95% CI 1.6–10.5; p = 0.002) and 23.9% (relative risk versus PBO was 3.5; 95% CI 1.7–7.5; p < 0.001) of patients receiving ruxolitinib. However, those studies included exclusively patients with 10% or less of total body surface area depigmentation, and more than 70% of patients across treatment groups had stable disease at baseline.[22] Patients with rapidly progressive or spreading vitiligo defined as a large number of either new lesions or enlargement of lesions within the past 3 months may require systemic agents to achieve disease control and/or improvement.[14,15] Systemic corticosteroids and other immunosuppressants, such as azathioprine, have been used to treat widespread or

active vitiligo; however, the risks of long-term systemic corticosteroid treatment should be fully considered before being implemented, and long-term safety and efficacy data are limited for azathioprine in patients with vitiligo.[14] Findings from a phase 2b study of ritlecitinib, an oral JAK3/TEC inhibitor, demonstrated differences in the LS mean percent change from baseline in F-VASI at 24 weeks (50 mg without loading dose; –18.5 versus 2.1; $p < 0.001$) compared with PBO, however, a significant difference in the LS mean percent change from baseline in T-VASI was not demonstrated.[23]

Upadacitinib is approved for the treatment of several immune-mediated diseases[20] and has demonstrated efficacy in dermatologic conditions such as atopic dermatitis.[24] Infections, herpes zoster, thromboembolic events (including MACE), VTE, and abnormal laboratory values have been associated with JAK inhibitors, including upadacitinib.[25] Available long-term safety data from an integrated analysis of MACE and VTE during studies investigating upadacitinib 15 mg or upadacitinib 30 mg versus an active comparator in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis indicated that rates of MACE and VTE with upadacitinib treatment were consistent with previously reported data for patients receiving conventional synthetic and biologic therapies.[26] Furthermore, an integrated analysis of four studies in patients with atopic dermatitis receiving upadacitinib indicated MACE and VTE were less common (<0.1 per 100 PYs) in this patient population compared with rheumatoid arthritis (MACE 0.6–1.0 per 100 PYs; VTE 0.4–0.5 per 100 PYs), and while increased rates of herpes zosters cases have been reported in patients with atopic dermatitis who were receiving upadacitinib, most infections were non-serious with only localized cutaneous involvement.[27] Decreases in haemoglobin and neutrophil levels, as well as abnormal findings on laboratory tests (eg, elevations of serum transaminase and creatine phosphokinase levels) with upadacitinib have been reported, and these findings were consistent with changes reported for other JAK inhibitor use.[25] The safety profile of upadacitinib at doses analysed in this study was consistent with findings in other dermatology studies of upadacitinib,[24,28] as well as those observed in rheumatoid arthritis.[20] No new important safety signals were identified during the course of this study.

While the results of this phase 2 dose-ranging study are promising, this study is not without limitations. A large percentage of each treatment group was White, and thus additional studies are needed in underrepresented populations. However, subgroup analyses based on race and Fitzpatrick skin types yielded similar improvements to the overall population. Eligibility criteria for this dose-ranging study were selected with safety in mind and thus, like most clinical trials, the population may not fully reflect the vitiligo patient population in the real-world setting. Additionally, this study evaluated upadacitinib as monotherapy, while many patients with vitiligo conventionally receive a combination of therapies.[12] Because improvements in depigmentation did not reach a plateau through week 52, the current study may not have fully demonstrated the efficacy of upadacitinib in non-segmental vitiligo. Considering that each treatment arm had fewer than 50 patients, the observed treatment difference across dose subgroups may be influenced by variation, and the results should be interpreted with caution. Furthermore, while this sample size was adequately powered to detect treatment differences in this study, investigation in a larger patient population is warranted. Thus, additional phase 3 studies of vitiligo are necessary to confirm and further explore the efficacy and safety of upadacitinib in patients with extensive non-segmental vitiligo.

Overall, the results of this study provide insights into the efficacy of upadacitinib compared with PBO for the treatment of adults with extensive non-segmental vitiligo. Both UPA11 and UPA22 demonstrated efficacy based on F-VASI and were associated with a high patient-reported improvement on the Patient's GIC-V. Although UPA6 provided numerical improvement for most assessments, UPA6 failed to show statistical improvement in F-VASI. Upadacitinib is the first oral JAK1 inhibitor to demonstrate significant repigmentation of vitiligo lesions on the face (based on F-VASI) and total body (based on T-VASI) at 24 and 52 weeks. Upadacitinib may offer a new and effective systemic treatment option for adults with extensive non-segmental vitiligo. Based on the results from this phase 2 dose-ranging study and exposure-response modelling, the efficacy and safety of upadacitinib 15 mg are being investigated in adults and adolescents with non-segmental vitiligo in an ongoing phase 3 trial (Viti-Up; ClinicalTrials.gov, NCT06118411).

Contributors

TP participated in conceptualization (equal); investigation (equal); method development (equal); and writing, review, and editing of the manuscript (equal). KE participated in study investigation (equal) and writing, review, and editing of the manuscript (equal). IH participated in study conceptualization (equal); method development (equal); and writing, review, and editing of the manuscript (equal). NvG participated in method development (equal) and writing, review, and editing of the manuscript (equal). BJS participated in formal analysis (lead); investigation (lead); method development (equal); data validation (lead); visualization (lead); and writing, review, and editing of the manuscript (lead). XW participated in data curation (lead); formal analysis (lead); study investigation (lead); methodology development (equal); data validation (lead); visualization (equal); and writing, review, and editing of the manuscript (equal). XH participated in data curation (equal); formal analysis (equal); study investigation (lead); method development (lead); visualization (equal); and writing, review, editing of the manuscript (equal). AMS participated in conceptualization (equal); formal analysis (supporting); method development (supporting); visualization (supporting); and writing, review, editing of the manuscript (equal). DR participated in conceptualization (equal); investigation (equal); method development (equal); and writing, review, and editing of the manuscript (equal). JEH participated in conceptualization (equal); method development (equal); and writing, review, and editing of the manuscript (equal). HSC participated in conceptualization (lead); formal analysis (lead); investigation (equal); method development

(lead); supervision (lead); visualization (lead); and writing, review, and editing of the manuscript (equal). AGP participated in method development (equal) and writing, review, and editing of the manuscript (equal). BJX, TP, and XH accessed and verified the data. All authors participated in reviewing and interpreting the data and in developing the manuscript. All authors had permission to access the raw data, final responsibility for the decision to submit for publication, and approved the final manuscript.

Data sharing statement

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized individual and trial-level data (analysis data sets), as well as other information (eg, protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal and statistical analysis plan (SAP) and execution of a data sharing agreement (DSA). Data requests can be submitted at any time after approval in the United States and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://vivli.org/ourmember/abbvie/, then select "Home".

Declaration of interests

TP is a consultant for AbbVie, Almirall, Amgen, Bristol Myers Squibb, Calypso, Galderma, Incyte Corporation, Janssen, Eli Lilly, Novartis, Pfizer, Roivant, UCB, and VYNE Therapeutics. He has received grants and/or honoraria from AbbVie, ACM Pharma, Almirall, Amgen, Astellas, Bristol Myers Squibb, Calypso, Celgene, Galderma, Genzyme/Sanofi, GlaxoSmithKline, Incyte Corporation, Janssen, LEO Pharma, Eli Lilly, Novartis, Pfizer, Roivant, Sun Pharmaceuticals, UCB, and VYNE Therapeutics. He is the cofounder of YUKIN Therapeutics; and has patents on WNT agonists or GSK3b antagonist for repigmentation of vitiligo and the use of CXCR3B blockers in vitiligo. KE is a consultant for AbbVie, Incyte Corporation, La Roche-Posay, Pfizer, Pierre Fabre, Sanofi, and Viela Bio. IH is a consultant for AbbVie, Almirall, Avita, Boehringer Ingelheim, Galderma, Incyte, Jansen, Novartis, Pfizer, Sonoma, UCB, and Union Therapeutics. He is an investigator for Avita, Incyte, Lenicura, L'Oréal/Laroche Posay, and Pfizer, and a board member and past president of the Hidradenitis Suppurativa Foundation and Global Vitiligo Foundation. NvG is a consultant and/or investigator for AbbVie, Pfizer, Incyte, MDS/Merck, and Sunpharma and has received grants from AbbVie, Incyte, Pfizer, and COURD-COUSIN Collaboration (C3). She is the chair of the Vitiligo International Task Force group. DR has served as a consultant, spoken for, or conducted trials for the following companies: AbbVie, Abcuro, AltruBio, Amgen, Boehringer Ingelheim, Bristol Meyers Squibb, Celgene, Concert, CSL Behring, Dermavant, Dermira, Galderma, Incyte, Janssen, Kyowa Kirin, Lilly, Merck, Nektar, Novartis, Pfizer, RAPT, Regeneron, Recludix, Revolo Biotherapeutics, Sanofi, Sun Pharmaceuticals, UCB, Viela Bio, and Zura Bio. JEH is a consultant for AbbVie, Aldena, Almiral, Avita, Biologics MD, Genzyme/Sanofi, Granular Therapeutics, Incyte, Klirna, LEO Pharma, Matchpoint Therapeutics, Merck, NIRA Biosciences, Pfizer, Sun Pharmaceuticals, Temprian Therapeutics, Vimela Therapeutics, and Vividion Therapeutics. He is an investigator for Genzyme/Sanofi, Incyte, LEO Pharma, Pfizer, and Sun Pharmaceuticals; and holds equity stock (founder) in Aldena, Klirna, NIRA Biosciences, and Vimela Therapeutics. AGP is a consultant for AbbVie, Arcutis, Avita, Immune Tolerance Network, Incyte, Pfizer, Thalocan, WCG/Trifecta, Twi Pharmaceuticals, Villaris, Vimela, and VYNE Therapeutics. He is an investigator for Incyte; and holds stock options in Tara Medical and Zerigo Health. BJS, XW, XH, AMS, and HSC are full-time employees of AbbVie and may own stock and/or options and patents.

Acknowledgements

AbbVie funded this study and participated in the study design, research, data collection, analysis, interpretation of data, reviewing, and approval of the manuscript. All authors had access to relevant data and participated in the drafting, review, and approval of this manuscript. No honoraria or payments were made for authorship.

AbbVie and authors thank all the trial investigators and the patients who participated in this clinical trial. Statistical support was provided by Xiaofei Hu, a full-time employee of AbbVie. Medical writing support was provided by Sharon Bryant, DPT, and Lamara D. Shrode, PhD, CMPP™, of JB Ashtin, and funded by AbbVie.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102655.

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