

Reimbursement Recommendation

Ruxolitinib (Opzelura)

Indication: For the topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 12 years of age and older whose disease is not adequately controlled with conventional topical prescription therapies (topical corticosteroids, topical calcineurin inhibitors) or when those therapies are not advisable

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 should not be reimbursed by public drug plans for the topical treatment of mild to moderate atopic dermatitis (AD) in adult and pediatric patients 12 years of age and older whose disease is not adequately controlled with conventional topical prescription therapies (topical corticosteroids [TCS], topical calcineurin inhibitors [TCI]) or when those therapies are not advisable.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 2 clinical trials showed that Opzelura treatment improved the severity of AD compared with placebo in adult and adolescent patients with mild to moderate AD. However, it is unclear if these patients were representative of patients whose disease is not adequately controlled with TCS and/or TCI, or for whom such treatment(s) is not advisable, which is the patient population expected to receive Opzelura in clinical practice.
- No evidence that directly compared Opzelura to currently available treatments for mild to moderate AD was submitted. The submitted indirect evidence in patients with moderate AD was uncertain due to limitations of the analyses. The study was also not conducted in the patient population expected to receive Opzelura in clinical practice.

Additional Information

What Is AD?

AD is a condition that affects the skin and causes dry, red skin that is extremely itchy. Constant scratching causes the skin to split and bleed, which can lead to infections. Oozing and weeping sores occur in more severe forms. Severe AD can be physically incapacitating and cause anxiety or depression. In Canada, the prevalence of AD is estimated to vary from 1.8% to 3.5% in adults and from 9.4% to 15.8% in adolescents.

Unmet Needs in AD

There is a need for additional topical treatment options that are effective in reducing the severity and symptoms of AD and are safe and easy to apply on different parts of the body, including sensitive areas.

Summary

How Much Does Opzelura Cost?

Treatment with Opzelura is expected to cost approximately \$8,608 to \$12,912 per patient in the first year of treatment and \$2,152 to \$8,608 per patient in subsequent years.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that ruxolitinib 1.5% cream not be reimbursed for the topical treatment of mild to moderate AD in adult and pediatric patients 12 years of age and older whose disease is not adequately controlled with conventional topical prescription therapies (TCS, TCI) or when those therapies are not advisable.

Rationale for the Recommendation

CDEC acknowledged the potential need for additional treatment options that effectively reduce the severity and symptoms of AD and are safe; however, CDEC identified several limitations and uncertainties in the submitted evidence that did not allow the committee to determine whether ruxolitinib 1.5% cream will provide a clinically meaningful benefit in the patient population under review.

Evidence for ruxolitinib cream was reviewed based on the Health Canada indication, which limits usage to patients with mild to moderate AD whose disease is not adequately controlled with TCS and/or TCI, and those who are not candidates for those treatments. However, the 2 double-masked, randomized, vehicle-controlled trials (TRuE-AD1, N = 631; TRuE-AD2, N = 618) enrolled patients who had mild to moderate AD without restricting trial entry based on response to prior TCS and/or TCI treatments. Although the results of the pivotal trials suggested added clinical benefits with 8 weeks of ruxolitinib 1.5% cream treatment, compared to vehicle cream, in achieving Investigator Global Assessment (IGA) treatment success (TS) and at least a 75% reduction from baseline in the Eczema Area and Severity Index (EASI) (known as EASI-75) in patients aged 12 years and older with mild to moderate AD, the trial populations were not reflective of the anticipated use of ruxolitinib cream based on the indication under review. Post hoc subgroup analyses in patients with a recent history of TCS and/or TCI treatment were submitted as supporting evidence; however, the proportion of patients in the subgroup analyses that had an inadequate response to TCS and/or TCI remains unknown. Additionally, the results of these post hoc subgroup analyses were inconclusive due to methodological limitations, including a lack of sample size consideration and control for multiplicity.

There was a lack of direct comparative evidence for ruxolitinib cream versus active treatments used in Canada for the treatment of mild to moderate AD. Indirect comparative evidence submitted for review included 1 sponsor-submitted network meta-analysis (NMA), which assessed the efficacy of ruxolitinib 1.5% cream versus dupilumab, abrocitinib, and upadacitinib in patients with moderate AD. The results of this analysis were inconclusive due to imprecise results and important limitations that prevented verification of whether the underlying assumptions of homogeneity and consistency were met. Additionally, subgroup analyses in patients whose disease is not adequately controlled with, or who are not candidates for, TCS and/or TCI were not reported from the indirect treatment comparison. No comparative studies were submitted comparing ruxolitinib cream with off-label systemic immunosuppressants in patients with moderate AD. Overall, CDEC was unable to determine the comparative efficacy and safety of ruxolitinib 1.5% cream relative to currently available treatments for mild to moderate AD.

Patients identified a need for effective treatments that can reduce disease severity and the number of flares, improve quality of life, have fewer side effects, and offer a simplified treatment regimen by allowing topical application on multiple body areas, including sensitive areas. Based on the evidence reviewed, CDEC concluded that ruxolitinib cream meets the need for an additional topical treatment option, but the committee could not determine whether ruxolitinib cream would adequately reduce disease severity and number of flares, improve quality of life, and have fewer side effects due to the uncertainties around the treatment effect of ruxolitinib cream compared to currently available treatments in the patient population under review.

Discussion Points

- Reconsideration request:** The sponsor requested a reconsideration of the initial draft recommendation to not reimburse for the topical treatment of mild to moderate AD in adult and pediatric patients 12 years of age and older whose disease is not adequately controlled with conventional topical prescription therapies (TCS, TCI) or when those therapies are not advisable. The 4 issues outlined by the sponsor in the request for reconsideration that were discussed by CDEC included considering whether the trial patient populations aligned with the indicated and anticipated-use population, revising the language used in statements regarding the evidence base of direct and indirect comparisons versus active treatments, acknowledging clinically important treatment effects of ruxolitinib cream on the Dermatology Life Quality Index (DLQI), and considering available evidence for the long-term safety of ruxolitinib cream.
- Lack of robust comparative evidence versus comparator treatments:** During the initial meeting and the reconsideration meeting, CDEC discussed that although they recognized the value that both patients and clinicians place in having a choice of treatment options for mild to moderate AD, the absence of robust comparative efficacy and safety data versus currently available treatments — specifically in patients who have inadequate control with, or an inadequate response to, TCS and/or TCI preclude assessment of all factors necessary to balance all outcomes and unmet needs. Based on the input from the clinical experts consulted for this review, phototherapy, systemic immunosuppressants, biologics, and Janus kinase (JAK) inhibitors are currently used in clinical practice following inadequate response to, or ineligibility for, TCS or TCI. The committee noted that there was no direct or indirect evidence assessing the clinical benefits of ruxolitinib cream relative to other active therapies in the patient population under review (i.e., adult and pediatric patients 12 years of age and older whose disease is not adequately controlled with conventional topical prescription therapies or when those therapies are not advisable).
- Limitations of the subgroup analyses:** During the initial meeting, considering the post hoc subgroup analyses from the pivotal trials in patients who received TCS and/or TCI within 30 days before screening, CDEC noted that these analyses were conducted regardless of patients' status of disease control with, or response to, prior TCS and/or TCI treatment. Therefore, CDEC concluded at the initial meeting that the population included in the trials was not aligned with the patient population under review. Additional ad hoc subgroup analyses of pivotal trial participants who discontinued

prior TCS or TCI therapies due to toxicity, side effects, or lack of efficacy (not included in the initial submission) were presented by the sponsor as part of the reconsideration request. During the reconsideration meeting, CDEC noted that these ad hoc subgroup analyses may have the potential to address the treatment effects of ruxolitinib cream in the patient population under review; however, this new evidence could not be accepted or considered by CDEC during the reconsideration process for ruxolitinib cream in accordance with the *Procedures for CDA-AMC Reimbursement Reviews*. Without a comprehensive appraisal of the new evidence from CDA-AMC, CDEC noted that it remains unclear if ruxolitinib cream could meet the unmet needs.

- **Effects on health-related quality of Life (HRQoL) are uncertain:** During the initial meeting and the reconsideration meeting, CDEC discussed that there was evidence of low certainty from the TRuE-AD1 and TRuE-AD2 trials that ruxolitinib 1.5% cream may result in a clinically important improvement in dermatology-specific HRQoL in adults and little to no clinically important improvement in dermatology-specific HRQoL in adolescents at week 8 compared to vehicle cream, per Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessments. The clinical experts noted that it is plausible that the duration of follow-up at week 8 was insufficient for capturing the HRQoL effects of topical treatments in general, given that AD is a chronic condition that waxes and wanes over time. CDEC acknowledged this limitation of the dermatology-specific HRQoL analyses and noted that, in addition, the analyses were associated with methodological limitations (differential dropouts between treatment groups and a risk of randomization not being fully preserved in the Children's DLQI [CDLQI] responder analysis). Additionally, the comparative HRQoL effects of ruxolitinib cream versus other active treatments for mild to moderate AD are unknown because HRQoL outcomes were not assessed in the sponsor-submitted NMA. Therefore, no definitive conclusions could be drawn on the comparative effectiveness of ruxolitinib cream on HRQoL versus active therapies for the indicated population.
- **Long-term efficacy and safety are uncertain:** During the initial meeting and the reconsideration meeting, CDEC also considered results from the long-term safety period of the pivotal trials, which suggested that the observed clinical benefits of ruxolitinib cream could potentially be sustained through 52 weeks, and no notable safety concerns were identified. However, analyses beyond week 8 were noncomparative. Overall, no firm conclusion could be drawn on the results of the long-term safety period due to the absence of a control group, potential risk of selection bias, and considerable loss to follow-up (approximately 20%) in both trials. Additionally, clinical expert input indicated that the duration of follow-up may be inadequate for capturing the long-term safety of ruxolitinib cream, particularly for potentially rare adverse events (AEs) (e.g., malignancies, major adverse cardiovascular events). Additional safety studies of ruxolitinib cream (not included in the initial submission) were presented by the sponsor as part of the reconsideration request. During the reconsideration meeting, CDEC noted that these new safety studies could not be accepted or considered by CDEC during the reconsideration process, in accordance with the *Procedures for CDA-AMC Reimbursement Reviews*.

Background

AD is a chronic relapsing-remitting skin condition characterized by itching, inflammation, dryness, recurrent eczematous lesions, erythematous papules, and lichenification. The intense itch associated with AD can lead to sleep disturbances, mental health burden, and reduced quality of life for patients and caregivers. In Canada, the prevalence of AD is estimated to vary from 1.8% to 3.5% in adults and from 9.4% to 15.8% in adolescents. Currently available topical treatments for patients with mild to moderate AD include TCS and nonsteroidal topical treatments (i.e., TCI and topical phosphodiesterase type 4 inhibitors). Patients who do not achieve adequate disease control with topical treatments could receive phototherapy, off-label systemic immunosuppressant treatments (methotrexate, cyclosporine, mycophenolate mofetil, azathioprine), and advanced systemic therapies (e.g., dupilumab, upadacitinib, and abrocitinib). According to the clinical experts consulted by CDA-AMC, limitations of the currently available nonsteroidal topical treatments include poor efficacy in some patients and in body areas with thicker skin, potential application site reactions, difficult application for treatments in ointment formulation (tacrolimus), and high treatment costs.

Ruxolitinib 1.5% cream has been approved by Health Canada for topical treatment of mild to moderate AD in adult and pediatric patients 12 years of age and older whose disease is not adequately controlled with conventional topical prescription therapies (TCS, TCI) or when those therapies are not advisable. Ruxolitinib is a Janus kinase inhibitor. It is available as a 1.5% topical cream, and the dosage recommended in the product monograph is twice daily to affected skin areas up to a maximum of 20% of body surface area (BSA) for each application. The total BSA calculation excludes the scalp.

Sources of Information Used by the Committee

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

- A review of 2 phase III, double-masked, randomized controlled trials (RCTs) in adolescents and adults with mild to moderate AD, and their extension phases; 1 indirect treatment comparison study; and 1 phase II, open-label, single-arm study
- Patients' perspectives gathered by 3 patient groups, including input from the Eczema Society of Canada, and joint input from the Canadian Skin Patient Alliance and Eczema Quebec
- Input from public drug plans that participate in the reimbursement review process
- Two clinical specialists with expertise in diagnosing and treating patients with AD
- Input from 2 clinician groups, including the Canadian Dermatology Association and the Atlantic Dermatology Specialist Group
- 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

The information in this section is a summary of input provided by the patient and clinician groups who responded to the CDA-AMC call for input and from clinical experts consulted by CDA-AMC for the purpose of this review. Note that the patient and clinician group inputs were received at the time of the CDA-AMC call for input based on the initial reimbursement request (i.e., for the topical treatment of AD in patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable), which predates the reimbursement request update provided by the sponsor (i.e., for the topical treatment of mild to moderate AD in adult and pediatric patients 12 years of age and older whose disease is not adequately controlled with conventional topical prescription therapies [TCS, TCI] or when those therapies are not advisable).

Patient Input

Input from 2 patient groups was submitted. The Eczema Society of Canada is a registered Canadian charity with a mission of support, education, awareness, and research for people living with eczema. The Eczema Society of Canada gathered information from more than 3,000 patients in Canada living with AD and their caregivers and/or family members via survey questionnaires and one-on-one interviews. Other patient group input was jointly submitted by the Canadian Skin Patient Alliance and Eczema Quebec. The Canadian Skin Patient Alliance is a national nonprofit organization that engages in collaboration, advocacy, and education for people affected by skin, hair, and nail conditions. Eczema Quebec is a nonprofit organization dedicated to providing support, resources, and education to individuals and families affected by eczema in Quebec. The joint input was based on information gathered between February 2023 and October 2023 from various sources, including a literature review, patients, a report called “The Skin I’m In,” and collaboration with an academic institution. Some patients (number not specified) surveyed by Eczema Quebec indicated that they had experience with ruxolitinib cream treatment.

Both submissions of input highlighted that the signs and symptoms of AD, such as dry, itchy, inflamed skin that can lead to cracks, oozing, bleeding, and thickening of skin, affect many aspects of patients’ lives, such as physical, social, emotional, and professional aspects. Patients said itches can be extremely uncomfortable and painful and require frequent medical visits, specialized treatments, and ongoing care. Besides, the joint input by the Canadian Skin Patient Alliance and Eczema Quebec pointed out that AD is associated with other conditions such as asthma, seasonal allergies, environmental allergies, food intolerances, sleep disorders, anxiety, and depression. The inputs emphasized that caregivers and/or family members also share a significant burden of disease. The negative impact of AD on patients and their caregivers and/or families is amplified when AD is not well-controlled despite optimization of the treatment regimen and when cycling through or switching to different therapies. Based on the input by the Eczema Society of Canada, uncontrolled AD or flares could lead to emergency department visits and hospitalizations. The input also highlighted that, because AD can occur at a young age, it can have a significant impact on a youth’s performance at school, social life, and mental health. Based on the 2 submissions of input, patients expressed a need for new treatments that are safe, improve symptoms of AD, reduce flares, improve quality of life (e.g., better sleep quality; less psychological burden; the ability to carry out daily activities and

establish and maintain intimate relationships), as well as reduce or eliminate potential complications and secondary infections associated with AD. Other key outcomes reported to be important to patients included fast and durable relief, reduced skin thickening, ease of medication use, and affordability. In addition, patients also value treatments that do not require injections. Patients expressed a need for treatments suitable for application on not only the body but also the face and sensitive areas of the body, to allow a simplified regimen. The patient groups acknowledged that AD is a heterogeneous disease and requires a variety of treatments to fill gaps in therapeutic needs.

Clinician Input

Input From Clinical Experts Consulted by CDA-AMC

The clinical experts consulted for this review noted that currently available nonsteroidal topical treatments are not effective for all patients with AD and are inadequate for treating body areas with thick skin (e.g., palms and soles) or lichenification, are associated with application site reactions (burning and stinging), and are costly. As well, the clinical experts noted that a nonsteroidal topical treatment that is currently considered to be the most effective option (i.e., tacrolimus) is available in ointment formulation only, which is difficult to apply. One clinical expert anticipated that ruxolitinib would primarily serve as a second-line topical treatment following treatment failure with, or ineligibility to, TCS and/or TCI because of long-established treatment protocols favouring TCS and TCI as well as anticipated access challenges for ruxolitinib cream due to its higher drug cost relative to currently reimbursed topical treatments. The other clinical expert anticipated that ruxolitinib cream could also be used as a first-line topical treatment. This clinical expert further explained that TCI are associated with application site reactions and moderate efficacy. Provided that ruxolitinib cream is similarly or more effective and has fewer application site reactions than TCI, the clinical expert thought it would be reasonable to use ruxolitinib cream ahead of TCI, in particular for the face and groin, for which TCS treatment is inappropriate. The clinical experts noted that the determination of patients for whom the use of TCS and TCI is advisable primarily depends on reaction to previous use (i.e., these treatments are inadvisable in cases of intolerance). According to the clinical experts, there are very few contraindications to TCS and TCI (e.g., the use of all TCS, including hydrocortisone on the eyelids and long-term use of corticosteroids more potent than hydrocortisone on the face and intertriginous skin). In their experience, almost all topical treatment-naïve patients are eligible for TCS and TCI treatments. The clinical experts noted that depending on the severity of the symptoms and the treatment response in each anatomic location, ruxolitinib cream could be used as either monotherapy or in combination with other topical therapies (applied to different affected areas). The clinical experts noted that when used concurrently with other topical therapies, ruxolitinib cream could be applied to the same or different anatomic locations; most patients are expected to use 1 treatment at a time in a given location and different topicals to different parts of the body.

One clinical expert noted that patients with AD who have facial or intertriginous involvement, inadequate response to or intolerable AEs from TCS and/or TCI treatments, and 10% or BSA affected by AD, are most suited for treatment with ruxolitinib cream as monotherapy. In the second clinical expert's opinion, patients with AD could receive ruxolitinib cream treatment regardless of response to or eligibility for TCS and/or TCI

treatments. As well, the second clinical expert felt that patients with more than 10% BSA affected might still be eligible for ruxolitinib cream, provided that the cream is applied to no more than 10% to 20% of their BSA.

According to the clinical experts, there is no universal definition for adequate (or inadequate) response to TCS and TCI treatment. They noted that treatment response to TCS and TCI is typically determined by clinical judgment on a case-by-case basis and by patient satisfaction, although it might be reasonable to consider initiation of ruxolitinib cream treatment in patients whose skin fails to improve after 4 to 8 weeks of conventional topical therapy, including low-, mid-, or high-potency TCS, TCI, or crisaborole, as suggested in the sponsor's submission. From a clinical perspective, the clinical experts noted that ruxolitinib cream could also be considered before failure of existing topical treatments. The clinical experts noted that response to ruxolitinib cream treatment should similarly be assessed based on clinical judgment. They noted that EASI 75, which is the benchmark currently used for renewing reimbursement of systemic AD treatments may not be applicable to ruxolitinib cream. The clinical experts explained that given that ruxolitinib cream may be used in combination with other topical treatments (applied to different affected areas), it is impossible to attribute changes in EASI score to ruxolitinib cream treatment in these scenarios. It is reasonable to conduct a follow-up assessment at 8 weeks following treatment initiation, although a longer interval at 3 to 6 months may be more practical for patients with less severe disease, according to the clinical experts. Additionally, the clinical experts noted that, given Canada's medical resource constraints, particularly in terms of access to dermatology visits but also to family physician and other physician visits, shorter follow-up intervals may be impractical. The clinical experts noted that treatment discontinuation could be considered in patients who have an inadequate response or intolerable AEs to ruxolitinib cream treatment. The clinical experts noted that ruxolitinib cream could be prescribed by any health care provider with experience in diagnosing, treating, and monitoring patients with AD; this would principally include general dermatologists, pediatricians, pediatric dermatologists, allergists, family practitioners, and nurse practitioners.

Clinician Group Input

The Canadian Dermatology Association, represented by 3 clinicians, and the Atlantic Dermatology Specialist Group, represented by 11 clinicians, prepared 2 separate input submissions. Consistent with the input from the clinical experts consulted by CDA-AMC, the clinician groups indicated that some patients receiving existing treatments experience uncontrolled disease, side effects, poor tolerability with ointment formulation, or poor treatment adherence due to the need to apply different topical products to different body locations. They agreed that there is an unmet need for a new topical therapy that is effective, better tolerated, and in a cream formulation. The clinician groups also noted that an effective topical therapy is needed to prevent the need to escalate to phototherapy or systemic treatments, which are associated with limitations (e.g., limited efficacy, accessibility, and drug coverage; side effects; monitoring requirements; high treatment cost). Both clinician groups also agreed that the main treatment goals include reducing itch and inflammation (short- and long-term), achieving skin clearance, minimizing tolerability and safety issues, and improving quality of life (e.g., sleep, anxiety, and depression). The clinician groups and clinical experts agreed that an ideal topical treatment would be in a cosmetically appropriate base, convenient to use, and accessible.

In general, 2 clinician groups and the clinical experts consulted by CDA-AMC agreed that ruxolitinib cream could be used in patients with AD who are not adequately controlled with topical prescription therapies (i.e., TCS, TCI) or when those therapies are not advisable. However, the Atlantic Dermatology Specialist Group and the clinical experts noted that there is potential for the ruxolitinib treatment to be used as a first-line treatment in some patients. The clinician groups noted that eligible patients include those with mild to moderate AD affecting up to 20% of their BSA, severe localized AD, and moderate-to-severe AD (EASI score greater than 16 and at least 10% BSA affected), and those who cannot access or have contraindications to phototherapy or systemic therapies. Consistent with the input from the clinical experts consulted by CDA-AMC, the clinician groups noted that ruxolitinib cream could be used as either monotherapy or adjunct therapy (to systemic therapy if eligible and tolerated) for continuous or as-needed use. While the clinician groups felt that ruxolitinib cream could be used on any body sites in patients with up to 20% BSA affected, 1 of the clinical experts consulted by CDA-AMC felt that use of ruxolitinib cream should be mainly limited to face and intertriginous skin only and applied to no more than 10% BSA due to potential systemic absorption and high treatment cost.

Both clinician groups and the clinical experts noted that the treatment response is typically assessed by signs and symptoms (e.g., itch and inflammation), BSA, extent of involvement of special sites (hands, feet, face, skin folds, or perineal area), and patient-reported outcomes, (e.g., HRQoL, functional impact). The clinician groups and 1 of the clinical experts consulted by CDA-AMC agreed that after a trial period of 8 weeks, if there is an inadequate improvement in signs and symptoms of disease, recurrent flares, worsening of disease, or intolerance and/or side effects, then discontinuation of the treatment would be considered. The clinician groups' input also indicated that a 3- to 6-month follow-up for response assessment in patients receiving topical treatments could be more favourable in clinical practice, except in patients with more severe disease, for whom an 8-week assessment interval would be appropriate. The clinician groups agreed that generalist or primary care physicians, as well as specialists (e.g., dermatologists, allergy and immunology specialists) and pediatricians who are comfortable with the diagnosis and management of AD, should prescribe, treat, and monitor patients who receive ruxolitinib cream.

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 cream:

- Considerations for initiation of therapy
- Considerations for prescribing of therapy
- Generalizability of trial populations to the broader populations in the jurisdictions
- Care provision issues
- System and economic 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 sponsor-conducted systematic literature review identified 2 identically designed, pivotal, phase III, double-masked, RCTs (TRuE-AD1, N = 631; TRuE-AD2, N = 618) aiming to assess the efficacy and safety of ruxolitinib cream relative to vehicle cream, as monotherapy, in adolescents and adults aged 12 years or older with AD of mild (IGA score of 2) or moderate (IGA score of 3) severity, and 3% to 20% of BSA affected by AD. Patients were randomized to receive ruxolitinib 1.5% cream, ruxolitinib 0.75% cream, or vehicle cream monotherapy in a 2:2:1 ratio for an 8-week vehicle-controlled period, followed by a 44-week long-term safety period. In the long-term safety period, patients who initially received vehicle cream in the vehicle-controlled period were rerandomized to 1 of the 2 ruxolitinib cream treatment groups to receive treatment on an as-needed basis, whereas patients who initially received ruxolitinib cream continued to receive the same intervention as needed. In both trials, the primary end point was the proportion of patients achieving IGA-TS (i.e., an IGA score of 0 or 1 with at least a 2 grade improvement from baseline) at week 8, and the key secondary end points were proportion of patients achieving EASI-75, at least a 4-point improvement (i.e., reduction) from baseline in Itch Numeric Rating Scale (NRS) score, at least a 6-point improvement (i.e., reduction) from baseline in Patient-Reported Outcomes Measurement Information System (PROMIS) Short Form — Sleep Disturbance (8b — 24-hour recall) score, and at least a 6-point improvement (i.e., reduction) from baseline in PROMIS Short Form — Sleep-Related Impairment (8a — 24-hour recall) score, at week 8.

At baseline, the majority of patients in both trials were adults (TRuE-AD1, 80.5%; TRuE-AD2, 80.3%) and had an IGA score of 3 (TRuE-AD1, 75.9%; TRuE-AD2, 74.1%). The mean total percent BSA affected by AD was 9.5% in the TRuE-AD1 trial and 10.0% in the TRuE-AD2 trial. Prior TCI treatment was noted in 24.1% and 18.8% of patients in the TRuE-AD1 and TRuE-AD2 trials, respectively. Prior medium-, high-, or super-high-potency TCS treatment was noted in 43.7%, 34.9%, and 8.9% of patients, respectively, in the TRuE-AD1 trial, and in 41.1%, 30.4%, and 7.0% of patients, respectively, in the TRuE-AD2 trial. The proportion of patients who had inadequate disease control with TCS and/or TCI, or for whom such treatments are not advisable, was not reported. A small proportion of patients received prior systemic immunosuppressants, phototherapy, dupilumab, and systemic JAK inhibitor treatment.

Efficacy Results

Note that the efficacy and safety results of the ruxolitinib 0.75% cream group are not presented in this report because this strength of ruxolitinib cream is not approved by Health Canada for the treatment of AD and is not of interest to this review. In addition, the study inclusion and exclusion criteria did not restrict entry based on prior experience with topical treatments, and the sponsor was unable to provide subgroup data in the patient population as per the Health Canada indication (patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable) upon the review team's request. However, the sponsor provided post hoc analyses using the pooled data from both trials by topical treatment history (TCS only, TCI only, TCS plus TCI — regardless of treatment time frame and in patients who received topical treatment within 30 days before screening) as supportive evidence for select

outcomes. Results of the full study population, along with the post hoc subgroup analyses, are presented in the following text.

IGA Score

IGA Treatment Success

The proportion of patients achieving IGA-TS at week 8 was the primary end point in both trials. At week 8, the between-group difference comparing ruxolitinib 1.5% cream with vehicle cream was 38.7% (95% confidence interval [CI], 29.9% to 47.4%; $P < 0.0001$) in the TRuE-AD1 trial and 43.7% (CI, 35.6% to 51.8%; $P < 0.0001$) in the TRuE-AD2 trial, both of which were in favour of ruxolitinib 1.5% cream. Results of the prespecified exploratory subgroup and sensitivity analyses were consistent in direction with the primary analysis in both trials. Subgroup analyses in both trials seem to suggest a higher IGA-TS response rate at week 8 in patients with a baseline IGA score of 3 (versus IGA score of 2), with an EASI score greater than 7 (versus EASI score 7 or less), and in Europe (versus in North America).

A post hoc subgroup analysis by topical treatment history showed results consistent with the primary analysis across subgroups (TCS only, TCI only, TCS plus TCI — regardless of treatment time frame and in patients who received topical treatment within 30 days before screening).

IGA-TS was not assessed at week 52 in either trial.

IGA Score of 0 or 1

The proportion of patients achieving an IGA score of 0 or 1 was a secondary end point at week 52 in both trials. At week 52, the proportions of patients achieving an IGA score of 0 or 1 in the vehicle cream to ruxolitinib 1.5% cream group and in the ruxolitinib 1.5% cream to ruxolitinib 1.5% cream group were 73.7% and 75.4%, respectively, in the TRuE-AD1 trial, and 74.4% and 80.1%, respectively, in the TRuE-AD2 trial.

In a post hoc subgroup analysis by topical treatment history, the vehicle cream to ruxolitinib 1.5% cream group achieved a similar IGA score 0 or 1 response rate at week 52 as the ruxolitinib 1.5% cream to ruxolitinib 1.5% cream group across patients who received TCS only, TCI only, and TCS and TCI — regardless of treatment time frame, and in patients who received topical treatment within 30 days before screening.

EASI Score

EASI-75

The proportion of patients achieving EASI-75 at week 8 was a key secondary end point and was adjusted for multiplicity in both trials. At week 8, the between-group difference comparing ruxolitinib 1.5% cream with vehicle cream was 37.5% (95% CI, 27.8% to 47.1%; $P < 0.0001$) in the TRuE-AD1 trial and 47.4% (95% CI, 38.5% to 56.4%; $P < 0.0001$) in the TRuE-AD2 trial, both of which were in favour of ruxolitinib 1.5% cream. In both trials, the results of the sensitivity analyses were consistent with the primary analysis. Results of the prespecified subgroup analyses were consistent in direction of effect with the primary analysis. Subgroup analyses in both trials seem to suggest a higher EASI-75 response rate at week 8 in patients with a baseline EASI score greater than 7 (versus an EASI score of 7 or less).

A post hoc subgroup analysis by topical treatment history showed results consistent in direction with the primary analysis across subgroups (TCS only, TCI only, TCS plus TCI — regardless of treatment time frame and in patients who received topical treatment within 30 days before screening).

EASI-75 was not assessed at week 52 in either trial.

Percent BSA Affected by AD

Change from baseline in AD-affected percent BSA at weeks 8 and 12 were secondary end points and were not adjusted for multiplicity in either trial. At week 8, the between-group least squares mean difference comparing ruxolitinib 1.5% cream with vehicle cream was -3.7% (95% CI, -4.7% to -2.8%) in the TRuE-AD1 trial and -4.5% (95% CI, -5.5% to -3.6%) in the TRuE-AD2 trial.

In both trials, the reduction in AD-affected percent BSA was sustained at week 52 in patients who continued to receive ruxolitinib 1.5% cream in the long-term safety period (ruxolitinib 1.5% cream to ruxolitinib 1.5% cream group). The vehicle cream to ruxolitinib 1.5% cream group achieved AD-affected percent BSA similar to that of the ruxolitinib 1.5% cream to ruxolitinib 1.5% cream group at week 52 in both trials. In a post hoc subgroup analysis by topical treatment history, the vehicle cream to ruxolitinib 1.5% cream group achieved a similar total percent BSA affected by AD at week 52 as the ruxolitinib 1.5% cream to ruxolitinib 1.5% cream group across patients who received TCS only, TCI only, and TCS and TCI (regardless of treatment time frame and in patients who received topical treatment within 30 days before screening).

Itch NRS Score

At Least a 4-Point Improvement in Itch NRS From Baseline

The proportion of patients with at least 4 points of improvement in Itch NRS from baseline (among patients with a baseline score of at least 4; vehicle cream: n = 78 in the TRuE-AD1 trial, n = 80 in the TRuE-AD2 trial; ruxolitinib: n = 161 in the TRuE-AD1 trial, n = 146 in the TRuE-AD2 trial) at week 8 was a key secondary end point and was adjusted for multiplicity in both trials. At week 8, the between-group difference comparing ruxolitinib 1.5% cream with vehicle cream was 36.8% (95% CI, 25.7% to 47.9%; $P < 0.0001$) in the TRuE-AD1 trial and 34.4% (95% CI, 23.0% to 45.9%; $P < 0.0001$) in the TRuE-AD2 trial, both of which were in favour of ruxolitinib 1.5% cream. A post hoc subgroup analysis by topical treatment history showed results consistent in direction with the primary analysis across subgroups (TCS only, TCI only, TCS plus TCI — regardless of treatment time frame and in patients who received topical treatment within 30 days before screening).

This end point was not assessed at week 52 in either trial.

Patient-Oriented Eczema Measure (POEM)

Change From Baseline in POEM

Change from baseline in POEM score at weeks 8 and 52 were secondary end points and were not adjusted for multiplicity in either trial. At week 8, the between-group least squares mean differences comparing ruxolitinib 1.5% cream with vehicle cream were -6.3 (95% CI, -7.6 to -5.0) in the TRuE-AD1 trial and -5.9 (95% CI, -7.2 to -4.7) in the TRuE-AD2 trial.

In both trials, reduction in POEM score was sustained at week 52 in patients who continued to receive ruxolitinib 1.5% cream in the long-term safety period (ruxolitinib 1.5% cream to ruxolitinib 1.5% cream group). The vehicle cream to ruxolitinib 1.5% cream group achieved a mean POEM score similar to that of the ruxolitinib 1.5% cream to ruxolitinib 1.5% cream group at week 52 in both trials.

PROMIS Short Form — Sleep Disturbance

At Least a 6-Point Improvement (24-Hour Recall)

The proportion of patients with at least a 6-point improvement in PROMIS Short Form — Sleep Disturbance score (24-hour recall) from baseline (among patients with a baseline score of at least 6; vehicle cream: n = 116 in the TRuE-AD1 trial, n = 110 in the TRuE-AD2 trial; ruxolitinib: n = 238 in the TRuE-AD1 trial, n = 211 in the TRuE-AD2 trial) at week 8 was a key secondary end point and was adjusted for multiplicity in both trials. The between-group difference comparing ruxolitinib 1.5% cream with vehicle cream was 12.8% (95% CI, 5.3% to 20.3%; P = 0.0039) in the TRuE-AD1 trial, in favour of ruxolitinib 1.5% cream. In the TRuE-AD2 trial, the between-group difference was 6.5% (95% CI, -2.9% to 15.9%; P = 0.2359), which did not favour either study intervention; no superiority testing was conducted for the efficacy end point that was lower in the statistical testing hierarchy (i.e., proportion of patients with at least 6 points of improvement in PROMIS Short Form — Sleep-Related Impairment score at week 8). This end point was not assessed at week 52 in either trial.

PROMIS Short Form — Sleep-Related Impairment

At Least a 6-Point Improvement (24-Hour Recall)

The proportion of patients with at least a 6 point improvement in PROMIS Short Form — Sleep Impairment score (24-hour recall) from baseline (among patients with a baseline score of at least 6; vehicle cream: n = 114 in the TRuE-AD1 trial, n = 111 in the TRuE-AD2 trial; ruxolitinib: n = 245 in the TRuE-AD1 trial, n = 212 in the TRuE-AD2 trial) at week 8 was a key secondary end point in both trials. This end point was included in the statistical testing hierarchy, but no superiority testing was conducted due to prior failure in the hierarchy. At week 8, the between-group difference comparing ruxolitinib 1.5% cream with vehicle cream was 8.4% (95% CI, 0.4% to 16.4%) in the TRuE-AD1 trial and 9.6% (95% CI, 1.4% to 18.4%) in the TRuE-AD2 trial. This end point was not assessed at week 52 in either trial.

DLQI and CDLQI Scores

Change From Baseline in DLQI

Change in DLQI score from baseline (among patients aged 16 years or older; vehicle cream: n = 82 in the TRuE-AD1 trial, n = 87 in the TRuE-AD2 trial; ruxolitinib: n = 201 in the TRuE-AD1 trial, n = 185 in the TRuE-AD2 trial) at weeks 8 and 52 were secondary end points and were not adjusted for multiplicity in either trial. At week 8, the between-group least squares mean difference comparing ruxolitinib 1.5% cream with vehicle cream was -4.5 (95% CI, -5.6 to -3.4) in the TRuE-AD1 trial and -2.8 (95% CI, -3.7 to -1.8) in the TRuE-AD2 trial. Results of the responder analysis (proportion of patients achieving at least 4-point improvement in DLQI score) at week 8 were similarly in favour of ruxolitinib cream in both trials

In both trials, improvement (i.e., reduction) from baseline in DLQI score was sustained at week 52 in patients who continued to receive ruxolitinib 1.5% cream in the long-term safety period (ruxolitinib 1.5% cream to ruxolitinib 1.5% cream group). The vehicle cream to ruxolitinib 1.5% cream group achieved a mean DLQI score similar to that of the ruxolitinib 1.5% cream to ruxolitinib 1.5% cream group at week 52 in both trials.

Change From Baseline in CDLQI

Change in CDLQI score from baseline (among patients younger than 16 years; vehicle cream: n = 16 in the TRuE-AD1 trial, n = 11 in the TRuE-AD2 trial; ruxolitinib: n = 28 in the TRuE-AD1 trial, n = 25 in the TRuE-AD2 trial) at weeks 8 and 52 were secondary end points and were not adjusted for multiplicity in either trial. At week 8, the between-group least squares mean difference comparing ruxolitinib 1.5% cream with the vehicle cream was -2.3 (95% CI, -4.4 to -0.1 points) in the TRuE-AD1 trial and -3.1 points (95% CI, -6.3 to 0.1 points) in the TRuE-AD2 trial.

In both trials, improvement (i.e., reduction) from baseline in CDLQI score was sustained at week 52 in patients who continued to receive ruxolitinib 1.5% cream in the long-term safety period (ruxolitinib 1.5% cream to ruxolitinib 1.5% cream group). The vehicle cream to ruxolitinib 1.5% cream group achieved a mean CDLQI score similar to that of the ruxolitinib 1.5% cream to ruxolitinib 1.5% cream group at week 52 in both trials.

Harms Results

Adverse Events

In the vehicle-controlled period, the proportion of patients who reported at least 1 treatment-emergent AE (TEAE) was lower in the ruxolitinib 1.5% cream group compared with the vehicle cream group in both trials (TRuE-AD1, 29.2% versus 34.9%; TRuE-AD2, 23.6% versus 31.5%). The difference appears to be partly attributable to including AD as a harm. In the long-term safety period, the proportion of patients who reported at least 1 TEAEs was higher in the ruxolitinib 1.5% cream group (53.5%) compared with the vehicle cream group (48.9%) in the TRuE-AD1 trial but lower compared with the vehicle cream group in the TRuE-AD2 trial (ruxolitinib, 54.3%; vehicle cream, 65.4%).

The most common TEAEs of ruxolitinib 1.5% cream were upper respiratory tract infection, nasopharyngitis, and headache in the vehicle-controlled and long-term safety periods.

Serious AEs

In the vehicle-controlled period, serious TEAEs were reported in 2 (1.6%) patients in the vehicle cream group and 2 (0.8%) patients in the ruxolitinib 1.5% cream group in the TRuE-AD1 trial. In the TRuE-AD2 trial, no patients reported serious TEAEs in the vehicle cream group, and 1 (0.4%) patient reported a serious TEAE in the ruxolitinib 1.5% cream group. A similarly low frequency of serious TEAEs was noted in both treatment arms of the trials in the long-term safety period.

Withdrawals Due to AEs

In the vehicle-controlled period, study treatment withdrawal due to TEAEs was reported in 5 (4.0%) patients in the vehicle cream group and 3 (1.2%) patients in the ruxolitinib 1.5% cream group in the TRuE-AD1 trial, and in 3 (2.4%) patients in the vehicle cream group and 1 (0.4%) patient in the ruxolitinib 1.5% cream group in the TRuE-AD2 trial. TEAEs leading to discontinuing ruxolitinib cream treatment included papule, generalized pruritus, urticaria (1 [0.4%] patient each in the TRuE-AD1 trial), and cerebrovascular accident (1 [0.4%] patient in the TRuE-AD2 trial). In the long-term safety period of both studies, no patients withdrew from study treatment due to TEAEs.

Mortality

No deaths were reported during the vehicle-controlled and long-term safety periods in either trial.

Critical Appraisal

The trials used adequate methods of randomization and allocation concealment. There were a few small baseline imbalances in patient characteristics that may be compatible with chance and were not believed to have substantially impacted study results. The trials were adequately masked to reduce bias; however, there is a small potential for bias in the measurement of patient-reported outcomes (i.e., Itch NRS, POEM, PROMIS Short Form — Sleep Disturbance, PROMIS Short Form — Sleep-Related Impairment, DLQI, and CDLQI scores), leading to inflated efficacy of ruxolitinib cream due to possible unmasking if patients become aware of their assignments based on treatment response. Responder analyses of IGA-TS, EASI-75, Itch NRS, and PROMIS Short Form — Sleep Disturbance and Sleep-Related Impairment scores at week 8 were controlled for multiplicity, while other outcomes (IGA 0 or 1, change from baseline in percent BSA affected by AD, POEM, DLQI, and CDLQI scores) were not and were at an increased risk of type I error (false-positive results). At least 30% of patients were excluded from each treatment group in the Itch NRS responder analysis (due to the baseline Itch NRS score being less than 4 points), which could potentially impact randomization, although the extent and direction of the resulting bias are unclear. There is a risk of potential attrition bias in favour of ruxolitinib cream with respect to continuous secondary end points in the vehicle-controlled period, given that study treatment discontinuation in the vehicle cream group was notably higher compared with the ruxolitinib cream group. Implicit imputation using mixed models for repeated measures under the missing-at-random assumption was applied to account for missing data, although it is unclear if the missing-at-random assumption holds when the reasons for patient withdrawal (most common reason for discontinuation) were not documented; as well, no sensitivity analysis was conducted. The end point of change from baseline in CDLQI scores was based on a small size in both treatment groups, which could lead to instability of the treatment effect estimates. There is a lack of sample size consideration and control for multiplicity for subgroup analyses, which precludes definitive conclusions on subgroup effects. No firm conclusion can be drawn from the results of the long-term safety period due to the absence of a control group, potential selection bias, and sizable loss to follow-up (approximately 20%) in both trials.

The sponsor's funding request (aligned with the Health Canada indication) was for the topical treatment of mild to moderate AD in adult and pediatric patients 12 years of age and older whose disease is not adequately controlled with conventional topical prescription therapies (TCS, TCI) or when those therapies

are not advisable. However, the inclusion and exclusion criteria of the pivotal trials did not restrict entry based on prior experience with TCS and TCI treatment. Post hoc subgroup analyses in patients with a recent history of TCS and/or TCI treatment were submitted by the sponsor as supporting evidence. Nonetheless, in consultation with the clinical experts, the review team considered it to be unclear if this subgroup population could adequately reflect most patients expected to receive ruxolitinib cream in clinical practice (i.e., patients with AD who are inadequately controlled with TCS and/or TCI treatment or for whom these treatments are inadvisable). The clinical experts considered that the baseline patient characteristics in the pivotal studies were generally reflective of the patient population eligible for ruxolitinib cream in clinical practice, although the proportion of patients with mild disease (IGA score of 2), previous TCI treatment, and previous TCS treatment of medium-, high-, or super-high-potency in the trials appear to be lower than expected in clinical practice. As per clinical expert input, the duration of the safety follow-up of 52 weeks was inadequate for capturing the long-term safety of ruxolitinib cream (including rare harms), given that AD is a lifelong condition requiring treatment over many years. The absence of head-to-head evidence comparing ruxolitinib cream with relevant comparators (systemic immunosuppressants, biologics, and JAK inhibitors) in patients with moderate AD, and evidence for ruxolitinib cream in combination with other topical therapies, represents gaps in evidence in the treatment of AD. Generalizability of study results to the adolescent patient population in clinical practice could potentially be limited by the small proportion of adolescents enrolled in the trials (approximately 20%). Of note, a similarly small proportion of adolescent patients was observed in other clinical trials for AD treatments.

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 the 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.

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:

- Severity and extent of AD (proportion of patients achieving IGA-TS, IGA 0/1, and EASI-75; change in percent BSA affected by AD from baseline)
- Symptom control (proportion of patients achieving at least a 4-point improvement in Itch NRS score from baseline, at least a 6-point improvement in PROMIS Short Form — Sleep Disturbance score from baseline, at least a 6-point improvement in PROMIS Short Form — Sleep-Related Impairment score from baseline; change in POEM score from baseline)
- HRQoL (change in DLQI and CDLQI scores from baseline)
- Harms (serious AEs).

The GRADE summary of findings for ruxolitinib 1.5% cream versus the vehicle cream for the treatment of patients with AD is presented in [Table 1](#).

Table 1: Summary of Findings for Ruxolitinib 1.5% Cream Versus Vehicle Cream for Patients With Mild to Moderate Atopic Dermatitis Whose Disease Is Not Adequately Controlled With Topical Therapies or When Those Therapies Are Not Advisable

Outcome and follow-up	Patients (studies), N	Absolute effect	Certainty	What happens
Extent and severity of disease				
IGA-TS (i.e., IGA score 0 [clear] or 1 [almost clear] with ≥ 2 -point reduction from baseline), proportion of patients achieving IGA-TS (95% CI) Follow-up: 8 weeks	725 (2 RCTs)	TRuE-AD1: - Ruxolitinib: 538 per 1,000 (NR) - Vehicle cream: 151 per 1,000 (NR) - Difference: 387 more per 1,000 (299 more to 474 more per 1,000) TRuE-AD2: - Ruxolitinib: 513 per 1,000 (NR) - Vehicle cream: 76 per 1,000 (NR) - Difference: 437 more (356 more to 518 more per 1,000)	Moderate ^{a,b}	Ruxolitinib 1.5% cream likely results in a clinically important increase in IGA-TS response when compared with placebo.
IGA score (5-point scale, 0 [clear] to 4 [severe]), proportion of patients achieving IGA score of 0 (clear) or 1 (almost clear) (95% CI) Follow-up: 52 weeks	423 (noncomparative from 2 RCTs)	TRuE-AD1: - Ruxolitinib: 754 per 1,000 (NR) - Vehicle cream to ruxolitinib: 737 per 1,000 (NR) - Difference: NA TRuE-AD2: - Ruxolitinib: 801 per 1,000 (NR) - Vehicle cream to ruxolitinib: 744 per 1,000 (NR) - Difference: NA	Very low ^c	The evidence is very uncertain about the effect of ruxolitinib 1.5% cream on achieving an IGA score of 0 or 1 when compared with any comparator.
EASI score (0 [clear] to 72 [very severe]), proportion of patients achieving EASI-75 (i.e., at least 75% reduction in score from baseline) (95% CI) Follow-up: 8 weeks	725 (2 RCTs)	TRuE-AD1: - Ruxolitinib: 621 per 1,000 (NR) - Vehicle cream: 246 per 1,000 (NR) - Difference: 375 more per 1,000 (278 more to 471 more per 1,000) TRuE-AD2: - Ruxolitinib: 618 per 1,000 (NR) - Vehicle cream: 144 per 1,000 (NR) - Difference: 474 more (385 more to 564 more per 1,000)	Moderate ^{a,b}	Ruxolitinib 1.5% cream likely results in a clinically important increase in EASI-75 response when compared with placebo.
LSM change from baseline in AD-affected %BSA, % (95% CI) Follow-up: 8 weeks	652 (2 RCTs)	TRuE-AD1: - Ruxolitinib: -6.7% (NR) - Vehicle cream: -3.0% (NR) - Difference: -3.7% (-4.7% to -2.8%)^d	Low ^{b,e,f}	Ruxolitinib 1.5% cream may result in little to no clinically important difference in percent BSA-affected by AD

Outcome and follow-up	Patients (studies), N	Absolute effect	Certainty	What happens
		TRuE-AD2: - Ruxolitinib: -6.7% (NR) - Vehicle cream: -2.2% (NR) - Difference: -4.5% (-5.5% to -3.6%)^d		when compared with placebo.
Change from baseline in AD-affected %BSA, % (95% CI) Follow-up: 52 weeks	424 (noncomparative from 2 RCTs)	TRuE-AD1: - Ruxolitinib: -8.1% (NR) - Vehicle cream to ruxolitinib: -4.9% (NR) - Difference: NA TRuE-AD2: - Ruxolitinib: -8.4% (NR) - Vehicle cream to ruxolitinib: -6.8% (NR) - Difference: NA	Very low ^c	The evidence is very uncertain about the effect of ruxolitinib 1.5% cream on percent BSA affected by AD when compared with any comparator.
Symptom control				
Itch NRS score (0 [no itch] to 10 [worst imaginable itch]), proportion of patients with ≥ 4 point improvement from baseline (95% CI) Follow-up: 8 weeks	465 (2 RCTs)	TRuE-AD1: - Ruxolitinib: 522 per 1,000 (NR) - Vehicle cream: 154 per 1,000 (NR) - Difference: 368 more per 1,000 (257 more to 479 more per 1,000) TRuE-AD2: - Ruxolitinib: 507 per 1,000 (NR) - Vehicle cream: 163 per 1,000 (NR) - Difference: 344 more per 1,000 (230 more to 459 more per 1,000)	Low ^{b,g}	Ruxolitinib 1.5% cream may result in a clinically important increase in the proportion of patients with ≥ 4 point improvement in Itch NRS score when compared with placebo.
POEM score (0 [clear] to 28 [very severe]), LSM change from baseline in score (95% CI) Follow-up: 8 weeks	635 (2 RCTs)	TRuE-AD1: - Ruxolitinib: -11.5 (NR) - Vehicle cream: -5.2 (NR) - Difference: -6.3 (-7.6 to -5.0)^d TRuE-AD2: - Ruxolitinib: -10.0 (NR) - Vehicle cream: -4.0% (NR) - Difference: -5.9 (-7.2 to -4.7)^d	Low ^{b,e,h}	Ruxolitinib 1.5% cream may result in a clinically important improvement in POEM score when compared with placebo.
POEM score (0 [clear] to 28 [very severe]), change from baseline in score (95% CI) Follow-up: 52 weeks	412 (noncomparative from 2 RCTs)	TRuE-AD1: - Ruxolitinib: -10.6 (NR) - Vehicle cream to ruxolitinib: -7.0 (NR) - Difference: NA TRuE-AD2: - Ruxolitinib: -10.7 (NR) - Vehicle cream to ruxolitinib: -6.3	Very low ^c	The evidence is very uncertain about the effect of ruxolitinib 1.5% cream on POEM score when compared with any comparator.

Outcome and follow-up	Patients (studies), N	Absolute effect	Certainty	What happens
		(NR) • Difference: NA		
PROMIS Short Form — Sleep Disturbance score (8 [no disturbance] and 40 [severe disturbance]), proportion of patients with ≥ 6 -point improvement (24-hour recall) from baseline (95% CI) Follow-up: 8 weeks	675 (2 RCTs)	TRuE-AD1: • Ruxolitinib: 223 per 1,000 (NR) • Vehicle cream: 95 per 1,000 (NR) • Difference: 128 more per 1,000 (53 more to 203 more per 1,000) TRuE-AD2: • Ruxolitinib: 256 per 1,000 (NR) • Vehicle cream: 191 per 1,000 (NR) • Difference: 65 more per 1,000 (29 less to 159 more per 1,000)	Low ^{a,b,i}	Ruxolitinib 1.5% cream may result in a clinically important increase in proportion of patients with ≥ 6 -point improvement in PROMIS Short Form — Sleep Disturbance score when compared with placebo.
PROMIS Short Form — Sleep-Related Impairment score (8 [no impairment] and 40 [severe impairment]), proportion of patients with ≥ 6 -point improvement (24-hour recall) from baseline (95% CI) Follow-up: 8 weeks	682 (2 RCTs)	TRuE-AD1: • Ruxolitinib: 216 per 1,000 (NR) • Vehicle cream: 132 per 1,000 (NR) • Difference: 84 more per 1,000 (4 more to 164 more per 1,000) ^j TRuE-AD2: • Ruxolitinib: 231 per 1,000 (NR) • Vehicle cream: 135 per 1,000 (NR) • Difference: 96 more per 1,000 (14 more to 184 more per 1,000) ^j	Low ^{a,b,k}	Ruxolitinib 1.5% cream may result in a clinically important increase in the proportion of patients with ≥ 6 -point improvement in PROMIS Short Form — Sleep Disturbance score when compared with placebo.
HRQoL				
DLQI score (0 [best] to 30 [worst]), LSM change from baseline in score (95% CI) Follow-up: 8 weeks	555 (2 RCTs)	TRuE-AD1: • Ruxolitinib: -7.5 (NR) • Vehicle cream: -3.1 (NR) • Difference: -4.5 (-5.6 to -3.4) ^d TRuE-AD2: • Ruxolitinib: -6.3 (NR) • Vehicle cream: -3.5 (NR) • Difference: -2.8 (-3.7 to -1.8) ^d	Low ^{b,e,l}	Ruxolitinib 1.5% cream may result in a clinically important improvement in DLQI score when compared with placebo.
DLQI score (0 [best] to 30 [worst]), change from baseline in score (95% CI) Follow-up: 52 weeks	362 (noncomparative from 2 RCTs)	TRuE-AD1: • Ruxolitinib: -7.7 (NR) • Vehicle cream to ruxolitinib: -4.8 (NR) • Difference: NA TRuE-AD2: • Ruxolitinib: -7.3 (NR) • Vehicle cream to ruxolitinib: -3.2 (NR) • Difference: NA	Very low ^c	The evidence is very uncertain about the effect of ruxolitinib 1.5% cream on DLQI score when compared with any comparator.

Outcome and follow-up	Patients (studies), N	Absolute effect	Certainty	What happens
CDLQI score (0 [best] to 30 [worst]), LSM change from baseline in score (95% CI) Follow-up: 8 weeks	80 (2 RCTs)	TRuE-AD1: - Ruxolitinib: -6.1 (NR) - Vehicle cream: -3.8 (NR) - Difference: -2.3 (-4.4 to -0.1)^d TRuE-AD2: - Ruxolitinib: -4.4 (NR) - Vehicle cream: -1.3 (NR) - Difference: -3.1 (-6.3 to 0.1)^d	Low ^{b,m}	Ruxolitinib 1.5% cream may result in little to no clinically important improvement in CDLQI score when compared with placebo.
CDLQI score (0 [best] to 30 [worst]), change from baseline in score (95% CI) Follow-up: 52 weeks	50 (noncomparative from 2 RCTs)	TRuE-AD1: - Ruxolitinib: -9.7 (NR) - Vehicle cream to ruxolitinib: -0.4 (NR) - Difference: NA TRuE-AD2: - Ruxolitinib: -6.6 (NR) - Vehicle cream to ruxolitinib: -6.4 (NR) - Difference: NA	Very low ^c	The evidence is very uncertain about the effect of ruxolitinib 1.5% cream on CDLQI score when compared with any comparator.
Harms				
Serious adverse events Follow-up: 8 weeks	749 (2 RCTs)	TRuE-AD1: - Ruxolitinib: 8 per 1,000 (NR) - Vehicle cream: 16 per 1,000 (NR) - Difference: NR TRuE-AD2: - Ruxolitinib: 4 per 1,000 (NR) - Vehicle cream: 0 per 1,000 (NR) - Difference: NR	Moderate ⁿ	Ruxolitinib 1.5% cream likely results in little to no clinically important difference in serious adverse events when compared with placebo.
Serious adverse events Follow-up: 52 weeks	545 (noncomparative from 2 RCTs)	TRuE-AD1: - Ruxolitinib: 13 per 1,000 (NR) - Vehicle cream to ruxolitinib: 21 per 1,000 (NR) - Difference: NA TRuE-AD2: - Ruxolitinib: 14 per 1,000 (NR) - Vehicle cream to ruxolitinib: 0 per 1,000 (NR) - Difference: NA	Very low ^c	The evidence is very uncertain about the effect of ruxolitinib 1.5% cream on the frequency of serious adverse events when compared with any comparator.

AD = atopic dermatitis; BSA = body surface area; CDLQI = Children's Dermatology Life Quality Index; CI = confidence interval; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; HRQoL = health-related quality of life; IGA = Investigator Global Assessment; IGA-TS = Investigator Global Assessment Treatment Success; LSM = least squares mean; NA = not applicable; NR = not reported; NRS = Numeric Rating Scale; POEM = Patient-Oriented Eczema Measure; PROMIS = Patient-Reported Outcomes Measurement Information System; RCT = randomized controlled trial.

Note: Study limitations (which refers 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.

^aDid not rate down for study limitations. There was a notable imbalance in the mean number of flares in the past 12 months at baseline between treatment groups in the TRuE-AD1 trial, which could potentially result in a bias in favour of ruxolitinib cream as per clinical expert input. Such an imbalance was not observed in the identically designed TRuE-AD2 study, which showed similar results to the TRuE-AD1 trial. The imbalance noted in the TRuE-AD1 trial was compatible with chance.

^bRated down 1 level for serious indirectness. The clinical experts consulted for this review anticipated that, in most patients, ruxolitinib cream would be used when AD is inadequately controlled with TCS and/or TCI treatment or these treatments are inadvisable. It is unclear if the trial population was reflective of the patient population in clinical practice because the inclusion and exclusion criteria of the trial did not restrict entry based on prior experience with TCS and TCI treatment. Other considerations included the lower proportion of patients with mild disease (IGA score of 2) at baseline in trials versus clinical practice. Baseline IGA score is a potential treatment effect modifier as per clinical expert input.

^cIn the absence of a comparator arm, conclusions about efficacy relative to any comparator cannot be drawn, and the certainty of evidence started at very low without an opportunity to rate up.

^dStatistical testing for this outcome was not adjusted for multiplicity. The results are considered as supportive evidence.

^eRated down 1 level for serious study limitations. Study treatment discontinuation in the vehicle-controlled period was notably higher in the vehicle cream group compared to the ruxolitinib cream group in both trials, which could potentially lead to attrition bias in favour of ruxolitinib cream. It is unclear if the imputation method used was appropriate to account for missing data. Did not rate down for imbalance in mean number of flares at baseline, which was considered by the review team to be compatible with chance.

^fThe clinical experts consulted for this review indicated that a 5% to 10% between-group difference could be considered clinically important. Based on the lower limit of the minimal important difference (MID) estimates (i.e., 5% difference), did not rate down for imprecision; the 95% CI in the TRuE-AD2 trial included the possibility of benefit and no difference; however, this was not considered to be a source of serious imprecision due to its proximity to -5%. Note that if the upper limit of the MID (i.e., 10% difference) was used instead, the review team would not rate down imprecision, given that both 95% CIs excluded the possibility of benefit. The overall rating of certainty would remain as low.

^gRated down 1 level for serious study limitations. A large proportion of patients with a baseline score of less than 4 (at least 30% in each treatment group) were excluded from the analysis, which could potentially impact randomization. The extent and direction of the resulting bias is, however, unclear.

^hLiterature-identified MID estimates ranged between 3.4 and 5 points. Did not rate down imprecision regardless of whether the lower or upper limit of MID estimates was used. Based on the lower limit of MID estimates (i.e., 3.4-point difference), both 95% CIs included the possibility of benefit. Based on the upper limit of MID estimates (i.e., 5-point difference), although the upper boundary of the 95% CI in the TRuE-AD1 and TRuE-AD2 trials was -5.0 and -4.7 respectively, this was not considered to be a source of serious imprecision due to its proximity to -5.

ⁱRated down 1 level for serious imprecision. Based on clinical expert input, 50 more per 1,000 patients achieving at least a 6-point improvement (24-hour recall) from baseline in PROMIS Short Form — Sleep Disturbance score could be considered clinically important. The 95% CI in the TRuE-AD2 trial included the possibility of benefit and no difference.

^jNo formal statistical testing was conducted due to prior failure in the statistical testing hierarchy (PROMIS Short Form — Sleep Disturbance score). The findings can be considered supportive.

^kRated down 1 level for serious imprecision. Based on clinical expert input, 50 more per 1,000 patients achieving at least a 6-point improvement (24-hour recall) from baseline in PROMIS Short Form — Sleep Impairment score could be considered clinically important. Both 95% CIs included the possibility of benefit and no difference.

^lLiterature-identified MID estimates ranged between 3 and 5 points. The review team considered the treatment effect to be clinically important, given that the point estimates in both trials were above or in close proximity to the lower limit of the MID estimate (i.e., 3-point difference). The upper bound of the CI in the TRuE-AD1 trial indicates no clinically important difference, but the review team recognized that there is some uncertainty about whether the literature-identified MID could be reliably applied to the analysis of the between-group difference in change from baseline and, thus, did not rate down on imprecision.

^mRated down 1 level for serious study limitations. There is a potential that the prognostic balance provided by the randomization is not fully preserved in this analysis because it was conducted in a small subset of patients, with no stratification involved. Literature-identified MID estimates ranged between 6 and 8 points. Based on the lower limit of MID estimates (i.e., 6-point difference), the review team did not rate down further for imprecision even though the lower boundary of the 95% CI was -6.3; this was not considered to be a source of serious imprecision due to its proximity to -6. Note that the rating of imprecision remains the same if the upper limit of MID estimates (i.e., 8-point difference) was used instead.

ⁿRated down 1 level for serious indirectness. The duration of follow-up of 8 weeks is inadequate for capturing potential rare serious adverse events of ruxolitinib cream, as per clinical expert input.

Source: Clinical Study Reports for the TRuE-AD1 and TRuE-AD2 trials. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

Both the TRuE-AD1 and TRuE-AD2 trials had a 44-week extension phase assessing the efficacy and safety of ruxolitinib cream in patients who completed the 8-week vehicle-controlled period. Evidence from the extension phase was submitted as part of the pivotal trials and is summarized in the Systematic Review section.

Indirect Comparisons

Description of Study

In the absence of head-to-head evidence comparing ruxolitinib cream to other relevant therapies used in the treatment of mild to moderate AD, the sponsor submitted 1 indirect treatment comparison indirectly

comparing the treatment effect of ruxolitinib 1.5% cream to dupilumab, abrocitinib, and upadacitinib in patients with moderate AD, defined by the sponsor as an IGA score of 3, EASI score of 16 or higher, and percent affected BSA of 10% or higher, via a frequentist NMA. Study outcomes included the proportion of patients achieving IGA-TS, EASI-75, and improvement in Itch NRS score of at least 4. No information on comparative harms was submitted. A total of 8 studies were included in the NMA.

Efficacy Results

IGA Treatment Success

There was insufficient evidence to show a difference comparing ruxolitinib cream versus upadacitinib 30 mg and 15 mg and versus dupilumab 300 mg because the 95% CIs for the odds ratios (ORs) were wide (comparing ruxolitinib 1.5% cream versus upadacitinib 30 mg, OR = 2.10 [95% CI, 0.10 to 44.41]; versus upadacitinib 15 mg, OR = 3.60 [95% CI, 0.17 to 76.04]; versus dupilumab 300 mg, OR = 6.69 [95% CI, 0.32 to 140.26]). Comparisons with abrocitinib 200 mg and 100 mg were not present in the evidence network for IGA-TS.

Eczema Area and Severity Index 75

There was insufficient evidence to show a difference comparing ruxolitinib cream versus upadacitinib 30 mg and 15 mg, dupilumab 300 mg, and abrocitinib 200 mg and 100 mg because the 95% CIs for the ORs were wide (comparing ruxolitinib 1.5% cream versus upadacitinib 30 mg, OR = 1.56 [95% CI, 0.22 to 11.03]; versus upadacitinib 15 mg, OR = 2.56 [95% CI, 0.36 to 18.12]; versus dupilumab 300 mg, OR = 3.36 [95% CI, 0.47 to 23.87]; versus abrocitinib 200 mg, OR = 1.52 [95% CI, 0.17 to 13.39]; versus abrocitinib 100 mg OR = 3.10 [95% CI, 0.35 to 27.32]).

Itch NRS-4

There was insufficient evidence to show a difference comparing ruxolitinib cream versus upadacitinib 30 mg and 15 mg and versus dupilumab 300 mg because the 95% CIs for the ORs were wide (upadacitinib 30 mg versus ruxolitinib 1.5% cream, OR = 2.42 [95% CI, 0.46 to 12.79]; upadacitinib 15 mg versus ruxolitinib 1.5% cream, OR = 1.65 [95% CI, 0.31 to 8.74]; dupilumab 300 mg versus ruxolitinib 1.5% cream, OR = 1.19 [95% CI, 0.22 to 6.32]). Comparisons with abrocitinib 200 mg and 100 mg were not present in the evidence network for Itch NRS-4.

Harms Results

Harms outcomes were not assessed.

Critical Appraisal

The validity of the results of the NMA was uncertain because the key assumptions of the analysis, homogeneity, and consistency could not be determined due to insufficient reporting of baseline patient characteristics in the moderate-only subgroup and a sparse network without a closed loop connecting ruxolitinib cream. For trials for which the information was available, there was evidence of heterogeneity in patient populations (i.e., age group; history of disease control with, or eligibility for, topical AD treatment) between studies. Only 4 of 12 included studies reported baseline patient characteristics of the moderate-only subgroup; heterogeneity in disease severity and duration of AD diagnosis were noted between these

studies and were not accounted for. These limitations result in uncertainty in the relative treatment effect estimates between ruxolitinib cream and the comparators. It is worth noting that there is a risk of missing results in the synthesis, given that close to half of the studies initially identified by the systematic literature review were excluded due to the absence of available results for subgroups consisting solely of moderate severity. Lastly, the absence of comparative evidence between ruxolitinib cream monotherapy and systemic immunosuppressants in patients with moderate AD, and the absence of comparative evidence for ruxolitinib cream as a combination therapy (in combination with other topical treatments), represent gaps in evidence in the treatment of AD.

Studies Addressing Gaps in the Evidence From the Systematic Review

Description of Studies

One phase II, open-label study (SCRATCH-AD) at a single Canadian site has been provided as supportive evidence regarding short-term clinical benefits of ruxolitinib 1.5% cream in adults with AD to control itch and reduce severity. The maximum study duration per participant was approximately 80 days, including the run-in period in which participants had a baseline mean Peak Pruritus NRS (PP-NRS) score of at least 4.0 during days -7 to -1. Other key inclusion criteria were BSA involvement of 1% to 20% and an IGA score of 2 or more on day 1. Key exclusion criteria were significant flares in the previous 4 weeks, known immune deficiency or immunocompromised condition, use of any systemic corticosteroids or phototherapy, JAK inhibitor use within 4 weeks prior, and dupilumab use within 26 weeks before the run-in period. Patients received ruxolitinib 1.5% cream applied topically twice daily (morning and evening, with approximately 12 hours between applications) from day 1 until the day before the day 29 visit. The primary end point was change from baseline PP-NRS at day 2 (24-hour recall period after the first application), and all data were analyzed descriptively. Concomitant use of emollient was permitted. No other concomitant AD treatments were permitted.

Of 84 individuals who were screened, 35 (41.7%) did not pass the screening. Forty-nine participants applied ruxolitinib 1.5% at least once (safety population), and 46 patients completed the run-in period, met all entry criteria, and had a baseline and at least 1 postbaseline PP-NRS or mPP-NRS assessment (modified intention-to-treat population). In the safety population (n = 49), the average age of participants was 35.6 years (standard deviation [SD] = 14.77 years), and the majority of participants were female (71.4%) and white (85.7%). At baseline, mean total percent BSA affected was 10.11% (SD = 5.34) and mean baseline EASI score was 7.23 (SD = 3.21). A mean PP-NRS score was 6.83 (SD = 1.4), and the majority of participants (87.8%) had an IGA score of 3. During the study period, the median cumulative dose was 110.30 g (range = 2.4 to 335.9, n = 48), and the majority of participants (73.5%) used emollients and protectives, other analgesics and antipyretics (36.7%), NSAIDs and antirheumatic products (28.6%), inhaled adrenergics (22.4%), and vitamins A and D, including combinations of the 2 (20.4%).

Efficacy Results

On day 2, a mean 3.37-point (SD = 1.85 points) or 50.57% (95% CI, 58.75% to 42.39%) reduction from baseline in PP-NRS (worst itch in the previous 24 hours) score was noted in the modified intention-to-treat population. The mean daily PP-NRS score decreased by 4.78 points (SD not reported) by day 7, with a

continued decrease; that is, a 5.68-point reduction (SD not reported) by day 29. In the modified intention-to-treat population, increasing proportions of participants achieved IGA-TS at days 8, 15, and 29; that is, 45.5% (95% CI, 30.4% to 61.2%), 71.1% (95% CI, 55.7% to 83.6%), and 77.3% (95% CI, 62.2% to 88.5%), respectively. The mean change from baseline in IGA score at days 8, 15, and 29 was -1.4 (SD = 0.73), -2.0 (SD = 0.87), and -2.2 (SD = 0.90), respectively.

Harms Results

Approximately one-third of participants (n = 15, 30.6%) had at least 1 TEAE. The most frequently reported TEAEs were COVID-19 (6.1%), and back pain, nasopharyngitis, headache, and upper respiratory infection (4.1% each). One participant (2.0%) had an application site reaction (acne), which resolved with no change to study treatment. There were no deaths, serious AEs, or TEAEs leading to study treatment interruption or discontinuation.

Critical Appraisal

The main limitation of the SCRATCH-AD trial was the single-arm design. The lack of a relevant comparator renders it impossible to draw causal conclusions about the comparative efficacy of ruxolitinib 1.5% cream with respect to other treatment options or to vehicle cream. Interpretation of the changes from baseline is complicated because they may be due to the intervention, concomitant treatments, a placebo effect, and/or natural history. Additionally, there is a potential risk of bias due to the open-label design. Patients were aware of the treatment and self-reported subjective outcomes, which may have resulted in overestimation of the change from baseline. The analyses were done in fewer than 50 patients (safety and modified intention-to-treat populations), which could add uncertainty to the efficacy results. Because the SCRATCH-AD trial was conducted in a single study site located in Quebec, its study findings largely have a good generalizability to the clinical practice in Canada, except for less-than-ideal representation of the Indigenous population in which AD is common.

Economic Evidence

Cost and Cost-Effectiveness

Table 2: Summary of the Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	- Base case: Patients 12 years of age and older with mild or moderate AD (aligned with the TRuE-AD pivotal trials) - Scenario analysis: Patients 12 years of age and older with moderate AD
Treatment	Ruxolitinib cream
Dose regimen	Applied twice daily to affected skin areas (maximum of 20% BSA for each application) for 8 weeks, and as needed thereafter

Component	Description
Submitted price	\$1,075.97 per 100 g tube
Submitted treatment costs	First year: \$ [REDACTED] per person (based on [REDACTED] tubes per year) ^a Subsequent years: \$ [REDACTED] per person (based on [REDACTED] tubes per year) ^a
Comparator(s)	Base case: • No active treatment^b Moderate AD scenario: • Abrocitinib • Dupilumab • Upadacitinib
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (50 years)
Key data source	Effectiveness of ruxolitinib cream was informed by the TRuE-AD1 and TRuE-AD2 trials in the sponsor's base case. In the moderate AD scenario analysis, the effectiveness of abrocitinib, dupilumab, and upadacitinib was informed by the sponsor-conducted NMA.
Key limitations	• Ruxolitinib cream is indicated for patients whose AD is not adequately controlled with conventional topical prescription therapies (TCS, TCI) or when those therapies are not advisable. Efficacy inputs for the sponsor's economic evaluation were obtained from the TRuE-AD 1 and TRuE-AD2 trials, which did not restrict eligibility based on prior treatment experience. Although the sponsor provided subgroup data for patients with a history of TCS and TCI use, these data were not used in the economic model. • 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 patients who do not achieve adequate disease control with topical treatments may try, for example, systemic immunosuppressants (e.g., methotrexate, cyclosporine) or advanced systemic therapies (i.e., abrocitinib, upadacitinib, dupilumab). • It is uncertain whether ruxolitinib cream provides a clinical benefit relative to other treatments for mild to moderate AD due to limitations in the clinical evidence submitted by the sponsor. There have been no head-to-head trials of ruxolitinib cream to any relevant comparator, and the sponsor deemed that an ITC for the full indicated population was not feasible. The CDA-AMC clinical review concluded that the submitted ITC for the moderate AD subgroup was insufficient to determine whether ruxolitinib cream would be associated with different clinical outcomes relative to abrocitinib, dupilumab, and upadacitinib, owing to methodological limitations and imprecision. • The long-term effectiveness of ruxolitinib cream is highly uncertain owing to a lack of clinical data beyond 52 weeks, and treatment effectiveness waning was not considered by the sponsor. If long-term effectiveness is lower than anticipated, patients who continue to use ruxolitinib cream may require more tubes per year than assumed in the sponsor's analysis, and hence, the drug acquisition costs will be higher than predicted. • The sponsor assumed that [REDACTED] tubes of ruxolitinib cream would be used in the first year of treatment, which is less than would be required based on observations from the TRuE-AD trials ([REDACTED] tubes, based on mean weight of ruxolitinib cream of [REDACTED] g in TRuE-AD1 and [REDACTED] g in TRuE-AD2). Clinical expert input received by CDA-AMC indicated that the amount of ruxolitinib cream required is expected to fluctuate over time based on the frequency and extent of AD flares. • The sponsor assumed that all patients who do not have an adequate treatment response at

Component	Description
	the end of the 8-week induction period or who later discontinue initial treatment will receive dupilumab as subsequent therapy, which implicitly assumes that patients with mild AD will have progressed to moderate AD after 8 weeks of no active treatment. The cost savings predicted by the sponsor's base case with ruxolitinib cream compared to no active treatment are due to the lower drug acquisition costs of subsequent treatment. However, whether any cost savings will be realized in clinical practice is highly uncertain because there are several agents that are less costly than dupilumab that could be used as subsequent therapy (e.g., immunosuppressants). • In the sponsor's model, from week 12 onward, patients could discontinue ruxolitinib cream or no active treatment on the basis of AEs or inadequate treatment response. CDA-AMC notes that it is not possible to discontinue no active treatment in practice; discontinuation because of a lack of response is accounted for at week 8 in the model; long-term AEs are unlikely to occur for patients who do not receive active treatment; and discontinuation rates from the 8-week pivotal trials are unlikely to be applicable over the entire 50-year model horizon. • The cost-effectiveness of ruxolitinib cream in adolescents is uncertain. The estimated effectiveness and utility values used in the sponsor's analyses were based on clinical trials that enrolled predominantly adult patients. As noted in the CDA-AMC clinical review, this may limit the generalizability of study results to adolescents in clinical practice. Clinical expert input received by CDA-AMC indicated that adherence to topical treatments may be lower among adolescents, which may affect drug acquisition costs and, hence, cost-effectiveness estimates.
CDA-AMC reanalysis results	• CDA-AMC undertook reanalyses that addressed some of the identified limitations, including excluding subsequent treatment, aligning the number of ruxolitinib cream tubes in the first year of treatment with observations from the TRuE-AD pivotal trials, and adopting a 1-year horizon. CDA-AMC was unable to address the remaining limitations, including uncertainty as to whether the trial population (and hence the cost-effectiveness estimates) adequately reflect the Health Canada indication. • Results suggest that ruxolitinib cream is more costly (incremental costs: \$6,747) and more effective (incremental QALYs: 0.04) than no active treatment, resulting in an ICER of \$151,361 per QALY gained. A price reduction of at least 68% would be required for ruxolitinib cream to be cost-effective compared to no active treatment at a willingness-to-pay threshold of \$50,000 per QALY gained.

AD = atopic dermatitis; AE = adverse event; BSA = body surface area; CDA-AMC = Canada's Drug Agency; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; LY = life-year; NMA = network meta-analysis; QALY = quality-adjusted life-year; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid.

^aTreatment cost was estimated by the sponsor based on observations from the TRuE-AD trials (BSA affected by AD, cream used per BSA affected, reduction in BSA affected by AD, and percentage of days on treatment).

^bIn the base case, the sponsor compared ruxolitinib cream to vehicle cream (from the TRuE-AD trials), which contained no active ingredient (i.e., ruxolitinib).

Budget Impact

CDA-AMC identified several key limitations with the sponsor's analysis. The treatment cost of ruxolitinib was underestimated in that the number of tubes used was not aligned with observations from the TRuE-AD trials. Higher ruxolitinib cream usage in the first year of treatment (compared to subsequent years) was not considered, which underestimated ruxolitinib acquisition costs. The market share and displacement of comparators were uncertain. The prices of comparators paid by public drug plans were also uncertain.

The CDA-AMC reanalysis included aligning the eligible population with the Health Canada indication (mild to moderate AD) and aligning the number of tubes of ruxolitinib cream used in year 1 with data from the TRuE-AD trials. Based on CDA-AMC reanalyses, reimbursing ruxolitinib cream for use by patients with

mild to moderate AD may be cost-saving to the public drug plans (3-year cost savings of \$39,727,424). This estimate was driven by the displacement of dupilumab, which has a higher annual cost than ruxolitinib cream (based on the sponsor's submitted price of ruxolitinib cream and the public list price of dupilumab). However, if the price paid by the public drug plans for dupilumab is at least 32% lower than the public list price, reimbursing ruxolitinib cream for mild to moderate AD will not be cost-saving. In the mild AD subgroup, the CDA-AMC scenario analysis suggested that reimbursement of ruxolitinib cream was expected to be associated with incremental costs to the public drug plans, given that the more expensive advanced systemic treatments are not indicated for this subgroup, and ruxolitinib cream would displace less costly treatments (e.g., systemic immunosuppressants).

Request for Reconsideration

The sponsor filed a request for reconsideration of the draft recommendation for ruxolitinib cream for the topical treatment of mild to moderate AD in adult and pediatric patients 12 years of age and older whose disease is not adequately controlled with conventional topical prescription therapies (TCS, TCI) or when those therapies are not advisable. In their request, the sponsor identified the following issues:

- The sponsor states that CDA-AMC and CDEC did not recognize that the evidence provided is aligned with the indicated and anticipated-use population and have thus disregarded all evidence for efficacy and safety, including intent-to-treat analyses, subgroup analyses, and indirect comparisons.
- Supporting evidence (not included in the initial submission) presented by the sponsor in the reconsideration request included ad hoc subgroup analyses of the participants of the TRuE-AD1 and TRuE-AD2 trials who discontinued prior TCS or TCI therapies due to toxicity, side effects, or lack of efficacy. The analysis indicated that [REDACTED] out of [REDACTED] patients in the pooled ruxolitinib 1.5% cream group and [REDACTED] out of [REDACTED] patients in the pooled vehicle cream group (from TRuE-AD1 and TRuE-AD2 trials) who discontinued prior TCS or TCI therapies due to toxicity, side effects, or lack of efficacy. Results of the analysis showed that, in the patient subgroup, [REDACTED] of patients achieved IGA-TS at week 8 in the ruxolitinib 1.5% cream group compared to [REDACTED] in the vehicle cream group ([REDACTED]). The proportions of patients achieving EASI-75 in this subgroup were [REDACTED] in the ruxolitinib 1.5% cream group and [REDACTED] in the vehicle cream group ([REDACTED]). Other subgroup analyses presented in the reconsideration request included analyses of a patient subgroup that had a prior TCS or TCI in the last 30 days before screening and discontinued prior TCS or TCI therapies due to toxicity, side effects, or lack of efficacy, and a subgroup of patients with moderate AD who discontinued prior TCS or TCI therapies due to toxicity, side effects, or a lack of efficacy. The submitted data were made available to CDEC for the purpose of reconsideration. However, evidence from the new ad hoc subgroup analyses was not critically appraised by the CDA-AMC review team.
- The sponsor states that CDA-AMC and CDEC should recognize that the submitted evidence provides comparative indirect evidence versus relevant active comparators and direct evidence versus placebo aligned with the indicated and intended population.

- The sponsor notes that CDA-AMC acknowledged the treatment effect for DLQI to be clinically important within Table 3 of the recommendation, but this was not reflected within the HRQoL discussion throughout the recommendation.
- The sponsor notes that CDA-AMC acknowledged the long-term safety data that exist for ruxolitinib 1.5% cream but did not consider it, citing it was out of scope. CDA-AMC noted analyses beyond week 8 were noncomparative; however, according to the sponsor, obtaining comparative data past this point would raise ethical concerns.
 - Supporting evidence (not included in the initial submission) presented by the sponsor in the reconsideration request included additional TRuE-AD1 and TRuE-AD2 safety data, long-term safety data reported for vitiligo, the real-world use study, the maximum-use study for AD, and the low systemic absorption as presented in the preclinical study. The submitted data were made available to CDEC for the purpose of reconsideration. However, these studies were not critically appraised by the CDA-AMC review team.

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 AD
- Feedback on the draft recommendation from 2 patient groups, including the Eczema Society of Canada and the Canadian Skin Patient Alliance
- Feedback on the draft recommendation from 2 clinician groups, including the Canadian Dermatology Association and a group of clinicians in Alberta
- Feedback on the draft recommendation from the public drug plans that participate in the reimbursement review process
- Feedback on the draft recommendation from the sponsor.

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

CDEC Information

Members of the Committee at the Initial Meeting

Dr. Peter Jamieson (Chair), Dr. Sally Bean, Daryl Bell, Dan Dunskey, 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.

Members of the Committee at the Reconsideration Meeting

Dr. Peter Jamieson (Chair), Dr. Sally Bean, Daryl Bell, Dan Dunskey, 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.

Initial meeting date: November 27, 2024

Regrets: One expert committee member did not attend.

Conflicts of interest: None

Reconsideration Meeting date: April 24, 2025

Regrets: One expert committee member 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

Canada's Drug Agency (CDA-AMC) is a pan-Canadian health organization. Created and funded by Canada's federal, provincial, and territorial governments, we're responsible for driving better coordination, alignment, and public value within Canada's drug and health technology landscape. We provide Canada's health system leaders with independent evidence and advice so they can make informed drug, health technology, and health system decisions, and we collaborate with national and international partners to enhance our collective impact.

Disclaimer: CDA-AMC has taken care to ensure that the information in this document was accurate, complete, and up to date when it was published, but does not make any guarantee to that effect. Your use of this information is subject to this disclaimer and the Terms of Use at cda-amc.ca.

The information in this document is made available for informational and educational purposes only and should not be used as a substitute for professional medical advice, the application of clinical judgment in respect of the care of a particular patient, or other professional judgments in any decision-making process. You assume full responsibility for the use of the information and rely on it at your own risk.

CDA-AMC does not endorse any information, drugs, therapies, treatments, products, processes, or services. The views and opinions of third parties published in this document do not necessarily reflect those of CDA-AMC. The copyright and other intellectual property rights in this document are owned by the Canadian Agency for Drugs and Technologies in Health (operating as CDA-AMC) and its licensors.

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