Efficacy and safety of upadacitinib in adults and adolescents for treatment of non-segmental vitiligo (Viti-Up): results of two phase 3 randomised controlled studies

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Lancet 2026; 408: 636–48

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Summary

Background Non-segmental vitiligo is an autoimmune inflammatory disease characterised by loss of melanocytes leading to skin depigmentation. No systemic therapies have been approved, and additional therapeutic options are needed. Here, we report the efficacy and safety of upadacitinib, a selective once-daily Janus kinase inhibitor, in adults and adolescents with non-segmental vitiligo.

Methods Viti-Up includes two phase 3, global, multicentre, randomised, double-blind, placebo-controlled studies conducted at 138 institutions in 18 countries in Asia, Europe, North America, and South America. Eligible patients were adults and adolescents aged 12 years or older with non-segmental vitiligo involving the face and body with a Facial Vitiligo Scoring Index (F-VASI) of 0·5 or greater and Total Vitiligo Area Scoring Index (T-VASI) of 5 to less than 50. Patients were randomly assigned (2:1) to receive either upadacitinib 15 mg or placebo orally once daily. The coprimary efficacy endpoints for both studies were T-VASI 50 (≥50% reduction in T-VASI score from baseline) at week 48 and F-VASI 75 (≥75% reduction in F-VASI score from baseline) at week 48 (ie, clinically meaningful repigmentation). Efficacy endpoints were analysed in the intention-to-treat population; safety endpoints were assessed in all randomly assigned patients who received at least one dose of study drug during the 48-week double-blind period. Viti-Up is registered on ClinicalTrials.gov, NCT06118411, and is ongoing.

Findings Between Dec 19, 2023, and Oct 14, 2024, 750 individuals were assessed for eligibility. 308 individuals in Viti-Up-1 (206 assigned to upadacitinib and 102 assigned to placebo; 156 [51%] female and 152 [49%] male) and 306 in Viti-Up-2 (205 assigned to upadacitinib and 101 assigned to placebo; 151 [49%] female and 155 [51%] male) were randomly assigned. At week 48, a greater proportion receiving upadacitinib versus placebo reached the coprimary endpoints of T-VASI 50 (Viti-Up-1: upadacitinib 40 [19%] participants *vs* placebo six [6%]; Viti-Up-2: upadacitinib 44 [21%] *vs* placebo six [6%]; p<0·001) and F-VASI 75 (Viti-Up-1: upadacitinib 52 [25%] *vs* placebo six [6%]; Viti-Up-2: upadacitinib 48 [23%] *vs* placebo seven [7%]; p<0·001). There were no reports of adjudicated major adverse cardiovascular events, adjudicated venous thromboembolic events, adjudicated gastrointestinal perforations, active tuberculosis, lymphoma, non-melanoma skin cancer, or opportunistic infections other than herpes zoster in either study. Safety data were consistent with the overall upadacitinib safety profile.

Interpretation Upadacitinib 15 mg daily provides clinically meaningful repigmentation of both the face and total body for adults and adolescents with non-segmental vitiligo, with no new safety signals identified.

Funding AbbVie.

Introduction

Vitiligo is a chronic, immune-mediated inflammatory disease characterised by skin depigmentation resulting from an autoimmune-induced loss of melanocytes.[1–4] Vitiligo has a global lifetime estimated prevalence of 0·36% based on physician diagnosis, with a higher rate of 0·55% based on self-reporting by patients.[5] Non-segmental vitiligo, the most common form of the disease, is characterised by patchy areas of bilateral depigmentation and exhibits a progressive as well as unpredictable course.[1] Non-segmental vitiligo has a significant negative impact on quality of life, and patients with non-segmental vitiligo often experience anxiety, depression, suicidal ideation, and difficulties with social interactions and relationships.[6] The psychosocial burden of the disease is especially increased in women younger than 30 years, those with darker skin, and those with more visibly affected areas, especially the face.[6,7] Moreover, in some cultures, vitiligo is a heavily stigmatising disease precluding social acceptance.[7–9] Although therapeutic interventions exist, many patients remain unsatisfied with their current treatment

Research in context

Evidence before this study

Vitiligo management is challenging, with no current approved systemic therapies. Inhibition of the Janus kinase (JAK) pathway has been proposed as a therapeutic approach to treat vitiligo given its central role in vitiligo pathogenesis. A PubMed search for articles published in English between Jan 1, 2000, and Feb 1, 2026, using the terms "vitiligo" AND "Janus kinase" was performed, yielding 231 results. By using "clinical trial" as the Medical Subject Headings term or article type, we identified six relevant studies. An additional search focusing on clinical trials evaluating oral or systemic treatments for vitiligo yielded few results. The topical JAK inhibitor ruxolitinib is an approved treatment for non-segmental vitiligo in patients aged 12 years or older; notably, its application is limited to 10% of body surface area and does not prevent new lesions in untreated areas. In a phase 2 dose-ranging monotherapy study, the oral JAK inhibitor upadacitinib demonstrated superiority over placebo for treatment of non-segmental vitiligo based on measures of repigmentation of the face and body as assessed by Facial Vitiligo Area Scoring Index (F-VASI) and Total Vitiligo Area Scoring Index (T-VASI).

Added value of this study

To the best of our knowledge, Viti-Up-1 and Viti-Up-2 are the first phase 3 clinical trials to report the efficacy and safety of a systemic once-daily oral selective JAK1 inhibitor (upadacitinib) for the treatment of non-segmental vitiligo. The coprimary efficacy endpoints of T-VASI 50 (≥50% reduction in T-VASI score from baseline) and F-VASI 75 (≥75% reduction in F-VASI score from baseline) at 48 weeks of treatment were met in two phase 3 clinical trials. No new safety signals beyond the known profile of upadacitinib were reported.

Implications of all the available evidence

Results of the current study demonstrate that upadacitinib is a safe, effective treatment for adults and adolescents with non-segmental vitiligo.

regimens, and there is a great need for more effective therapeutic options, including systemic therapies.[1]

Conventional treatment for non-segmental vitiligo has historically relied on topical therapies, including corticosteroids and calcineurin inhibitors, as well as phototherapy.[10,11] The recent approval of ruxolitinib, a topical Janus kinase (JAK) 1 and 2 inhibitor, represents a substantial advancement, because this is the only approved pharmacological treatment for vitiligo.[12] It can be used alone or in combination with phototherapy, but its use is restricted to a maximum of 10% of the body surface area.[13,14] Although systemic therapies such as oral corticosteroids or conventional non-corticosteroid immunosuppressants are sometimes used off-label for actively progressing or extensive vitiligo in clinical practice, no systemic therapy is currently approved for vitiligo. As a result, a considerable unmet therapeutic need remains, requiring the development and approval of effective systemic therapy options.

Janus kinases are involved in the pathogenesis of many immune-mediated inflammatory diseases, including vitiligo.[2] Inhibition of the JAK-STAT pathway holds promise for the treatment of vitiligo by disrupting autoimmune-induced melanocyte loss.[2] Upadacitinib (brand name Rinvoq; AbbVie, North Chicago, IL, USA) is an oral, once-daily, reversible JAK inhibitor with greater inhibitory potency for JAK1 than JAK2, JAK3, or tyrosine kinase 2, which has been approved for the treatment of several immune-mediated inflammatory diseases, including atopic dermatitis.[15,16] In a phase 2 clinical trial, upadacitinib treatment led to substantial repigmentation of facial and total body lesions in patients with non-segmental vitiligo.[17] Here, we report the primary results up to week 48 from two phase 3 randomised clinical trials (Viti-Up-1 and Viti-Up-2) assessing the efficacy and safety of upadacitinib monotherapy for the treatment of non-segmental vitiligo in adults and adolescents.

Methods

Study design

Viti-Up comprised two phase 3, global, randomised, double-blind, placebo-controlled, multicentre studies (Viti-Up-1 and Viti-Up-2), which include a 35-day screening period; a 48-week, placebo-controlled, double-blind treatment period (period A); a 112-week open-label extension period (period B); and a 30-day follow-up period (appendix p 12) The study was conducted at 138 institutions in 18 countries in Asia, Europe, North America, and South America. Independent ethics committees or institutional review boards at each site approved the study protocol (appendix pp 3–7), informed consent forms, and recruitment materials before patient enrolment. The study protocol and statistical analysis plans are provided in the appendix (pp 21–271). Studies were 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. Viti-Up is registered with ClinicalTrials.gov, NCT06118411, and is ongoing. Patients did not participate in the design of this study.

Participants

Eligible participants were individuals aged 12 years or older at screening with non-segmental vitiligo involving the face and body (Facial Vitiligo Area Scoring Index [F-VASI] of ≥0·5 and Total Vitiligo Area Scoring Index [T-VASI] of 5 to <50, respectively, at both screening and

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See Online for appendix

baseline), for whom treatment had failed with at least one topical corticosteroid and/or at least one topical calcineurin inhibitor per investigator judgement or had signs of active vitiligo. Active vitiligo was defined as the presence of at least one lesion with at least one of confetti-like depigmentation, trichrome pattern, or Koebner phenomenon type 2B, and/or the documented evidence of new lesions or progression or enlargement of existing lesions within the 6 months before baseline. Patients with F-VASI of at least 0·5 and T-VASI of 10 to less than 50 were eligible to enrol without requirement for previous topical therapy failure or signs of active vitiligo.

Patients with skin conditions that might interfere with the evaluation of vitiligo, patients with uncontrolled thyroid disease, and patients with more than 33% leukotrichia on the face or on the body were not eligible. Exclusion due to previous therapies included any previous use of a systemic JAK inhibitor or permanent skin bleaching agent, as well as permanent tattooing, transplantation, or grafting for vitiligo. Patients were required to discontinue systemic vitiligo therapy for a period of 30 days before and topical therapies at least 60 days before receiving the first dose of study drug. Phototherapy had to be discontinued at least 84 days before the first dose of study drug. All patients provided written informed consent before screening. Sex and race or ethnicity were self-reported by patients.

Randomisation and masking

Patients were randomly assigned (2:1) to receive upadacitinib 15 mg or placebo orally once daily. Interactive Response Technology was used to assign a randomisation number that encoded the patient's treatment group assignment according to randomisation schedules that were generated separately for Viti-Up-1 and Viti-Up-2. Patient randomisation was stratified by age at screening (12 to <18 years or ≥18 years), baseline disease severity (T-VASI ≤10 or T-VASI >10 to <50), and baseline status of active vitiligo (yes or no). Patients received either upadacitinib 15 mg or placebo once daily for 48 weeks (period A); during the 112-week open-label extension period (period B), patients previously receiving placebo were switched to upadacitinib 15 mg after week 48. Starting at week 12, patients receiving upadacitinib or placebo with worsening vitiligo, defined as an increase of 25% or greater in T-VASI from baseline, were switched to open-label upadacitinib 15 mg. The AbbVie study team was masked until the week 48 primary analysis. Patients, study investigators, and study site personnel were masked to treatment throughout the study. Study drug tablets were identical in appearance.

Procedures

Patients received a single daily, orally administered 15 mg tablet of upadacitinib or placebo. Efficacy was assessed at weeks 8, 12, 18, 24, 30, 36, 42, and 48. Safety was monitored throughout the study and until 30 days after the last dose of study drug. Vitiligo Area Scoring Index (VASI) is a composite measure of vitiligo disease extent that incorporates body surface area and degree of depigmentation. Investigators assessed body surface area and degree of depigmentation via skin examination and use of a Wood's lamp. Numerical values for body surface area and degree of depigmentation entered by investigators were used to automatically calculate T-VASI and F-VASI in the electronic data capture system. Details of protocol deviations can be found in the appendix (p 8).

Outcomes

The coprimary efficacy endpoints for both studies were T-VASI 50 (≥50% reduction in T-VASI score from baseline) at week 48 and F-VASI 75 (≥75% reduction in F-VASI score from baseline) at week 48. Scores for T-VASI and F-VASI, which quantify the percentage of depigmented areas of skin, are standard measures of improvement (reduction) in vitiligo.[4,18] Secondary endpoints were: F-VASI 50 at week 48; F-VASI 75 at week 24; percentage change from baseline in F-VASI at week 24; percentage change from baseline in T-VASI at week 48; F-VASI 90 at week 48; T-VASI 75 at week 48; occurrence of no increase from baseline in T-VASI at both week 8 and week 12 among patients with active vitiligo at baseline; and occurrence of each of the following: Physician's Global Impression of Change—Vitiligo (PhGIC-V) of "Much better (1)" at week 48, Patient's Global Impression of Change—Vitiligo (PaGIC-V) of "Much better (1)" at week 48, and Vitiligo Noticeability Scale score of "A lot less noticeable (4)" or "No longer noticeable (5)" at week 48.[19,20] An additional secondary endpoint related to 3D digital imaging was included in a select number of patients in Viti-Up-1, the results of which are not reported here and will be addressed in a future publication.

Safety was assessed as the number and proportion of patients experiencing treatment-emergent adverse events, serious adverse events, treatment-emergent adverse events related to study drug, treatment-emergent adverse events leading to discontinuation of study treatment, treatment-emergent adverse events of special interest prespecified based on previous observations in patients receiving upadacitinib, and treatment-emergent adverse events leading to death. Adverse events of special interest were identified using a standard definition based on information derived from multiple sources, including preclinical data, the known safety profile of the JAK class (including upadacitinib), evolving safety data, and events of regulatory interest. Events were categorised as serious if they could result in death, hospitalisation or prolongation of hospitalisation, congenital anomaly, or persistent or significant disability or incapacity; were life-threatening; or could require medical or surgical intervention to prevent a serious outcome. Events were rated for severity for each adverse event according to the

National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. If no specific grading criteria were provided for the reported event, the event was rated as severe based on meeting criteria from grades 3–5 as follows: grade 3, severe or medically significant but not immediately life-threatening, hospitalisation or prolongation of hospitalisation indicated, disabling, or limiting self-care activities of daily (refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not being bedridden); grade 4, life-threatening consequences, or urgent intervention indicated; grade 5, death related to adverse event.

An independent, external adjudication committee of physician experts in each of cardiovascular events and gastrointestinal perforation reported cardiovascular events (including major adverse cardiovascular events and venous thromboembolic events) and gastrointestinal perforation events in a blinded manner as defined by the Cardiovascular Adjudication Committee and Gastrointestinal Adjudication Charter. Laboratory assessments and physical examinations, including vital sign measurements, were conducted throughout the study.

Statistical analysis

In each of Viti-Up-1 and Viti-Up-2, approximately 270 adult and adolescent patients were planned to be randomly assigned (2:1) to upadacitinib or placebo. This design provided greater than 90% power to simultaneously detect differences for the coprimary endpoints of T-VASI 50 and F-VASI 75 at week 48 (two-sided α=0·05), based on the assumptions that week 48 response rates for upadacitinib versus placebo were 28·8% versus 6·0% for T-VASI 50, and 37·7% versus 6·0% for F-VASI 75. These response-rate assumptions were derived from the primary analysis results of a previous phase 2 study using a linear extrapolation method.[17] All efficacy endpoints were analysed in the intention-to-treat population, which included all patients randomly assigned at baseline in the groups to which they were assigned, for period A. Safety was assessed in all randomly assigned patients who received at least one dose of study drug during period A. Coprimary and binary secondary endpoints were analysed using the Cochran-Mantel-Haenszel test, adjusting for the actual values of three stratification factors: age at screening (12 to <18 years or ≥18 years), baseline disease severity (T-VASI ≤10 or T-VASI >10), and baseline status of active vitiligo (yes or no). Continuous secondary endpoints were analysed using an ANCOVA model including treatment groups, the actual values of the three aforementioned stratification factors, and the relevant baseline values. The statistical comparisons of upadacitinib versus placebo were done in hierarchical order under a two-sided significance level of 0·05. All analyses were performed using SAS version 9.4. An independent data monitoring committee was appointed to periodically review unmasked study data to identify potential safety risks and ensure the continued protection of participants.

For binary endpoints, non-responder imputation, while incorporating multiple imputation to handle any missing

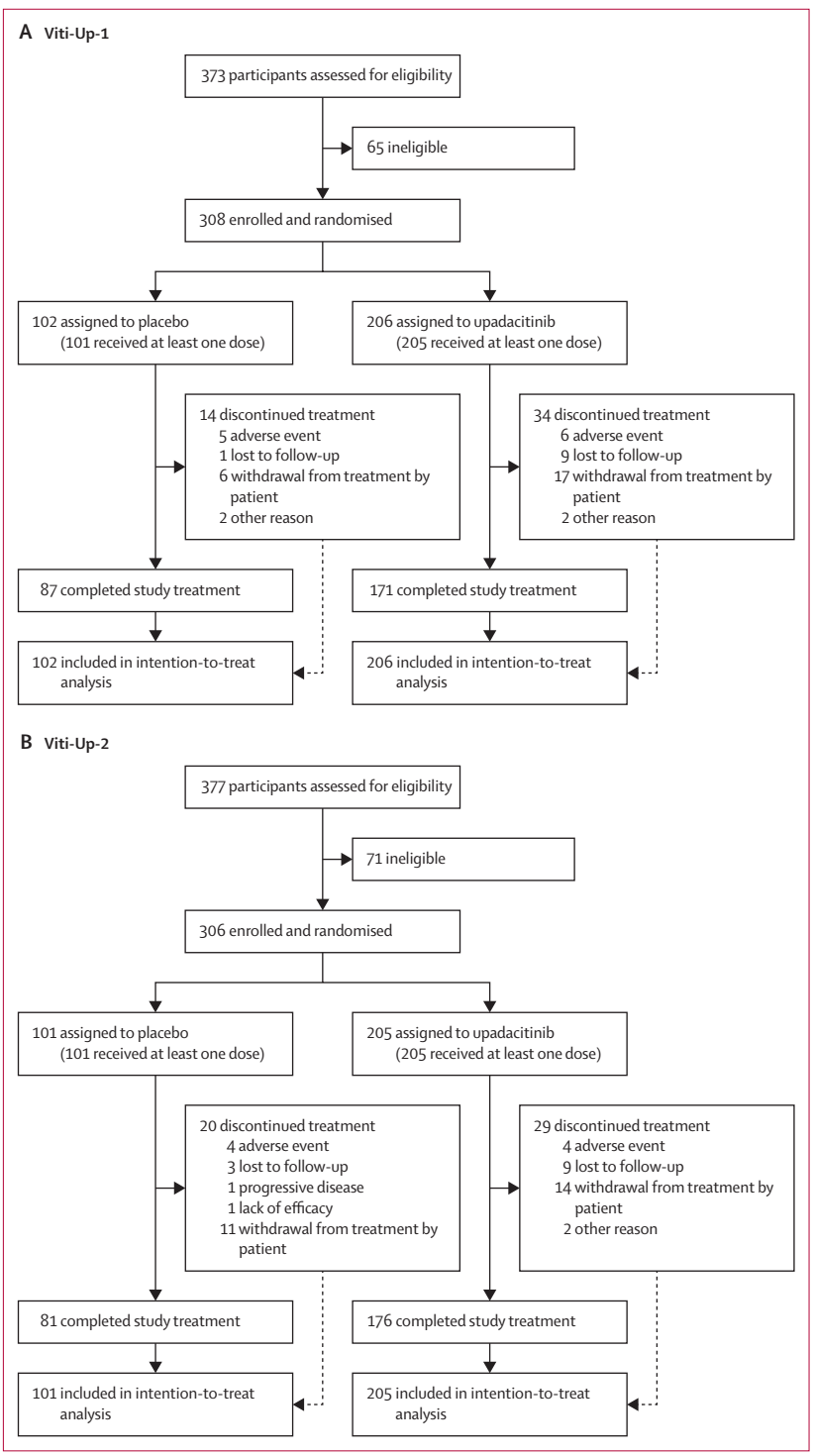

Figure 1: **Trial profiles**
Flow of participants in Viti-Up-1 (A) and Viti-Up-2 (B). In Viti-Up-1, one patient in each group chose not to receive a dose after randomisation.

data that can be reasonably assumed to be missing at random, was the primary approach. Because there were no missing data observed that could be reasonably assumed to be missing at random, non-responder imputation was used. For continuous endpoints, multiple imputation was the primary approach for handling missing data, with the exception of missing data after treatment discontinuation due to lack of efficacy, which were handled by return-to-baseline. Patients were considered as non-responders at visits affected by intercurrent events for binary endpoints; data affected by intercurrent events were handled with return-to-baseline for continuous endpoints. Missing safety data were not imputed.

Role of the funding source

The design, study conduct, financial support, and study drugs for this study were provided by AbbVie. AbbVie performed data analyses and interpretation of results. The funder participated in writing, reviewing, and approval of the manuscript. All authors had full access to the data, and reviewed and approved the final version. A medical writer, employed by AbbVie, assisted with manuscript preparation under the authors' direction.

Results

Between Dec 19, 2023, and Oct 14, 2024, 750 individuals were assessed for eligibility, of whom 614 met inclusion criteria and were enrolled. 308 patients in Viti-Up-1 (23 adolescents aged 12–17 years; 285 adults aged ≥18 years) and 306 patients in Viti-Up-2 (30 adolescents; 276 adults) were randomly assigned to upadacitinib (Viti-Up-1, n=206; Viti-Up-2, n=205) or placebo (Viti-Up-1, n=102; Viti-Up-2, n=101; figure 1). The current results include the 48-week placebo-controlled period A; period B is ongoing.

Demographics and baseline disease characteristics were generally balanced between treatment groups

	Viti-Up-1			Viti-Up-2		
	Placebo group (N=102)	Upadacitinib group (N=206)	Total (N=308)	Placebo group (N=101)	Upadacitinib group (N=205)	Total (N=306)
Sex						
Female	48 (47%)	108 (52%)	156 (51%)	44 (44%)	107 (52%)	151 (49%)
Male	54 (53%)	98 (48%)	152 (49%)	57 (56%)	98 (48%)	155 (51%)
Age, years	43·6 (14·7)	44·9 (15·4)	44·5 (15·1)	45·6 (15·7)	44·1 (15·3)	44·6 (15·4)
Race or ethnicity*						
Asian	23 (23%)	41 (20%)	64 (21%)	10 (10%)	23 (11%)	33 (11%)
Black	2 (2%)	9 (4%)	11 (4%)	6 (6%)	6 (3%)	12 (4%)
Hispanic or Latino	21 (21%)	60 (29%)	81 (26%)	33 (33%)	67 (33%)	100 (33%)
White	74 (73%)	152 (74%)	226 (73%)	85 (84%)	170 (85%)†	255 (84%)†
Adolescent (≥12 to <18 years)	8 (8%)	15 (7%)	23 (7%)	8 (8%)	22 (11%)	30 (10%)
BMI, kg/m²	26·0 (4·3)	26·3 (5·7)	26·2 (5·3)	26·8 (5·2)	25·9 (5·1)	26·2 (5·1)
Active vitiligo	63 (62%)	141 (68%)	204 (66%)	59 (58%)	119 (58%)	178 (58%)
T-VASI >10	73 (72%)	149 (72%)	222 (72%)	68 (67%)	141 (69%)	209 (68%)
F-VASI	1·1 (0·7)	1·0 (0·6)	1·1 (0·6)	1·0 (0·6)	1·1 (0·7)	1·1 (0·6)
T-VASI	20·7 (12·9)	18·7 (11·7)	19·4 (12·1)	17·6 (11·6)	16·5 (10·1)	16·8 (10·6)
Fitzpatrick skin type						
Type ≤II	17 (17%)	42 (20%)	59 (19%)	38 (38%)	80 (39%)	118 (39%)
Type >III	38 (37%)	85 (41%)	123 (40%)	20 (20%)	53 (26%)	73 (24%)
Type I	1 (1%)	4 (2%)	5 (2%)	5 (5%)	8 (4%)	13 (4%)
Type II	16 (16%)	38 (18%)	54 (18%)	33 (33%)	72 (35%)	105 (34%)
Type III	47 (46%)	79 (38%)	126 (41%)	43 (43%)	72 (35%)	115 (38%)
Type IV	31 (30%)	64 (31%)	95 (31%)	15 (15%)	41 (20%)	56 (18%)
Type V	6 (6%)	15 (7%)	21 (7%)	5 (5%)	10 (5%)	15 (5%)
Type VI	1 (1%)	6 (3%)	7 (2%)	0	2 (1%)	2 (1%)
Previous topical therapy for vitiligo‡	54 (53%)	117 (57%)	171 (56%)	64 (63%)	118 (58%)	182 (59%)
Previous phototherapy for vitiligo§	35 (34%)	67 (33%)	102 (33%)	32 (32%)	67 (33%)	99 (32%)
Vitiligo disease diagnosis duration, years	16·7 (14·4)	16·7 (14·8)	16·7 (14·6)	15·6 (12·0)	15·7 (12·6)	15·7 (12·4)
VitiQoL total score	33·3 (24·2)	36·2 (26·3)	35·3 (25·6)	34·4 (24·7)	38·1 (24·7)	36·9 (24·7)

Data are n (%) or mean (SD). F-VASI=Facial Vitiligo Area Scoring Index. T-VASI=Total Vitiligo Area Scoring Index. VitiQoL=Vitiligo-Specific Quality-of-Life Instrument. *Participants could choose multiple options. †Four participants did not report race or ethnicity in the upadacitinib group; percentages have been calculated from available data. ‡Includes topical corticosteroids and topical calcineurin inhibitors. §Previous phototherapy includes phototherapy, photochemotherapy, and laser (phototherapy equivalent).

Table 1: **Demographics and baseline characteristics**

(table 1). At baseline, 141 (68%) and 119 (58%) of patients receiving upadacitinib in Viti-Up-1 and Viti-Up-2, respectively, and 63 (62%) and 59 (58%) of patients receiving placebo, respectively, had active vitiligo. Mean baseline T-VASI was 18·7 (SD 11·7) and 16·5 (10·1) for patients receiving upadacitinib in Viti-Up-1 and Viti-Up-2, respectively, and 20·7 (12·9) and 17·6 (11·6) for patients receiving placebo, respectively. Mean baseline F-VASI scores were 1·0 (0·6) and 1·1 (0·7) for patients receiving upadacitinib in Viti-Up-1 and Viti-Up-2, respectively, and 1·1 (0·7) and 1·0 (0·6) for patients receiving placebo, respectively. Disease duration was 16·7 years (SD 14·8) and 15·7 years (12·6) for patients receiving upadacitinib in Viti-Up-1 and Viti-Up-2, respectively, and 16·7 years (14·4) and 15·6 years (12·0) for patients receiving placebo, respectively. Across all treatment groups in Viti-Up-1, the proportion of patients with Fitzpatrick skin type I–II was 19%, with type III was 41%, and with type IV–VI was 40%. In Viti-Up-2, the respective proportions were 39%, 38%, and 24% (table 1). Proportions of patients with each Fitzpatrick skin type are provided in table 1.

The overall rate of study treatment premature discontinuation was low (Viti-Up-1, 48 [16%]; Viti-Up-2, 49 [16%]). In both studies, the most frequent primary reason was withdrawal from treatment by patient. Premature discontinuation of study treatment due to adverse event, lack of efficacy, progressive disease, or mandatory discontinuation for progressing vitiligo occurred infrequently (figure 1).

At week 48, in both Viti-Up-1 and Viti-Up-2, upadacitinib demonstrated superior efficacy versus placebo in reaching the coprimary endpoints of T-VASI 50 (40 [19%] *vs* six [6%] in Viti-Up-1; 44 [21%] *vs* six [6%] in Viti-Up-2; p<0·001 for both studies) and F-VASI 75 (52 [25%] *vs* six [6%] in Viti-Up-1; 48 [23%] *vs* seven [7%] in Viti-Up-2; p<0·001 for both studies; figure 2).

The upadacitinib group demonstrated superiority over placebo in reaching F-VASI 75 at week 24 (31 [15%] *vs* two [2%] in Viti-Up-1; 23 [11%] *vs* one [1%] in Viti-Up-2; p<0·001 for both studies; table 2). Responses to upadacitinib were observed as early as week 8 (five [2%] *vs* none, nominal p=0·035 in Viti-Up-1; four [2%] *vs* none, nominal p=0·041 in Viti-Up-2), at which time a numerically greater proportion of patients reached F-VASI 75 compared with placebo (appendix p 13). A significantly greater proportion of patients receiving upadacitinib versus placebo reached F-VASI 50 at week 48 in both Viti-Up-1 and Viti-Up-2 (99 [48%] *vs* 13 [13%] in Viti-Up-1; 89 [43%] *vs* 13 [13%] in Viti-Up-2; p<0·001 for both studies). Numerical differences between upadacitinib and placebo in reaching F-VASI 50 were seen as early as week 8 (17 [8%] *vs* one [1%], nominal p<0·001 in Viti-Up-1; 11 [5%] *vs* none, nominal p<0·001 in Viti-Up-2; appendix p 14). In both Viti-Up-1 and Viti-Up-2, a significantly greater proportion of

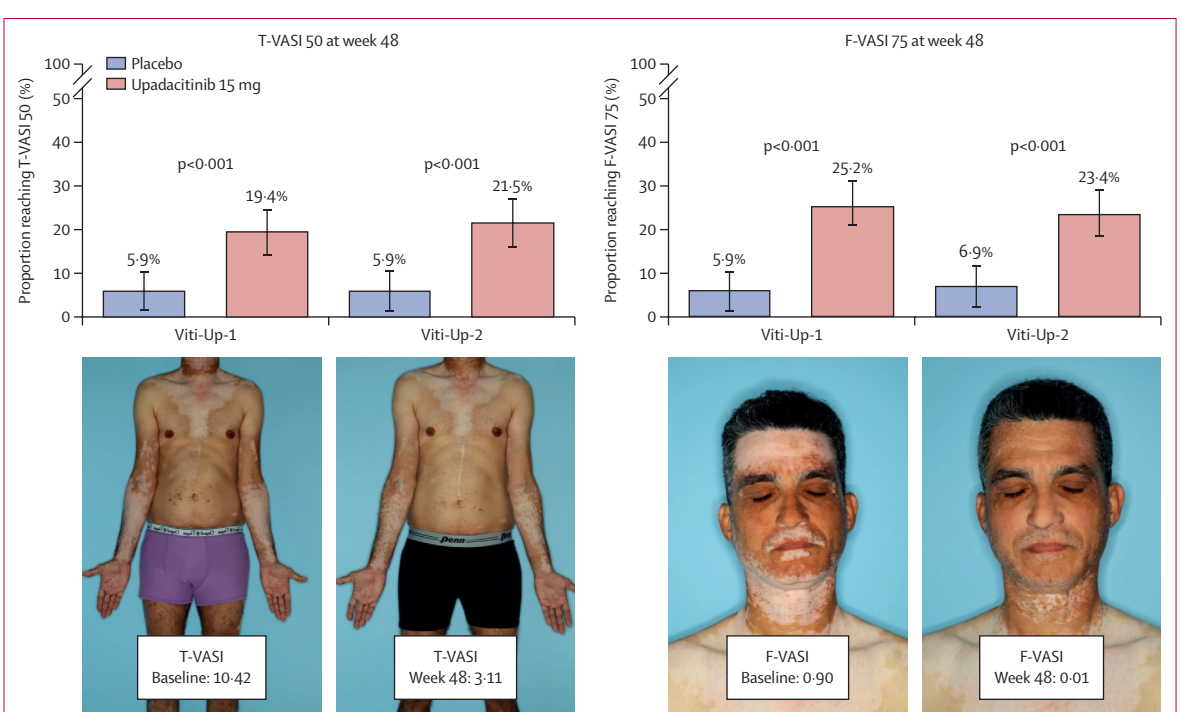

Figure 2: **Proportions of patients who reached coprimary endpoints at week 48 and representative clinical images**
Non-responder imputation while incorporating multiple imputation was the primary approach to handle missing data; however, as no missing data were observed that could be reasonably assumed to be missing at random, non-responder imputation was used instead. Patients were considered non-responders at visits affected by intercurrent events. F-VASI=Facial Vitiligo Area Scoring Index. T-VASI=Total Vitiligo Area Scoring Index.

patients reached the more stringent endpoint of F-VASI 90 in the upadacitinib group versus the placebo group (32 [16%] *vs* two [2%], p<0·001 in Viti-Up-1; 25 [12%] *vs* three [3%], p=0·001 in Viti-Up-2) at week 48. At week 24, upadacitinib demonstrated significantly greater improvement (reduction) from baseline in F-VASI versus placebo (upadacitinib –42% [SE 4] *vs* placebo –13% [5] in Viti-Up-1; upadacitinib –28% [3] *vs* placebo –2% [4] in Viti-Up-2; p<0·001 for both studies). Greater reductions in F-VASI from baseline were observed for upadacitinib versus placebo as early as week 8 (upadacitinib –16% [SE 3] *vs* placebo –4% [3] in Viti-Up-1; –7% [2] *vs* 3% [3] in Viti-Up-2), and continued to improve up to week 48 (upadacitinib 15 mg –55% [SE 5] *vs* placebo –20% [5] in Viti-Up-1; –45% [4] *vs* –11% [6] in Viti-Up-2; nominal p<0·001 for both studies; figure 3).

At week 48, upadacitinib demonstrated a significantly greater improvement (reduction) from baseline in T-VASI versus placebo (–29% [SE 4] *vs* –9% [5] in Viti-Up-1; –33% [3] *vs* –13% [4] in Viti-Up-2; p<0·001 for both studies; table 2, figure 3). Greater proportions of patients treated with upadacitinib reached T-VASI 50 compared with placebo as early as week 8 in Viti-Up-2 (upadacitinib four [2%] *vs* placebo none, nominal p=0·044) and week 24 in Viti-Up-1 (18 [9%] *vs* three [3%], nominal p=0·14; appendix p 13). The percentage change from baseline in T-VASI was greater in the upadacitinib group versus the placebo group beginning at week 8 in Viti-Up-1 (–6% [SE 1] *vs* –3% [2]; nominal p=0·021) and at week 12 in Viti-Up-2 (–8% [2] *vs* –2% [2]; nominal p=0·001). Responses to upadacitinib versus placebo continued to improve up to week 48 based on the percentage change from baseline in T-VASI (Viti-Up-1: –29% [SE 4] *vs* –9% [5]; Viti-Up-2: –33% [3] *vs* –13% [4]; p<0·001 for both studies; table 2, figure 3). Numerically greater proportions of patients treated with upadacitinib reached T-VASI 75 at week 48 compared with placebo in both studies (Viti-Up-1: ten [5%] *vs* three [3%], p=0·40; Viti-Up-2: ten [5%] *vs* two [2%], p=0·26). Among patients characterised as having active vitiligo at baseline, the proportions of patients assessed as having no increase (ie, no worsening) from baseline in T-VASI at both week 8 and week 12 were significantly greater for those receiving upadacitinib versus placebo in Viti-Up-1 (107 [76%] *vs* 38 [60%]; p=0·025) and Viti-Up-2 (90 [76%] *vs* 36 [61%]; p=0·042) indicating that upadacitinib stabilised disease extent.

Physicians reported that a significantly greater proportion of patients receiving upadacitinib versus placebo reached a PhGIC-V of "Much better (1)" at week 48 in both Viti-Up-1 (41 [20%] *vs* six [6%]; p<0·001) and Viti-Up-2 (34 [17%] *vs* one [1%]; p<0·001). Similarly, a significantly greater proportion of patients receiving upadacitinib vs placebo reached a PaGIC-V score of "Much better (1)" in both studies (Viti-Up-1: 32 [16%] *vs* four [4%]; Viti-Up-2: 37 [18%] *vs* one [1%];

	Viti-Up-1				Viti-Up-2			
	Placebo group (N=102)	Upadacitinib group (N=206)	Adjusted difference *vs* placebo (95% CI)	p value	Placebo group (N=101)	Upadacitinib group (N=205)	Adjusted difference *vs* placebo (95% CI)	p value
Coprimary endpoints								
T-VASI 50 (≥50% reduction from baseline) at week 48	6 (6%)	40 (19%)	13·1 (6·3 to 19·8)	<0·001	6 (6%)	44 (21%)	14·7 (7·5 to 21·9)	<0·001
F-VASI 75 (≥75% reduction from baseline) at week 48	6 (6%)	52 (25%)	18·7 (11·5 to 25·9)	<0·001	7 (7%)	48 (23%)	16·9 (9·2 to 24·5)	<0·001
Secondary endpoints								
F-VASI 50 at week 48	13 (13%)	99 (48%)	33·8 (24·8 to 42·9)	<0·001	13 (13%)	89 (43%)	30·1 (20·8 to 39·4)	<0·001
F-VASI 75 at week 24	2 (2%)	31 (15%)	13·1 (7·7 to 18·5)	<0·001	1 (1%)	23 (11%)	10·6 (5·8 to 15·5)	<0·001
F-VASI 90 at week 48	2 (2%)	32 (16%)	13·0 (7·8 to 18·3)	<0·001	3 (3%)	25 (12%)	9·4 (3·7 to 15·1)	0·001
Percentage change from baseline in F-VASI at week 24, LSM (SE)	–13% (5)	–42% (4)	–29% (–38 to –21)	<0·001	–2% (4)	–28% (3)	–26% (–34 to –18)	<0·001
Percentage change from baseline in T-VASI at week 48, LSM (SE)	–9% (5)	–29% (4)	–19% (–28 to –11)	<0·001	–13% (4)	–33% (3)	–20% (–29 to –12)	<0·001
T-VASI 75 at week 48	3 (3%)	10 (5%)	1·7 (–2·2 to 5·5)	0·40	2 (2%)	10 (5%)	2·2 (–1·6 to 6·0)	0·255
No increase from baseline in T-VASI at both week 8 and week 12 among participants with actively progressing vitiligo at baseline								
N	63	141	..	..	59	119	..	..
n (%)	38 (60%)	107 (76%)	15·8 (2·0 to 29·7)	0·025	36 (61%)	90 (76%)	14·9 (0·5 to 29·2)	0·042
PhGIC-V of "Much better (1)" at week 48	6 (6%)	41 (20%)	12·8 (6·2 to 19·4)	<0·001	1 (1%)	34 (17%)	15·4 (10·2 to 20·6)	<0·001
PaGIC-V of "Much better (1)" at week 48	4 (4%)	32 (16%)	11·2 (5·1 to 17·3)	<0·001	1 (1%)	37 (18%)	16·9 (11·3 to 22·5)	<0·001
VNS score of "A lot less noticeable (4)" or "No longer noticeable (5)" at week 48	2 (2%)	26 (13%)	10·5 (5·3 to 15·8)	<0·001	1 (1%)	30 (15%)	13·9 (8·7 to 19·1)	<0·001

Data are n (%) unless otherwise indicated. T-VASI=Total Vitiligo Area Scoring Index. F-VASI=Facial Vitiligo Area Scoring Index. LSM=least squares mean. PhGIC-V=Physician's Global Impression of Change—Vitiligo. PaGIC-V=Patient's Global Impression of Change—Vitiligo. VNS=Vitiligo Noticeability Scale. 95% CIs for adjusted differences and p values were calculated according to the Cochran–Mantel–Haenszel test adjusted for strata and based on a non-responder imputation approach for binary endpoints, and an ANCOVA model based on a return-to-baseline multiple imputation approach for continuous endpoints.

Table 2: **Coprimary and secondary endpoints**

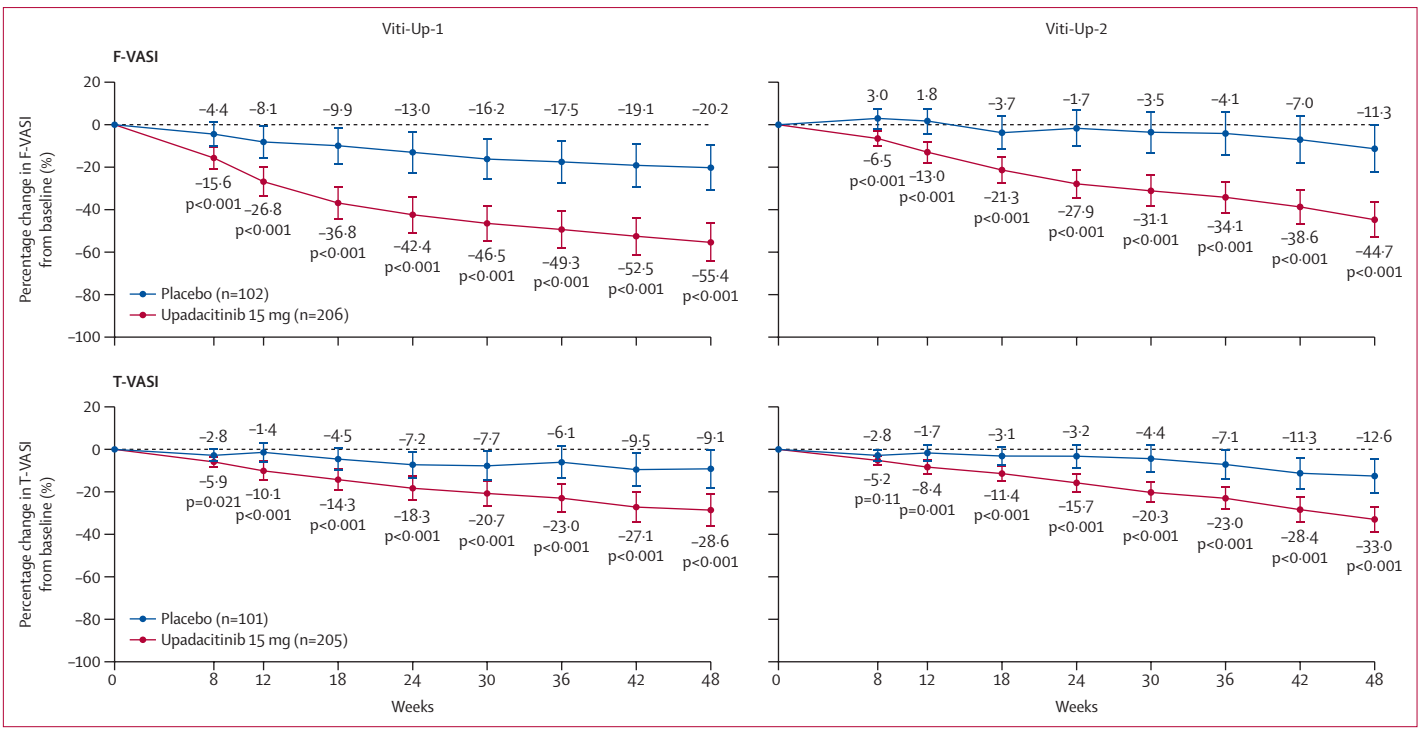

Figure 3: **Change from baseline in F-VASI and T-VASI across 48 weeks**
Multiple imputation was the primary approach for handling missing values, with the exception of missing data after discontinuation of study treatment due to lack of efficacy, which were handled by return-to-baseline. F-VASI=Facial Vitiligo Area Scoring Index. T-VASI=Total Vitiligo Area Scoring Index.

p<0·001 for both studies) at week 48. Additionally, a greater proportion of patients receiving upadacitinib versus placebo reached a Vitiligo Noticeability Scale score of "A lot less noticeable (4)" or "No longer noticeable (5)" at week 48 in Viti-Up-1 (26 [13%] *vs* two [2%]; p<0·001) and Viti-Up-2 (30 [15%] *vs* one [1%]; p<0·001). Responses were greater for upadacitinib versus placebo as early as week 8 (Viti-Up-1) and week 12 (Viti-Up-2) for the PhGIC-V, week 24 (Viti-Up-1) and week 8 (Viti-Up-2) for the PaGIC-V, and week 24 in both studies for the Vitiligo Noticeability Scale (appendix pp 15–17). Results for secondary endpoints are summarised in table 2.

Safety was assessed in all randomly assigned patients who received at least one dose of study drug during period A, which included 306 patients in Viti-Up-1 and 306 in Viti-Up-2. The incidence and nature of safety events were similar across studies and treatment groups. Up to week 48 of study treatment, the proportions of patients with treatment-emergent adverse events were 166 (81%) of 205 and 143 (70%) of 205 in the upadacitinib groups of Viti-Up-1 and Viti-Up-2, respectively, and 61 (60%) of 101 and 63 (62%) of 101 in the placebo groups, respectively (table 3). Treatment-emergent adverse events designated by the investigator as having a reasonable possibility of being related to study treatment were reported in 100 (49%) and 60 (29%) patients receiving upadacitinib and in 28 (28%) and 22 (22%) of those receiving placebo. The proportions of patients experiencing severe adverse events were 14 (7%) and six (6%) for upadacitinib and 12 (6%) and three (3%) for placebo; serious adverse events were reported by eight (4%) and four (2%) patients receiving upadacitinib and four (4%) and one (1%) patients receiving placebo. Six (3%) and four (2%) patients receiving upadacitinib and five (5%) and four (4%) patients receiving placebo experienced an adverse event leading to discontinuation of study treatment. No deaths were reported for patients receiving upadacitinib; one death (due to drowning) occurred in a patient receiving placebo in Viti-Up-2. The most common treatment-emergent adverse events (reported in ≥5% of participants) were upper respiratory tract infection, acne, nasopharyngitis, and headache (table 3). Across the two studies, all acne events were non-serious and non-severe (grade 1 or 2), and only one led to study treatment discontinuation. Acne events due to upadacitinib have been fully characterised in atopic dermatitis.[21]

For treatment-emergent adverse events of special interest up to week 48 of study treatment, there were no reports of adjudicated major adverse cardiovascular events, adjudicated venous thromboembolic events, adjudicated gastrointestinal perforations, active tuberculosis, lymphoma, non-melanoma skin cancer, or opportunistic infections other than herpes zoster in either study (table 3). Four serious infections were reported in three patients receiving upadacitinib in

	Viti-Up-1		Viti-Up-2	
	Placebo group (N=101)	Upadacitinib group (N=205)	Placebo group (N=101)	Upadacitinib group (N=205)
Any TEAE	61 (60%)	166 (81%)	63 (62%)	143 (70%)
Any TEAE related to study drug according to investigator	28 (28%)	100 (49%)	22 (22%)	60 (29%)
Any severe TEAE	6 (6%)	14 (7%)	3 (3%)	12 (6%)
Any serious TEAE	4 (4%)	8 (4%)	1 (1%)	4 (2%)
Any TEAE leading to discontinuation of study drug	5 (5%)	6 (3%)	4 (4%)	4 (2%)
Any TEAE leading to death	0	0	1 (1%)*	0
TEAEs of special interest				
Serious infections	0	3 (1%)	0	0
Herpes zoster	0	4 (2%)	1 (1%)	3 (1%)
Malignancy (all types)	1 (1%)	1 (<1%)	1 (1%)	0
Non-melanoma skin cancer	0	0	0	0
Malignancies excluding non-melanoma skin cancer	1 (1%)	1 (<1%)†	1 (1%)	0
Lymphoma	0	0	0	0
Hepatic disorders	4 (4%)	8 (4%)	2 (2%)	3 (1%)
Anaemia	0	3 (1%)	1 (1%)	2 (1%)
Neutropenia	3 (3%)	8 (4%)	1 (1%)	5 (2%)
Lymphopenia	1 (1%)	1 (<1%)	1 (1%)	4 (2%)
Bone fractures	1 (1%)	5 (2%)	0	3 (1%)
Retinal detachment	0	0	0	0
Serious hypersensitivity reactions	0	0	0	0
Adjudicated major adverse cardiovascular events	0	0	0	0
Adjudicated venous thromboembolic events	0	0	0	0
Opportunistic infections	0	0	0	0
Active tuberculosis	0	0	0	0
Adjudicated gastrointestinal perforations	0	0	0	0
Renal dysfunction	0	0	0	0
Most frequently reported TEAEs (≥5% of patients in any treatment group)				
Upper respiratory tract infection	8 (8%)	29 (14%)	11 (11%)	20 (10%)
Acne	5 (5%)	23 (11%)	3 (3%)	24 (12%)
Nasopharyngitis	8 (8%)	21 (10%)	14 (14%)	36 (18%)
Headache	5 (5%)	18 (9%)	5 (5%)	17 (8%)

Data are n (%). Adjudicated refers to review by an independent panel of medical experts. Events were categorised as serious if they could result in death, hospitalisation or prolongation of hospitalisation, congenital anomaly, persistent or significant disability or incapacity, were life-threatening, or could require medical or surgical intervention to prevent a serious outcome. Events were rated for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. TEAE=treatment-emergent adverse event. *Cause of death was drowning. †Genital neoplasm, malignant, in 69-year-old female participant 46 days after start of upadacitinib.

Table 3: **Treatment-emergent adverse events across 48 weeks**

Viti-Up-1 (1% of patients; bronchitis and influenza in one patient, complicated appendicitis and parainfluenza virus infection in two other patients, none of which led to study treatment discontinuation). No serious infections were reported in Viti-Up-2 for any patients receiving upadacitinib or placebo. Herpes zoster was reported in four (2%) and three (2%) patients receiving upadacitinib in Viti-Up-1 and Viti-Up-2, respectively, with no reports for patients receiving placebo in Viti-Up-1 and one (1%) for a patient receiving placebo in Viti-Up-2. There were no cases of disseminated herpes zoster. In Viti-Up-1, one case of malignancy excluding non-melanoma skin cancer was reported in each of the placebo and upadacitinib groups; in Viti-Up-2, there was one report in the placebo group and none in the upadacitinib group. One patient (female, 69 years old) receiving upadacitinib in Viti-Up-1 developed a malignant genital neoplasm identified 46 days after starting the study treatment, making the temporal association of this event with the study treatment implausible. Reports of bone fractures were uncommon; all occurred in the setting of trauma and were numerically higher in patients receiving upadacitinib (five [2%] and three [1%]) compared with placebo (one [1%] and none).

For laboratory-related adverse events of special interest, numerically higher proportions of patients receiving upadacitinib versus placebo in one or both studies had reports of anaemia (Viti-Up-1: upadacitinib three [2%] and placebo none; Viti-Up-2: upadacitinib two [1%] and placebo one [1%]), lymphopenia (Viti-Up-1: one [1%] and one [1%]; Viti-Up-2: four [2%] and one [1%]), and neutropenia (Viti-Up-1: eight [4%] and placebo three [3%]; Viti-Up-2: five [2%] and one [1%]). The proportion of patients with adverse events of hepatic disorders was similar between the treatment groups (Viti-Up-1: upadacitinib eight [4%] and placebo four [4%]; Viti-Up-2: three [1%] and two [2%]) and were generally due to transitory liver enzyme elevations, of which none met Hy's law criteria for drug-induced liver injury. No cases of renal dysfunction were reported. No laboratory-related adverse events were considered serious (table 3). Potentially clinically significant laboratory value decreases in neutrophil count showed no association with the occurrence of serious infections (appendix p 9).

Discussion

In both Viti-Up-1 and Viti-Up-2, the efficacy, safety, and tolerability of upadacitinib were demonstrated in adults and adolescents with non-segmental vitiligo. The coprimary endpoints of T-VASI 50 and F-VASI 75 at week 48 were reached by a greater proportion of patients receiving upadacitinib than placebo. Additionally, the secondary endpoints of F-VASI 50 at week 48, F-VASI 75 at week 24, F-VASI 90 at week 48, and PhGIC-V of "Much better (1)" at week 48 were met by a greater proportion of patients receiving upadacitinib compared with placebo.

Upadacitinib demonstrated a statistically significantly greater percentage change (reduction) from baseline in F-VASI at week 24 and in T-VASI at week 48. Repigmentation by upadacitinib continued to increase up to week 48 of both studies as evidenced by both percentage change from baseline and specified categorical (eg, T-VASI 50) VASI endpoints. Of note, no apparent plateau in the degree of improvement in VASI endpoints was observed at week 48, signalling the potential for continued increases in repigmentation with

longer duration of therapy, which will be verified in longer term analyses of these studies.

The Viti-Up study used T-VASI 50 as the primary responder endpoint to examine meaningful total body repigmentation, similar to other published non-segmental vitiligo studies.[17,22] T-VASI 50 has been shown to reflect clinically meaningful improvement in repigmentation through qualitative patient interviews and quantitative psychometric analyses.[23,24] Of note, some studies have pointed to lower thresholds (T-VASI 30 and T-VASI 42) for clinical meaningfulness,[17,25] whereas others have pointed to the need to reach higher thresholds of repigmentation (75%).[25–27] The optimal long-term threshold for treatments used as monotherapy or in combination with modalities such as narrow-band ultraviolet B (UVB) phototherapy warrants further prospective investigation.

Patient-reported outcomes continued to improve with upadacitinib up to week 48. Of note, greater proportions of patients receiving upadacitinib compared with placebo indicated the status of their non-segmental vitiligo as "Much better" (PaGIC-V) and either "A lot less noticeable" or "No longer noticeable" (Vitiligo Noticeability Scale) at week 48. Observed improvements in repigmentation and in patient-reported outcomes in the current study demonstrate the clinical utility of upadacitinib as a systemic therapy for vitiligo.[23]

Given that repigmentation in non-segmental vitiligo is known to take a considerable amount of time, particularly in the absence of adjunctive targeted phototherapy (narrow-band UVB), the improvements in VASI scores seen as early as week 8 for F-VASI 75 and T-VASI 50 for patients receiving upadacitinib compared with placebo were notable. Additionally, in both studies, 14% of patients on upadacitinib reached F-VASI 90 at week 48, highlighting the potential to reach complete or near-complete repigmentation with upadacitinib treatment of non-segmental vitiligo. Patients, including those with extensive vitiligo, have the opportunity for profound depth of response with upadacitinib.

Several factors may influence the potential for and speed of repigmentation of vitiligo, including age, Fitzpatrick skin type, disease duration, ultraviolet light exposure, disease activity (active *vs* stable), and anatomic area of involvement.[28–31] The Viti-Up study populations had a long disease duration (mean 16 years) and considerable disease extent based on baseline VASI scores. Additionally, approximately 62% had active disease at baseline. In the current study, comprising patients meeting the criteria of baseline T-VASI scores ranging from 5 to a maximum of 50, and both active and stable disease, upadacitinib demonstrated efficacy in the treatment of non-segmental vitiligo over placebo.

Upadacitinib did not demonstrate a difference from placebo in the achievement of T-VASI 75 at week 48. Given the multiple variables affecting repigmentation, increased duration of treatment or combination treatment might be required to reach this higher level of response in total body repigmentation.[32,33] For vitiligo, the need to treat for many years to optimise results has been well demonstrated,[34] and combination treatment with phototherapy (eg, narrow-band UVB) can enhance response as previously reported with both oral and topical JAK inhibitors (baricitinib and ruxolitinib). Furthermore, according to expert recommendations, the combination of topical or systemic immunomodulatory agents with narrow-band UVB phototherapy could achieve better efficacy.[10,35]

Stabilisation is a treatment goal and key pillar of vitiligo treatment.[10,11] For patients, prevention of disease spread is paramount. A systemic therapy targeting the immune dysregulation that causes vitiligo has the potential to stabilize disease and thereby limit disease progression (the appearance of new or expanding lesions). In Viti-Up-1 and Viti-Up-2, greater proportions of patients with active vitiligo taking upadacitinib had no increase in T-VASI at weeks 8 and 12 compared with baseline, suggesting that treatment with upadacitinib can potentially stabilise disease extent in patients with active vitiligo by limiting increases in disease extent. The unpredictable course of vitiligo and the associated fear of new or expanding vitiligo lesions that many experience contribute to the burden for patients with vitiligo.[36–38] Considering the profound psychosocial impact (or burden) that non-segmental vitiligo can have on patients, disease management should prioritise reducing this burden, improving patient perception of disease, and, ultimately, ameliorating health-related quality of life.[7] Results of the Viti-Up studies demonstrate that upadacitinib positively affects patient perception of their disease.

Upadacitinib is the first systemic JAK inhibitor to be used in two phase 3, 48-week, randomised, placebo-controlled studies in patients with non-segmental vitiligo. Both studies showed consistent safety outcomes with no reports of major adverse cardiovascular events, venous thromboembolic events, opportunistic infections, active tuberculosis, or gastrointestinal perforations, and low rates of serious infections and herpes zoster. The observed safety profile of upadacitinib was overall consistent with published long-term safety outcomes from studies of upadacitinib in atopic dermatitis that indicated no increase in safety risks over time;[39] no new safety signals were identified across 48 weeks in Viti-Up-1 or Viti-Up-2.

As a systemic therapy, upadacitinib provides a therapeutic option for groups in whom vitiligo cannot be addressed by current topical therapies or phototherapy. Such groups might include: patients for whom topical therapy phototherapy use could be challenging, inadequate, or both; patients with active non-segmental vitiligo; and patients with more extensive and/or widespread depigmentation. Ruxolitinib 1·5% cream is an approved therapy for

patients with vitiligo, but its application is limited to 10% of the body surface area,[14] resulting in a notable unmet clinical need for approved therapies for patients with non-segmental vitiligo with more extensive disease.

In general, long-term topical therapy use is perceived by patients to be inconvenient, particularly for inaccessible and/or extensive lesions. Because treatment of vitiligo is chronic and requires persistence, adherence to topical therapy might be challenging because patients report the use of topical medications as being more difficult than taking oral medications.[40,41] This can be particularly relevant for treatments requiring application more than once daily. Current guidelines recommend the use of systemic therapy for actively progressing disease to achieve stabilisation of disease activity and prevent spread.[10] Approximately 62% of the Viti-Up population had active vitiligo at baseline, and upadacitinib demonstrated efficacy over placebo in the ability to stabilise vitiligo disease extent in this group. Based on its ability to systemically treat non-segmental vitiligo, without limitations to body surface area or the need to reapply and manage frequent topical therapy applications, upadacitinib provides patients with an alternative that can potentially stabilise their disease, provide repigmentation of the face and total body, improve health-related quality of life, and reduce psychosocial burden.

The current studies are not without limitations. As with most clinical trials, the population in these studies might not reflect the full range of the non-segmental vitiligo patient population in a real-world setting. Additionally, this study evaluated upadacitinib as monotherapy, but many patients being treated for non-segmental vitiligo might utilise a combination of treatments, which would not be reflected in the current studies. Numbers of patients with high Fitzpatrick skin type were low, and a large percentage of each treatment group was White, suggesting additional studies are needed in under-represented populations. In the two studies, treatment effect of upadacitinib on repigmentation continued until week 48 without reaching plateau; therefore, the full potential of upadacitinib in achieving repigmentation in non-segmental vitiligo warrants assessment at a later timepoint of continued therapy. At the time of the development of the current study, there was no consensus on the definition of active vitiligo. The recently published consensus statement by the INTERCEPT Study Group indicates that active vitiligo can be identified clinically by the presence of new or spreading patches, confetti-like depigmentation, trichrome vitiligo or poorly defined borders, and Koebner phenomenon; the definition of active vitiligo used in the current study aligns with this definition.[42] Given the importance of vitiligo disease activity and its stabilisation, it is anticipated that the definitions of active vitiligo and rapidly progressing vitiligo will continue to be refined as new prospective data are published and the understanding of these concepts evolves.

In conclusion, the results of the two phase 3 Viti-Up studies demonstrate the efficacy and safety of upadacitinib as a systemic therapy for non-segmental vitiligo in adults and adolescents and address the core outcomes of repigmentation and safety.[43] Improvements in repigmentation, as well as patient-reported outcomes, were observed. Upadacitinib demonstrated efficacy based on VASI and was associated with high physician-reported and patient-reported improvement, as measured by PhGIC-V and PaGIC-V. Upadacitinib, an oral JAK inhibitor, is the first systemic therapy to demonstrate significant repigmentation of the face and total body at week 48 in a phase 3 clinical trial in patients with non-segmental vitiligo, with no new safety signals. Data suggest that upadacitinib can stabilise disease extent in patients with active non-segmental vitiligo; further investigation of upadacitinib's potential impacts on disease activity is needed. Upadacitinib might offer a new and effective systemic therapy option for adults and adolescents with non-segmental vitiligo. Additional Viti-Up data addressing core outcomes, including maintenance of repigmentation, will be forthcoming.

Contributors

TP, KE, NvG, IH, AGP, DR, XH, AMS, HSC, HDT, SP, BJS, and JS participated in conceptualisation. XH, XW, MW, YY, HSC, SP, and BJS participated in data curation. SS, IF, XH, XW, MW, YY, AMS, HDT, SP, and BJS participated in the formal data analysis. TP, VHP, RKS, NvG, IH, LX, TS, SD, MR, SS, IF, XH, XW, MW, YY, AMS, HDT, SP, BJS, and JS participated in study investigation. TP, KE, NvG, IH, AGP, DR, SS, IF, XH, XW, MW, YY, AMS, HSC, HDT, SP, BJS, and JS participated in methodology. VHP, RKS, SS, IF, XH, XW, MW, YY, AMS, HSC, HDT, SP, and BJS participated in validation. SS, IF, XH, XW, MW, YY, AMS, HDT, SP, and BJS participated in data visualisation. SP and BJS wrote the original manuscript draft. All authors participated in review and editing of manuscript drafts, had full access to all the data in the study, and had final responsibility for the decision to submit the manuscript for publication.

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, honoraria, or both 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, Takeda, UCB, and VYNE Therapeutics. He is the cofounder of NIKAIA Pharmaceuticals and founder of SUNLUTION; and has patents on WNT agonists or GSK3b antagonist for repigmentation of vitiligo and the use of CXCR3B blockers in vitiligo. VHP has served as an advisor, consultant, and/or speaker for AbbVie, Actelion, Amgen, Apogee Therapeutics, Aralez, Arcutis, Aspen, Bausch Health, BioJAMP/JAMP Pharma, BioScript Solutions, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Celltrion, Cipher, CorEvitas, Eczema Society of Canada, Galderma, GlaxoSmithKline, Homeocan, Incyte, J&J Innovative Medicine, Janssen, Johnson & Johnson, Knight Therapeutics, LEO Pharma, Lilly, Medexus, Nia Health, Novartis, Organon, Paladin, Pediapharm, Pfizer, Regeneron, Sanofi Genzyme, Sun Pharmaceuticals, Tribute, and UCB. He has also served as an investigator for AbbVie, AnaptysBio, Apogee Therapeutics, Arcutis, Arena, Asana, Bausch Health, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Concert, CorEvitas, Dermavant, Dermira, Galderma, Incyte, J&J Innovative Medicine, Janssen, Leo Pharma, Lilly, Meiji Pharma,

Nektar Therapeutics, Nimbus Lakshmi, Novartis, Pfizer, Q32 Bio, RAPT Therapeutics, Regeneron, Reistone, Roche, Sanofi Genzyme, Sun Pharmaceuticals, Takeda, UCB, and VYNE Therapeutics; and received grants from AbbVie, Bausch Health, Janssen, LEO Pharma, Novartis, and Sanofi Genzyme. RKS has served as a consultant or speaker for Amgen, Burt's Bees, Sanofi, Bristol Myers Squibb, Arbonne, Trace Minerals, Codex Labs, Pfizer, Phothera, Almirall, Nutraceutical Wellness, Lilly, Galderma, Incyte, Novartis, Arcutis, Janssen, AbbVie, Leo Pharma, UCB, Sun Pharmaceuticals, and Regeneron Pharmaceuticals. KE is a consultant for AbbVie, Incyte Corporation, La Roche-Posay, Pfizer, Pierre Fabre, Sanofi, and Viela Bio. NvG has received grants from and/or is a consultant and/or investigator for AbbVie, Incyte, Merck/MSD, Pfizer, Bristol Myers Squibb, Boehringer Ingelheim, Takeda, Teva, and Sun Pharmaceuticals; and is chair of the Vitiligo Task Force for the European Academy of Dermatology and Venereology (EADV). IH is a consultant for AbbVie, Almirall, Avita, Boehringer Ingelheim, Galderma, Incyte, Janssen, Novartis, Pfizer, Merck, UCB, Lilly, and Teva. He is an investigator for AbbVie, Avita, Incyte, Lenicura, L'Oréal/La Roche-Posay, Merck, Takeda, Teva, and Pfizer; and is a board member and former President of the Hidradenitis Suppurativa Foundation and Global Vitiligo Foundation. AGP has served as an investigator for Avita, Clinuvel, and Incyte; as a consultant for AbbVie, Avita, Boehringer Ingelheim, Incyte, Lilly, Pfizer, Sun Pharmaceuticals, Vimela, Vyne, and WCG; and is a shareholder for Tara Medical. DR has served as a consultant, spoken for, or conducted trials for the following companies: AbbVie, Abcuro, Almirall, AltruBio, Amgen, Arena, Astria, Boehringer Ingelheim, Bristol Meyers Squibb, Celgene, Concert, CSL Behring, Dermavant, Dermira, Dualitas, Edesa Biotech, EMD Serono, Forte Biosciences, Galderma, Incyte, Inmagene, Janssen, Kymera, Kyowa Kirin, Lilly, Merck, Nektar, Novartis, Pfizer, RAPT, Regeneron, Recludix, Revolo Biotherapeutics, Sanofi, Sun Pharmaceuticals, Takeda, UCB, VielaBio, and Zura Bio. LX is a consultant for AbbVie, Galderma, Merz, Solta, Skinceutical, Beiersdof, P&G, Botanee, JAKA, and Unilever. TS has consulted for, spoken for, or collaborated on research with AbbVie, Pfizer, J-TEC, Maruho, and Pola. He is the President of the Japanese Society of Vitiligo. SD has served as a consultant and/or investigator for AbbVie as well as Pfizer, Incyte, Eli Lilly, Galderma, L'Oreal, Alumis, and Apogee and has held multiple leadership roles in dermatology and health care. MR has received grants and/or honoraria from and/or served as a consultant, spoken for, or conducted trials for the following companies: AbbVie, LEO Pharma, Dermavant, Incyte, Janssen, Pfizer, Dren Bio, ITN, Elixiron, Sanofi, Biogen, Incyte, Abeona Therapeutics, Edesa Biotech, Atlas Venture, Inzen, ROME Therapeutics, Almirall, Medicxi, Related Sciences, and VisualDx. SS, IF, XH, XW, MW, YY, AMS, HSC, HDT, SP, and BJS are employees of AbbVie and may own stocks or stock options. AMS is a co-inventor on AbbVie patents. JS has received grants and/or honoraria from AbbVie, Almirall, Boehringer Ingelheim, Incyte, LEO Pharma, Lilly, Novartis, Pfizer, Pierre Fabre, Sanofi, and Silab; and has a patent on MMP9 inhibitors and uses thereof in the prevention or treatment of a depigmenting disorder and three-dimensional model of depigmenting disorder.

Data sharing

AbbVie is committed to responsible data sharing regarding the clinical trials it sponsors. This includes access to anonymised, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols, clinical study reports, synopses, or statistical analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. 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, statistical analysis plan, and execution of a Data Use Agreement. Data requests can be submitted at any time after indication regulatory approval in the USA and Europe. For more information on the process or to submit a request, visit https://vivli.org/ourmember/abbvie/ then select Home.

Acknowledgments

AbbVie and the authors thank all study investigators for their contributions and the patients who participated in this study. AbbVie funded the research for this study and provided writing support for this manuscript. Medical writing assistance was provided by Elin M Grissom of AbbVie.

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