Canadian Journal of Health Technologies

Canada's Drug Agency
L'Agence des médicaments du Canada

August 2025 Volume 5 Issue 8

Drugs Health Technologies Health Systems

Reimbursement Recommendation

Ruxolitinib (Opzelura)

Indication: Topical treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older

Sponsor: Incyte Biosciences Canada Corporation

Final recommendation: Do not reimburse

Summary

What Is the Reimbursement Recommendation for Opzelura?

Canada's Drug Agency (CDA-AMC) recommends that Opzelura not be reimbursed by public drug plans for topical treatment of nonsegmental vitiligo in adult and pediatric patients aged 12 years and older.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 2 clinical trials demonstrated that about 30% of patients using Opzelura saw significant improvement in facial repigmentation, compared to around 8% to 11% using a placebo. More patients also reported that their vitiligo became less noticeable or no longer noticeable than those who received placebo. However, the impact of vitiligo on daily life varies, and the treatment did not lead to meaningful improvements in overall health-related quality of life (HRQoL).
- The studies only compared Opzelura to a placebo; therefore, there is no data on how it performs against other commonly used treatments.
- The Canadian Drug Expert Committee (CDEC) recognized that vitiligo can seriously affect people's lives, especially those with darker skin tones, who may face stigma, loss of identity, and low self-esteem. Most trial participants had lighter skin tones, and the treatment did not improve their HRQoL. These limitations make it difficult to know how effective Opzelura would be for those most affected by vitiligo.

Additional Information

What Is Nonsegmental Vitiligo?

Vitiligo is a long-term condition where the skin loses its colour due to the immune system attacking pigment-producing cells. It affects up to 2% of people worldwide and about 0.5% to 1% in Canada. Nonsegmental vitiligo, the most common type, causes symmetrical white patches and accounts for about 80% of cases. Vitiligo can have a major emotional impact, leading to anxiety, depression, and social stigma, especially in children and people where skin tone changes are more stigmatized.

Unmet Needs in Nonsegmental Vitiligo

Patients with nonsegmental vitiligo need a treatment that is easy to use, affordable, and provides reliable, long-lasting repigmentation with fewer side effects. There is a need for better options that improve both the appearance of vitiligo and the overall HRQoL for those affected.

Summary

How Much Does Opzelura Cost?

Treatment with Opzelura is expected to cost approximately $29,051 per patient per year.

Recommendation

CDEC recommends that ruxolitinib not be reimbursed for topical treatment of nonsegmental vitiligo in adult and pediatric patients aged 12 years and older.

Rationale for the Recommendation

Two phase III, multicentre, double-blind, vehicle-controlled randomized controlled trials (RCTs) (TRuE-V1 [n = 330] and TRuE-V2 [n = 344]) designed to evaluate the efficacy and safety of 1.5% ruxolitinib topical cream, applied twice daily to depigmented areas for the treatment of nonsegmental vitiligo in adult and pediatric patients aged 12 years and older, suggest that treatment with ruxolitinib topical cream likely results in a clinically important improvement in the Facial Vitiligo Area Scoring Index score (F-VASI) score compared with vehicle cream, indicating better repigmentation. Among patients who applied ruxolitinib topical cream, the proportions of patients who responded based on the improvement of 75% in the F-VASI (F-VASI75) score, 29.8% of patients in the TRuE-V1 trial, and 30.9% of patients in the TRuE-V2 trial resulted in a between-group difference in response rate versus vehicle cream of 22.3% (95% confidence interval [CI], 14.2% to 30.5%; P < 0.0001) in the TruE-V1 trial and 19.5% (95% CI, 10.5% to 28.4%; P = 0.0004) in the TruE-V2 trial at week 24. Results for Total Vitiligo Area Scoring Index (T-VASI) score improvements were of smaller magnitude. Results for patient-reported noticeability, assessed as a key secondary outcome using the Vitiligo Noticeability Scale (VNS), suggest that a higher proportion of patients who applied ruxolitinib topical cream achieved the scores of 4 (a lot less noticeable) or 5 (no longer noticeable) versus patients who applied vehicle cream for more than 24 weeks; among patients who applied ruxolitinib topical cream, the proportions of patients who responded were 25% in the TRuE-V1 trial and 21% in the TRuE-V2 trial, resulting in a between-group difference in response rate versus vehicle cream of 21.2% (95% CI, 14.3% to 28.1%; P = 0.0002) in the TruE-V1 trial and 15.5% (95% CI, 8.5% to 22.6%; P = 0.0013) in the TruE-V2 trial. However, the impact of vitiligo on daily life varies among individuals and objective response based on repigmentation should be considered alongside HRQoL findings. Despite improving the appearance of vitiligo in some patients, ruxolitinib topical cream did not alleviate the negative impact of the disease on patients' lives in the overall study population as measured by HRQoL metrics. In addition, the TRuE-V1 and TRuE-V2 trials included a vehicle control group; therefore, there is no direct evidence comparing ruxolitinib topical cream to other currently used therapies for vitiligo. No indirect evidence was submitted, and the sponsor rated the feasibility of conducting robust evidence synthesis as low. CDEC and the clinical experts noted that this lack of comparative evidence is a significant limitation, as current off-label treatments are well accepted and routinely prescribed according to the clinical experts consulted. Therefore, the comparative efficacy and safety of ruxolitinib topical cream remain unknown.

CDEC acknowledged that nonsegmental vitiligo can profoundly impact patients, often leading to stigma and social isolation where the condition may be misunderstood or viewed negatively, leading to fear, discrimination, and emotional distress. This effect is especially pronounced in individuals with darker skin tones, where the condition can result in loss of identity and decreased self-esteem, profoundly affecting their HRQoL. Patient feedback highlights the need for accessible and tolerable therapies capable of delivering

reliable repigmentation, that reduces patchiness and delivers lasting comprehensive results. The patient group input noted that there is an unmet need for additional, effective treatment options, particularly in patients with darker skin tones who could not achieve satisfactory improvements with the currently available therapies, and who experience a negative impact of the condition on their HRQoL. CDEC noted that whether ruxolitinib topical treatment can address these important unmet needs is uncertain due to the lack of improvement in HRQoL and limitations in the external validity of the available evidence, where most study participants had lighter skin tones based on the Fitzpatrick skin type classification, and many had conditions that did not substantially interfere with daily life, as indicated by the lower-than-expected use of prior therapies despite long-lasting disease and relatively low baseline HRQoL impairment. These factors prevent definitive conclusions about ruxolitinib topical treatment's effect on those with the greatest unmet needs.

Discussion Points

- **Reconsideration request**: The sponsor requested a reconsideration of the initial draft recommendation to not reimburse ruxolitinib topical treatment for nonsegmental vitiligo in adult and pediatric patients aged 12 years and older. There were 5 issues outlined by the sponsor in the request for reconsideration that were discussed by CDEC. The sponsor emphasized that repigmentation is the primary treatment goal in nonsegmental vitiligo. They expressed concern that the unmet need in this condition has not been fully acknowledged. In their view, both the VNS and repigmentation outcomes should be considered when assessing clinical value and HRQoL. The sponsor also noted that conducting indirect treatment comparisons (ITCs) with other therapies is not feasible. Finally, they asserted that the treatment demonstrates consistent efficacy across different skin types (according to the Fitzpatrick Scale skin type classification).
- **Unmet needs**: During the initial and reconsideration meetings, CDEC acknowledged that nonsegmental vitiligo can profoundly affect patients, especially those with darker skin tones, leading to stigma, social isolation, loss of identity, and decreased self-esteem. The condition can significantly impact HRQoL, often causing depression, anxiety, and an increased risk of suicide. Vitiligo also imposes an economic burden due to costs for medications, clothing, and camouflage makeup, as well as lost productivity. Current off-label treatments have limitations, such as incomplete or uneven repigmentation and loss of response over time. Many patients become refractory or discontinue treatments due to toxicity. Patient group input highlights the need for more accessible and tolerable treatments capable of delivering reliable repigmentation that reduces patchiness and delivers lasting comprehensive results. There is an unmet need for better treatment options, particularly for patients with darker skin tones who have not achieved satisfactory improvements with existing therapies. However, the effectiveness of ruxolitinib topical cream in addressing these needs is uncertain due to the lack of improvement in HRQoL and limitations in generalizability of the available evidence to these patients. During the reconsideration meeting, CDEC acknowledged the feedback received from the clinician and patient groups who stated that nonsegmental vitiligo is an autoimmune condition with both visible and invisible impacts, affecting the skin and mental health, and often occurring

alongside other autoimmune diseases. CDEC acknowledged the psychological toll is especially severe in adolescents, who face high rates of anxiety, depression, bullying, and even suicidal ideation, and that many patients experience social withdrawal, which can disrupt family life, work, and financial stability. However, CDEC discussed that partial repigmentation is not always linked to improvements in HRQoL, as the psychological impact of vitiligo often persists as long as the condition remains visible. Patients expressed a desire for treatments that are effective, easy to use, and capable of delivering reliable, lasting repigmentation. They also prioritized fewer side effects, better affordability, and greater accessibility — ideally through at-home or simplified options. While it is true that no therapies are currently approved in Canada specifically for repigmentation in nonsegmental vitiligo, CDEC heard from the clinical experts consulted that topical corticosteroids and calcineurin inhibitors (with or without phototherapy) are commonly used and are referred to as treatment options in the treatment guidelines. Therefore, whether ruxolitinib topical cream meaningfully addresses the identified unmet needs remains uncertain based on the current evidence.

- **GRADE assessment**: CDEC discussed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment of selected outcomes from the TRuE-V1 and TRuE-V2 trials that concluded with moderate certainty that topical treatment with ruxolitinib would likely result in a clinically important increase in the proportion of patients achieving F-VASI75, an improvement of 90% in the F-VASI (F-VASI90), and VNS of “4- A lot less noticeable” or “5-No longer noticeable” over 24 weeks compared to vehicle cream, while ruxolitinib topical cream may not result in a clinically important improvement in HRQoL as measured with the Vitiligo-Specific Quality of Life instrument (VitiQoL) over 24 weeks compared to vehicle cream.
- **Clinical meaningfulness of the results**: The difference between ruxolitinib topical cream and vehicle cream in terms of repigmentation was considered clinically meaningful; however, CDEC noted that the overall impact of objective response on patients’ daily lives is difficult to assess. Given that nonsegmental vitiligo can range from being barely perceptible to cosmetically distressing, individual priorities will vary, making the minimal objective response needed for a meaningful impact highly variable across patients depending on how the disease affects their daily lives. In clinical practice, treatment is targeted at improving quality of life, therefore going beyond surface area of involvement and degree of repigmentation. As such, both patients and clinicians emphasize the importance of reliable repigmentation that reduces patchiness and provides lasting, comprehensive results. During the initial and reconsideration meetings, CDEC discussed that partial repigmentation in areas such as cheeks and neck may not be meaningful if no improvement is seen in resistant areas around the eyes and mouth for example; hence, HRQoL is impacted as long as the disease is visible.
- **HRQoL**: HRQoL was measured using the Dermatology Life Quality Index (DLQI) or the Child Dermatology Life Quality Index (CDLQI) as other secondary outcomes and VitiQoL as the exploratory outcome; as such, the studies were not designed to test for differences in HRQoL. Results did not suggest benefits from ruxolitinib topical cream. CDEC discussed that the differences between ruxolitinib topical cream and vehicle cream, as well as the within-group changes, were not clinically meaningful. Therefore, CDEC noted that despite repigmentation making the condition less noticeable

in some patients, ruxolitinib topical cream did not alleviate the impact of vitiligo on HRQoL in the overall study population. The clinical experts noted to CDEC that several factors which may have an important impact on patients are not captured by the Vitiligo Area Scoring Index (VASI) score, such as disease site visibility, repigmentation heterogeneity, and cultural influences, where the condition may be misunderstood or viewed negatively, leading to fear, discrimination, and emotional distress. CDEC also noted that baseline HRQoL values suggest relatively low impairment in the trial population, which may not represent patients whose condition substantially interferes with daily life. During the reconsideration meeting, CDEC discussed the request to consider both the VNS and repigmentation outcomes when assessing clinical value and HRQoL. As previously outlined, repigmentation is only 1 treatment goal and it also needs to ultimately improve psychosocial impact on HRQoL. CDEC also noted that the VNS is a subjective, patient-reported outcome that focuses on the visibility of pigmentation but does not necessarily correlate with improvements in HRQoL. As a global assessment based on patient perception, VNS does not indicate whether repigmentation has occurred in high-impact areas such as the face or hands, which are more closely tied to psychosocial burden. In lighter skin tones, minor changes like redness may be more noticeable, potentially inflating VNS scores and limiting its usefulness in assessing clinically meaningful outcomes. CDEC and the clinical experts noted that VNS cannot serve as a surrogate for HRQoL and noted that there is a lack of demonstrated improvement in disease-specific HRQoL, as measured by VitiQoL in the trials.

- **Primary treatment goal**: During the reconsideration meeting, CDEC discussed what is considered as the primary treatment goal in nonsegmental vitiligo and noted that the main burden of vitiligo is psychological, making HRQoL the most important measure of treatment impact. While ruxolitinib topical cream led to repigmentation in some patients in the trials, it did not show clear improvements in HRQoL. Repigmentation extent is only 1 part of disease severity, factors like lesion location, activity, and skin type (according to the Fitzpatrick Scale skin type classification) also matter. VASI scores measure how much skin is affected but don’t reflect the impact of vitiligo in highly visible areas like the face and hands, which are harder to treat. Finally, CDEC acknowledged the clinician group’s feedback suggesting that any degree of repigmentation significantly improves HRQoL. However, CDEC noted that this claim is not strongly supported by evidence, as results from both trials did not demonstrate meaningful improvements in any HRQoL outcomes with ruxolitinib topical cream.
- **Comparative evidence**: While it is accurate that no therapies are currently approved in Canada specifically for repigmentation in patients with nonsegmental vitiligo, the clinical experts acknowledged that topical corticosteroids and calcineurin inhibitors, with or without phototherapy, are commonly used and effective in some patients. Despite the pivotal trials being vehicle-controlled, there is an existing standard of care. The absence of direct or indirect comparative evidence is a significant limitation, not only for evaluating the relative efficacy (in terms of repigmentation and HRQoL) and safety of ruxolitinib topical cream, but also for determining its appropriate place in therapy.
- **Responders analysis**: Findings from post-hoc analyses in patients who received ruxolitinib topical cream, which compared the change in VitiQoL and DLQI from baseline to week 24 among patients

who achieved various levels of F-VASI and those who did not, suggest that patients who achieve at least F-VASI75 may observe improvement in their HRQoL; however, whether the improvement in HRQoL is clinically meaningful is uncertain. In addition, interpretation of these findings is limited by the post-hoc nature of the analyses.

- **Skin type and race**: CDEC discussed the subgroup analyses by skin type (according to the Fitzpatrick Scale skin type classification) and race, which are relevant to vitiligo treatment. Although vitiligo affects all races and skin tones, it is more visible in individuals with darker skin tones, impacting their quality of life more. However, few patients with darker skin tones were included in the studies. Of the 661 patients in the TRuE-V1 and TRuE-V2 trials, only 4.7% were Black or African American, 3.9% were Asian, 0.3% were American Indian or Alaska Native, and 0.3% were Native Hawaiian or Pacific Islander. As for skin type according to the Fitzpatrick Scale skin type classification, 6.5% of patients had a skin type of V (i.e., dark brown) and 2.0% of patients had a skin type of VI (i.e., deeply pigmented dark brown to darkest brown). CDEC discussed that these subgroups were underpowered, so findings should be viewed as supplemental. During the reconsideration meeting, CDEC acknowledged that individuals with darker skin tones may experience greater psychological and social impacts from vitiligo, and that patients with different skin tones have different experiences with vitiligo. However, the current evidence base is limited by the underrepresentation of individuals with darker skin tones in the clinical trials. Future research should address this limitation to ensure more inclusive and generalizable findings. The clinical experts noted to CDEC that vitiligo tends to be more visible and distressing in patients with darker skin tones, underscoring a potentially greater unmet need in these populations. Furthermore, the clinical meaningfulness of repigmentation may differ by skin type (according to the Fitzpatrick Scale skin type classification); partial repigmentation might be acceptable in patients with lighter skin tones, but in patients with darker skin tones, residual uneven pigmentation can remain highly visible and stigmatizing, potentially diminishing perceived treatment benefit.
- **Long-term efficacy**: The 24-week, double-blind controlled period for the TRuE-V1 and TRuE-V2 trials was followed by a 28-week open-label extension; therefore, totalling 52 weeks. The TRuE-V long-term extension (LTE) study assessed long-term efficacy and safety over an additional 104 weeks. The median ruxolitinib topical cream exposure in TRuE-V LTE was 364 days. CDEC noted that findings were consistent with evidence from the double-blind duration, showing continued improvement in F-VASI and T-VASI scores over time. Ruxolitinib topical cream maintained repigmentation even after discontinuation in patients who achieved F-VASI90. Patients who experienced disease relapse regained responses within 12 weeks of re-treatment. However, improvements in F-VASI did not correlate with HRQoL, for which no clinically meaningful improvement was observed, and uncertainty remains due to the uncontrolled, open-label nature of the extension studies and limited evidence beyond the follow-up duration.

Background

Vitiligo is a chronic autoimmune disorder that causes progressive depigmentation of the skin due to the loss of melanocytes, affecting up to 2% of the global population, with prevalence in Canada estimated between 0.5% and 1%. It is categorized into nonsegmental vitiligo (presenting as symmetrical patches), segmental vitiligo (affecting 1 side of the body), and mixed forms (displaying characteristics of both forms), with nonsegmental vitiligo being the most common accounting for approximately 80% of vitiligo cases. It can also have an unpredictable progression, often starting before age 12 years and peaking around age 30 years. The pathogenesis of vitiligo involves autoimmune mechanisms targeting melanocytes, driven by increased oxidative stress and inflammatory pathways, leading to immune-mediated destruction.

Lesions often appear on the face, hands, and genital areas, and are often triggered by stress. Flares are also common, especially in individuals with more extensive skin involvement or darker skin tones. Additionally, about 25% of patients have autoimmune comorbidities, with thyroid disease being the most frequent. The psychosocial impact of vitiligo is profound, often leading to depression, anxiety, and social stigma, especially when lesions are visible. Children and those with darker skin tones in communities with stronger stigma are particularly vulnerable. Vitiligo also carries both direct and indirect economic costs, including treatment expenses and lost productivity. Diagnosis is based on physical exams, clinical history, and laboratory tests, with biopsies used in rare cases. Due to the association with autoimmune conditions, thyroid function and tests for other autoimmune disorders are often assessed.

Ruxolitinib 1.5% topical cream was approved by Health Canada for the topical treatment of nonsegmental vitiligo in adult and pediatric patients aged 12 years and older. The recommended dosage is a thin layer of 1.5% ruxolitinib topical cream applied twice daily to affected skin areas, covering up to a maximum of 10% of the body surface area per application. Satisfactory repigmentation may require more than 24 weeks of treatment. If meaningful repigmentation is not observed by 24 weeks, re-evaluation by a health care provider is recommended.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 2 phase III, multicentre, double-blind, vehicle-controlled RCTs identically designed to evaluate the efficacy and safety of 1.5% ruxolitinib topical cream, applied twice daily to depigmented areas, for the treatment of nonsegmental vitiligo in adult and pediatric patients aged 12 years and older; and 3 LTE studies
- patients' perspectives gathered by 1 patient group, the Canadian Skin Patient Alliance in collaboration with Vitiligo Voices Canada
- input from public drug plans that participate in the reimbursement review process
- two clinical specialists with expertise diagnosing and treating patients with vitiligo

- input from 2 clinician groups, the Canadian Dermatology Association in collaboration with the Dermatologist Association of Ontario and Dermatology Association of Saskatchewan (8 clinicians contributed to the input), and the Southwestern Ontario Dermatologists Group (4 clinicians contributed to the input)
- a review of the pharmacoeconomic model and report submitted by the sponsor
- information submitted as part of the sponsor's request for reconsideration (described subsequently)
- feedback on the draft recommendation.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

Input was submitted by the Canadian Skin Patient Alliance in collaboration with Vitiligo Voices Canada regarding the current review of ruxolitinib topical cream for nonsegmental vitiligo, based on a survey conducted in Canada between September 26 and October 15, 2024, with 19 respondents.

Participants were primarily from Ontario and Alberta, with others from British Columbia, Newfoundland and Labrador, Yukon, Quebec, Nova Scotia, and New Brunswick. Respondents were predominantly white, and about one-half were aged 55 years or older.

According to the input, the impact of vitiligo extends beyond physical symptoms, affecting identity, emotional well-being, sense of belonging, and social interactions. Young individuals faced bullying and social stigma, while many respondents struggled with anxiety due to the unpredictable nature of the condition. Severe mental health consequences, such as depression and suicidal ideation, were also reported, with challenges exacerbated for individuals with darker skin tones who faced heightened judgment due to sociocultural beauty standards.

Current treatment options were seen as inadequate. Respondents reported frustration with inconsistent results, side effects, high costs, and access barriers particularly for patients living in rural area due to the need for frequent clinic visits. The patients who provided input through the patient groups noted that topical corticosteroids, the first-line therapy, were largely ineffective, as were other treatments like vitamin D derivatives and immunomodulators. Some patients reported limited effectiveness with depigmentation therapy (monobenzone) and narrowband UVB phototherapy, though responses varied, and these treatments posed challenges due to frequent clinic appointments and additional costs. Notably, none of the respondents had experience with ruxolitinib topical cream.

Survey respondents emphasized the need for a treatment that is effective, easy to use, and capable of delivering reliable repigmentation with lasting results. They also prioritized fewer side effects, increased affordability, and greater accessibility, ideally through at-home or simpler solutions.

Clinician Input

Input From Clinical Experts Consulted for This Review

Vitiligo can range from being barely perceptible to cosmetically distressing, with patients coming from different walks of life having different perceptions of their condition. The disease site and degree of repigmentation matter, as areas affected by vitiligo in visible sites will be more difficult to hide and therefore more impactful for the patient. Partial repigmentation is not necessarily associated with improvement in HRQoL, as the visibility of vitiligo can still negatively affect a patient's HRQoL.

The clinical experts emphasized that the choice of treatment will be based on the impact that the disease has on a patient's life. Options include conservative camouflage, which is usually not well accepted by patients and does not modify disease mechanisms or provide any sort of disease improvement. The mainstays of treatment are topical corticosteroids and calcineurin inhibitors, which address the underlying inflammatory attack on the melanocytes. Other alternative treatments include phototherapy, which may be also combined with topical treatments. However, according to the clinical experts, approximately one-half of patients routinely seen in clinical practice become refractory due to disease resistance, while some other patients have to discontinue treatments due to unacceptable toxicity.

As none of the other current therapies are approved by Health Canada for the treatment of nonsegmental vitiligo, the clinical experts indicated that topical ruxolitinib could potentially be a first-line therapy for nonsegmental vitiligo, or that it could be reserved as a second-line option for patient refractory or intolerance to current mainstay treatments. They noted that the absence of comparative evidence against the drugs currently used in clinical practice was considered a substantial limitation. The experts also highlighted that the place in therapy for ruxolitinib topical cream would depend on whether it can provide clinically meaningful improvements for patients who have the highest unmet need. These patients were identified as those with darker skin tones, who are likely to experience a greater impact on HRQoL due to the increased visibility of the condition, as well as those with affected lip-tip, periocular, and/or perioral regions, which are highly visible and often resistant to repigmentation.

The clinical experts expect ruxolitinib topical cream to be discontinued if there is a lack of efficacy or disease progression after 24 weeks or once the skin is fully repigmented. The clinical expert noted that referring patients to a specialist, such as a dermatologist, is preferable. They also indicated that it would be appropriate to restrict the amount of medication used by patients, limiting administration to 10% of the body surface area.

Clinician Group Input

Two clinician groups, comprising a total of 12 clinicians, provided input for this review: the Canadian Dermatology Association in collaboration with the Dermatologist Association of Ontario and the Dermatology Association of Saskatchewan (8 clinicians contributed to the input), and the Southwestern Ontario Dermatologists Group (4 clinicians contributed to the input).

Both groups agreed that, aside from ruxolitinib topical cream, no effective treatments for vitiligo are available in Canada. Current options include off-label use of corticosteroids, calcineurin inhibitors, and

narrowband UVB phototherapy, with systemic drugs and surgical grafting considered for more severe cases. Despite these treatments, vitiligo remains difficult to manage, with no cure and a high recurrence rate. The core treatment goals, as outlined by both groups, are to achieve visible repigmentation and halt disease progression, although attaining high levels of repigmentation remains challenging. The Canadian Dermatology Association highlighted the need for maintenance therapy to prevent relapse, while the Southwestern Ontario group suggested reducing stress on melanocytes to improve outcomes.

Both groups described 1.5% ruxolitinib topical cream as a transformative first-line therapy for vitiligo in patients aged 12 years and older. It targets the underlying disease mechanisms and has a favourable safety profile, allowing for prolonged maintenance use.

Treatment response for vitiligo is typically assessed based on repigmentation and disease progression. The primary outcome measures include the VASI, Investigator Global Assessment, VNS, and global impression scales.

Regarding treatment discontinuation, the Canadian Dermatology Association experts suggested stopping treatment after 6 months without repigmentation, while others recommended extending it to 18 months. The Southwestern Ontario group stressed that, after 1 year, an inadequate response based on patient-reported outcomes, physician assessments, disease progression, and adverse events should lead to discontinuation. Both groups agreed that vitiligo can be diagnosed by any physician, but dermatologists are ideally suited for diagnosis, treatment selection, and monitoring to ensure the best long-term outcomes.

Drug Program Input

Input was obtained from the drug programs that participate in the reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a recommendation for ruxolitinib topical cream:

- considerations for initiation of therapy
- considerations for prescribing of therapy
- care provision issues.

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Clinical Evidence

Systematic Review

Description of Studies

The TRuE-V1 (n = 330) and TRuE-V2 (n = 344) studies were phase III, multicentre, double-blind, vehicle-controlled RCTs identically designed to evaluate the efficacy and safety of 1.5% ruxolitinib topical cream,

applied twice daily to depigmented areas, for the treatment of nonsegmental vitiligo in adult and pediatric patients aged 12 years and older.

The primary outcome was the proportion of patients achieving an improvement of F-VASI75 at week 24. Additional levels of VASI thresholds were assessed as secondary end points in the trials. The VASI score evaluates the objective response to treatment, capturing the overall surface area of vitiligo involvement and the degree of repigmentation. However, the VASI score is a validated instrument that is not routinely used in clinical practice. Evidence in the literature suggests that a reduction of F-VASI75, and a reduction of 50% in the baseline T-VASI score, would likely result in a clinically meaningful change in repigmentation for patients with nonsegmental vitiligo. Patient-reported noticeability was assessed as a key secondary outcome using the VNS, a validated instrument for which scores of 4 (a lot less noticeable) or 5 (no longer noticeable) have been used as the minimal clinically important difference (MCID).

HRQoL was assessed in the studies using the DLQI and the CDLQI as other secondary outcomes, while the VitiQoL as exploratory outcome. The DLQI is a 10-item questionnaire designed to assess the impact of skin conditions on an adult's life, while the CDLQI is a similar questionnaire for children. The instrument covers domains such as symptoms, daily activities, relationships, work or school, and emotional well-being. The maximum total DLQI-CDLQI score is 30, with higher scores denoting a greater negative impact on quality of life. The VitiQoL is a specialized, patient-reported HRQoL assessment tool designed to measure the impact of vitiligo on a patient’s life. The total score can range from 0 to a maximum of 90, where higher scores denote a greater negative impact on quality of life.

Efficacy Results

Vitiligo Area Scoring Index

For the primary outcome, which was the proportion of patients achieving an improvement of F-VASI75 score, treatment with ruxolitinib topical cream was associated with a between-group difference in response rate of 22.3% (95% CI, 14.2% to 30.5%; P < 0.0001) in the TruE-V1 trial and 19.5% (95% CI, 10.5% to 28.4%; P = 0.0004) in the TruE-V2 trial over 24 weeks versus vehicle cream. In absolute effects, 60 patients (30.8%) who applied ruxolitinib topical cream achieved the outcome compared to 7 patients (7.8%) who applied vehicle cream in the TRuE-V1 trial. In the TRuE-V2 trial, 62 patients (31.2%) who applied ruxolitinib topical cream achieved the outcome compared to 11 patients (11.2%) who applied vehicle cream.

F-VASI75 has been reported in the literature as a threshold for treatment success based on perceptions of patients with vitiligo and dermatologists; however, no MCID for between-group differences were reported. The presence of an important effect was informed by the clinical expert consulted for this review. The difference between treatments was considered clinically meaningful in terms of repigmentation, but the clinical experts noted that the overall impact was difficult to assess. In clinical practice, partial repigmentation measured by, for example, the F-VASI score, may not necessarily be associated with a meaningful change for patients, as long as the disease remains visible. The minimal clinically important objective response can be highly variable across patients depending on how the disease impacts their daily lives. Therefore, evidence of moderate certainty suggests that treatment with ruxolitinib topical cream likely results in a clinically important increase in the proportions of patients achieving F-VASI75 compared to vehicle cream.

Topical treatment with ruxolitinib was also likely associated with a clinically important increase in the proportions of patients achieving other thresholds of VASI scores, such as the F-VASI90, over 24 weeks compared to vehicle cream. A total of 31 patients (15.9%) who applied ruxolitinib topical cream in the TRuE-V1 trial achieved F-VASI90 compared with 2 patients (2.2%) who applied vehicle cream; in the TRuE-V2 trial, 33 patients (16.6%) who applied ruxolitinib topical cream achieved the outcome compared with 1 patient (1.0%) who applied vehicle cream. The between-group difference in response rate was 13.2% (95% CI, 7.5% to 18.8%; P = 0.0038) in the TruE-V1 trial and 15.0% (95% CI, 9.3% to 20.7%; P = 0.0065) in the TruE-V2 trial. As previously mentioned, results for improvement from baseline of at least 50% in total body VASI scores were consistent. However, results for the more conservative threshold of at least 75% in total body VASI (T-VASI75) were deemed unlikely to constitute a meaningful change for patients according to the clinical experts.

Vitiligo Noticeability Scale

Patient-reported noticeability, assessed using the VNS, suggest that treatment with ruxolitinib topical cream likely results in a clinically important increase in the proportions of patients achieving a VNS of “4- A lot less noticeable” or “5-No longer noticeable” over 24 weeks compared to vehicle cream. Among patients who applied ruxolitinib topical cream, the proportions of those who responded were 25% in the TRuE-V1 trial and 21% in the TRuE-V2 trial, resulting in a between-group difference in response rate versus vehicle cream of 21.2% (95% CI, 14.3% to 28.1%; P = 0.0002) in the TruE-V1 trial and 15.5% (95% CI, 8.5% to 22.6%; P = 0.0013) in the TruE-V2 trial. Uncertainty was introduced by the absence of a reported MCID for differences between treatments in the literature, and as was the case for the VASI, a less noticeable condition may not necessarily be associated with a meaningful change for patients as long as the disease remains visible.

Health-Related Quality of Life

The clinical experts consulted for this review indicated that the treatment of vitiligo is targeted at improving current and future HRQoL rather than focusing on surface area of involvement and degree of repigmentation. This was also consistent with patient and clinician input, all of whom highlighted the importance of improving the psychosocial impact of the disease on quality of life. In the trials, HRQoL was measured using DLQI or CDLQI as other secondary outcomes and VitiQoL as exploratory outcome. Statistical testing was not adjusted for multiplicity and results should be considered as supportive evidence.

Results suggest that treatment with ruxolitinib topical cream may not result in a clinically important improvement in HRQoL, as measured with the VitiQoL over 24 weeks compared to vehicle cream. The mean between-group difference in change from baseline through 24 weeks in VitiQoL was −0.28 (95% CI, −4.51 to 3.95; P = 0.8976) in the TRuE-V1 trial, and −3.52 (95% CI, −7.60 to 0.57; P = 0.0915) in the TRuE-V2 trial. Consistently, results for HRQoL assessed using the DLQI and CDLQI were not deemed clinically meaningful. There is currently no MCID established for these instruments in patients with vitiligo based on the literature; therefore, the absence of an important effect was informed by the clinical expert consulted for this review. This indicates that despite observing an objective response to ruxolitinib topical cream in terms of overall surface area of involvement and degree of repigmentation making the condition less noticeable in

some patients, ruxolitinib topical cream did not improve the impact of the disease on HRQoL in the overall study population. Findings from post-hoc analyses in patients who received ruxolitinib topical cream, which compared the change in VitiQoL and DLQI from baseline to week 24 among patients who achieved various levels of F-VASI and those who did not, suggest that patients may observe improvement in their HRQoL with at least an F-VASI75 improvement; however, whether the improvement in HRQoL is clinical meaningful is uncertain. In addition, interpretation of these findings is limited by the post-hoc nature of the analyses.

Harms Results

A relatively high proportion of patients receiving ruxolitinib topical cream in the TRuE-V1 (46%) and TRuE-V2 (50%) studies experienced at least 1 adverse event (AE). The most common treatment-emergent AEs (TEAEs) were related to application site reactions (i.e., acne, pruritus, rash, and exfoliation) and infections. Serious AEs (SAEs) were uncommon. Topical treatment with ruxolitinib appeared to be well tolerated, as there were few discontinuations due to AEs. No death was reported throughout the trials' duration. Findings for the treatment extensions in the TRuE-V1 and TRuE-V2 studies, as well as from the TRuE-V LTE trial, were consistent with those from the pivotal trials. Overall, the clinical expert indicated that the harms profile of ruxolitinib topical cream did not raise any new safety signal, or any particular safety concern. However, as with most clinical trials, the studies were not powered to detect infrequent AEs, or those with a lag time.

Critical Appraisal

Interpretation of the findings is limited by the fact that the key efficacy evidence for ruxolitinib topical cream is focused on objective response to treatment. Because vitiligo can range from being barely perceptible to cosmetically distressing, and because different individuals are likely to have different priorities and objectives when assessing the magnitude of response to treatment, the clinical meaningfulness of objective response is uncertain. As the TRuE-V1 and TRuE-V2 studies included a vehicle control group, there is no direct evidence comparing ruxolitinib topical cream to other currently used therapies for vitiligo. Therefore, the comparative effectiveness and safety of ruxolitinib topical cream relative to other treatment options available, which were considered overall well accepted and routinely prescribed according to the clinical experts, are unknown.

The TRuE-V1 and TRuE-V2 studies may be considered generalizable to a selected sample of individuals living in Canada with vitiligo. Most patients included in the studies were white and had a lighter skin tone. However, vitiligo is particularly visible in patients with darker skin tones and as such, is likely to present with an increased impact on quality of life in these patients. As only a few patients with darker skin tones were included in the studies, the effect of ruxolitinib topical cream on these patients is uncertain. In addition, there is a possibility that the trial population may not be representative of patients whose condition interferes substantially with their daily life, considering the lower-than-expected use of prior therapies despite a long-lasting disease duration, as well as the relatively low level of HRQoL impairment at baseline. There were only a few adolescents enrolled in the trials; therefore, there is limited data to interpret in this younger age group. The follow-up duration of 24 weeks was considered relatively short, as the disease generally improves over a longer period of time. Though considered sufficient by the clinical experts to capture improvements in objective response, treatment with ruxolitinib topical cream is likely to last in the long-term and evidence beyond the studies follow-up duration is limited.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group:

- Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.
- When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.
- For the GRADE assessments, findings from the TRuE-V1 and TRuE-V2 studies were considered together and summarized narratively per outcome because these studies were similar in population, interventions, design, and outcome measures.
- The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:
  - improvements in F-VASI
  - patient-reported decrease in noticeability (VNS)
  - HRQoL (VitiQoL)
  - harms.

Table 1 presents the GRADE summary of findings for ruxolitinib topical cream versus vehicle cream.

Table 1: Summary of Findings for Ruxolitinib Topical Cream Versus Vehicle Cream for Patients With Vitiligo

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Vehicle cream	Ruxolitinib topical cream	Difference		
F-VASI							
Proportions of patients achieving F-VASI75 Follow-up: 24 weeks	N = 394, ruxolitinib topical cream N = 188, vehicle cream (2 RCTs)	TRuE-V1 trial: OR = 5.28; 95% CI, 2.341 to 11.903 TRuE-V2 trial: OR = 3.45; 95% CI, 1.737 to 6.835	TRuE-V1 trial: 74 per 1,000 patients TRuE-V2 trial: 114 per 1,000 patients	TRuE-V1 trial: 298 per 1,000 patients TRuE-V2 trial: 309 per 1,000 patients	TRuE-V1 trial: 223 more per 1,000 patients 95% CI, 142 to 305 TRuE-V2 trial: 195 more per 1,000 patients 95% CI, 105 to 284	Moderate[a]	Ruxolitinib topical cream likely results in a clinically important increase in the proportions of patients achieving F-VASI75 over 24 weeks compared to vehicle cream.
Proportions of patients achieving F-VASI90 Follow-up: 24 weeks	N = 394, ruxolitinib topical cream N = 188, vehicle cream (2 RCTs)	TRuE-V1 trial: OR = 8.49; 95% CI, 1.997 to 36.048 TRuE-V2 trial: OR = 15.29; 95% CI, 2.150 to 108.739	TRuE-V1 trial: 22 per 1,000 patients TRuE-V2 trial: 13 per 1,000 patients	TRuE-V1 trial: 153 per 1,000 patients TRuE-V2 trial: 163 per 1,000 patients	TRuE-V1 trial: 132 more per 1,000 patients 95% CI, 75 to 188 TRuE-V2 trial: 150 more per 1,000 patients 95% CI, 93 to 207	Moderate[a]	Ruxolitinib topical cream likely results in a clinically important increase in the proportions of patients achieving F-VASI90 over 24 weeks compared to vehicle cream.
VNS							
Proportion of patients achieving a VNS of “4- A lot less noticeable” or “5-No longer	N = 394, ruxolitinib topical cream N = 188,	TRuE-V1 trial: OR = 9.53; 95% CI,	TRuE-V1 trial: 33 per 1,000 patients TRuE-V2 trial:	TRuE-V1 trial: 245 per 1,000 patients TRuE-V2 trial:	TRuE-V1 trial: 212 more per 1,000 patients 95% CI, 143 to 281	Moderate[b]	Ruxolitinib topical cream likely results in a clinically important increase in the proportions of patients achieving a VNS of “4- A lot less noticeable” or “5-No

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Vehicle cream	Ruxolitinib topical cream	Difference		
noticeable” Follow-up: 24 weeks	vehicle cream (2 RCTs)	2.900 to 31.290 TRuE-V2 trial: OR = 4.86; 95% CI, 1.851 to 12.755	49 per 1,000 patients	205 per 1,000 patients	TRuE-V2 trial: 155 more per 1,000 patients 95% CI, 85 to 226		longer noticeable” over 24 weeks compared to vehicle cream.
HRQoL							
Change from baseline in VitiQoL Follow-up: 24 weeks	N = 394, ruxolitinib topical cream N = 188, vehicle cream (2 RCTs)	NA	TRuE-V1 trial: LSM (SE) = −6.18 (1.77) TRuE-V2 trial: LSM (SE) = −2.66 (1.70)	TRuE-V1 trial: LSM (SE) = −6.45 (1.21) TRuE-V2 trial: LSM (SE) = −6.18 (1.20)	TRuE-V1 trial: LSM difference = −0.28; 95% CI, −4.51 to 3.95 TRuE-V2 trial: LSM difference = −3.52; 95% CI, −7.60 to 0.57	Low[c]	Ruxolitinib topical cream may not result in a clinically important improvement in HRQoL as measured with the VitiQoL over 24 weeks compared to vehicle cream.
Harms							
Patients with SAEs Follow-up: 24 weeks	N = 449, ruxolitinib topical cream N = 224, vehicle cream (2 RCTs)	NR	TRuE-V1 trial: 9 per 1,000 patients TRuE-V2 trial: 0 per 1,000 patients	TRuE-V1 trial: 27 per 1,000 patients TRuE-V2 trial: 9 per 1,000 patients	TRuE-V1 trial: 18 more per 1,000 patients TRuE-V2 trial: 9 more per 1,000 patients	Moderate[d]	Ruxolitinib topical cream likely did not result in a clinically important increase in SAEs over 24 weeks compared to vehicle cream.

CI = confidence interval; F-VASI = Facial Vitiligo Area Scoring Index; F-VASI75 = a ≥ 75% improvement on the Facial Vitiligo Area Scoring Index; F-VASI90 = a ≥ 90% improvement on the Facial Vitiligo Area Scoring Index; HRQoL = health-related quality of life; LSM = least square means; MCID = minimal clinically important difference; NA = not applicable; NR = not reported; OR = odds ratio; RCT = randomized controlled trial; SAEs = serious adverse events; SE = standard error; VitiQoL = Vitiligo-Specific Quality of Life; VNS = Vitiligo Noticeability Scale.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a]VASI: Rated down 1 level for imprecision, due to uncertainty surrounding the outcome measure and MCID. The F-VASI score is not used in clinical practice; the instrument was developed specifically for clinical trial assessment. Validation studies were identified from the literature. While F-VASI75 has been suggested as a threshold for treatment success based on perceptions of patients with vitiligo and dermatologists, no MCID for between-group differences were reported. The presence of an important effect was informed by the clinical expert consulted for this review, but was deemed difficult to assess, as partial repigmentation measured by the F-VASI score may not necessarily be associated with a meaningful change for patients as long as the disease remains visible.

[b]VNS: Rated down 1 level for imprecision, due to uncertainty surrounding the outcome measure and MCID. While the VNS is a validated instrument, for which scores of 4 (a lot less noticeable) or 5 (no longer noticeable) have been used as the MCID, no MCID for between-group differences were reported. The presence of an important effect was informed by the clinical expert consulted for this review, but was deemed difficult to assess, as a less noticeable condition may not necessarily be associated with a meaningful change for patients as long as the disease remains visible.

[c]HRQoL: Rated down 2 levels for imprecision. The VitiQoL was assessed as an exploratory outcome. Statistical testing for the VitiQoL was not adjusted for multiplicity in the trial and should be considered as supportive evidence. In addition, there is currently no MCID established for this instrument in the literature; the absence of an important effect was informed by the clinical expert consulted for this review. The uncertainty surrounding the MCID precluded definite judgment on whether the bounds of the CI suggest a meaningful effect on either side of the null.

[d]Harms: Rated down 1 level for imprecision, because of the low number of events in the study.

Sources: Incyte Corporation, 2021

Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

TRuE-V1 and TRuE-V2 Open-Label Treatment Extension Studies

Description of Studies

In the pivotal TRuE-V1 and TRuE-V2 RCTs, the double-blind controlled period was followed by a 28-week open-label treatment extension. Patients initially randomized to vehicle cream crossed over to ruxolitinib topical cream, while patients initially randomized to ruxolitinib topical cream received an additional 28 weeks of treatment with an active drug, as long as they completed the week 24 assessments with no safety concerns. During the treatment extension period, patients continued to treat depigmented areas identified for treatment at baseline even if the area fully repigmented.

Efficacy Results

The proportions of patients who achieved all of the predefined thresholds of reduction in the VASI score (i.e., ≥ 25% improvement on the F-VASI [F-VASI25], ≥ 50% improvement on the F-VASI [F-VASI50], F-VASI75, F-VASI90, and T-VASI75) were numerically higher in all treatment arms when compared to the corresponding proportions during the double-blind period. However, in the treatment extension period, no statistical analysis was reported to assess whether the change from week 24 to week 52 was statistically significant, or to assess the magnitude of the between-group difference. Similar results were obtained in the proportions of patients who achieved a VNS of “4- A lot less noticeable” or “5-No longer noticeable.” Results for HRQoL, assessed using the DLQI-CDLQI and the VitiQoL, suggest that within-group changes observed from baseline to week 52 were small and not clinically meaningful according to the clinical experts.

Harms Results

The proportions of patients who experienced at least 1 AE during the treatment extension ranged from 33.7% to 41.2% across treatment arms in the 2 trials. Few patients experienced SAEs. One patient discontinued due to application site eczema. No deaths were reported during the treatment extension.

Critical Appraisal

Conclusions regarding the efficacy and safety of ruxolitinib topical cream in the longer-term are noncomparative due to the single-arm nature of the TRuE-V1 and TRuE-V2 open-label treatment extensions. The same limitations pertaining to the uncertain clinical impact of the F-VASI score and selected patient population, which were highlighted for the double-blind controlled period of the studies, also apply to the extension period.

TRuE-V Long-Term Extension Trial

Description of Studies

The TRuE-V LTE is a phase III, double-blind, vehicle-controlled, randomized withdrawal trial designed to assess the long-term efficacy and safety of ruxolitinib topical cream in patients with vitiligo. It follows the TRuE-V1 and TRuE-V2 studies and includes 2 cohorts: cohort A evaluates the duration of response after withdrawing ruxolitinib topical cream, and cohort B assesses the maintenance of response with continued treatment. The LTE study had a duration of 52 weeks, followed by a 30-day safety follow-up.

Cohort A followed a randomized withdrawal design, providing data on the duration of response after discontinuation and the maintenance of response with continued treatment. Participants who achieved complete or near-complete facial repigmentation (F-VASI90 or higher) at week 52 in either of the TRuE-V1 or TRuE-V2 studies were assigned to this cohort. They were randomized in a 1:1 ratio to either continue with 1.5% ruxolitinib topical cream or switch to vehicle cream during the LTE. Participants in cohort A who experienced disease relapse (defined as less than F-VASI75) received open-label ruxolitinib topical cream as rescue treatment until week 104 or the end of the trial. Cohort B included participants who did not achieve F-VASI90 or higher at week 52 in the parent studies. These participants continued treatment with 1.5% ruxolitinib topical cream for the entire LTE period. Both clinician groups remained blinded in cohort A until after the primary analysis (week 104), while the treatment in cohort B was open-label.

The primary outcome of the TRuE-V LTE study was the time to relapse in cohort A, defined as a loss of F-VASI75 response. The key secondary outcome was the time to maintain F-VASI90. Additional secondary outcomes included the proportion of patients achieving F-VASI50, F-VASI75, F-VASI90, a VNS score of “4 – A lot less noticeable” or “5 – No longer noticeable,” T-VASI75, and the time to regain F-VASI90 and F-VASI75 following relapse. Other secondary outcomes included changes in DLQI, CDLQI, and VitiQoL from week 52, and time to regain F-VASI75 and F-VASI90 following relapse. Safety outcomes were consistent with the parent studies, TRuE-V1 and TRuE-V2.

Statistical analyses were exploratory with no alpha control, and CIs were at 95%. Data from participants with noncompliance or incorrect randomization were excluded. Primary and secondary analyses used the intent to treat in LTE population, and time-to-event data were analyzed using Kaplan-Meier and Cox models. Relapse incidence, subgroup analyses, and safety outcomes were summarized descriptively.

Efficacy Results

Primary End Point: Time to Relapse (Less Than F-VASI75)

In cohort A, a lower proportion of patients using ruxolitinib topical cream experienced disease relapse (14.5%) compared to the vehicle cream group (28.6%). The risk of relapse was lower in the ruxolitinib topical cream group (hazard ratio [HR] = 0.422; 95% CI, 0.180 to 0.990; P = 0.0414).

Key Secondary End Point: Time to Maintain F-VASI90 Response

The majority of patients who achieved complete or near-complete face repigmentation in cohort A in the parent studies maintained this level of repigmentation with continued ruxolitinib topical cream application beyond week 52. Of the cohort of patients who received vehicle cream, 55.4% lost their F-VASI90 response. The median time to loss of F-VASI90 in the group of patients who received vehicle cream was 195.0 days (95% CI, 113.0 to 372.0). Of the cohort of patients who applied ruxolitinib topical cream in the double-blind period, then continued treatment with ruxolitinib topical cream and achieved an F-VASI90 response, 23.6% lost their F-VASI90 response. The median time to loss of F-VASI90 response in this cohort was not evaluable. The risk of losing F-VASI90 response was lower for patients who continued to use ruxolitinib topical cream compared with patients who applied vehicle cream (HR = 0.316; 95% CI, 0.165 to 0.606; P = 0.0003).

Additional Secondary and Exploratory End Points

In cohort B, 86.4%, 66.1%, and 33.9% achieved F-VASI50, F-VASI75, and F-VASI90, respectively, with ruxolitinib topical cream at week 104, compared to 69.9%, 47.3%, and 28.0% in those who switched to ruxolitinib topical cream.

In cohort A, the proportion of participants continuing with 1.5% ruxolitinib topical cream who achieved T-VASI75 was 42.1% at week 52 and 55.3% at week 104. Among participants using vehicle cream, 38.6% achieved T-VASI75 at week 52 and 39.1% at week 104.

In cohort B, for those who continued using 1.5% ruxolitinib topical cream, at week 52, 12.2% achieved T-VASI75 and by week 104, 30.5% achieved this threshold. Among participants initially randomized to vehicle cream who switched to 1.5% ruxolitinib topical cream during the TRuE-V LTE study, 3.4% achieved T-VASI75 at week 52 and 18.3% at week 104.

In cohort A, the proportion of participants receiving blinded treatment who reported a VNS score of 4 (a lot less noticeable) or 5 (no longer noticeable) remained generally stable compared to week 52. Among participants receiving 1.5% ruxolitinib topical cream, 50.0% reported a score of 4 or 5 at week 104, compared to 42.1% at week 52. Among participants receiving vehicle cream, 56.5% reported a score of 4 or 5 at week 104, compared to 49.1% at week 52.

In cohort B, the proportion of participants achieving a VNS score of 4 or 5 for those who continued using 1.5% ruxolitinib topical cream remained generally stable (43.3% at week 104 versus 35.3% at week 52). The VNS score of 4 or 5 increased from week 52 to week 104 for those initially randomized to vehicle cream who switched to 1.5% ruxolitinib topical cream during the TRuE-V LTE study (30.1% at week 104 versus 11.9% at week 52).

As for quality of life, there were no significant changes in the DLQI scores for cohort A, while cohort B showed slight improvements in CDLQI scores, regardless of whether patients continued or switched to ruxolitinib topical cream. There were also improvements in VitiQoL scores for cohort B, but no clear pattern was observed in cohort A.

In exploratory end points, the median time to regain F-VASI75 was 85.0 days for patients who experienced disease relapse and switched to open-label rescue treatment, whereas 62.5% of patients using ruxolitinib topical cream regained F-VASI75, with a median time of 205.0 days.

Harms Results

The overall incidences of TEAEs and application site reactions for cohort A were higher among patients who applied ruxolitinib topical cream (55.2% and 6.9%, respectively) compared with the vehicle cream treatment group (36.2% and 3.4%, respectively). One participant treated with 1.5% ruxolitinib topical cream in cohort A (1.7%) had a serious TEAE, and no participant had a TEAE with a fatal outcome or a TEAE leading to study drug discontinuation.

The overall incidences of TEAEs and application site reactions in cohort B were 50.9% and 8.5%, respectively, among patients who continued receiving 1.5% ruxolitinib topical cream, compared to 50.0% and

5.1% for participants initially randomized to vehicle cream who switched to 1.5% ruxolitinib topical cream during the LTE study. The incidence of serious TEAEs was 3.1% in patients treated with 1.5% ruxolitinib topical cream and 3.4% in those initially treated with vehicle cream. The only TEAE leading to study drug discontinuation in cohort B was [redacted] accident in 1 participant that the investigator assessed as unlikely to be related to the study drug.

Critical Appraisal

Internal Validity

Cohort A of the TRuE-V-LTE trial employed appropriate random allocation using an interactive response technology system. Allocation concealment was ensured, and both patients and investigators remained blinded to treatment assignment until the study's conclusion. Baseline characteristics between groups were well balanced, supporting the validity of comparisons. The single-arm design of cohort B introduces potential bias in assessing efficacy outcomes, as both participants and investigators were aware of the treatment being administered. This lack of blinding could lead to detection bias. Additionally, the single-arm nature of the study inherently carries a high risk of bias, which may influence the assessment of subjective treatment outcomes. No conclusion can be made on the comparative efficacy and safety.

Participants selected for the TRuE-V-LTE trial represented a subsample of the parent trials, consisting of those who completed the parent trials without safety concerns following ruxolitinib topical cream use. This selection process may have introduced a risk of selection bias, as it could limit the representativeness of the wider patient population in the study.

The TRuE-V-LTE trial had a high dropout rate, and unlike the pivotal trials, imputation methods to address missing data were not employed, increasing the risk of attrition bias. The substantial number of missing participants may have skewed the results and impacted the interpretation of the findings.

External Validity

The TRuE-V LTE trial consisted of patients who took part in the pivotal studies (TRuE-V1 and TRuE-V2 studies); it is reasonable to expect that the same strengths and limitations related to generalizability apply to the extension studies. While the studies were conducted in centres in Europe and North America, the patient population of those studies may be reflective of the population in Canada, and the clinical evidence is generalizable to the setting in Canada.

Indirect Comparisons

As the TRuE-V1 and TRuE-V2 studies included a vehicle control group, there is no direct evidence comparing ruxolitinib topical cream to the currently used off-label therapies for the treatment of vitiligo that would inform the reimbursement question. In addition, no indirect evidence was submitted by the sponsor. Though potential studies were identified to perform an ITC, the sponsor rated the feasibility of conducting robust evidence synthesis as low, limiting the feasibility of an ITC. As a result, the comparative efficacy and safety of ruxolitinib topical cream compared with any off-label therapies for the treatment of vitiligo is unknown.

Studies Addressing Gaps in the Evidence From the Systematic Review

No studies addressing gaps were submitted by the sponsor.

Economic Evidence

Cost and Cost-Effectiveness

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Patients 12 years of age and older with NSV
Treatment	Ruxolitinib topical cream
Dose regimen	Applied twice daily to affected skin areas (maximum of 10% of BSA for each application) for 24 weeks and as needed thereafter
Submitted price	$1,075.97 per 100 g tube
Submitted treatment cost	$1,156.88 per 28-day cycle or $15,091 per year
Comparator	No active treatment (i.e., vehicle cream)[a]
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (61 years)
Key data sources	• Comparative clinical efficacy at week 24 and safety were derived from data pooled from the double-blinded phase of the TRuE-V1 and TRuE-V2 trials. • Long-term clinical efficacy of ruxolitinib topical cream was obtained from the open-label extension phase of the TRuE-V1 and TRuE-V2 trials at week 52 and from the TRuE-V LTE study at week 104. Because there was no comparative clinical data beyond week 24, the relative effects observed at week 24 were applied to vehicle cream at weeks 52 and 104.
Key limitations	• The sponsor's base case compared ruxolitinib topical cream to no active treatment, which is not a relevant comparator for decision-making. Clinical expert input received by CDA-AMC for this review noted that there are multiple alternative treatments such as topical corticosteroids, topical calcineurin inhibitors, and phototherapy used to manage NSV in clinical practice; however, these treatments were not included as comparators by the sponsor. • The model is structured according to change in F-VASI scores although its appropriateness is uncertain. According to clinical expert input received, F-VASI is not used in clinical practice to guide treatment decisions and does not capture all patient-important outcomes relating to treatment. • TRuE-V1 and TRuE-V2 trials included few patients from populations that were considered to have the greatest unmet needs, such as patients with a pronounced contrast between depigmented and unaffected skin, and patients whose condition substantially interferes with their daily lives. The generalizability of the effects of ruxolitinib topical cream on these patients is therefore uncertain. As such, the cost-effectiveness of ruxolitinib topical cream may not be representative of its use in patient populations in whom ruxolitinib topical cream is most likely to be used in clinical practice.

Component	Description
	• The sponsor's mapped health utilities lacked face validity. Both the baseline and patients who responded utility values were higher than the general population in Canada. The sponsor also assumed that patients who did not respond experienced a persistent decrease in health utility that is lower than their baseline values. • The sponsor adopted a mean daily dose of [redacted] for ruxolitinib topical cream; however, the daily dose used in the TRuE-V1 and TRuE-V2 trials was much higher. The mean daily dose of ruxolitinib topical cream ranged from [redacted] to [redacted] per day during the double-blind controlled period of the trials (24-week duration), and from [redacted] to [redacted] per day in the extension period of the trials (28-week duration). The sponsor's estimate is an underestimation of the daily dose and the treatment cost of ruxolitinib topical cream.
CDA-AMC reanalysis results	• CDA-AMC undertook reanalyses that addressed some of the identified limitations, including assuming utilities for patients who did not respond would be identical to baseline utilities and adopting a higher daily dose for ruxolitinib topical cream. CDA-AMC was unable to address other key limitations, including the exclusion of relevant comparators, concerns with the appropriateness of F-VASI scores, and the overall external validity of the pivotal trials. • In the CDA-AMC base case, ruxolitinib topical cream is associated with an ICER of $535,419 per QALY gained compared with no active treatment (incremental costs = $39,038; incremental QALYs = 0.07). A price reduction of approximately 90% is required for ruxolitinib topical cream (from $1,076 to $108 per 100 g tube) to be considered cost-effective compared to no active treatment at a WTP threshold of $50,000 per QALY gained.

BSA = body surface area; F-VASI = Facial Vitiligo Area and Severity Index; ICER = incremental cost-effectiveness ratio; LTE = long-term extension; LY = life-year; NSV = nonsegmental vitiligo; QALY = quality-adjusted life-year; WTP = willingness to pay.

[a]In the base case, the sponsor compared ruxolitinib topical cream to vehicle cream (from the TRuE-V1 and TRuE-V2 trials), which contained no active ingredient.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis: the proportion of patients with nonsegmental vitiligo seeking care was underestimated; clinical experts anticipated a higher uptake of ruxolitinib topical cream than the sponsor's estimate, suggesting that the market share of ruxolitinib topical cream may have been underestimated; the displacement of comparators by ruxolitinib topical cream was uncertain; treatment cost of ruxolitinib topical cream was underestimated because the modelled daily dose was much lower compared with observations from the TRuE-V trials; the use of the compliance rate to estimate actual drug costs underestimated drug costs; and relevant comparators (i.e., topical calcineurin inhibitors, phototherapy and combination therapy) were excluded.

CDA-AMC reanalysis included increasing the proportion of patients with nonsegmental vitiligo seeking care, increasing the market share of ruxolitinib topical cream, adjusting the market capture of ruxolitinib topical cream to reflect expert feedback, and adopting a higher daily dose and assuming perfect compliance for all drugs. Based on the CDA-AMC base case, the 3-year budget impact was expected to be $1,833,254,114 (year 1 = $438,355,337; year 2 = $606,815,718; year 3 = $788,083,059) should the public drug plans reimburse ruxolitinib topical cream for the topical treatment of patients aged 12 years and older with nonsegmental vitiligo. CDA-AMC was unable to address the exclusion of relevant comparators, although given the differences between treatment costs, its inclusion is only expected to have a small impact on lowering the budget impact. The estimated budget impact was most sensitive to the uncertainties in market share assumptions for ruxolitinib topical cream.

Request for Reconsideration

The sponsor filed a request for reconsideration of the draft recommendation for ruxolitinib topical treatment of nonsegmental vitiligo in adult and pediatric patients aged 12 years and older. In their request, the sponsor identified the following issues:

- The sponsor stated that primary treatment goal in nonsegmental vitiligo is repigmentation.
- The sponsor is of the view that that the unmet need was not fully recognized.
- The sponsor is of the view that VNS and repigmentation should be considered when evaluating clinical value and HRQoL.
- The sponsor stated that it is not feasible to conduct ITCs against other treatments.
- The sponsor is of the view that efficacy is consistent across skin types (according to the Fitzpatrick Scale skin type classification).

In the meeting to discuss the sponsor's request for reconsideration, CDEC considered the following information:

- information from the initial submission related to the issues identified by the sponsor
- feedback from 2 clinical specialists with expertise in diagnosing and treating patients with nonsegmental vitiligo
- feedback on the draft recommendation from 1 patient group, the Canadian Skin Patient Alliance
- feedback on the draft recommendation from 6 clinician groups: North York Dermatology Clinic; Vitiligo Treatment and Research Centre at the University of British Columbia and Vancouver General Hospital; Canadian Dermatology Association and Dermatology Association of Ontario; Southwestern Ontario Dermatologists Group; Diverse Skin Types and Pigmentation Disorders Clinic at the Women's College Hospital; and the Atlantic Group of Dermatologists
- feedback on the draft recommendation from the public drug plans that participate in the reimbursement review process.

All feedback received in response to the draft recommendation is available on the CDA-AMC website.

CDEC Information

Initial Meeting Date: March 26, 2025

Members of the Committee

Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice Chair), Dr. Sally Bean, Daryl Bell, Dan Dunsky, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed.

Regrets: Five expert committee members did not attend.

Conflicts of interest: None

Reconsideration Meeting Date: July 24, 2025

Members of the Committee

Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice Chair), Dr. Sally Bean, Daryl Bell, Dan Dunsky, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed.

Regrets: Seven expert committee members did not attend.

Conflicts of interest: None

Canada's Drug Agency
L'Agence des médicaments du Canada
Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

ISSN: 2563-6596

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.