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

Reimbursement Recommendation

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(Draft)

Ruxolitinib (Opzelura)

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

Sponsor: Incyte Biosciences Canada Corporation

Recommendation: Do Not Reimburse

Version: 1.0
Publication Date: April 2025

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Recommendation

The CDA-AMC Canadian Drug Expert Committee (CDEC) recommends that ruxolitinib not be reimbursed for topical treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older.

Rationale for the Recommendation

Two phase 3, multicenter, double-blind (DB) 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 12 years of age and older, suggest that treatment with ruxolitinib likely results in a clinically important improvement in the Facial Vitiligo Area Scoring Index score (F-VASI) score compared with vehicle, indicating better repigmentation. Among patients who applied ruxolitinib, the proportions of responders based on improvement of 75% in the facial VASI score (F-VASI75) 29.8% in TRuE-V1 and 30.9% in TRuE-V2, resulting in a between-group difference in response rate versus vehicle of 22.3% (95% CI; 14.2 to 30.5; p<0.0001) in TruE-V1 and 19.5% (95% CI; 10.5 to 28.4; p=0.0004) in TruE-V2 at week 24. Results for total body VASI improvements (T-VASI) 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 achieved the scores of 4 (a lot less noticeable) or 5 (no longer noticeable) versus patients who applied vehicle over 24 weeks; among patients who applied ruxolitinib, the proportions of responders was 25% in TRuE-V1 and 21% in TRuE-V2, resulting in a between-group difference in response rate versus vehicle of 21.2% (95% CI; 14.3 to 28.1; p=0.0002) in TruE-V1 and 15.5% (95% CI; 8.5 to 22.6; p=0.0013) in TruE-V2. However, the impact of vitiligo on daily life varies among individuals and objective response based on repigmentation should be considered alongside health-related quality of life (HRQoL) findings. Despite improving the appearance of vitiligo in some patients, ruxolitinib did not alleviate the negative impact of the disease on patients' lives in the overall study population as measured by HRQoL metrics. In addition, TRuE-V1 and TRuE-V2 included a vehicle control group, so there is no direct evidence comparing ruxolitinib 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 remain unknown.

CDEC acknowledged that nonsegmental vitiligo can profoundly impact patients, often leading to stigma and social isolation due to significant cultural implications. This effect is especially pronounced in individuals with a darker skin colour, 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 color 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 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 colour based on Fitzpatrick skin type, and many had conditions that did not substantially interfere with daily life, as indicated by the 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's effect on those with the greatest unmet needs.

Discussion Points

- **Unmet needs**: CDEC acknowledged that nonsegmental vitiligo can profoundly affect patients, especially those with darker skin color, 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 color who have not achieved satisfactory improvements with existing therapies. However, the effectiveness of ruxolitinib 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.

- **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 treatment with ruxolitinib would likely results in a clinically important increase in the proportions of patients achieving F-VASI75, F-VASI90, and VNS of “4- A lot less noticeable” or “5-No longer noticeable” over 24 weeks compared to vehicle, while ruxolitinib may not result in a clinically important improvement in HRQoL as measured with the VitiQoL over 24 weeks compared to vehicle.

- **Clinical meaningfulness of the results**: The difference between ruxolitinib and vehicle 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 non segmental 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. 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, and hence HRQoL is impacted as long as the disease is visible.

- **HRQoL**: HRQoL was measured using DLQI or CDLQI as other secondary outcomes and VitiQoL as exploratory outcome; as such, the studies were not designed to test for differences in HRQoL. Results did not suggest benefits from ruxolitinib. CDEC discussed that the differences between ruxolitinib and vehicle, 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 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 VASI score, such as disease site visibility, repigmentation heterogeneity, and cultural influences. 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.

- **Responders analysis**: Findings from post-hoc analyses in patients who received ruxolitinib, 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 a F-VASI75 may observe improvement in their HRQoL; 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.

- **Skin type and race**: CDEC discussed the subgroup analyses by skin type and race, which are relevant to vitiligo treatment. Although vitiligo affects all races and skin color types, it is more visible in individuals with darker colour of skin, impacting their quality of life more. However, few patients with darker skin color were included in the studies. Out of 661 patients in TRuE-V1 and TRuE-V2, 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 colour according to the Fitzpatrick Scale skin type, 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.

- **Long term efficacy**: The 24-week, DB controlled period for TRuE-V1 and TRuE-V2 was followed by a 28-week open-label extension, therefore totaling 52 weeks. The TRuE-V LTE study assessed long-term efficacy and safety over an additional 104 weeks. The median ruxolitinib exposure in TRuE-V LTE was 364 days. CDEC noted that findings were consistent with evidence from the DB duration, showing continued improvement in F-VASI and T-VASI scores over time. Ruxolitinib maintained repigmentation even after discontinuation in patients who achieved F-VASI90. Relapsed patients regained responses within 12 weeks of retreatment. 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 Canada's prevalence estimated between 0.5% and 1%. It is categorized into nonsegmental vitiligo (presenting as symmetrical patches), segmental vitiligo (affecting one side of the body), and mixed forms (displaying characteristics of both forms), with nonsegmental vitiligo being the most common which accounts for approximately 80% of vitiligo cases. It can also have an unpredictable progression, often starting before age 12 and peaking around age 30. 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 or from cultures 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% 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 ruxolitinib 1.5% cream applied twice daily to affected skin areas, covering up to a maximum of 10% of the body surface area (BSA) 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 healthcare provider is recommended.

Sources of Information Used by the Committee

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

- a review of two phase 3, multicenter, double-blind (DB) vehicle-controlled randomized controlled trials (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 12 years of age and older; and 3 long-term extension studies
- patients' perspectives gathered by one patient group, the Canadian Skin Patient Alliance (CSPA) in collaboration with Vitiligo Voices Canada (VVC)
- 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 two clinician groups, the Canadian Dermatology Association (CDA) 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

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

An input was submitted by the Canadian Skin Patient Alliance (CSPA) in collaboration with Vitiligo Voices Canada (VVC) regarding the current review of ruxolitinib 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, Yukon, Quebec, Nova Scotia, and New Brunswick. Respondents were predominantly white/Caucasian, and about half of them were aged 55 or older.

According to the input, Vitiligo's impact 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 condition's unpredictable nature. Severe mental health consequences, such as depression and suicidal thoughts, 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 of frequent clinic visits. The patients 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 NB-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.

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 health-related quality of life (HRQoL), as the visibility of vitiligo can still negatively affect patients' HRQoL.

The clinical experts emphasized that the choice of treatment will be based on the impact that the disease has on patients' 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. According to the clinical experts however, approximately half of the 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 non-segmental vitiligo, or that it could be reserved as a second-line option for patient refractory or intolerant to current mainstay treatments. They noted that the absence of comparative

evidence against the agents currently used in clinical practice was considered a substantial limitation. The experts also highlighted that the place in therapy for ruxolitinib 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 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 (CDA) 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).

Both groups agreed that, aside from ruxolitinib, 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 agents 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, though attaining high levels of repigmentation remains challenging. The CDA highlighted the need for maintenance therapy to prevent relapse, while the Southwestern Ontario group stressed reducing stress on melanocytes to improve outcomes.

Both groups described ruxolitinib 1.5% cream as a transformative first-line therapy for vitiligo in patients aged 12 and older. It targets the underlying disease mechanisms and has a favorable 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 Vitiligo Area Severity Index (VASI), Investigator Global Assessment (IGA), Vitiligo Noticeability Scale (VNS), and global impression scales.

Regarding treatment discontinuation, CDA experts suggested stopping treatment after six months without repigmentation, while others recommended extending it to 18 months. The Southwestern Ontario group stressed that, after one 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:

- 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

Two studies were reviewed: TRuE-V1 (n = 330) and TRuE-V2 (n = 344) were phase 3, multicenter, double-blind (DB) vehicle-controlled randomized controlled trials (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 12 years of age and older.

The primary outcome was the proportion of patients achieving an improvement of at least 75% from baseline in the Facial Vitiligo Area Scoring Index score (F-VASI) at Week 24. Additional levels of VASI thresholds were assessed as secondary endpoints 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. The VASI score is a validated instrument that is however not routinely used in clinical practice. Evidence in the literature suggests that a reduction of 75% in the baseline F-VASI score (F-VASI75), and a reduction of 50% in the baseline T-VASI score (T-VASI50), 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 Vitiligo Noticeability Scale (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).

Health-related quality of life (HRQoL) was assessed in the studies using the Dermatology Life Quality Index (DLQI) and the Child Dermatology Life Quality Index (CDLQI) as other secondary outcomes, while the Vitiligo-Specific Quality-of-Life instrument (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 patients' lives. 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 – VASI

For the primary outcome, which was the proportion of patients achieving an improvement of at least 75% from baseline in F-VASI score (F-VASI75), treatment with ruxolitinib was associated with a between-group difference in response rate of 22.3% (95% CI; 14.2 to 30.5; $p < 0.0001$) in TruE-V1 and 19.5% (95% CI; 10.5 to 28.4; $p = 0.0004$) in TruE-V2 over 24 weeks versus vehicle. In absolute effects, 60 patients (30.8%) who applied ruxolitinib achieved the outcome compared to 7 patients (7.8%) who applied vehicle in TRuE-V1. In TRuE-V2, 62 patients (31.2%) who applied ruxolitinib achieved the outcome compared to 11 patients (11.2%) who applied vehicle.

A 75% improvement in F-VASI 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-groups 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 such as measured by 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 impact their daily lives. Therefore, evidence of moderate certainty suggests that treatment with ruxolitinib likely results in a clinically important increase in the proportions of patients achieving F-VASI75 compared to vehicle.

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. A total of 31 patients (15.9%) who applied

ruxolitinib in TRuE-V1 achieved F-VASI90 compared with 2 patients (2.2%) who applied vehicle; in TRuE-V2, 33 patients (16.6%) who applied ruxolitinib achieved the outcome compared with 1 patient (1.0%) who applied vehicle. The between-group difference in response rate was 13.2% (95% CI; 7.5 to 18.8; p = 0.0038) in TruE-V1 and 15.0% (95% CI; 9.3 to 20.7; p = 0.0065) in TruE-V2. Results for improvement from baseline of at least 50% in total body VASI scores (T-VASI50) were consistent with the above. However, results for the more conservative threshold of T-VASI75 were deemed unlikely to constitute a meaningful change for the patients according to the clinical experts.

Vitiligo Noticeability Scale – VNS

Patient-reported noticeability, assessed using the VNS, suggest that treatment with ruxolitinib 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. Among patients who applied ruxolitinib, the proportions of responders was 25% in TRuE-V1 and 21% in TRuE-V2, resulting in a between-group difference in response rate versus vehicle of 21.2% (95% CI; 14.3 to 28.1; p = 0.0002) in TruE-V1 and 15.5% (95% CI; 8.5 to 22.6; p = 0.0013) in TruE-V2. Uncertainty was introduced by the absence of a reported MCID for differences between treatments in the literature, and by the fact that 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 – HRQoL

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 may not result in a clinically important improvement in HRQoL, as measured with the VitiQoL over 24 weeks compared to vehicle. 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 TRuE-V1, and -3.52 (95% CI; -7.60 to 0.57; p = 0.0915) in TRuE-V2. 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 in terms of overall surface area of involvement and degree of repigmentation making the condition less noticeable in some patients, ruxolitinib 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, 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 a 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 in TRuE-V1 (46%) and TRuE-V2 (50%) experienced at least one AE. The most common treatment-emergent AEs were related to application site reactions (i.e., acne, pruritus, rash, and exfoliation) and infections. SAEs were uncommon. 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 TRuE-V1 and TRuE-V2, as well as from the TRuE-V LTE, were consistent with those from the pivotal trials. Overall, the clinical expert indicated that the harms profile of ruxolitinib did not raise any new safety signal, or any particular safety concern. As with most clinical trials, the studies were however 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 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 TRuE-V1 and TRuE-V2 included a vehicle control group, there is no direct evidence comparing ruxolitinib to other currently used therapies for vitiligo. Therefore, the comparative effectiveness and safety of ruxolitinib relative to other treatment options available, which were considered overall well accepted and routinely prescribed according to the clinical experts, are unknown.

TRuE-V1 and TRuE-V2 may be considered generalizable to a selected sample of individuals living in Canada with vitiligo. The majority of patients included in the studies were White and had a lighter skin color. Vitiligo however, is particularly visible in patients with darker color of skin and as such, is likely to present with an increased impact on quality of life in these patients. Since only few patients with a darker color of skin were included in the studies, the effect of ruxolitinib in these patients is uncertain. In addition, there is a possibility that the trial population may not be representative of patients whose condition interfere 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 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 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 TRuE-V1 and TRuE-V2 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 versus vehicle.

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

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Vehicle	Ruxolitinib	Difference		
F-VASI							
Proportions of patients achieving F-VASI75 Follow-up: 24 weeks	N = 394, ruxolitinib N = 188, vehicle (2 RCTs)	TRuE-V1: OR = 5.28 (2.341, 11.903) TRuE-V2: OR = 3.45 (1.737, 6.835)	TRuE-V1: 74 per 1,000 patients TRuE-V2: 114 per 1,000 patients	TRuE-V1: 298 per 1,000 patients TRuE-V2: 309 per 1,000 patients	TRuE-V1: 223 more per 1,000 patients (142, 305) TRuE-V2: 195 more per 1,000 patients (105, 284)	Moderate[a]	Ruxolitinib likely results in a clinically important increase in the proportions of patients achieving F-VASI75 over 24 weeks compared to vehicle.
Proportions of patients achieving F-VASI90 Follow-up: 24 weeks	N = 394, ruxolitinib N = 188, vehicle (2 RCTs)	TRuE-V1: OR = 8.49 (1.997, 36.048) TRuE-V2: OR = 15.29 (2.150, 108.739)	TRuE-V1: 22 per 1,000 patients TRuE-V2: 13 per 1,000 patients	TRuE-V1: 153 per 1,000 patients TRuE-V2: 163 per 1,000 patients	TRuE-V1: 132 more per 1,000 patients (75, 188) TRuE-V2: 150 more per 1,000 patients (93, 207)	Moderate[a]	Ruxolitinib likely results in a clinically important increase in the proportions of patients achieving F-VASI90 over 24 weeks compared to vehicle.
VNS							
Proportion of patients achieving a VNS of "4- A lot less noticeable" or "5-No longer noticeable" Follow-up: 24 weeks	N = 394, ruxolitinib N = 188, vehicle (2 RCTs)	TRuE-V1: OR = 9.53 (2.900, 31.290) TRuE-V2: OR = 4.86 (1.851, 12.755)	TRuE-V1: 33 per 1,000 patients TRuE-V2: 49 per 1,000 patients	TRuE-V1: 245 per 1,000 patients TRuE-V2: 205 per 1,000 patients	TRuE-V1: 212 more per 1,000 patients (143, 281) TRuE-V2: 155 more per 1,000 patients (85, 226)	Moderate[b]	Ruxolitinib 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.
HRQoL							
Change from baseline in VitiQoL Follow-up: 24 weeks	N = 394, ruxolitinib N = 188, vehicle (2 RCTs)	N/A	TRuE-V1: LSM (SE) = -6.18 (1.77) TRuE-V2: LSM (SE) = -2.66 (1.70)	TRuE-V1: LSM (SE) = -6.45 (1.21) TRuE-V2: LSM (SE) = -6.18 (1.20)	TRuE-V1: LSM difference = -0.28 (-4.51, 3.95) TRuE-V2: LSM difference = -3.52 (-7.60, 0.57)	Low[c]	Ruxolitinib may not result in a clinically important improvement in HRQoL as measured with the VitiQoL over 24 weeks compared to vehicle.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Vehicle	Ruxolitinib	Difference		
Harms							
Patients with SAEs Follow-up: 24 weeks	N = 449, ruxolitinib N = 224, vehicle (2 RCTs)	NR	TRuE-V1: 9 per 1,000 patients TRuE-V2: 0 per 1,000 patients	TRuE-V1: 27 per 1,000 patients TRuE-V2: 9 per 1,000 patients	TRuE-V1: 18 more per 1,000 patients TRuE-V2: 9 more per 1,000 patients	Moderate[d]	Ruxolitinib likely did not result in a clinically important increase in SAEs over 24 weeks compared to vehicle.

CI = confidence interval; F-VASI = Facial Vitiligo Area Scoring Index; HRQoL = health-related quality of life; LSM = least square means; N/A = 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 a 75% improvement in F-VASI has been suggested as a threshold for treatment success based on perceptions of patients with vitiligo and dermatologists, no MCID for between-groups 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-groups 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 judgement 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

Description of studies

In the pivotal RCTs TRuE-V1 and TRuE-V2, the DB controlled period was followed by a 28-week open-label treatment extension. Patients initially randomized to vehicle cream crossed over to ruxolitinib, while patients initially randomized to ruxolitinib received an additional 28 weeks of treatment with 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 the predefined thresholds of reduction in the VASI score (i.e., F-VASI25, F-VASI50, F-VASI75, F-VASI90, and T-VASI75) were numerically higher in all treatment arms when compared to the corresponding proportions during the DB period. In the treatment-extension period however, 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 from baseline to week 52 observed 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 two 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 in the longer-term are non-comparative 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 DB controlled period of the studies, also apply to the extension period.

TRuE-V Long-Term Extension

Description of studies

The TRuE-V Long-Term Extension (LTE) is a phase 3, double-blind, vehicle-controlled, randomized withdrawal trial designed to assess the long-term efficacy and safety of ruxolitinib cream in patients with vitiligo. It follows the TRuE-V1 and TRuE-V2 studies and includes two cohorts: Cohort A, which evaluates the duration of response after withdrawing ruxolitinib cream, and Cohort B, which 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 (greater than or equal to F-VASI90) at Week 52 in either TRuE-V1 or TRuE-V2 were assigned to this cohort. They were randomized in a 1:1 ratio to either continue 1.5% ruxolitinib cream or switch to vehicle cream during the LTE. Participants in Cohort A who experienced a relapse (defined as less than F-VASI75) received open-label ruxolitinib cream as rescue treatment until Week 104 or the end of the trial (EOT). Cohort B included participants who did not achieve greater than or equal to F-VASI90 at Week 52 in the parent studies. These participants continued treatment with 1.5% ruxolitinib 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 in relapsed patients. 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 confidence intervals were at 95%. Data from participants with noncompliance or incorrect randomization were excluded. Primary and secondary analyses used the ITT-Ext 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 endpoint: Time to relapse (<F-VASI75)

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

Key secondary endpoint: Time to maintain F-VASI90 response

The majority of patients who achieved complete or near-complete repigmentation of the face in Cohort A in the parent studies maintained this level of repigmentation with continued ruxolitinib 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 cream in the double-blind period, then continued treatment with ruxolitinib 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 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 endpoints

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

In Cohort A, the proportion of participants continuing on 1.5% ruxolitinib 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 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 ruxolitinib 1.5% 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 proportions of participants on 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 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 cream remained generally stable (43.3% at Week 104 vs 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 ruxolitinib 1.5% cream during the TRuE-V LTE study (30.1% at Week 104 vs 11.9% at Week 52).

As for quality of life, there were no significant changes in the Dermatology Life Quality Index (DLQI) scores for Cohort A, while Cohort B showed slight improvements in Children's Dermatology Life Quality Index (CDLQI) scores, regardless of whether patients

continued or switched to ruxolitinib. There were also improvements in Vitiligo-Specific Quality of Life (VitiQoL) scores for Cohort B, but no clear pattern was observed in Cohort A.

In exploratory endpoints, the median time to regain F-VASI75 was 85.0 days for patients who experienced relapse and switched to open-label rescue treatment, whereas 62.5% of patients on ruxolitinib 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 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 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 cream, compared to 50.0% and 5.1% for participants initially randomized to vehicle cream who switched to ruxolitinib 1.5% cream during the LTE study. The incidence of serious TEAEs was 3.1% in patients treated with 1.5% ruxolitinib 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, in addition no conclusion can be made on the comparative efficacy and safety.

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

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 (the 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 Canadian population and the clinical evidence is generalizable to the Canadian setting.

Indirect Comparisons

As TRuE-V1 and TRuE-V2 included a vehicle control group, there is no direct evidence comparing ruxolitinib 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 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

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Patients 12 years of age and older with non-segmental vitiligo (NSV)
Treatment	Ruxolitinib 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)[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 was derived from data pooled from the double-blinded phase of the TRuE-V1 and TRuE-V2 trials • Long term clinical efficacy of ruxolitinib 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 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 normal skin, and patients whose condition interfere substantially with their daily lives. The generalizability of the effects of ruxolitinib in these patients is therefore uncertain. As such, the cost-effectiveness of ruxolitinib may not be representative of its use in patients populations in whom ruxolitinib is most likely to be used in clinical practice. • The sponsor's mapped health utilities lacked face validity. Both the baseline and responder utility values were higher than the general Canadian population. The sponsor also assumed that non-responders experienced a persistent decrease in health utility that is lower than their baseline values. • The sponsor adopted a mean daily dose of [redacted] grams for ruxolitinib, however, the daily dose used in the TRuE-V1 and TRuE-V2 trials was much higher. The mean daily dose of ruxolitinib ranged from [redacted] grams to [redacted] grams per day during the double-blind controlled period of the trials (24-week duration), and from [redacted] grams to [redacted] grams per day in the extension period of the trials (28-

Component	Description
	week duration). The sponsor's estimate is an underestimation of the daily dose and the treatment cost of ruxolitinib.
CDA-AMC reanalysis results	• CDA-AMC undertook reanalyses that addressed some of the identified limitations, including assuming utilities for non-responders would be identical to baseline utilities and adopting a higher daily dose for ruxolitinib. 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 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 (from $1,076 to $108 per 100 gram 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 = non-segmental vitiligo; QALY= quality-adjusted life-year; WTP = willingness to pay

[a] In the base case, the sponsor compared ruxolitinib 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 NSV patient seeking care was underestimated; clinical experts anticipated a higher uptake of ruxolitinib than sponsor's estimate, suggesting that the market share of ruxolitinib may have been underestimated; the displacement of comparators by ruxolitinib was uncertain; treatment cost of ruxolitinib was underestimated because the modelled daily dose was much lower compared with observations from the TRuE-V trials; the use of 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 NSV patients seeking care, increasing the market share of ruxolitinib, adjusting the market capture of ruxolitinib to reflect expert feedback, 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 cream for the topical treatment of patients aged 12 years and older with NSV. 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.

CDEC Information

Members of the Committee:

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

Meeting date: March 26, 2025

Regrets:

5 expert committee members did not attend.

Conflicts of interest:

None