



# Ruxolitinib cream for treatment of vitiligo: a randomised, controlled, phase 2 trial

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## Summary

**Background** Vitiligo is a chronic autoimmune disease resulting in skin depigmentation and reduced quality of life. There is no approved treatment for vitiligo repigmentation and current off-label therapies have limited efficacy, emphasising the need for improved treatment options. We investigated the therapeutic potential of ruxolitinib cream in patients with vitiligo and report the efficacy and safety results up to 52 weeks of double-blind treatment.

**Methods** We did a multicentre, randomised, double-blind, phase 2 study for adult patients with vitiligo in 26 US hospitals and medical centres in 18 states. Patients with depigmentation of 0·5% or more of their facial body surface area (BSA) and 3% or more of their non-facial BSA were randomly assigned (1:1:1:1) by use of an interactive response technology system to receive ruxolitinib cream (1·5% twice daily, 1·5% once daily, 0·5% once daily, or 0·15% once daily) or vehicle (control group) twice daily on lesions constituting 20% or less of their total BSA for 24 weeks. Patients in the control group in addition to patients in the 0·15% once daily group who did not show a 25% or higher improvement from baseline in facial Vitiligo Area Scoring Index (F-VASI) at week 24 were re-randomised to one of three higher ruxolitinib cream doses (0·5% once daily, 1·5% once daily, 1·5% twice daily). Patients in the 0·5% once daily, 1·5% once daily, or 1·5% twice daily groups remained at their original dose up to week 52. Patients, investigators, and the study sponsor (except members of the interim analysis and primary endpoint analysis data monitoring teams) remained masked to treatment assignment throughout the study. The primary endpoint was the proportion of patients achieving a 50% or higher improvement from baseline in F-VASI (F-VASI50) at week 24, assessed in the intention-to-treat population. The study is registered with ClinicalTrials.gov, NCT03099304.

**Findings** Between June 7, 2017, and March 21, 2018, 205 patients were screened for eligibility, 48 were excluded and 157 patients (mean age, 48·3 years [SD 12·9]; 73 [46%] male and 84 [54%] female) were randomly assigned to either an intervention group or the control group. 32 (20%) of 157 were assigned to the control group, 31 (20%) to the 0·15% once daily group, 31 (20%) to the 0·5% once daily group, 30 (19%) to the 1·5% once daily group, and 33 (21%) to the 1·5% twice daily group. F-VASI50 at week 24 was reached by significantly more patients given ruxolitinib cream at 1·5% twice daily (15 [45%] of 33) and 1·5% once daily (15 [50%] of 30) than were treated with vehicle (one [3%] of 32). Four patients had serious treatment-emergent adverse events (one patient in the 1·5% twice daily group developed subdural haematoma; one patient in the 1·5% once daily group had a seizure; one patient in the 0·5% once daily group had coronary artery occlusion; and one patient in the 0·5% once daily group had oesophageal achalasia), all of which were unrelated to study treatment. Application site pruritus was the most common treatment-related adverse event among patients given ruxolitinib cream (one [3%] of 33 in the 1·5% twice daily group; three [10%] of 30 in the 1·5% once daily group; three [10%] of 31 in the 0·5% once daily group; and six [19%] of 31 in the 0·15% once daily group) with three [9%] of 32 patients showing application site pruritus in the control group. Acne was noted as a treatment-related adverse event in 13 (10%) of 125 patients who received ruxolitinib cream and one (3%) of 32 patients who received vehicle cream. All treatment-related adverse events were mild or moderate in severity and similar across treatment groups.

**Interpretation** Treatment with ruxolitinib cream was associated with substantial repigmentation of vitiligo lesions up to 52 weeks of treatment, and all doses were well tolerated. These data suggest that ruxolitinib cream might be an effective treatment option for patients with vitiligo.

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## Introduction

Vitiligo is a chronic autoimmune disease characterised by depigmented patches of skin that result from the loss of melanocytes.<sup>1,2</sup> The global prevalence of vitiligo is

approximately 0·5–2%, which varies geographically.<sup>3</sup> Patients with vitiligo have a reduced quality of life and often have psychosocial and autoimmune comorbidities.<sup>4–6</sup> Vitiligo is caused by the infiltration of affected areas with

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## Research in context

### Evidence before this study

A PubMed search for publications of clinical trials between Jan 1, 1997, and April 4, 2017, using the terms “vitiligo” and “repigmentation” with an emphasis on topical therapy yielded few results in large patient populations. No language restrictions were applied to the search. Among prospective studies evaluating treatment of vitiligo lesions with topical therapies, the majority evaluated corticosteroids or calcineurin inhibitors, or both. Few studies evaluated targeted immunotherapy for the treatment of vitiligo, but promising preliminary results, especially facial repigmentation, were reported with the use of Janus kinase (JAK) inhibitors. Controlled studies reporting the use of topical corticosteroids and calcineurin inhibitors, currently used off-label, included relatively small patient populations, and results indicated inadequate repigmentation with safety limitations on duration of use.

### Added value of this study

This phase 2 study is the first, to our knowledge, to report results from a large, prospective, randomised, vehicle-controlled study evaluating the efficacy and safety of any targeted immunomodulatory agent (including JAK inhibitors) in adult patients with vitiligo. A greater proportion of patients receiving any dose of ruxolitinib cream than vehicle met the primary endpoint of a 50% or greater improvement from baseline in facial Vitiligo Area Scoring Index (F-VASI50)

at week 24, compared with vehicle. Continuous improvement was seen following 52 weeks of ruxolitinib cream monotherapy. Additionally, 45% of patients with baseline total body surface area 20% or less (and could therefore treat all depigmented skin) who received 1.5% ruxolitinib cream twice daily had a 50% or greater improvement from baseline in total Vitiligo Area Scoring Index (T-VASI50; total body assessment, including the face) at week 52. Ruxolitinib cream was well tolerated and application site reactions during treatment were few.

### Implications of all the available evidence

There is no approved treatment for repigmentation of vitiligo lesions. Results from this randomised, double-blind, phase 2 study provide support for the use of JAK inhibitors in the treatment of vitiligo and a rationale for continued investigation of ruxolitinib cream in randomised phase 3 trials. The data generated in this study could provide additional evidence for the use of F-VASI and T-VASI instruments for quantification of repigmentation in future vitiligo clinical trials, on the basis of post-hoc confirmation of instrument validity and reliability using phase 2 data reported here. Identification of biomarkers predictive of patients expected to respond to ruxolitinib cream treatment would be of considerable value and worthy of continued investigation. The use of ruxolitinib cream monotherapy in patients with vitiligo could lead to effective and sustained repigmentation.

activated melanocyte antigen-specific CD8<sup>+</sup> T cells that drive cytotoxicity and disease pathogenesis.<sup>2</sup> Recruitment of autoreactive CD8<sup>+</sup> T cells to melanocytes is mediated by interferon  $\gamma$  (IFN $\gamma$ ) through the IFN $\gamma$ -induced chemokines C-X-C motif chemokine ligand (CXCL) 9 and 10, a signalling pathway regulated by Janus kinase (JAK) 1 and 2.<sup>7-9</sup> CXCL9 and CXCL10 have been validated as biomarkers of vitiligo activity; the concentration of both these factors are increased in the skin and blood of patients with vitiligo compared with healthy controls, and in patients with active versus stable vitiligo.<sup>10-13</sup>

Inhibitors of JAK signalling suppress inflammatory cytokine signalling and are under investigation as potential treatment options for several dermatological diseases, including vitiligo.<sup>14-17</sup> A previous study reported that keratinocytes sense IFN $\gamma$  in vitiligo lesions and are the primary producers of CXCL9 and CXCL10, which promote T-cell recruitment.<sup>18</sup> Thus, topical administration of a JAK inhibitor is a rational approach to diminish local inflammation and facilitate endogenous repigmentation in patients with vitiligo.

Ruxolitinib cream is a JAK1 and JAK2 inhibitor,<sup>19</sup> which has shown preliminary efficacy in vitiligo treatment. In open-label studies,<sup>16,17</sup> application of 1.5% ruxolitinib cream twice daily significantly improved facial Vitiligo Area Scoring Index (F-VASI) scores from

baseline. We did a randomised, dose-ranging, 156-week, phase 2 study to further investigate the therapeutic potential of ruxolitinib cream in patients with vitiligo. Here, we report the efficacy and safety results up until 52 weeks of double-blind treatment.

## Methods

### Study design and participants

This randomised, double-blind, dose-ranging, phase 2 study was done across 26 US hospitals and medical centres in 18 states (appendix pp 4–5).

Patients aged 18–75 years (inclusive) with a diagnosis of vitiligo and depigmented areas that included at least 0.5% facial body surface area (BSA) and at least 3% non-facial BSA were eligible for inclusion. Further inclusion criteria were discontinuation of all agents used to treat vitiligo from screening up until the final follow-up visit; however, over-the-counter preparations deemed acceptable by the investigator and camouflage makeups were permitted. Exclusion criteria included any dermatological disease confounding vitiligo assessment, previous use of JAK inhibitor therapy, and use of the following therapies for vitiligo: any biological or experimental therapy within 12 weeks or five half-lives of screening, phototherapy within 8 weeks of screening, or immunomodulating oral or systemic medication

See Online for appendix

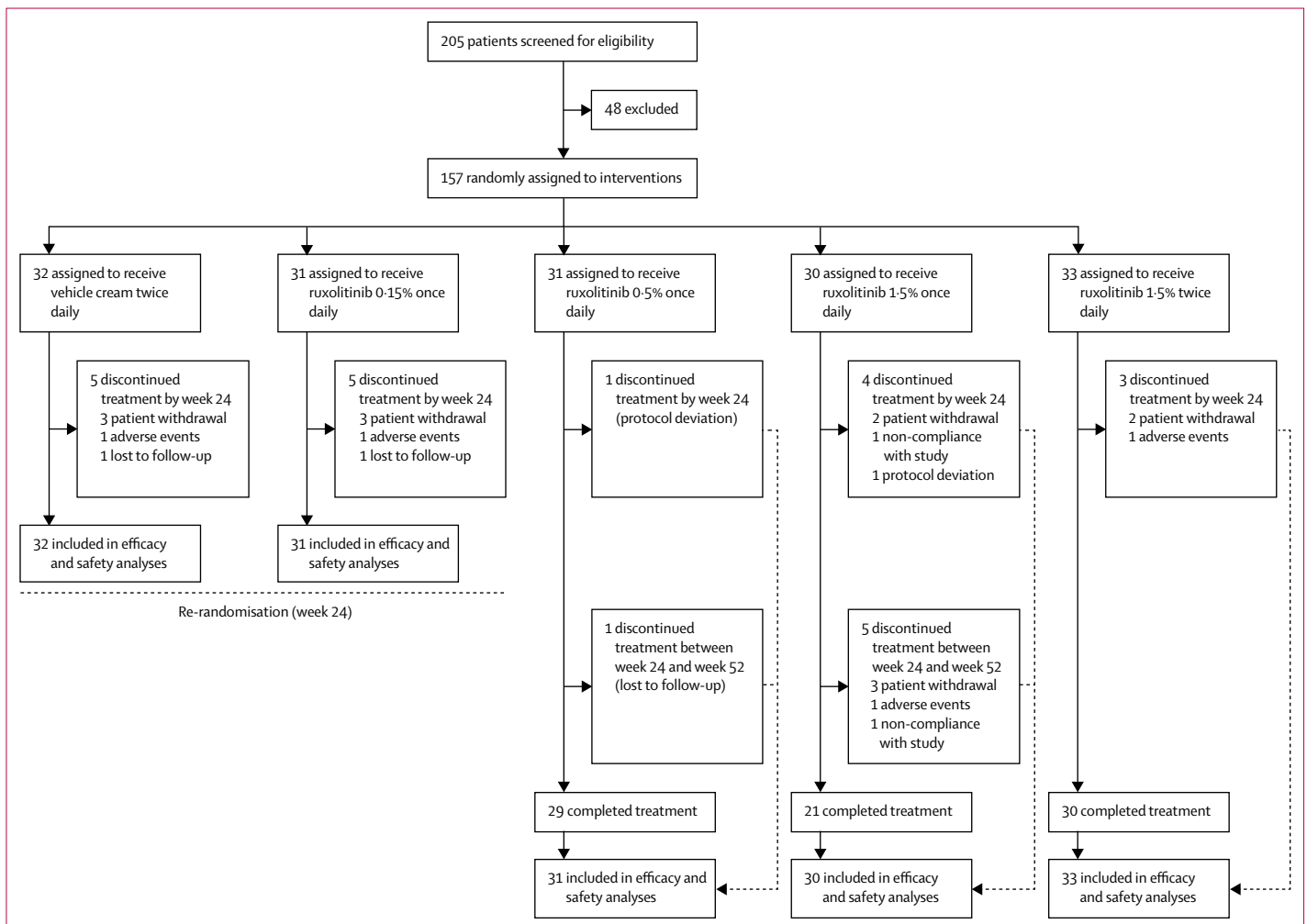
within 4 weeks of screening. Further exclusion criteria were a clinically substantially abnormal thyroid-stimulating hormone or free T4 concentration at screening; presence of cytopenia defined as a leucocyte count less than  $3.0 \times 10^9$  per L ( $<2.5 \times 10^9$  per L for African American patients), neutrophil count less than the lower limit of normal, lymphocyte count less than  $0.8 \times 10^9$  per L, haemoglobin concentration less than 10 g/dL, and platelet count less than  $100 \times 10^9$  per L. Full eligibility criteria are provided in the appendix (pp 13–14).

The study was done in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice and the principles embodied by the Declaration of Helsinki. All patients provided written informed consent.

The protocol (appendix pp 42–121) was approved by the institutional review board or ethics committee at each participating centre.

**Randomisation and masking**

The study used an interactive response technology system for the management of study enrolment. The system assigned the patient study numbers, tracked patient visits, randomised according to defined parameters, and maintained treatment masking. The system used a configurable stratification algorithm with limits set to patient age ( $\leq 30$  and  $>30$  years). Patients were randomly assigned to one of four dose strengths of ruxolitinib cream (1.5% twice daily, 1.5% once daily, 0.5% once daily, 0.15% once daily) or vehicle cream twice daily (control group) in a 1:1:1:1 ratio. Patients who received ruxolitinib cream once daily also received vehicle cream once daily to maintain masking. Patients, investigators, and the study sponsor (except members of the interim analysis and primary endpoint analysis data monitoring teams) remained masked to each patient’s treatment assignment throughout the study. Emergency unmasking could occur if an adverse event required the investigator to learn the patient’s treatment assignment.



**Figure 1: Trial profile**

Part 1 of the study was double-blind vehicle-controlled (up to week 24) and part 2 was a double-blind extension period (up to week 52).

## Procedures

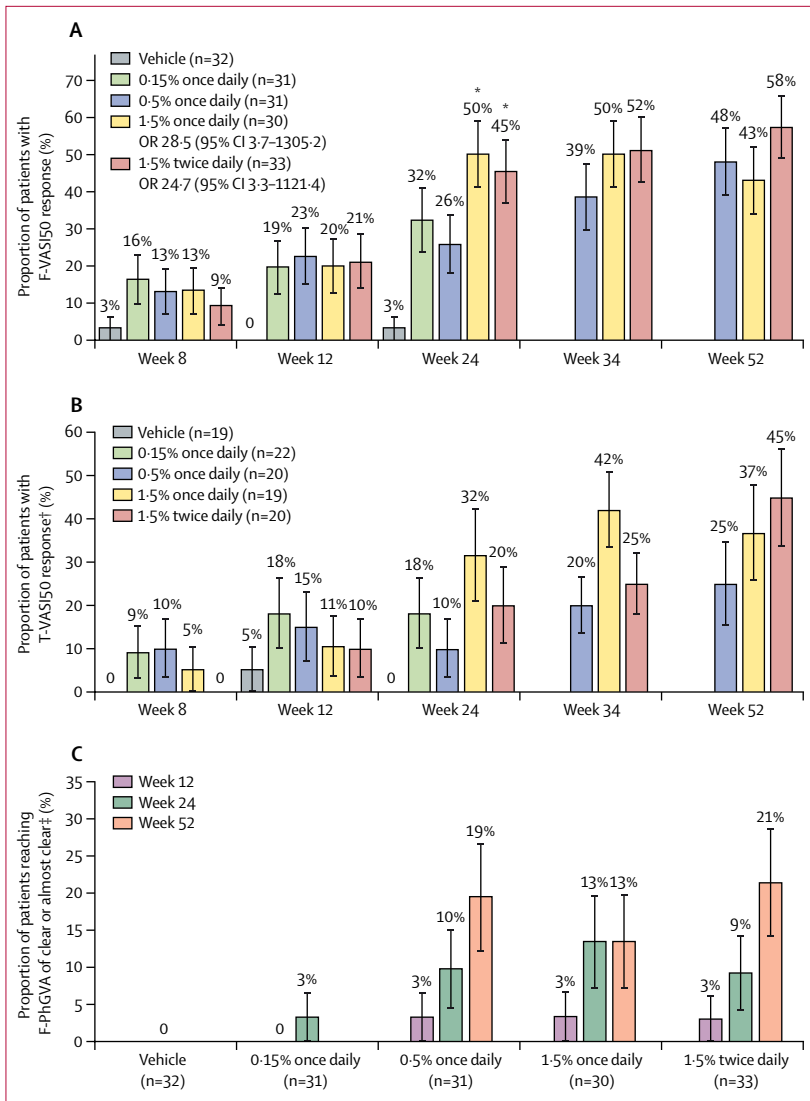
This phase 2 study comprised three parts spanning 156 weeks. During the double-blind, vehicle-controlled period (part 1), eligible patients were randomly assigned

(1:1:1:1) to receive ruxolitinib cream 1·5% twice daily, 1·5% once daily, 0·5% once daily, 0·15% once daily, or vehicle twice daily, with treatment application limited to 20% or less of patient's total BSA (T-BSA), for 24 weeks.

	Control (vehicle twice daily; n=32)	Ruxolitinib cream				Total (n=157)
		0·15% once daily group (n=31)	0·5% once daily group (n=31)	1·5% once daily group (n=30)	1·5% twice daily group (n=33)	
Age, years	46·3 (13·1)	45·1 (11·5)	53·8 (14·3)	46·7 (11·7)	49·5 (12·3)	48·3 (12·9)
≤30	4 (13%)	2 (6%)	3 (10%)	2 (7%)	4 (12%)	15 (10%)
>30	28 (88%)	29 (94%)	28 (90%)	28 (93%)	29 (88%)	142 (90%)
Sex						
Male	12 (38%)	13 (42%)	19 (61%)	11 (37%)	18 (55%)	73 (46%)
Female	20 (63%)	18 (58%)	12 (39%)	19 (63%)	15 (45%)	84 (54%)
Race						
White	26 (81%)	29 (94%)	25 (81%)	23 (77%)	29 (88%)	132 (84%)
Black	5 (16%)	0	4 (13%)	2 (7%)	3 (9%)	14 (9%)
Asian	1 (3%)	0	1 (3%)	2 (7%)	1 (3%)	5 (3%)
Other	0	2 (6%)	1 (3%)	3 (10%)	0	6 (4%)
Baseline F-VASI	1·21 (0·85)	1·19 (0·75)	1·22 (0·71)	1·45 (0·98)	1·26 (0·81)	1·26 (0·82)
Baseline T-VASI	19·40 (18·51)	14·57 (9·05)	18·43 (15·36)	20·55 (18·49)	16·94 (14·26)	17·96 (15·45)
Facial BSA*	1·44 (0·84)	1·35 (0·86)	1·40 (0·76)	1·67 (0·95)	1·55 (0·89)	1·48 (0·86)
Total BSA	23·54 (20·96)	17·56 (10·93)	22·96 (21·45)	24·81 (20·06)	21·46 (16·82)	22·05 (18·38)
Duration of disease, years	15·4 (1·5–37·6)	13·7 (0·3–67·9)	10·8 (1·7–59·0)	14·7 (0·3–56·0)	13·5 (0·8–47·8)	14·0 (0·3–67·9)
Diagnosed in childhood†	8 (25%)	7 (23%)	6 (19%)	4 (13%)	10 (30%)	35 (22%)
Type of vitiligo						
Segmental	5 (16%)	2 (6%)	2 (6%)	0	2 (6%)	11 (7%)
Non-segmental	27 (84%)	29 (94%)	29 (94%)	30 (100%)	31 (94%)	146 (93%)
Disease stability‡						
Progressive	21 (66%)	20 (65%)	12 (39%)	16 (53%)	20 (61%)	89 (57%)
Stable	11 (34%)	11 (35%)	19 (61%)	14 (47%)	13 (39%)	68 (43%)
Skin type						
I	1 (3%)	1 (3%)	1 (3%)	2 (7%)	1 (3%)	6 (4%)
II	7 (22%)	11 (35%)	12 (39%)	8 (27%)	12 (36%)	50 (32%)
III	10 (31%)	9 (29%)	9 (29%)	9 (30%)	13 (39%)	50 (32%)
IV	8 (25%)	8 (26%)	4 (13%)	7 (23%)	4 (12%)	31 (20%)
V	2 (6%)	2 (6%)	2 (6%)	3 (10%)	1 (3%)	10 (6%)
VI	4 (13%)	0	3 (10%)	1 (3%)	2 (6%)	10 (6%)
Other autoimmune disorders						
Thyroid disorders	11 (34%)	6 (19%)	5 (16%)	9 (30%)	8 (24%)	39 (25%)
Juvenile diabetes	0	0	0	0	2 (6%)	2 (1%)
Pernicious anaemia	1 (3%)	0	0	0	0	1 (1%)
Previous therapy						
Topical corticosteroids	16 (50%)	16 (52%)	12 (39%)	14 (47%)	14 (42%)	72 (46%)
Calcineurin inhibitors	18 (56%)	14 (45%)	13 (42%)	11 (37%)	14 (42%)	70 (45%)
Phototherapy	14 (44%)	5 (16%)	13 (42%)	11 (37%)	12 (36%)	55 (35%)
Excimer laser therapy	4 (13%)	2 (6%)	6 (19%)	5 (17%)	3 (9%)	20 (13%)
Photochemotherapy	1 (3%)	1 (3%)	2 (6%)	4 (13%)	4 (12%)	12 (8%)
Vitamin D derivatives	2 (6%)	1 (3%)	2 (6%)	1 (3%)	1 (3%)	7 (4%)
Surgical techniques	0	0	0	0	1 (3%)	1 (1%)
Other	8 (25%)	3 (10%)	2 (6%)	1 (3%)	3 (9%)	17 (11%)

Data are n (%), mean (SD), or median (range). BSA=body surface area. F-VASI=facial Vitiligo Area Scoring Index. T-VASI=total Vitiligo Area Scoring Index. \*Percentage of total BSA. †Data missing for one patient in the 1·5% twice daily group. ‡Determination of disease stability was based on investigator judgment.

**Table 1: Baseline characteristics**



**Figure 2: Efficacy of varying doses of ruxolitinib cream or vehicle cream** (A) F-VASI50 response. (B) T-VASI50 response. (C) F-PhGVA of clear or almost clear. Part 1 of the study was double-blind vehicle-controlled (up to week 24) and part 2 was a double-blind extension period (up to week 52). Error bars indicate SE. F-PhGVA=facial Physician's Global Vitiligo Assessment. F-VASI50=facial Vitiligo Area Scoring Index improvement of 50% or more. OR=odds ratio. T-BSA=total body surface area. T-VASI50=total Vitiligo Area Scoring Index improvement of 50% or more. \*p<0.0001 vs vehicle at week 24. †T-VASI50 response is reported for the subset of patients with baseline T-BSA of 20% or less because treatment was limited to lesions constituting 20% or less of T-BSA. ‡No patients had F-PhGVA values of clear or almost clear at baseline.

In the double-blind extension period (part 2), patients initially randomly assigned to vehicle and to 0.15% once daily who did not achieve at least a 25% improvement from baseline in F-VASI score were randomly assigned to one of three higher dosing groups (0.5% once daily, 1.5% once daily, 1.5% twice daily) for an additional 28 weeks. Re-randomised patients were only analysed up to week 24 in their originally assigned group. Patients initially randomly assigned to 1.5% twice daily, 1.5% once daily, or 0.5% once daily maintained the same treatment until week 52. After week 52, all patients could

receive open-label ruxolitinib cream 1.5% twice daily for an additional 104 weeks (part 3), with optional concurrent treatment with narrow-band ultraviolet light B phototherapy. Upon conclusion of part 3, a 24-week safety follow-up was done. This report describes results until the 52-week double-blind period (parts 1 and 2).

VASI assessment and monitoring of adverse events were done at baseline and at weeks 4, 8, 12, 18, 24, 28, 34, 40, 46, and 52 (or end of treatment or upon early termination). Patient's Global Vitiligo Assessment (PaGVA), Physician's GVA (PhGVA), and Patient Global Impression of Change-Vitiligo (PaGIC-V) were administered at baseline and weeks 12, 24, 40, and 52.

**Outcomes**

The primary endpoint was the proportion of patients given ruxolitinib cream who had a 50% or higher improvement from baseline in F-VASI score (F-VASI50) at week 24 versus vehicle. Key secondary endpoints were the proportion of patients achieving a facial PhGVA (F-PhGVA) of clear (completely repigmented, no signs of vitiligo) or almost clear (only specks of depigmentation present) at week 24 and the proportion achieving a 50% or higher improvement from baseline in total Vitiligo Area Scoring Index<sup>20</sup> (T-VASI50) at week 52. Other secondary endpoints included mean percentage change from baseline in F-VASI (ie, F-VASI75 and F-VASI90) and T-VASI scores and mean percentage change in facial BSA (F-BSA) and T-BSA over the treatment period, proportion of patients in each F-PhGVA and total PhGVA (T-PhGVA) and facial and total PaGVA (F-PaGVA and T-PaGVA) category during the treatment periods, proportion of patients in each PaGIC-V category during treatment periods, and safety and tolerability assessments done by monitoring adverse events and laboratory data. The reliability and validity of F-VASI and T-VASI instruments as measures of treatment efficacy were confirmed post hoc using data from this phase 2 study. A reliability and validity report for the VASI instrument (primary and key secondary endpoints) is available in the appendix (pp 30–40). Exploratory endpoints assessed included the percentage change in serum CXCL10 and IFN $\gamma$  protein concentrations and broader proteomic analysis of the serum samples. Post-hoc subgroup analyses were done to assess total body lesions among patients with baseline T-BSA 20% or less (ie, patients who could treat all areas of depigmented skin).

**Statistical analysis**

A sample size of 150 randomly assigned patients (approximately 30 patients per group) was determined to provide sufficient statistical power to detect the difference between ruxolitinib cream 1.5% twice daily and vehicle (appendix p 3). For the primary and key secondary endpoints, comparisons between the ruxolitinib groups and vehicle were done using exact logistic regression, including stratification factors. Type I error was controlled using the Bonferroni–Holm procedure at an overall



two-sided  $\alpha$  of 0.05 to determine the superiority of ruxolitinib cream 1.5% twice daily or 1.5% once daily versus vehicle. Statistics used for the exploratory analyses of biomarkers are described in the appendix (p 3). All other secondary and exploratory analyses were summarised using descriptive statistics. All randomly assigned patients who received at least one dose of ruxolitinib cream or vehicle were included in the efficacy (intention-to-treat population) and safety (safety population) analyses (data cutoff, April 30, 2019). Secondary outcomes were assessed using the intention-to-treat population, with the exception of the subanalyses that examined total body lesions in patients with baseline BSA of 20% or less. Statistical analyses were done with SAS software version 9.4. No external data monitoring committee was used; however, an internal data monitoring committee examined the interim analysis. The study is registered with ClinicalTrials.gov, NCT03099304.

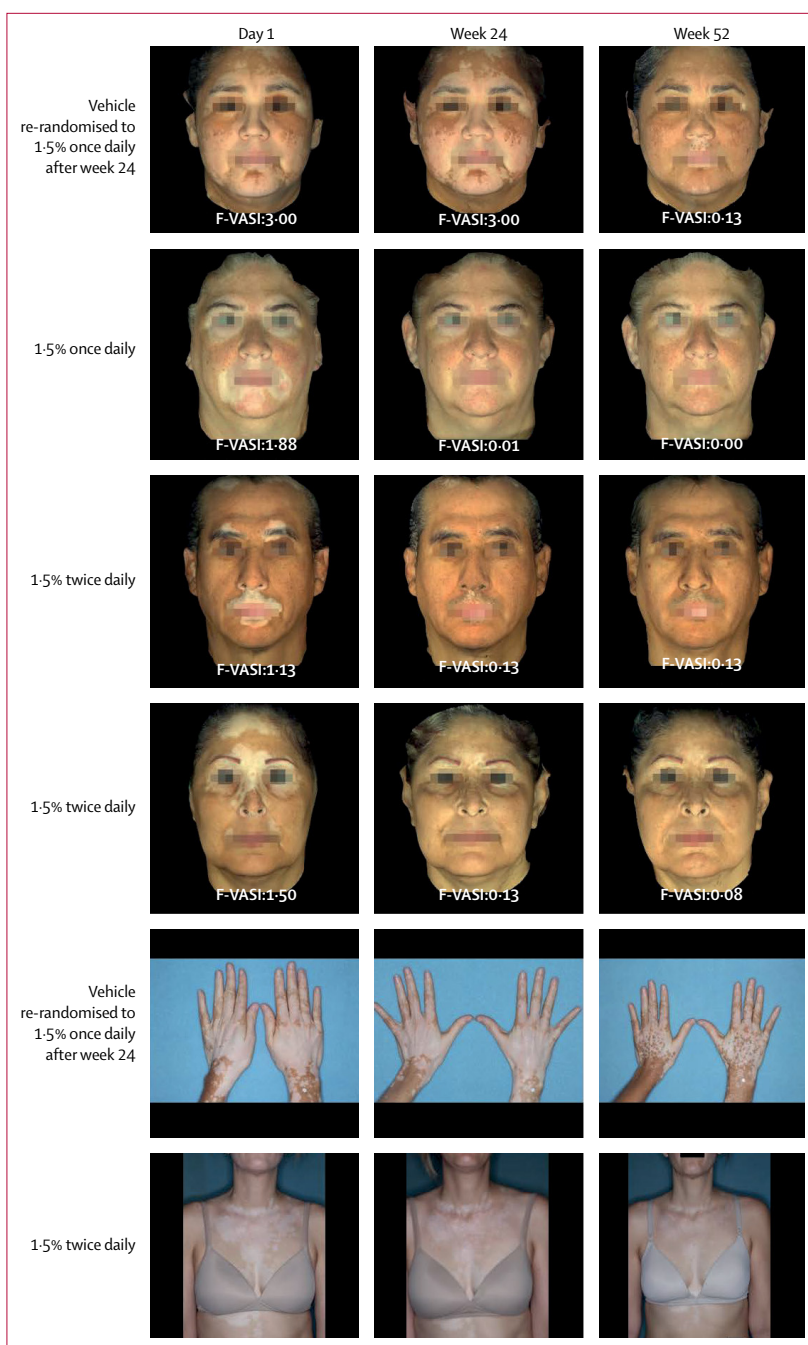
#### Role of the funding source

The sponsor participated in study design development and collaborated with authors in analysing and interpreting the data and writing the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

#### Results

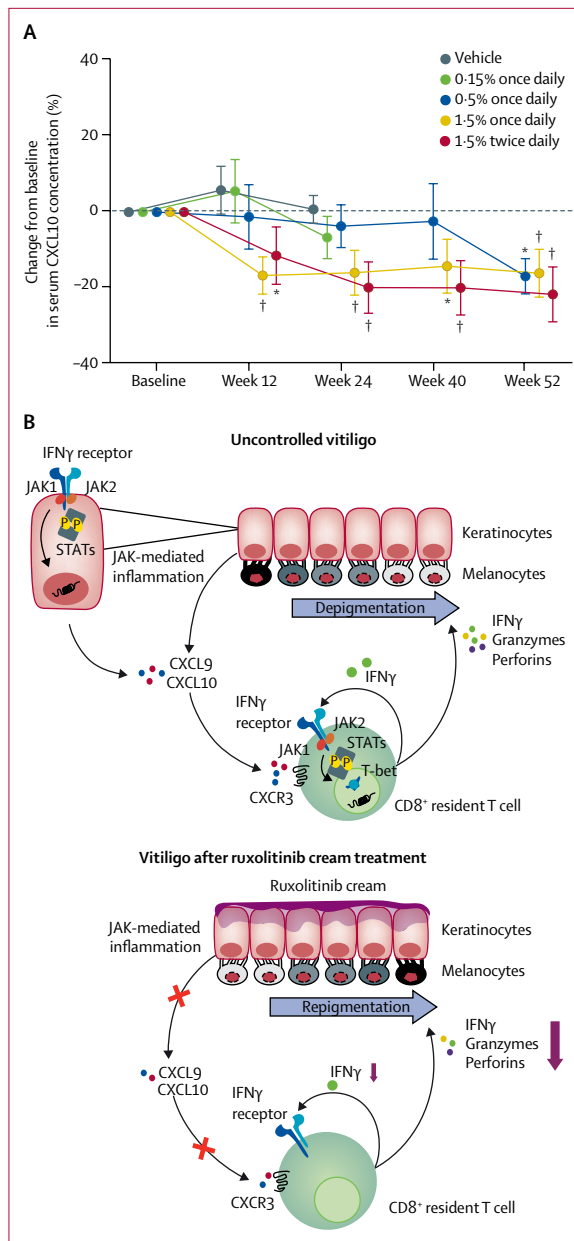
Between June 7, 2017, and March 21, 2018, 205 patients were screened for eligibility, 48 were excluded and 157 patients were randomly assigned to receive ruxolitinib cream or vehicle (figure 1). 32 were assigned to receive vehicle cream twice daily and 125 to receive ruxolitinib (31 to the 0.15% once daily group, 31 to the 0.5% once daily group, 30 to the 1.5% once daily group, and 33 to the 1.5% twice daily group). By week 24, 18 (11%) of the 157 patients had discontinued study treatment, and discontinuation rates were low up until week 52). Primary reasons for discontinuation up to week 24 were withdrawal in ten (6%) patients, adverse events in three (2%) patients, two (1%) patients were lost to follow-up, two (1%) had a protocol deviation, and one (1%) for non-compliance with study drug. The mean age was 48.3 years (SD 12.9) and the median age was 49.0 years (range 18–73), 73 (46%) of 157 patients were men and 84 (54%) were women, and 132 (84%) were white. The distribution of baseline disease characteristics was similar across treatment groups (table 1). Most patients (93%) had non-segmental vitiligo and skin types II–III (64%). Median disease duration was 14.0 years (range 0.3–67.9). The mean percentage of T-BSA involvement at baseline was 22.05% (SD 18.38%) and for F-BSA 1.48% (0.86%). The baseline mean T-VASI score was 17.96 (SD 15.45) and the mean F-VASI score was 1.26 (0.82).

The primary endpoint, week 24 F-VASI50, was reached by significantly more patients given the two highest doses



**Figure 3:** Representative clinical images of patients during double-blind treatment with ruxolitinib F-VASI=facial Vitiligo Area Scoring Index. Patients provided consent to use their images.

of ruxolitinib cream (1.5% twice daily, 15 [45%] of 33 patients, odds ratio [OR] 24.7, 95% CI 3.3–1121.4;  $p=0.0001$ ; 1.5% once daily, 15 [50%] of 30 patients, OR 28.5, 95% CI 3.7–1305.2;  $p<0.0001$ ) and also by more patients who received the two lowest doses of ruxolitinib cream (0.5% once daily, eight [26%] of 31; 0.15% once daily, ten [32%] of 31) compared with vehicle (one [3%] of 32 patients; figure 2A). By week 52, 19 (58%) of 33 patients



**Figure 4: Effect of ruxolitinib cream on biomarkers in vitiligo**  
 (A) Percentage change in CXCL10 serum concentrations following 52 weeks of treatment. (B) Proposed mechanism of action for ruxolitinib cream in vitiligo. Data are mean percentage change (SE). Ruxolitinib cream reduces skin inflammation by inhibiting IFN $\gamma$ -mediated activation of keratinocytes leading to a reduction of IFN $\gamma$ , CXCL9, and CXCL10 in circulation. Subsequent reduction of CD8<sup>+</sup> T cells trafficking to the skin and the corresponding reduction of inflammatory mediators allows for recovery of melanocyte number and function, facilitating endogenous repigmentation. CXCL=C-X-C motif chemokine ligand. CXCR3=C-X-C motif chemokine receptor 3. IFN $\gamma$ =interferon  $\gamma$ . JAK=Janus kinase. STAT=signal transducer and activator of transcription. T-bet=T-box transcription factor expressed in T cells. \* $p < 0.05$  vs baseline; † $p < 0.01$  vs baseline. Exact p values for all comparisons are presented in the appendix (p 16).

treated with 1.5% twice daily reached F-VASI50, which was the highest response among the three ruxolitinib groups (1.5% twice daily, 1.5% once daily, 0.5% once

daily). Greater improvements from baseline in F-VASI were also attained in patients receiving 1.5% twice daily, with F-VASI75 reached by 30% of patients at week 24 and 52% at week 52, with dose-dependent responses (appendix p 15). F-VASI90 was reached by 33% of patients receiving 1.5% twice daily at week 52.

T-VASI50 at week 52, a key secondary endpoint, was reached by patients in the total population in a dose-dependent manner (1.5% twice daily, 12 [36%] of 33; 1.5% once daily, nine [30%] of 30; 0.5% once daily, eight [26%] of 31). Among patients who treated all depigmented skin (baseline T-BSA  $\leq 20\%$ ), nine (45%) of 20 achieved T-VASI50 response (1.5% twice daily) at week 52 (figure 2B). Mean percentage change from baseline in VASI (appendix p 6) and BSA (appendix p 7) showed clear separation from vehicle for face and total body starting as early as week 8 of treatment with most ruxolitinib cream doses.

The reliability and validity of F-VASI and T-VASI instruments as measures of treatment efficacy were confirmed in a post-hoc analysis. Clinically meaningful change was detected for F-VASI with a percentage change of 57% and T-VASI with a percentage change of 42% from baseline, using an approach anchored on the 7-point PaGIC-V scale (appendix pp 30–40).

The additional key secondary endpoint of reaching scores of clear or almost clear in the F-PhGVA at week 24 was attained only by patients given ruxolitinib cream (0.15% once daily, one [3%] of 31; 0.5% once daily, three [10%] of 31; 1.5% once daily, four [13%] of 30; 1.5% twice daily, three [9%] of 33; figure 2C). At week 52, more patients had clear to mild disease than at baseline in F-PhGVA and T-PhGVA assessments (appendix p 8). Similarly, more patients reported mild disease or no white patches in F-PaGVA and T-PaGVA after 52 weeks of treatment with ruxolitinib cream compared with baseline (appendix p 9). A larger proportion of patients with baseline T-BSA 20% or less who received ruxolitinib cream 1.5% twice daily noted very much or much improvement (scores of 1 or 2) of vitiligo per the PaGIC-V at week 24 than in the vehicle group (32% vs 12%), and this increased to 47% at week 52. Patients who received any dose of ruxolitinib cream showed visible improvement in repigmentation of facial and non-facial vitiligo lesions; repigmentation was most notable with 1.5% once daily and 1.5% twice daily, and patients showed continued improvement up until week 52 (figure 3).

Serum IFN $\gamma$  concentrations were less than the limit of detection throughout the study (data not shown). However, CXCL10 serum concentrations were significantly reduced following treatment with ruxolitinib cream 1.5% twice daily (figure 4A). Specifically, CXCL10 concentrations were reduced by 20% ( $p = 0.0011$ ) at week 24 and 22% ( $p = 0.0006$ ) at week 52 compared with baseline; these changes were not related to systemic concentrations of ruxolitinib (week 24,  $r^2 = 0.12$ ; week 52,  $r^2 = 0.11$ ; appendix p 10). This change suggests that repigmentation is associated with

	Control (vehicle twice daily; n=32)	Ruxolitinib cream			
		0.15% once daily group (n=31)	0.5% once daily group (n=31)	1.5% once daily group (n=30)	1.5% twice daily group (n=33)
Patients with treatment-emergent adverse events	20 (63%)	20 (65%)	26 (84%)	23 (77%)	23 (70%)
Most common treatment-emergent adverse events*					
Acne	1 (3%)	4 (13%)	5 (16%)	3 (10%)	6 (18%)
Viral upper respiratory tract infection	5 (16%)	3 (10%)	3 (10%)	6 (20%)	1 (3%)
Application site pruritus	3 (9%)	6 (19%)	3 (10%)	3 (10%)	1 (3%)
Pruritus	3 (9%)	1 (3%)	5 (16%)	4 (13%)	3 (9%)
Upper respiratory tract infection	0	1 (3%)	5 (16%)	1 (3%)	3 (9%)
Headache	3 (9%)	1 (3%)	0	3 (10%)	2 (6%)
Sinusitis	1 (3%)	2 (6%)	1 (3%)	2 (7%)	2 (6%)
Patients with treatment-related adverse events	12 (38%)	11 (35%)	12 (39%)	12 (40%)	10 (30%)
Most common treatment-related adverse events*					
Application site pruritus	3 (9%)	6 (19%)	3 (10%)	3 (10%)	1 (3%)
Acne	1 (3%)	1 (3%)	3 (10%)	3 (10%)	6 (18%)
Pruritus	2 (6%)	1 (3%)	4 (13%)	3 (10%)	2 (6%)
Patients with treatment-emergent adverse events leading to discontinuation†	1 (3%)	1 (3%)‡	0	1 (3%)	0
Patients with serious treatment-emergent adverse events§	0	0	2 (6%)	1 (3%)	1 (3%)

Data are n (%). \*Occurring in more than 5% of the total patient population. †Treatment-emergent adverse events leading to discontinuation were not related to treatment unless otherwise indicated. ‡Headache related to treatment. §No serious treatment-emergent adverse events were related to treatment.

**Table 2: Treatment-emergent adverse events up to 52 weeks of treatment**

reduced skin inflammation and subsequent release of inflammatory mediators into circulation (figure 4B).

To further characterise the effect of ruxolitinib cream treatment on the autoimmune nature of vitiligo, broad proteomic analysis of 1104 proteins was done on serum samples from 130 patients across dose groups. From baseline to week 24, 204 proteins were significantly modulated with 1.5% twice daily, 162 proteins with 1.5% once daily, 71 proteins with 0.5% once daily, and 29 proteins with 0.15% once daily groups compared with 56 proteins in the vehicle group (appendix pp 17–28). CXCL9 and CXCL10 were significantly downregulated in both the 1.5% once daily and 1.5% twice daily groups. Additionally, chemokine C-C motif ligand 18 (CCL18), matrix metalloprotease 12, and CD27, which are associated with skin inflammation and T-cell costimulation,<sup>21,22</sup> were modulated in the 1.5% once daily and 1.5% twice daily groups. Overall, pathway analysis showed an association between the therapeutic response to ruxolitinib cream in the skin and the capacity for immune cell trafficking in circulation.

The occurrences and types of treatment-emergent adverse events were similar across treatment groups (table 2). Four patients had serious treatment-emergent adverse events (1.5% twice daily, subdural haematoma [n=1]; 1.5% once daily, seizure [n=1]; 0.5% once daily, coronary artery occlusion [n=1] and oesophageal achalasia [n=1]) unrelated to study treatment. Application site pruritus was the most common treatment-related adverse

event among patients given ruxolitinib cream (1.5% twice daily, one [3%] of 33; 1.5% once daily, three [10%] of 30; 0.5% once daily, three [10%] of 31; 0.15% once daily, six [19%] of 31) and vehicle (three [9%] of 32; table 2). Acne was noted as a treatment-related adverse event in 13 (10%) of 125 patients who received ruxolitinib cream and in one (3%) of 32 who received vehicle. All treatment-related adverse events were mild (grade 1) or moderate (grade 2) in severity. Three patients had a treatment-emergent adverse event leading to treatment discontinuation (0.15% once daily and vehicle [both n=1], headache [related to treatment for 0.15% once daily]; 1.5% once daily [n=1], seizure).

There were no clinically relevant changes in laboratory values. Transient shifts within the normal range in haemoglobin (appendix p 11) and platelet (appendix p 12) concentrations were observed throughout double-blind treatment. At week 52, haemoglobin and platelet concentrations were generally similar to those observed at baseline. Ruxolitinib cream bioavailability was limited, corresponding to approximately 4–7% of the topical dose applied.

## Discussion

This is the first report, to our knowledge, from a large, prospective, randomised, vehicle-controlled study evaluating the efficacy and safety of a JAK inhibitor or any targeted immunomodulatory drug in adult patients with vitiligo. A substantially greater proportion of patients



receiving ruxolitinib cream (0·15% once daily, 0·5% once daily, 1·5% once daily, and 1·5% twice daily) than vehicle met the primary endpoint of F-VASI50 at week 24 (26–50% across ruxolitinib cream doses *vs* 3% for vehicle), with the two highest doses of 1·5% twice daily and 1·5% once daily showing a significant improvement. Continuous improvement was seen following 52 weeks of ruxolitinib cream monotherapy, with 1·5% twice daily producing the highest responses in F-VASI50 (58%), F-VASI75 (52%), and F-VASI90 (33%). Responses for F-VASI75 and F-VASI90 approximate desired patient outcomes of complete or near-complete repigmentation;<sup>23</sup> these responses paralleled improvements in PhGVA and PaGVA scores at week 52. Although not quantitatively assessed, clinical images of patients with substantial VASI improvement showed favourable subjective appearance of repigmentation.

Most patients in this study were older (median age, 49·0 years), had non-segmental vitiligo, had long standing and extensive disease, and had received previous treatment, suggesting this was a difficult-to-treat population. Although there was no BSA limitation for patients enrolled in this study, treatment was limited to lesions constituting 20% or less of T-BSA. T-VASI50 response at week 52 (key secondary endpoint) in the total population (1·5% twice daily, 36%) was increased when the analysis included only patients who could treat all areas of depigmented skin and had baseline T-BSA 20% or less (1·5% twice daily, 45%). Additionally, ruxolitinib cream was well tolerated, as occurrences and types of treatment-emergent adverse events were generally similar across ruxolitinib cream and vehicle treatment groups. Acne was more common in patients who received ruxolitinib cream and will be further assessed in phase 3 studies. Four serious treatment-emergent adverse events were observed, but all were deemed unrelated to treatment. All treatment-related adverse events were mild or moderate in severity.

Current topical treatments for vitiligo include corticosteroids and calcineurin inhibitors;<sup>24</sup> however, they are used off-label,<sup>25</sup> and few controlled studies in large populations have been done. Results of a meta-analysis of topical corticosteroid therapies (mean treatment duration, 8 months [range 2–21]) showed that 56% of 235 patients (six studies) receiving potent corticosteroids (class 3) showed more than 75% repigmentation, although methods of assessing repigmentation probably differed between studies.<sup>26</sup> In a meta-analysis of topical calcineurin inhibitors (median treatment duration, 3 months, [range 2–7]), 75% or higher repigmentation was seen in 18% of 520 patients (19 studies).<sup>27</sup> In the current study, early responses to ruxolitinib cream monotherapy are similar to calcineurin inhibitors at 24 weeks in small prospective studies (sample size, 12–42 patients)<sup>27,28</sup> and with phototherapy at 24 weeks and 52 weeks.<sup>29</sup> Long-term use of topical corticosteroids is associated with skin atrophy,<sup>26</sup> and calcineurin inhibitors are associated with local reactions (eg, burning).<sup>27</sup> In

contrast to other topical therapies, the results of this study indicate a low frequency of application site reactions after treatment with ruxolitinib cream. Long-term data for the current study (part 3) are forthcoming.

Inhibition of JAK-mediated IFN $\gamma$  signalling is a rational approach to the treatment of vitiligo. Because keratinocytes are the primary producers of chemokines that promote vitiligo pathogenesis,<sup>18</sup> targeting the local immune response with a topical treatment provides directed therapy with few systemic adverse effects. Because the IFN $\gamma$  pathway is central to vitiligo pathogenesis,<sup>9,18</sup> the reduction of IFN $\gamma$ -mediated biomarkers with topical application of ruxolitinib suggests the potential for disease disruption. Specifically, ruxolitinib cream treatment was associated with significant reductions in circulating concentrations of CXCL10, which primarily recruits CD8<sup>+</sup> T cells to the site of inflammation; CCL18, an inflammatory chemokine associated with inflammation in several dermatoses; and soluble CD27, a T-cell costimulatory molecule that promotes IFN $\gamma$  signalling. These observations suggest that longer duration treatment with ruxolitinib cream and the resulting repigmentation are associated with decreased keratinocyte-mediated inflammation and the subsequent release of skin-associated inflammatory mediators into circulation.

Our findings are consistent with those of earlier work showing that treatment of vitiligo reduced serum CXCL10 concentrations and the reduction occurred in parallel with disease stabilisation.<sup>11</sup> At 24 weeks, although clinical markers of efficacy (eg, F-VASI50) indicated similar improvement with 1·5% twice daily and 1·5% once daily administration, the chemokine profile showed maximal serum CXCL10 reduction with 1·5% twice daily. By week 52, clinical markers of efficacy showed maximal responses with 1·5% twice daily. Vitiligo therapy is a two-step process: arrest of immune autoreactivity followed by melanocyte recruitment,<sup>30</sup> with a time lag between these events before a clinical effect can be realised. As such, longer duration therapy seems to have allowed for clinical effect to more closely reflect altered IFN $\gamma$ -mediated pathogenesis.

Study limitations included that most patients were older than 30 years and had fairer skin types (ie, skin types I–III). There were small numbers of patients in each group, so confirmation of these findings in a larger patient population is needed. Quality of life was not assessed in this phase 2 study and should be explored in future analyses. Finally, additional analyses are needed to further elucidate any correlation between circulating chemokines and the number and function of skin-associated T cells, as well as changes in the skin chemokine concentrations.

In conclusion, study data up until week 52 suggest that ruxolitinib cream monotherapy is an effective treatment option for patients with vitiligo. The reduction of serum CXCL10 suggests that ruxolitinib might work by altering some of the key pathways involved in vitiligo pathogenesis. These results support suppression of

immune autoreactivity in the skin via topical JAK inhibition, which allows for recovery of melanocyte number and function. Longer duration therapy seems to be required for repigmentation, as objectively assessed using the VASI (ie, near-complete facial repigmentation as assessed by F-VASI75 and substantial total body repigmentation as assessed by T-VASI50); this finding is also supported by trends in the PhGVA and PaGVA data at week 52. All doses of ruxolitinib cream were well tolerated, and no treatment-related serious adverse events were reported. Additional long-term data from this trial (part 3; 104-week open-label treatment) will be reported once available.

#### Contributors

DR, AGP, ML, PG, IH, ABG, and JEH contributed to data acquisition, data interpretation, and manuscript writing. KB and FK contributed to study design, data analysis, data interpretation, and manuscript writing. KS contributed to study design, statistical analysis, data interpretation, and manuscript writing. TJ contributed to study design, data acquisition, and data interpretation related to the pharmacokinetic analyses and manuscript writing. MDH contributed to study design, data acquisition, and data interpretation related to the biomarker analyses and manuscript writing. All authors read and approved the final version of the manuscript for publication.

#### Declaration of interests

DR has received honoraria as a consultant for AbbVie, Celgene, Dermavant Sciences, Dermira, Eli Lilly and Company, Janssen, Novartis, Pfizer, Regeneron Pharmaceuticals, Sanofi, and Sun Pharmaceuticals; research support from AbbVie, Bristol-Myers Squibb, Celgene, Dermira, Eli Lilly and Company, Incyte, Janssen, Merck, Novartis, Pfizer, and Regeneron Pharmaceuticals; and has served as a paid speaker for AbbVie, Celgene, Eli Lilly and Company, Janssen, Novartis, Pfizer, Regeneron Pharmaceuticals, and Sanofi. AGP has served as an investigator for Aclaris Therapeutics, Immune Tolerance Network, Incyte, and Pfizer; a consultant for Incyte and Pfizer; and a board member who also holds stock options for Clarify Medical. ML is an employee of Mount Sinai Hospital, which receives research funds from AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, Celgene, Eli Lilly and Company, Incyte, Janssen, Johnson & Johnson, Kadmon, LEO Pharma, MedImmune, Novartis, Ortho Dermatologics, Pfizer, Scidem, UCB, and ViDac; and is a consultant for Allergan, Almirall, Arcutis, Avotres, BirchBioMed, Boehringer Ingelheim, Bristol-Myers Squibb, Cara Therapeutics, Castle Biosciences, Dermavant Sciences, Encore, Inozyme, LEO Pharma, Meiji, Menlo, Mitsubishi Pharma, Neuroderm, Pfizer, Dr Reddy, Theravance Biopharma, and Verrica Pharmaceuticals. PG has served as a consultant for Aclaris Therapeutics, Clarify Medical, DermaForce, Incyte, Proctor & Gamble, and Versicolor Technologies and a principal investigator for Aclaris Therapeutics, Allergan, Clinuvel Pharmaceuticals, Incyte, Johnson & Johnson, L'Oreal, Merz Pharma, Pfizer, Thync Global, and VT Cosmetics. IH has served as an advisory board member for AbbVie; a consultant for Incyte, Pfizer, and UCB; a principal investigator for AbbVie, Allergan, Bayer, Clinuvel Pharmaceuticals, Estée Lauder, Ferndale Laboratories, Galderma Laboratories LP, GE Healthcare, Incyte, Janssen, Janssen Biotech, Johnson & Johnson, Lencicure, LEO Pharma, Pfizer, and Unigen; a subinvestigator for Amgen, Bristol-Myers Squibb, Foamix Pharmaceuticals, and Janssen; president of the HS Foundation; and co-chair of the Global Vitiligo Foundation. ABG has received research or educational grants from Boehringer Ingelheim, Incyte, Janssen, Novartis, UCB, and Xbiotech and has served as a consultant or advisory board member for AbbVie, Avotres Therapeutics, Beiersdorf, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli Lilly and Company, Incyte, Janssen, LEO Pharma, Novartis, Sun Pharmaceutical Industries, UCB, Valeant, and Xbiotech. KB, FK, KS, TJ, and MDH are employees and shareholders of Incyte. JEH has served as a consultant for AbbVie, Aclaris Therapeutics, BiologicsMD, EMD Serono, Sanofi Genzyme, Janssen, Pfizer, Rheos Medicines, Sun Pharmaceuticals, TeVido BioDevices, The Expert Institute, 3rd Rock Ventures, and Villarís

Therapeutics; has served as an investigator for Aclaris Therapeutics, Celgene, Dermira, EMD Serono, Sanofi Genzyme, Incyte, LEO Pharma, Pfizer, Rheos Medicines, GSK, Sun Pharmaceuticals, TeVido BioDevices, and Villarís Therapeutics; holds equity in Rheos Medicines, TeVido BioDevices, and Villarís Therapeutics; is a scientific founder of Villarís Therapeutics; and has patents pending for IL-15 blockade for treatment of vitiligo, JAK inhibition with light therapy for vitiligo, and CXCR3 antibody depletion for treatment of vitiligo.

#### Data sharing

Access to individual patient-level data is not available for this study. The redacted study protocol is available in the appendix.

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