









## REVIEW ARTICLE

# Topical ruxolitinib: A new treatment for vitiligo

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## Abstract

Vitiligo is a chronic autoimmune skin disorder whose diagnosis is often psychologically upsetting. The efficacy of the available therapies, including topical corticosteroids and topical calcineurin inhibitors, has historically been limited and the management of vitiligo is still challenging. As vitiligo is a chronic disease limited to the skin, topical rather than systemic therapies may be preferable (especially among patients with localised lesions) to avoid the long-term side-effects of the latter. A topical formulation of ruxolitinib, a selective JAK1/2 inhibitor, has recently been approved in the United States for the treatment of non-segmental vitiligo in patients aged >12 years based on data from the phase III TRuE-V1 and TRuE-V2 clinical trials. The aim of this review is to describe the current evidence concerning the efficacy and safety of topical ruxolitinib in the treatment of vitiligo, and discuss issues regarding its use in younger children and pregnant or breastfeeding women, as well as the duration and durability of treatment. The promising results obtained so far suggest that 1.5% ruxolitinib cream is an effective means of treating vitiligo.

## INTRODUCTION

Vitiligo is a chronic autoimmune skin disorder with a highly unpredictable course that is characterised by the development of circumscribed depigmented macules and patches due to the acquired loss of functioning epidermal melanocytes.<sup>1</sup> It equally affects both sexes<sup>2</sup> and has an estimated global prevalence of 0.5%–2% in the general population.<sup>3</sup> Its diagnosis is often psychologically upsetting<sup>4</sup> (especially among patients with dark skin type whose lesions are more detectable),<sup>5</sup> and the disease can have other negative effects on the quality of life that are mainly related to its extent, progression, previous management and the length of time from its diagnosis.<sup>6</sup>

The severity of the disease can be assessed in terms of the extent of its involvement and residual depigmentation. The most frequently used methods in everyday clinical practice

are visual and photographic analyses but, as these are subjective, clinical trials usually use the vitiligo area severity index (VASI), which integrates body surface area (BSA) with a depigmentation score.<sup>7</sup> Furthermore, new means of scoring the evolution of vitiligo lesions have recently been validated.<sup>8</sup>

The efficacy of the available treatments has historically been limited and the management of vitiligo is still challenging. Treatment is chosen on a case-by-case basis, even if European and British guidelines are available mainly based on disease activity and severity. The first line of treatment (especially among patients with localised disease) usually involves the use of potent topical corticosteroids (TCS) or topical calcineurin inhibitors (TCI)<sup>9</sup> and systemic treatment with oral or intramuscular corticosteroids may be effective in stabilising the disease in those experiencing rapid progression.<sup>10</sup> Phototherapy with narrowband ultraviolet B (NB-UVB) may be administered two to three times weekly,

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alone or in combination with other treatments, in order to promote repigmentation.<sup>11</sup> Another option is laser therapy, which is supported by encouraging efficacy and safety data, but its application is still limited because of its costs and the fact that it is only suitable for the treatment of small areas.<sup>12</sup>

The aim of this review is to describe the current evidence supporting the efficacy and safety of topical ruxolitinib, the first Food and Drug Administration (FDA)-approved treatment for vitiligo, and discuss still open questions regarding its possibly more widespread use.

## TOPICAL RUXOLITINIB AND THE PRE-CLINICAL BACKGROUND

Opzelura® is a white to off-white, oil-in-water, solubilised emulsion containing 1.5% ruxolitinib phosphate (Table 1).

As ruxolitinib is a Janus kinase (JAK) 1/2 inhibitor, it interferes with the signal transducers and activators of transcription (STAT) pathway mediating the signalling of more than 60 of the inflammatory cytokines involved in immune function, including growth factors, interferons and interleukins (IL).<sup>13</sup> More specifically, JAKs phosphorylate cytokine receptors and consequently recruit STAT transcription, which translocates into the nucleus and modulates gene expression.

The pharmacokinetics of ruxolitinib cream has been evaluated in three double-blind studies of patients with atopic dermatitis, which demonstrated that plasma ruxolitinib concentrations after its twice-daily topical application did not lead to any systemic pharmacological activity.<sup>14</sup> A pre-clinical study investigated the plasma pharmacokinetics and skin distribution of ruxolitinib following its oral and topical administration of ruxolitinib in mini-pigs, and found that topical administration led to higher epidermal and dermal ruxolitinib concentrations than oral administration, and the sustained and nearly complete blockade of the JAK/STAT signalling pathway.<sup>15</sup> Ruxolitinib has also been tested in a complete battery of genotoxicity assays, which revealed no evidence of genotoxic potential in bacterial mutagenicity, in vitro chromosomal aberration and rat bone marrow micronucleus assays. Carcinogenicity studies (including a 104-week dermal carcinogenicity study on CD-1 mice) have

found no significant drug-related toxicity or tumours when 1.5% ruxolitinib cream is applied at a dose of 100 µL per day.<sup>16</sup>

## CLINICAL TRIALS

The efficacy of topical ruxolitinib in the treatment of vitiligo was assessed in various clinical trials before its approval by the FDA. Table 2 lists the key completed and ongoing trials.

### Completed clinical trials

#### Phase II trial NCT02809976

The first study to assess the use of topical ruxolitinib in the treatment of vitiligo was an open-label, proof-of-concept trial of its twice-daily administration to 11 patients with vitiligo affecting at least 1% of BSA.

This study demonstrated a 23% improvement in the total VASI (T-VASI) scores of all the enrolled patients at Week 20 (95% confidence interval [95% CI] 4–43;  $p=0.02$ ). The most significant response was a 76% improvement in facial VASI (F-VASI) at Week 20, especially in patients with significant facial involvement at baseline (95% CI 53–99;  $p=0.001$ ).

Only minor adverse events were reported: erythema, a rim of hyperpigmentation surrounding the vitiligo patches, transient papular eruptions and acne.<sup>17</sup> Moreover, a 32-week study extension with optional NB-UVB confirmed a statistically significant mean improvement in T-VASI of  $37.6\% \pm 31.2\%$  ( $p=0.011$ ) at Week 52.<sup>18</sup>

#### Phase II trial NCT03099304

This randomised, double-blind, vehicle-controlled study involved 157 vitiligo patients aged 18–75 years who were randomised to receive one of four different doses of topical ruxolitinib (0.15% once daily, 0.5% once daily, 1.5% once daily, 1.5% twice daily) or vehicle (1:1:1:1). The subjects all had vitiligo involving <20% of their baseline total BSA.

**TABLE 1** General characteristics of 1.5% ruxolitinib cream.

Alternative names	Opzelura®, INCB018424
Chemical name	(R)-3-(4-(7H-pyrrolo[2,3-d]pymiridin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate
Mechanism of action	Specifically inhibits JAK1 and JAK2 interfering with the STAT pathway
Route of administration	Topical
Indication and usage	<ul style="list-style-type: none"> <li>Non-segmental vitiligo covering up to 10% of BSA in patients aged &gt;12 years</li> <li>Short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients &gt;12 years whose disease is not adequately controlled with topical prescription therapies or when such therapies are not advisable.</li> </ul>
Most frequent adverse reactions	Application site acne, application site pruritus, nasopharyngitis, headache, application site rash, pyrexia
Warning and precautions	Serious infections, non-melanoma skin cancer, thrombosis, thrombocytopenia, anaemia and neutropenia

Abbreviations: BSA, body surface area; JAK1, Janus kinase 1; JAK2, Janus kinase 2; STAT, signal transducers and activators of transcription.

**TABLE 2** Key clinical trials of 1.5% ruxolitinib cream for the treatment of vitiligo.

Identifier	Indication	Purpose	Clinical trial phase	Number of subjects	Age of subjects (years)	Trial status	Location(s)
NCT02809976	Vitiligo	Efficacy	Phase II	11	≥18	Completed	USA
NCT03099304	Vitiligo	Efficacy, safety, and tolerability	Phase II	157	18–75	Completed	USA
NCT04052425 (TRuE-V1)	Non-segmental vitiligo	Efficacy and safety	Phase III	330	≥12	Completed	USA, Bulgaria, Canada, France, Germany, Italy, Poland, Spain
NCT04057573 (TRuE-V2)	Non-segmental vitiligo	Efficacy and safety	Phase III	344	≥12	Completed	USA, Bulgaria, Canada, France, Germany, Italy, Netherlands, Poland, Spain
NCT04896385 (TRuE-V MOA)	Vitiligo	Mechanism of action	Phase II	60	≥18	Ongoing	USA, Canada, France
NCT05247489	Non-segmental vitiligo	Efficacy and safety combined with NB-UVB	Phase II	50 <sup>a</sup>	12–99	Recruiting	USA, Canada
NCT04530344	Non-segmental vitiligo	Duration, safety, and maintenance of response	Phase III	458	≥12	Ongoing	USA, Bulgaria, Canada, France, Germany, Netherlands, Poland, Spain

Abbreviation: NB-UVB, narrowband ultraviolet B.

<sup>a</sup>Estimated enrolment.

After 24 and 52 weeks of treatment, an improvement in the F-VASI scores of ≥50% (F-VASI50), ≥75% (F-VASI75) and ≥90% (F-VASI90) was observed in more patients who received ruxolitinib cream than in those who received the vehicle. In particular, among those who received the 1.5% ruxolitinib cream twice daily, respectively 45% and 58% achieved F-VASI50 after 24 weeks and 58% at 52 weeks, respectively, 30% and 52% obtained F-VASI75, and 33% achieved F-VASI90 after week 52 weeks. The total VASI50 (T-VASI50) scores were achieved in a dose-dependent manner: 20% of the subjects who received 1.5% ruxolitinib cream twice daily achieved T-VASI50 after 24 weeks, and 45% after 52 weeks.<sup>19</sup>

A descriptive subgroup analysis did not identify any significant difference among the responders depending on race, skin type, disease status or T-BSA. However, those receiving twice-daily treatment with 1.5% ruxolitinib who achieved F-VASI50 by Week 24 were more frequently females (60.0% vs. 33.3%) and aged ≤50 years (58.8% vs. 31.3%). Furthermore, the patients with previously treated vitiligo refractory to phototherapy, corticosteroids, and topical calcineurin inhibitors also achieved F-VASI50.

The Week 52 achievement of T-VASI50 with twice-daily 1.5% ruxolitinib treatment was predominantly observed in patients with facial vitiligo, whereas the proportion of responders with upper or lower limb involvement was lower (60% vs. 52.9% and 52.6%). The lowest response rate was observed among the patients with hands or foot involvement (respectively 15.0% and 29.4% achieved T-VASI50).<sup>20</sup>

During the open-label phase starting at Week 104 of the study, optional concomitant NB-UVB therapy was permitted at different frequencies depending on the different centres. Among the 19 patients who added 12 weeks of NB-UVB therapy, the combination was well tolerated and the addition of NB-UVB improved facial and total body repigmentation.<sup>21</sup>

### Phase III trial NCT04052425 TRuE-V1 and NCT0457573 TRuE-V2

The efficacy and safety of topical ruxolitinib were evaluated in two multinational, phase III, double-blind, vehicle-controlled clinical trials (Topical Ruxolitinib Evaluation in Vitiligo Study 1 [TRuE-V1] and 2 [TRuE-V2]), which involved patients aged >12 years with non-segmental vitiligo involving <10% of their T-BSA.

The trials enrolled a total of 674 patients (330 patients in TRuE-V1 and 344 in TRuE-V2), who randomised (2:1) to apply 1.5% ruxolitinib cream or matching vehicle twice daily to all depigmented vitiligo lesions for 24 weeks, followed by the twice-daily application of 1.5% ruxolitinib cream during an additional 28-week, open-label treatment extension period. No additional vitiligo treatment was permitted. The primary and key secondary endpoints are summarised in Tables 3 and 4.

The primary endpoint was the achievement of F-VASI75, which was observed at Week 24 in 29.8% of the

**TABLE 3** Efficacy of 24 weeks' treatment with twice-daily 1.5% ruxolitinib cream in the subjects with non-segmental vitiligo enrolled in TRuE-V1 and TRuE-V2.

	TRuE-V1		TRuE-V2	
	1.5% ruxolitinib cream b.i.d.	Vehicle cream b.i.d.	1.5% ruxolitinib cream b.i.d.	Vehicle cream b.i.d.
VASI	<i>n</i> = 221 (variability)	<i>n</i> = 109 (variability)	<i>n</i> = 221 (variability)	<i>n</i> = 109 (variability)
F-VASI25 (Week 24)	69.8 (63.5, 76.2)	30.0 (20.8, 39.2)	63.9 (57.2, 70.6)	32.0 (23.0, 41.0)
F-VASI50 (Week 24)	51.2 (44.4, 58.0)	16.9 (9.3, 24.6)	51.4 (44.6, 58.3)	20.9 (12.9, 28.9)
F-VASI75 (Week 24)	29.8 (23.5, 36.1)	7.4 (2.2, 12.6)	30.9 (24.5, 37.3)	11.4 (5.2, 17.7)
F-VASI90 (Week 24)	15.3 (10.4, 20.2)	2.2 (0, 5.1)	16.3 (11.2, 21.5)	1.3 (0, 3.8)
T-VASI25 (Week 24)	48.8 (41.9, 55.6)	23.8 (15.2, 32.5)	50.2 (43.5, 57.12)	21.2 (12.9, 29.4)
T-VASI50 (Week 24)	20.6 (15.2, 26.0)	5.1 (0.6, 9.7)	23.9 (18.1, 29.8)	6.8 (1.9, 11.7)
T-VASI75 (Week 24)	4.1 (1.5, 6.7)	1.8 (0, 4.4)	8.0 (4.4, 11.6)	1.8 (0, 4.4)
T-VASI90 (Week 24)	0.5 (0, 1.3)	0.0 (NE)	1.0 (0, 2.3)	0.0 (NE)

Abbreviations: F-VASI, facial vitiligo area scoring index; NE, not evaluable; T-VASI, total body vitiligo area scoring index; VASI, vitiligo area scoring index.

**TABLE 4** Efficacy of 52 weeks' treatment with twice-daily 1.5% ruxolitinib cream in the subjects with non-segmental vitiligo enrolled in TRuE-V1 and TRuE-V2.

	TRuE-V1		TRuE-V2	
	1.5% ruxolitinib cream b.i.d.	Vehicle to week 24 weeks/1.5% Ruxolitinib cream b.i.d. after Week 24	1.5% ruxolitinib cream b.i.d.	Vehicle (up to Week 24 weeks)/1.5% ruxolitinib cream b.i.d. after Week 24
VASI	<i>n</i> = 173 (variability)	<i>n</i> = 82 (variability)	<i>n</i> = 177 (variability)	<i>n</i> = 82 (variability)
F-VASI25 (Week 52)	89.6 (84.1, 93.7)	74.4 (63.6, 83.4)	82.5 (76.1, 87.8)	71.6 (60.5, 81.1)
F-VASI50 (Week 52)	75.1 (68.0, 81.4)	56.1 (44.7, 67.0)	74.0 (66.9, 80.3)	49.4 (38.1, 60.7)
F-VASI75 (Week 52)	52.6 (44.9, 60.2)	26.8 (17.6, 37.8)	48.0 (40.5, 55.6)	29.6 (20.0, 40.8)
F-VASI90 (Week 52)	32.9 (26.0, 40.5)	12.2 (6.0, 21.3)	27.7 (21.2, 34.9)	16.0 (8.8, 25.9)
T-VASI25 (Week 52)	77.5 (70.5, 83.5)	56.1 (44.7, 67.0)	76.8 (69.9, 82.8)	53.1 (41.7, 64.3)
T-VASI50 (Week 52)	53.2 (45.5, 60.8)	31.7 (21.9, 42.9)	49.2 (41.6, 56.8)	22.2 (13.7, 32.8)
T-VASI75 (Week 52)	20.2 (14.5, 27.0)	9.8 (4.3, 18.3)	20.9 (15.2, 27.6)	8.6 (3.5, 17.0)
T-VASI90 (Week 52)	3.5 (1.3, 7.4)	2.4 (0.3, 8.5)	6.8 (3.6, 11.5)	1.2 (0, 6.7)

Abbreviations: F-VASI, facial vitiligo area scoring index; T-VASI, total body vitiligo area scoring index; VASI, vitiligo area scoring index.

ruxolitinib-treated patients in TRuE-V1 and 30.9% in TRuE-V2, and, respectively, 7.4% and 11.4% of the vehicle-treated patients (TRuE-V1: relative risk [RR] 4.0, 95% CI 1.9–8.4; *p*-value < 0.001; TRuE-V2: RR 2.7, 95% CI 1.5–4.9; *p*-value < 0.001). The secondary endpoints confirmed the superiority of the 1.5% ruxolitinib cream, which led to greater repigmentation after both 24 and 52 weeks.

The treatment-related adverse events (AEs) occurring during the double-blind period were mainly mild or moderate and were reported by 45.7% of the patients in the ruxolitinib group in TRuE-V1 and 50.0% in TRuE-V2, and by, respectively, 38.5% and 33.9% of the patients in the vehicle group. Table 5 lists the most frequently reported AEs after 24 weeks.

Serious AEs were reported by 14 patients who applied ruxolitinib cream at any time and none of these were considered by the investigators to be related to the trial agent.<sup>22</sup>

## Ongoing clinical trials

The mechanism of action of ruxolitinib cream is currently being evaluated in one phase II, double-blind, vehicle-controlled clinical trial (Topical Ruxolitinib Evaluation in Vitiligo Mechanism of Action [TRuE-V MOA], NCT04896385) which has enrolled 60 patients with non-segmental vitiligo aged >18 years. The primary outcome measure is the difference in any baseline-Week 24 change in immunity biomarkers (including CXCL10) between the ruxolitinib cream and vehicle cream group. The secondary outcome measures include the correlation between CXCL10 and VASI scores, the repigmentation response of target lesions and the number of treatment-emergent adverse events.<sup>23</sup>

The findings of previous studies suggest that treatment with 1.5% ruxolitinib cream may reduce serum CXCL10



**TABLE 5** Reported adverse reactions to treatment with 1.5% ruxolitinib cream during the 24-week double-blind period of TRuE-V1 and TRuE-V2.

Adverse reaction	1.5% Ruxolitinib cream (n = 449)	Vehicle (n = 224)
	No. (%)	No (%)
Any adverse event	215 (47.8)	81 (36.2)
Application site acne	26 (5.8)	3 (1.2)
Application site pruritus	23 (5.1)	6 (2.6)
Nasopharyngitis	19 (4.2)	5 (2.2)
Headache	17 (3.8)	6 (2.6)
Application site rash	7 (1.5)	2 (0.8)
Pyrexia	6 (1.3)	0
Application site exfoliation	5 (1.1)	1 (0.4)

concentrations and consequently affect CD8<sup>+</sup> T cells. The expected reduction in T cells migration to the skin and the corresponding reduction in inflammatory mediators could lead to a recovery in the number and function of melanocytes and have a positive effect on repigmentation.<sup>19</sup>

Another recruiting phase II clinical trial (NCT05247489) will evaluate the efficacy and safety of ruxolitinib cream with and without phototherapy in adolescents and adults whose area of non-segmental vitiligo does not exceed 10% of T-BSA. The participants enrolled will initially apply 1.5% ruxolitinib cream twice daily and, from Week 12 to 48, NB-UVB will be given three times per week to those who show a <25% improvement in T-VASI25.<sup>24</sup>

The third of the ongoing trails (NCT04530344) is a phase III, double-blind, vehicle-controlled, randomised withdrawal and treatment extension study designed to assess the long-term efficacy and safety of ruxolitinib cream in 458 of the patients previously enrolled in TRuE-V1 and TRuE-V2. The participants who completed the parent studies with an F-VASI90 outcome at Week 52 are to be randomised (1:1) to receive ruxolitinib cream or vehicle twice daily, whereas those who did not achieve F-VASI90 at Week 52 will continue ruxolitinib cream twice daily. The primary and secondary outcome measures will be evaluated after the extension period at Week 108.<sup>25</sup>

## ADVERSE EVENTS

Given the low plasma ruxolitinib concentrations measured after the topical application of ruxolitinib cream, it is expected that there will be few treatment-related AEs other than those affecting the site of the application.<sup>14</sup> The first insights into AEs related to topical ruxolitinib came from clinical trial assessing its efficacy in the treatment of atopic dermatitis.<sup>23</sup> Two double-blind, vehicle-controlled clinical trials (NCT03745638 Topical Ruxolitinib Evaluation in Atopic Dermatitis Study 1 [TRuE-AD1] and NCT03745651 Topical Ruxolitinib Evaluation in Atopic Dermatitis Study 2 [TRuE-AD2]) involving 499 adult aged ≥12 years, showed

that the most frequent AEs after 52 weeks' treatment were upper respiratory tract infections, nasopharyngitis, headache, bronchitis, rhinitis and application site reactions. Most of the AEs, other than application site reaction, were not related to treatment by the study investigators.<sup>26,27</sup>

The most complete data regarding ruxolitinib cream-related AEs occurring during the treatment of vitiligo come from the two phase III, double-blind, vehicle-controlled clinical trials NCT04052425 TRuE-V1 and NCT0457573 TRuE-V2. The AEs reported during the trial's 24-week double-blind periods were mild or moderate, and occurred in approximately one-half of the patients in the 1.5% ruxolitinib groups and one-third of those in the vehicle groups. The application site AEs that seemed to be treatment-related were acne, pruritus and exfoliation: after 24 weeks, acne was the most common in both the ruxolitinib and vehicle groups (5.8% vs. 1.2%), followed by pruritus (5.1% vs. 2.6%). Systemic AEs such as nasopharyngitis, headache, urinary tract infection and pyrexia were also described but their relation to treatment was considered uncertain as they occurred in <1% of the subjects in the treatment group, and their incidence was at least 1% lower than that reported in the vehicle group.

There were also reported AEs only in the ruxolitinib group and in the vehicle group, with an incidence of 0.5%–1%, and those were application site dermatitis, hypertension, anxiety, application site discoloration, application site folliculitis, contusion, contact dermatitis, diarrhoea, ear infections, gastritis, gastroenteritis, hordeolum, influenza-like illness, insomnia, nasal congestion and vomiting. None of the serious AEs were considered to be related to the trial agent by the investigators.<sup>22</sup>

## CURRENT APPROVAL STATUS AND FUTURE PERSPECTIVES

The twice-daily application of 1.5% ruxolitinib cream has been approved by FDA for the topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis and non-segmental vitiligo in non-immunocompromised aged >12 years whose disease is inadequately controlled by topical prescription therapies, or when these are not advisable.<sup>28</sup>

On 23 February 2023, the Committee for Medicinal Products for Human Use (CHMP), the European Medicines Agency (EMA)'s committee responsible for human medicines, adopted a positive opinion recommending the granting of a marketing authorisation for 1.5% ruxolitinib cream for the treatment of non-segmental vitiligo.

Furthermore, in April 2022, as there is a lack of evidence concerning the safety and effectiveness of topical ruxolitinib in the treatment of vitiligo patients aged <12 years, the EMA approved a paediatric investigation plan consisting of four clinical studies that is designed to be completed by June 2024. Study 1 (INCB 18424-306) is a double-blind, randomised, placebo-controlled trial aimed at evaluating the efficacy and safety of ruxolitinib cream in patients with non-segmental

vitiligo aged  $\geq 12$  years; studies 2 (INCB 18424-307) and 3 (INCB 18424-308) are extension studies aimed at assessing the long-term efficacy and safety of ruxolitinib cream; and study 4 (INCB 18424-309) is a double-blind, randomised, placebo-controlled trial aimed at evaluating the efficacy and safety of ruxolitinib cream in children with non-segmental vitiligo aged 6–11 years.<sup>29</sup> No information regarding the possible cost of the European treatment plan is currently available.

## DISCUSSION

Given the limited effectiveness and possible side-effects of existing treatments, and in order to address the unmet need to improve patients' quality of life, new safe and effective treatments are now required. The pathogenesis of vitiligo is still unclear and probably multi-factorial but, as cytotoxic T lymphocytes may be directly responsible for the destruction of melanocytes,<sup>30</sup> it seems that the immune system plays a central role. Recent pre-clinical and translational studies have shown that interferon- $\gamma$  (IFN- $\gamma$ ) signalling through the JAK pathway is one of the main pathogenetic drivers of the disease, and transcriptome analyses of the blood and skin of vitiligo patients have identified IFN- $\gamma$  induced C-X-C motif chemokine ligands 9 (CXCL9) and 10 (CXCL10) as key elements in melanocyte destruction.<sup>31,32</sup>

As the JAK/STAT signalling pathway is fundamental for the transduction of the IFN- $\gamma$  signals, JAK inhibition seems to be a promising therapeutic strategy. Some of the first human data concerning the efficacy of JAK inhibitors in vitiligo come from 10 patients whose vitiligo was treated with oral tofacitinib (a JAK1/3 inhibitor) and phototherapy in 2017.<sup>33</sup> A meta-analysis published in 2020 found that the proportion of patients with a repigmentation rate of  $>50\%$  is higher when JAK inhibitors are combined with NB-UVB phototherapy than when they are used alone (88% vs. 57.8%).<sup>34</sup>

However, as vitiligo is a chronic skin disease, it is more attractive to develop new topical therapies because of the possible systemic side-effects associated with long-term drug use of the above-mentioned small molecules. Consequently, a topical formulation of ruxolitinib (Opzelura®), a selective inhibitor of JAK1 and JAK2, has recently been approved by the FDA for the treatment of nonsegmental vitiligo in patients aged  $>12$  years based on data from the two phase III TRuE-V clinical trials. The recommended dose of ruxolitinib cream for the treatment of vitiligo is a thin layer spread twice daily on affected areas covering up to 10% of the body surface area. The formulation has also been previously approved for the topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis, and some new evidence suggests that it may be effective in treating cutaneous lichen planus and psoriasis.<sup>35,36</sup>

There were no approved treatments for vitiligo in the United States until the FDA approved the use of 1.5% ruxolitinib cream in June 2022. In Europe the management of

vitiligo is based on the most recent guidelines of the Vitiligo European Task Force<sup>37</sup> and the British Association of Dermatologists.<sup>38</sup> These suggest that once-daily TCS should be used in the first-line treatment of limited forms of vitiligo but, as these drugs require prolonged use, it is necessary to monitor patients for the local and systemic adverse effects that may arise after long-term treatment. Twice-daily TCIs can be considered as an alternative to TCS in adults and children with vitiligo as their safety profile is reportedly better than that of TCS, especially in relation to the risk of skin atrophy,<sup>39,40</sup> but their application should be discontinued in the case of superficial skin infections, malignancies, immunosuppression or extensive sun exposure. Another therapeutic option in patients with vitiligo is phototherapy, which has proved to be safe in children and adults, particularly in the case of NB-UVB radiation the current phototherapy of choice. It can stimulate repigmentation, but it is well known that the extremities are difficult to treat.<sup>41</sup> It is usually administered twice or three times a week, and continued for as long as there is ongoing repigmentation. The most frequent acute adverse reaction is skin type- and dose-dependent erythema, which usually occurs 12–24 h after irradiation. As vitiligo often affects exposed acral areas such as the face and hands, NB-UVB phototherapy is often used as part of a combined therapeutic strategy. However, the lack of information concerning the safety of long-term UVB exposure, and the existence of conflicting data concerning the incidence of melanoma and non-melanoma skin cancer in patients with vitiligo, may be a limiting factor of phototherapy.<sup>42,43</sup> Systemic therapies may benefit patients with unstable, widespread or recalcitrant vitiligo,<sup>10</sup> but it is important to remember that outcomes have varied widely and there is limited evidence supporting their use.<sup>44</sup> The use of systemic corticosteroids for up to 6 months is a first-line option only in the case of rapidly progressing disease.

As the first treatment for non-segmental vitiligo to be approved by the FDA, 1.5% ruxolitinib cream represents a therapeutic milestone that has strengthened the dermatological armamentarium.<sup>45</sup> The encouraging clinical trial data indicating a significant improvement in F-VASI and T-VASI scores reflect clinically relevant repigmentation although, like the other available treatments, ruxolitinib cream seems to be more effective in controlling vitiligo on the face than on the other parts of the body, possibly because of the different distribution of hair follicles and the more limited impact of the Koebner phenomenon.<sup>46</sup>

There is still a lack of real-life data concerning the effectiveness of topical ruxolitinib. In the real world, vitiligo patients are likely to be less compliant than motivated trial participants, particularly as the proposed treatment regimen consists of twice-daily applications for a long period of time, and this may affect treatment efficacy. It would also be useful to determine possible biomarkers that could be used to select the patients who are more likely to benefit from ruxolitinib treatment.

Furthermore, as most of the patients enrolled in the phase III clinical trials were Caucasians with skin types

I, II or III, little is known about the effects of the cream on patients with darker skin. A sub-analysis of the data from the phase II clinical trials suggests that the treatment was similarly effective on all phototypes, and it is theoretically unlikely that the activity of topical ruxolitinib in re-establishing melanocyte function is related to a specific skin type. There is also a lack of data concerning settings such as India or Africa, where the disease is seen as highly stigmatising and/or there is a higher burden of infectious diseases.

Topical ruxolitinib seems to be well tolerated and has given rise to few AEs. The most frequent local adverse effect is application site acne of uncertain pathogenesis, which is also common among patients treated with other systemic JAK inhibitors. However, one possible means of controlling JAK inhibitor-related acne is retinoid treatment.<sup>47</sup>

The findings of the open-label extensions of the clinical trials described above should provide further insights into the possible AEs associated with longer-term topical ruxolitinib, and the ongoing clinical trial aimed at investigating the mechanisms of action of topical ruxolitinib should improve our understanding of possible drug-related systemic AEs.

No study has yet compared ruxolitinib cream with traditional topical therapies such as TCS and TCIs, which would also be a useful means of determining the cost-effectiveness of the widespread use of topical ruxolitinib, and there is still a need to investigate the use of topical ruxolitinib in pregnant or breastfeeding women.

Although topical ruxolitinib has proven to be safe and effective for the treatment of vitiligo, the growing number of molecules currently investigated will ultimately benefit patients, allowing physicians to deliver patient-centred therapies, taking into account disease severity, co-morbidities and drugs side-effects. These promising approaches could broaden the possible therapeutic arsenal against vitiligo, in a *scenario* of growing evidence on the efficacy of topical ruxolitinib and the need of a personalised and patient-centred therapeutic approach.

Oral ruxolitinib has been approved by both the FDA and the EMA for the treatment of myelofibrosis, polycythaemia vera and acute graft-versus-host disease.<sup>48</sup> Only a few case reports suggest a potential role of oral ruxolitinib in the treatment of vitiligo, but it has been observed that pigmentation regresses following the discontinuation of treatment.<sup>34</sup> Other JAK-inhibitors are currently being evaluated in different stages of clinical trials for the treatment of vitiligo. These studies include both topical (e.g. ARQ-252,<sup>49</sup> cerdulatinib<sup>50</sup> and ATI-50002<sup>51</sup>) and systemic JAK-inhibitors (e.g. ritlecitinib,<sup>52,53</sup> upadacitinib<sup>54</sup> and baricitinib<sup>55</sup>). Furthermore, other potential therapeutic targets are being currently evaluated, including Wnt-signalling,<sup>56</sup> IL-15 pathway<sup>57</sup> and the heat shock protein 70.<sup>58</sup>

There is still considerable uncertainty concerning the duration of topical ruxolitinib treatment required to ensure the best pigmentation, and the durability of repigmentation after its withdrawal. However, the findings of the phase III

open-label extension (NCT04530344) should help to clarify these points.<sup>25</sup>

Moreover, it would be useful to determine the effect of topical ruxolitinib on skin-resident T cells during and after the discontinuation of treatment, in order to evaluate possible changes in the micro-environment and their effects on recurrent disease.<sup>59</sup> In the case of post-discontinuation depigmentation, further cycles of ruxolitinib may help to control the disease but it is also necessary to consider the risks of further AEs, increased costs, and reduced patient compliance.

Finally, EMA's proposed paediatric plan should help overcome the lack of information concerning the possible use of topical ruxolitinib in a patient population for which there are very few longitudinal data.

The current evidence suggests that ruxolitinib cream is an effective and well-tolerated means of treating vitiligo. However, only real-life data can ultimately confirm the feasibility of its use and its direct impact on the patients' quality of life.

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The authors have no conflict of interest to disclose.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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## REFERENCES

- Picardo M, Dell'Anna ML, Ezzedine K, Hamzavi I, Harris JE, Parsad D, et al. Vitiligo. *Nat Rev Dis Primers*. 2015;1:15011.
- Ezzedine K, Eleftheriadou V, Whitton M, van Geel N. Vitiligo. *Lancet*. 2015;386(9988):74–84.
- Alkhateeb A, Fain PR, Thody A, Bennett DC, Spritz RA. Epidemiology of vitiligo and associated autoimmune diseases in Caucasian probands and their families. *Pigment Cell Res*. 2003;16(3):208–14.
- Ezzedine K, Sheth V, Rodrigues M, Eleftheriadou V, Harris JE, Hamzavi IH, et al. Vitiligo is not a cosmetic disease. *J Am Acad Dermatol*. 2015;73(5):883–5.
- Linthorst Homan MW, Spuls PI, de Korte J, Bos JD, Sprangers MA, van der Veen JP. The burden of vitiligo: patient characteristics associated with quality of life. *J Am Acad Dermatol*. 2009;61(3):411–20.



6. Bibeau K, Pandya AG, Ezzedine K, Jones H, Gao J, Lindley A, et al. Vitiligo prevalence and quality of life among adults in Europe, Japan and the USA. *J Eur Acad Dermatol Venereol*. 2022;36(10):1831–44.
7. Kohli I, Veenstra J, Hamzavi I. Vitiligo assessment methods—vitiligo area scoring index and vitiligo European task force assessment. *Br J Dermatol*. 2015;172(2):318–9.
8. van Geel N, Depaep L, Vandaele V, Mertens L, van Causenbroeck J, de Schepper S, et al. Assessing the dynamic changes in vitiligo: reliability and validity of the vitiligo disease activity score (VDAS) and vitiligo disease improvement score (VDIS). *J Eur Acad Dermatol Venereol*. 2022;36(8):1334–41.
9. Bergqvist C, Ezzedine K. Vitiligo: a review. *Dermatology*. 2020;236(6):571–92.
10. Searle T, Al-Niaimi F, Ali FR. Vitiligo: an update on systemic treatments. *Clin Exp Dermatol*. 2021;46(2):248–58.
11. Zubair R, Hamzavi IH. Phototherapy for vitiligo. *Dermatol Clin*. 2020;38(1):55–62.
12. Post NF, Ezekwe N, Narayan VS, Bekkenk MW, van Geel N, Hamzavi I, et al. The use of lasers in vitiligo, an overview. *J Eur Acad Dermatol Venereol*. 2022;36(6):779–89.
13. Howell MD, Kuo FI, Smith PA. Targeting the Janus kinase family in autoimmune skin diseases. *Front Immunol*. 2019;10:2342.
14. Gong X, Chen X, Kuligowski ME, Liu X, Liu X, Cimino E, et al. Pharmacokinetics of ruxolitinib in patients with atopic dermatitis treated with ruxolitinib cream: data from phase II and III studies. *Am J Clin Dermatol*. 2021;22(4):555–66.
15. Persaud I, Diamond S, Pan R, Burke K, Harris J, Conlin M, et al. Plasma pharmacokinetics and distribution of ruxolitinib into skin following oral and topical administration in minipigs. *Int J Pharm*. 2020;590:119889.
16. Food and Drug Administration. Ruxolitinib cream – NDA multi-disciplinary review and evaluation. [accessed 2022 Dec 5]. Available from: <https://www.fda.gov/media/154307/download>
17. Rothstein B, Joshipura D, Saraiya A, Abdat R, Ashkar H, Turkowski Y, et al. Treatment of vitiligo with the topical Janus kinase inhibitor ruxolitinib. *J Am Acad Dermatol*. 2017;76(6):1054–60.e1.
18. Joshipura D, Alomran A, Zancanaro P, Rosmarin D. Treatment of vitiligo with the topical Janus kinase inhibitor ruxolitinib: a 32-week open-label extension study with optional narrow-band ultraviolet B. *J Am Acad Dermatol*. 2018;78(6):1205–7.e1.
19. Rosmarin D, Pandya AG, Lebwohl M, Grimes P, Hamzavi I, Gottlieb AB, et al. Ruxolitinib cream for treatment of vitiligo: a randomised, controlled, phase 2 trial. *Lancet*. 2020;396(10244):110–20.
20. Hamzavi I, Rosmarin D, Harris JE, Pandya AG, Lebwohl M, Gottlieb AB, et al. Efficacy of ruxolitinib cream in vitiligo by patient characteristics and affected body areas: descriptive subgroup analyses from a phase 2, randomized, double-blind trial. *J Am Acad Dermatol*. 2022;86(6):1398–401.
21. Pandya AG, Harris JE, Lebwohl M, Hamzavi IH, Butler K, Kuo FI, et al. Addition of narrow-band UVB phototherapy to ruxolitinib cream in patients with vitiligo. *J Invest Dermatol*. 2022;142(12):3352–5.e4.
22. Rosmarin D, Passeron T, Pandya AG, Grimes P, Harris JE, Desai SR, et al. Two phase 3, randomized, controlled trials of ruxolitinib cream for vitiligo. *N Engl J Med*. 2022;387(16):1445–55.
23. A study to evaluate the mechanism of action of ruxolitinib cream in subjects with vitiligo (TRuE-V MOA). NCT04896385. [accessed 2022 Dec 5]. Available from: <https://clinicaltrials.gov/ct2/show/NCT04896385?cond=TRuE-V+MOA&draw=2&rank=1>
24. A study to evaluate the safety and efficacy of ruxolitinib cream with phototherapy in participants with vitiligo. NCT05247489. [accessed 2022 Dec 5]. Available from: <https://clinicaltrials.gov/ct2/show/NCT05247489?cond=NCT05247489&draw=2&rank=1>
25. Assess the long term efficacy and safety of ruxolitinib cream in participants with vitiligo. NCT04530344. [accessed 2022 Dec 5]. Available from: <https://clinicaltrials.gov/ct2/show/NCT04530344?cond=NCT04530344&draw=2&rank=1>
26. Papp K, Szepletowski JC, Kirck L, Toth D, Eichenfield LF, Leung DYM, et al. Efficacy and safety of ruxolitinib cream for the treatment of atopic dermatitis: results from 2 phase 3, randomized, double-blind studies. *J Am Acad Dermatol*. 2021;85(4):863–72.
27. Papp K, Szepletowski JC, Kirck L, Toth D, Eichenfield LF, Forman SB, et al. Long-term safety and disease control with ruxolitinib cream in atopic dermatitis: results from two phase 3 studies. *J Am Acad Dermatol*. 2022;88(5):1008–16.
28. Food and Drug Administration. FDA approves topical treatment addressing repigmentation in vitiligo in patients aged 12 and older. [accessed 2022 Dec 5]. Available from: <https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-topical-treatment-addressing-repigmentation-vitiligo-patients-aged-12-and-older>
29. European Medicines Agency. [accessed 2022 Dec 5]. Available from: [https://www.ema.europa.eu/en/documents/pip-decision/p/0145/2021-ema-decision-16-april-2021-agreement-paediatric-investigation-plan-granting-deferral-granting\\_en.pdf](https://www.ema.europa.eu/en/documents/pip-decision/p/0145/2021-ema-decision-16-april-2021-agreement-paediatric-investigation-plan-granting-deferral-granting_en.pdf)
30. van den Boorn JG, Konijnenberg D, Dellelijn TA, van der Veen JP, Bos JD, Melief CJ, et al. Autoimmune destruction of skin melanocytes by perilesional T cells from vitiligo patients. *J Invest Dermatol*. 2009;129(9):2220–32.
31. Rashighi M, Agarwal P, Richmond JM, Harris TH, Dresser K, Su MW, et al. CXCL10 is critical for the progression and maintenance of depigmentation in a mouse model of vitiligo. *Sci Transl Med*. 2014;6(223):223ra23.
32. Regazzetti C, Joly F, Marty C, Rivier M, Mehl B, Reiniche P, et al. Transcriptional analysis of vitiligo skin reveals the alteration of WNT pathway: a promising target for repigmenting vitiligo patients. *J Invest Dermatol*. 2015;135(12):3105–14.
33. Liu LY, Strassner JP, Refat MA, Harris JE, King BA. Repigmentation in vitiligo using the Janus kinase inhibitor tofacitinib may require concomitant light exposure. *J Am Acad Dermatol*. 2017;77(4):675–82.e1.
34. Phan K, Phan S, Shumack S, Gupta M. Repigmentation in vitiligo using janus kinase (JAK) inhibitors with phototherapy: systematic review and meta-analysis. *J Dermatolog Treat*. 2022;33(1):173–7.
35. Brumfiel CM, Patel MH, Severson KJ, Zhang N, Li X, Quillen JK, et al. Ruxolitinib cream in the treatment of cutaneous lichen planus: a prospective, open-label study. *J Invest Dermatol*. 2022;142(8):2109–16.e4.
36. Tegtmeyer K, Ravi M, Zhao J, Maloney NJ, Lio PA. Off-label studies on the use of ruxolitinib in dermatology. *Dermatitis*. 2021;32(3):164–72.
37. Taieb A, Alomar A, Böhm M, Dell'anna M, de Pase A, Eleftheriadou V, et al. Guidelines for the management of vitiligo: the European dermatology forum consensus. *Br J Dermatol*. 2013;168(1):5–19.
38. Eleftheriadou V, Atkar R, Batchelor J, McDonald B, Novakovic L, Patel JV, et al. British Association of Dermatologists guidelines for the management of people with vitiligo 2021. *Br J Dermatol*. 2022;186(1):18–29.
39. Reitamo S, Rustin M, Harper J, Kalimo K, Rubins A, Cambazard F, et al. A 4-year follow-up study of atopic dermatitis therapy with 0.1% tacrolimus ointment in children and adult patients. *Br J Dermatol*. 2008;159(4):942–51.
40. Reitamo S, Rissanen J, Remitz A, Granlund H, Erkkö P, Autio P, et al. Tacrolimus ointment does not affect collagen synthesis: results of a single-center randomized trial. *J Invest Dermatol*. 1998;111(3):396–8.
41. Fai D, Cassano N, Vena GA. Narrow-band UVB phototherapy combined with tacrolimus ointment in vitiligo: a review of 110 patients. *J Eur Acad Dermatol Venereol*. 2007;21(7):916–20.
42. Rodrigues M. Skin cancer risk (nonmelanoma skin cancers/melanoma) in vitiligo patients. *Dermatol Clin*. 2017;35(2):129–34.
43. Gran S. Vitiligo and skin cancer: is it a question of ethnicity? *Br J Dermatol*. 2020;182(4):825–6.
44. Fatima S, Abbas T, Refat MA, Harris JE, Lim HW, Hamzavi IH, et al. Systemic therapies in vitiligo: a review. *Int J Dermatol*. 2022;62:279–89. <https://doi.org/10.1111/ijd.16114>
45. Eidsmo L. New hope for patients with vitiligo. *N Engl J Med*. 2022;387(16):1515–6.
46. Esmat SM, El-Tawdy AM, Hafez GA, Zeid OA, Abdel Halim DM, Saleh MA, et al. Acral lesions of vitiligo: why are they



- resistant to photochemotherapy? *J Eur Acad Dermatol Venereol.* 2012;26(9):1097–104.
47. Correia C, Antunes J, Filipe P. Management of acne induced by JAK inhibitors. *Dermatol Ther.* 2022;35(9):e15688.
  48. Kirito K. Recent progress of JAK inhibitors for hematological disorders. *Immunol Med.* 2022;1–12.
  49. Safety and efficacy of ARQ-252 cream 0.3% in subjects with non-segmental facial vitiligo. NCT04811131. Available from: <https://clinicaltrials.gov/ct2/show/record/NCT04811131?cond=ARQ-252&draw=2&rank=1>
  50. Safety and tolerability study of cerdulatinib gel, 0.37% in adults with vitiligo. NCT04103060. Available from: <https://clinicaltrials.gov/ct2/show/NCT04103060?cond=cerdulatinib&draw=2&rank=2>
  51. A study of ATI-50002 topical solution for the treatment of vitiligo. NCT03468855. Available from: <https://clinicaltrials.gov/ct2/show/NCT03468855?cond=ATI-50002&draw=2&rank=1>
  52. Ezzedine K, Peeva E, Yamaguchi Y, Cox LA, Banerjee A, Han G, et al. Efficacy and safety of oral ritlecitinib for the treatment of active non-segmental vitiligo: a randomized phase 2b clinical trial. *J Am Acad Dermatol.* 2023;88(2):395–403.
  53. A 52-week study of ritlecitinib oral capsules in adults and adolescents with vitiligo (active and stable) (Tranquillo). NCT05583526. Available from: <https://clinicaltrials.gov/ct2/show/NCT05583526?cond=ritlecitinib&draw=2&rank=5>
  54. Study to evaluate adverse events and change in disease activity with oral tablets of upadacitinib in adult participants with non-segmental vitiligo. NCT04927975. Available from: <https://clinicaltrials.gov/ct2/show/NCT04927975?cond=upadacitinib+vitiligo&draw=2&rank=1>
  55. Evaluation of effect and tolerance of the association of baricitinib and phototherapy versus phototherapy in adults with progressive vitiligo (BARVIT). NCT04822584. Available from: <https://clinicaltrials.gov/ct2/show/NCT04822584?cond=baricitinib+vitiligo&draw=2&rank=1>
  56. Lin X, Meng X, Lin J. The possible role of Wnt/ $\beta$ -catenin signalling in vitiligo treatment. *J Eur Acad Dermatol Venereol.* 2023;37:2208–21. <https://doi.org/10.1111/jdv.19022>
  57. Richmond JM, Strassner JP, Zapata L Jr, Garg M, Riding RL, Refat MA, et al. Antibody blockade of IL-15 signaling has the potential to durably reverse vitiligo. *Sci Transl Med.* 2018;10(450):eaam7710.
  58. Mosenson JA, Zloza A, Nieland JD, Garrett-Mayer E, Eby JM, Huelsmann EJ, et al. Mutant HSP70 reverses autoimmune depigmentation in vitiligo. *Sci Transl Med.* 2013;5(174):174ra28.
  59. Giri PS, Mistry J, Dwivedi M. Meta-analysis of alterations in regulatory T cells' frequency and suppressive capacity in patients with vitiligo. *J Immunol Res.* 2022;2022:6952299.

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