

Reimbursement Review

Ritlecitinib (Litfulo)

Sponsor: Pfizer Canada ULC

Therapeutic area: Alopecia areata

Summary

What Is Alopecia Areata?

- Alopecia areata (AA) is the second most common cause of nonscarring hair loss after female or male pattern baldness. The onset of hair loss in AA is rapid and the progression is unpredictable.
- AA is associated with a negative emotional and psychosocial burden on patients and their caregivers, including a loss of confidence in appearance, shame, and guilt.
- Globally, AA affects approximately 2% of the general population. The prevalence of AA in Canada is estimated to be between 0.1% and 0.58%. Among people living in Canada with AA, less than 5% are estimated to be living with severe disease.
- AA can occur at any age, but most people (83% to 88%) develop the disease before the age of 40 years, and approximately 70% of AA cases occur in people aged 10 to 25 years.

What Are the Treatment Goals and Current Treatment Options for AA?

- The clinical experts consulted for this review noted that the most important treatment goals for patients with severe AA include significant hair regrowth (including eyelashes, eyebrows, and facial hair in males), preserving pre-existing hair, reducing further hair loss, and improving quality of life (including the psychological well-being of patients).
- Current treatment options for severe AA in Canada include topical and intralesional corticosteroids, short-term oral corticosteroids, and JAK inhibitors (most notably baricitinib).
- Baricitinib is not indicated for the treatment of AA in children and adolescents and is currently not listed on public formularies despite receiving a reimbursement recommendation from Canada's Drug Agency (CDA-AMC). However, negotiations for baricitinib with the pan-Canadian Pharmaceutical Alliance have been concluded and a letter of intent was issued on November 10, 2025.
- Patients expressed a need for treatments that can lead to full and sustained hair regrowth and a lower risk of side effects for both adults and adolescents.

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What Is Litfulo and Why Did CDA-AMC Conduct This Review?

- Litfulo is a drug that is administered orally. It is a member of the class of drugs called selective JAK3 and tyrosine kinase expressed in hepatocellular carcinoma family inhibitors.
- Health Canada approved Litfulo on November 29, 2023, “for the treatment of adults and adolescents 12 years and older with severe AA.”
- CDA-AMC reviewed Litfulo to inform a recommendation to the participating public drug programs on whether it should be reimbursed for the Health Canada–approved indication.

How Did CDA-AMC Evaluate Litfulo?

- CDA-AMC reviewed the clinical evidence on the beneficial and harmful effects, as well as the economic evidence, of Litfulo versus other treatments used in Canada for the treatment of adults and adolescents with severe AA. Baricitinib was considered a relevant treatment to compare with Litfulo when reviewing the clinical evidence.
- CDA-AMC identified equity and ethical considerations relevant to Litfulo and AA.
- The review was informed by materials submitted by the sponsor, which included clinical and economic evidence.
- The review was also informed by 1 patient group submission in response to our call for input, and by input from the participating public drug programs regarding issues that may affect their ability to implement a recommendation. No clinician group input was received for this review.
- Two dermatologists with representation from Quebec and Ontario were consulted as part of the review process.

What Were the Findings?

Clinical Evidence

- CDA-AMC reviewed the following clinical evidence:
 - 1 pivotal phase IIb and III, randomized, double-blinded, placebo-controlled study (ALLEGRO-2b/3) comparing Litfulo to placebo in 261 adults and adolescents aged 12 years or older with severe AA; the study included a 24-week double-blinded, placebo-controlled phase followed by an additional 24-week extension phase during which all patients received Litfulo
 - 1 ongoing open-label phase III extension study (ALLEGRO-LT)

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- evaluating the long-term efficacy and safety of Litfulo in patients with severe AA
 - 1 indirect treatment comparison (ITC) using a network meta-analysis as the base case for the randomized controlled trial data and unanchored population-adjusted indirect comparisons (using a matching-adjusted indirect comparison) for the single-arm extension data.
- For the comparison of Litfulo versus placebo in adults and adolescents with severe AA based on the ALLEGRO-2b/3 study:
 - Treatment with Litfulo led to a greater proportion of patients achieving an improvement in scalp hair regrowth, as measured by a Severity of Alopecia Tool (SALT) score of 20 or less and a SALT score of 10 or less, compared with placebo.
 - A greater proportion of patients who received Litfulo achieved an improvement in eyebrow and eyelash hair regrowth, as measured by at least a 2-grade improvement or a score of 3 in the eyebrow or eyelash score, compared with placebo.
 - Compared to placebo, a higher proportion of patients who received Litfulo reported an overall improvement in their health status, as measured by the Patient Global Impression of Change, compared to placebo.
 - Mean changes in anxiety and depression scores at week 24 based on the Hospital Anxiety and Depression Scale were small, and differences were not statistically significant between the Litfulo and placebo groups.
 - Harms, including adverse events (AEs) and serious AEs, were generally similar between Litfulo and placebo, and reported AEs were consistent with the oral JAK inhibitor class.
- Results from the ALLEGRO-LT extension study suggested that treatment with Litfulo for 36 months led to improvements or the maintenance of scalp hair regrowth and eyebrow or eyelash hair regrowth; however, the evidence is uncertain due to the noncomparative design (open-label design). No new safety concerns were observed.
- For the comparison of Litfulo versus baricitinib in adults and adolescents with severe AA:
 - No direct comparative evidence versus relevant comparators was submitted. The sponsor-submitted ITC results suggest that the comparative efficacy of Litfulo relative to baricitinib for scalp hair regrowth (SALT score of 20 or less and SALT score of 10 or less)

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at week 24 is broadly similar, with no differences observed between treatments. However, credible intervals (Cris) were wide and included a null (no) effect, indicating imprecision and uncertainty in the magnitude of any potential differences. At week 24, indirect comparisons between Litfulo and baricitinib for anxiety and depression were highly uncertain, with no evidence of a between-treatment difference and wide Cris. Similarly, the safety profile (the risk of AEs, serious AEs, and discontinuation of treatment due to an AE) of Litfulo relative to baricitinib is uncertain due to the low frequency of AEs, which resulted in wide Cris.

- Based on the evidence available for this review, Litfulo represents another treatment option for adult patients with severe AA. There was also supportive evidence of the efficacy and safety of Litfulo compared to placebo in adolescent patients with severe AA, a population for whom targeted treatment options are currently limited.

Economic Evidence

- Litfulo is available as a 50 mg capsule. At the submitted price of \$1,390.76 per 28-capsule bottle, the annual cost of Litfulo is expected to be \$18,142 per patient, based on the Health Canada–recommended dosage.
- Key clinical efficacy data (i.e., change in SALT score categories) used to inform the economic model for Litfulo versus best supportive care were derived from the ALLEGRO-2b/3 study, which compared Litfulo with placebo in adults and adolescents aged 12 years and older with severe AA. Evidence submitted by the sponsor indicates that Litfulo is likely to increase the proportion of patients achieving improvement in scalp hair regrowth compared with placebo among patients with severe AA. For Litfulo versus baricitinib, the sponsor assumed equal clinical efficacy, informed by the sponsor-submitted ITC, which suggested broadly similar clinical efficacy for scalp hair regrowth.
- There is no robust evidence to suggest that Litfulo provides greater health benefit to patients than baricitinib. If there are no differences in health outcomes between Litfulo and baricitinib, then the total cost of Litfulo to the health system should not exceed that of baricitinib for the treatment of AA. CDA-AMC identified numerous key issues with the sponsor-submitted analysis, not all of which could be resolved by CDA-AMC, that deemed it uninformative for decision-making. Key remaining areas of uncertainty include the long-term efficacy of Litfulo

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compared with placebo and the impact of Litfulo on health-related quality of life.

- Using public list prices, CDA-AMC estimates that the budget impact of reimbursing Litfulo for the treatment of severe AA will be a savings of approximately \$11 million over the first 3 years of reimbursement compared to the amount currently spent on comparators, with an estimated expenditure of \$85 million on Litfulo over this period. The actual budget impact of reimbursing Litfulo will depend on the eligible patient population size, the market uptake of Litfulo, and the displacement of the comparators, all of which are uncertain.

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Abbreviations

AA	alopecia areata
AAPPO	Alopecia Areata Patient Priority Outcomes
AE	adverse event
AESI	adverse event of special interest
AT	alopecia totalis
AU	alopecia universalis
BMI	body mass index
BSC	best supportive care
CANAAF	Canadian Alopecia Areata Foundation
CDA-AMC	Canada's Drug Agency
CFB	change from baseline
CI	confidence interval
CrI	credible interval
CSPA	Canadian Skin Patient Alliance
EBA	eyebrow assessment
ELA	eyelash assessment
ESS	effective sample size
FAS	full analysis set
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HADS	Hospital Anxiety and Depression Scale
HR	hazard ratio
HRQoL	health-related quality of life
IPD	individual patient data
ITC	indirect treatment comparison
LS	least squares
LTE	long-term extension
MAIC	matching-adjusted indirect comparison
MID	minimal important difference
ML-NMR	multilevel network meta-regression
NMA	network meta-analysis
NRI	nonresponder imputation
OR	odds ratio
PGI-C	Patient Global Impression of Change

QALY	quality-adjusted life-year
RCT	randomized controlled trial
SAE	serious adverse event
SALT	Severity of Alopecia Tool
SD	standard deviation
SE	standard error
SIM	simulated treatment comparison
SLR	systematic literature review
TEAE	treatment-emergent adverse events
WDAE	withdrawal due to adverse event

Background

Context for the Review

The objectives of this report are as follows:

- Review and critically appraise the evidence submitted by the sponsor on the beneficial and harmful effects of ritlecitinib (Litfulo), 50 mg oral capsules, in the treatment of adults and adolescents 12 years and older with severe alopecia areata (AA). The focus will be placed on comparing ritlecitinib to relevant comparators in clinical practice in Canada and identifying gaps in the current evidence; this focus is outlined in [Table 1](#).
- Review and critically appraise the economic information submitted by the sponsor, including a cost-effectiveness analysis and budget impact analysis. The focus of the Economic Review is aligned with the scope of the Clinical Review, unless otherwise stated. For most reviews, a base case is developed by Canada's Drug Agency (CDA-AMC), informed by clinical expert input, the available clinical evidence, and the best interpretation of the economic evidence based on the information provided by the sponsor.

Table 1: Information on the Application Submitted for Review and on the CDA-AMC Review

Item	Description
Information on the application submitted for review	
Drug	Ritlecitinib (Litfulo), 50 mg, capsules, oral use
Sponsor	Pfizer Canada
Health Canada indication	For the treatment of adults and adolescents 12 years and older with severe AA.
Health Canada approval status	NOC
Health Canada review pathway	Standard review
NOC date	November 29, 2023
Mechanism of action	Selective JAK3 and TEC family kinase inhibitor
Recommended dosage	The recommended dosage of ritlecitinib is 50 mg orally once daily.
Submission type	Initial
Sponsor's reimbursement request	Per indication
Submitted price	\$1,390.76 per 28-capsule bottle
Information on the CDA-AMC review	
Review type	Standard
Clinical review focus^a	Population: as defined in the Health Canada indication Subgroups: adolescents aged 12 years to younger than 18 years Intervention: per recommended dosage Comparators: baricitinib Outcomes: SALT score of 20 or less, SALT score of 10 or less, 75% improvement in SALT score, a CFB in SALT score, the proportion of patients with PGI-C response, an EBA response, an ELA response, a CFB in AAPPO scales, a PGI-C response, a CFB in

Item	Description
	depression and anxiety subscales of the HADS, the proportion of patients with TEAEs, SAEs, and AESIs, withdrawals due to AEs, and deaths

AA = alopecia areata; AAPPO = Alopecia Areata Patient Priority Outcomes; AE = adverse event; AESI = adverse events of special interest; CDA-AMC = Canada's Drug Agency; CFB = change from baseline; EBA = eyebrow assessment; ELA = eyelash assessment; HADS = Hospital Anxiety and Depression Scale; NOC = Notice of Compliance; PGI-C = Patient Global Impression of Change; SAE = serious adverse event; SALT = Severity of Alopecia Tool; TEAE = treatment-emergent adverse event.

^aThe Economic Review aligns with the scope of the Clinical Review, unless otherwise stated.

Sources: The ALLEGRO-2b/3 trial Clinical Study Report.⁹³ Details included in the table are from the sponsor's Summary of Clinical Evidence.

Submission History for the Drug Under Review

CDA-AMC has not previously reviewed ritlecitinib through the reimbursement review process.

Sources of Information

The contents of the Reimbursement Review report are informed by materials submitted by the sponsor, input received from interested parties (patient groups, clinician groups, and drug programs), and input from clinical experts consulted for this review.

Calls for patient group and clinician group input are issued for each Reimbursement Review. One joint patient group submission from the Canadian Alopecia Areata Foundation (CANAAF) and the Canadian Skin Patient Alliance (CSPA) was received. No submissions from clinician groups were received for this review. Information for the patient group submission was compiled from peer-reviewed scientific literature, CANAAF's national patient surveys, and insights from long-standing support groups and youth programs. The submission also compiled information from CSPA-led initiatives, which included the Breaking Barriers workshop (2023), the Mental Health Symposium (2024), and the Mental Health Survey (2025). In addition, CANAAF incorporated findings from its 2023 and 2025 community surveys, as well as more than 15 years of support sessions. These findings reflected the experiences of individuals and families living in Canada of all ages, sexes, races, and ethnicities affected by AA. The full submissions received are available on the CDA-AMC [project landing page](#) in the consolidated input document. The drug programs provide input on each drug being reviewed through the reimbursement review process by identifying issues that may affect their ability to implement a recommendation.

Input from patient and clinician groups is considered throughout the review, including in the selection of outcomes to include in the Clinical Review and in the interpretation of the clinical and economic evidence. Relevant patient and clinician group input is summarized in the Disease Background, Current Management, and Unmet Needs and Existing Challenges sections.

Each review team includes at least 1 clinical expert with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process. Two dermatologists with expertise in the diagnosis and management of AA participated as part of the review team, with representation from Quebec and Ontario.

Disease Background

AA is a clinically heterogeneous autoimmune disease characterized by nonscarring hair loss.¹⁻³ AA is the second most common cause of nonscarring hair loss following female or male pattern baldness.⁴ Although the etiology of AA is not fully understood, evidence suggests that environmental or internal triggers may lead to collapse of hair follicle immune privilege and subsequent immune-mediated hair loss. This results in the characteristic hair loss associated with the disease.⁴⁻⁷ The clinical experts consulted by CDA-AMC for this review noted that AA is a type 1 interferon–driven autoimmune condition that is commonly associated with other immune-mediated comorbidities, including vitiligo, autoimmune thyroid disease, morphea, lichen sclerosus, and type 1 diabetes. Because the disease process does not destroy hair follicles, patients with AA retain the potential for hair regrowth.⁴ AA often follows an unpredictable pattern and can be acute and self-limiting or follow a prolonged, relapsing-remitting course.¹⁸ Most patients experience multiple episodes,^{4,8-11} which may present as acute, self-limiting occurrences lasting up to 6 or 12 months, or as chronic episodes (> 12 months).⁹⁻¹²

Globally, AA affects approximately 2% of the general population at some point in their lifetime.¹³ In 2024, the prevalence of AA in Canada was estimated to be between 0.1% and 0.58% based on data from the US, the UK, and South Korea.¹⁴⁻¹⁸ The Canadian Dermatology Association report estimates that among patients living in Canada with AA, less than 5% have severe disease.¹⁹ However, there are no clinical practice guidelines in Canada for the management of AA. AA is usually diagnosed clinically through a physical examination by a dermatologist.²⁰ The physical examination typically looks for characteristic patchy, nonscarring areas of hair loss, often with “exclamation mark” hairs at the periphery in patients who are in the early stages of the condition.^{21,22} In more complex cases of AA, diagnosis may be facilitated by biopsy and/or histology.²¹ Disease severity is primarily based on the extent of scalp hair loss, and blood tests may also be performed to assess differential diagnoses.²²

According to the patient group submission from the CANAAF and CSPA, patients with AA experience negative psychological, social, and functional effects related to unpredictable hair loss. Patients with AA often reported significant emotional distress, anxiety, and disruption of identity, as well as stigma and misinterpretation from peers regarding their hair loss; caregivers often experience sadness, guilt, or helplessness related to the condition. These negative effects were especially highlighted among adolescents, who reported experiences of being bullied by peers, social exclusion, and the avoidance of activities central to adolescent development. The patient group also noted that patients with AA face substantial financial and functional burdens, such as out-of-pocket costs related to wigs, wig maintenance, and cosmetic adaptations (including makeup and eyebrow and eyelash solutions), as well as productivity loss. In addition, adolescents living with AA may miss school, avoid extracurricular activities, or struggle academically due to emotional distress.

Current Management

Treatment Goals

According to the patient group submission from the CANAAF and the CSPA, the most important treatment goals for patients with AA are full and sustained hair regrowth and a reduction in side effects associated with treatment, while maintaining health-related quality of life (HRQoL).

The clinical experts consulted for this review noted that the most important treatment goals for patients with severe AA include complete (or nearly complete) regrowth of hair, preservation of pre-existing hair, reduction of further hair loss, control of underlying immune inflammation, and improvement in quality of life, including patients' psychological well-being. According to the clinical experts, preventing complications related to the loss of protective hair with important physiological functions, particularly involvement of the eyelashes and nasal hair, is also an important goal of AA treatment. Addressing the mental health and developmental effects of severe AA is a critical treatment goal, especially in adolescents, for whom personal identity, self-esteem, and social integration are actively forming. Given that patients with severe AA often face bullying, social withdrawal, academic underperformance, and significant psychological distress, effective disease control has the potential to mitigate these downstream consequences.

Current Treatment Options

The sponsor's Summary of Clinical Evidence noted that the treatment of AA is broadly categorized into topical, intralesional, and oral therapies, with topical and intralesional treatments typically used and oral systemic therapies reserved for more extensive disease. The clinical experts consulted by CDA-AMC noted that patients with severe AA are usually treated initially with mid- to high-potency topical corticosteroids and, where feasible, intralesional steroid injections, although these approaches are insufficient as monotherapy and are used mainly as adjuncts to systemic treatment. The most commonly used systemic options include off-label conventional immunosuppressants (e.g., cyclosporine, methotrexate, azathioprine, mycophenolate mofetil), which have limited efficacy, and JAK inhibitors (baricitinib, tofacitinib, upadacitinib, and abrocitinib). Tofacitinib, upadacitinib, and abrocitinib are only accessible if patients have concomitant atopic dermatitis. Short courses of oral corticosteroids (prednisone) may be used for rapidly progressive severe disease. Conventional immunosuppressants are used off-label for the treatment of severe AA,⁴¹ while tofacitinib, upadacitinib, and abrocitinib are JAK inhibitor treatments used off-label for the treatment of patients with severe AA. The clinical experts noted that systemic steroids are sometimes used in the short-term to manage aggressive flares, but they are not appropriate for long-term use.

Other known treatments for AA, including topical anthralin and contact immunotherapy with diphenylcyclopropenone, are not commonly used for treatment in Canada. Nonpharmacological interventions include camouflage techniques such as wigs, hairpieces, and eyebrow tattooing to help patients cope with AA.^{14,23,24} Platelet-rich plasma and a variety of botanical remedies (e.g., garlic gel, squill extract, coacillium) have also been explored in the treatment of AA.²⁵⁻²⁹

Key characteristics of ritlecitinib are summarized alongside other treatments available for severe AA in the Key Characteristics table in Appendix 1 in the Supplemental Material document.

Unmet Needs and Existing Challenges

The patient group submission from the CANAAF and the CSPA noted that despite a variety of treatments available for AA, effective treatment options remain limited for adolescents and for patients with severe disease (defined as a Severity of Alopecia Tool [SALT] score of 50% or greater). Patients reported that existing therapies are often associated with limited effectiveness and undesirable side effects, including scalp atrophy, hyperpigmentation, irritation, and allergic reactions. Systemic immunosuppressive treatments, such as methotrexate and azathioprine, were noted to be associated with a higher risk of organ toxicity, malignancy, and infection. Patients noted that certain modes of administration (e.g., painful intralesional injections and greasy topical formulations) are burdensome. In addition, the lack of public reimbursement for several treatments contributes to financial strain.

The patient input highlighted that current treatments do not adequately address key unmet needs in AA, particularly the psychological and social effects of persistent or insufficient hair regrowth. These gaps are most pronounced in children and adolescents, in whom incomplete disease control contributes to bullying, social isolation, and school-related challenges.

The 2 clinical experts consulted for this review reinforced these concerns, emphasizing that topical and intralesional corticosteroids are not appropriate for severe AA and that topical immunotherapy (e.g., diphenylcyclopropenone) is difficult to access in Canada, as it is available only in a small number of specialized centres. Off-label conventional systemic therapies, such as methotrexate and cyclosporine, were described as having limited efficacy and important safety concerns; cyclosporine was also noted to be costly and not publicly funded for AA. While targeted therapies, such as JAK inhibitors, represent an important advance, the clinical experts noted that baricitinib is currently indicated only for adults, leaving children and adolescents without access to this treatment option. Overall, the 2 clinical experts emphasized that although the primary treatment goal in severe AA is achieving meaningful and durable hair regrowth, this remains challenging in clinical practice in Canada due to the absence of clinical guidelines, limited access to effective and publicly reimbursed therapies, variable treatment response, and safety concerns with existing systemic options.

Considerations for Using the Drug Under Review

Contents within this section have been informed by input from the clinical experts consulted for the purpose of this review and from clinician groups, as well as the reimbursement conditions proposed by the sponsor (e.g., refer to the Initiation, Renewal, Discontinuation, and Prescribing Conditions Proposed by the Sponsor table in Appendix 1 in the Supplemental Material document available on the CDA-AMC [project landing page](#)). The implementation questions from the public drug programs and corresponding responses from the clinical experts consulted for this review are summarized in the Summary of Drug Program Input and Clinical Expert Responses table in Appendix 1 in the Supplemental Material document. The following information has been summarized by the review team.

Place in Therapy

The clinical experts consulted for the review noted that ritlecitinib should be considered as a first-line treatment option for severe AA. This is because topical treatments are not appropriate for the treatment of severe disease and conventional systemic therapies are either not effective or safe in the long term. In addition, the clinical experts emphasized that ritlecitinib not only improves hair regrowth, leading to enhanced quality of life, but also reduces itch (if the patient experiences it as a symptom). According to the 2 clinical experts, ritlecitinib should be used as a monotherapy; when the patient's hair regrowth improves but residual disease remains, topical or intralesional steroid therapies can be used concomitantly to treat limited residual areas.

Patient Population

The clinical experts noted that all patients with severe AA who have no contraindications to ritlecitinib will be best suited for treatment. According to the clinical experts consulted for the review, adolescents are less likely to have contraindications to ritlecitinib than adult patients. In addition, the psychological effect of AA is more pronounced in adolescents compared to adults, and adolescents may have a more urgent need for treatment than adult patients. Both clinical experts noted that patients with severe AA who have a contraindication to ritlecitinib would be least suitable for treatment with ritlecitinib.

Assessing the Response to Treatment

The clinical experts noted that based on their clinical experience, response to treatment is typically assessed based on improvement in the SALT score, which is usually used to monitor treatment response in clinical trials. They also indicated that a clinically meaningful response depends on the extent of hair loss at baseline. The clinical experts noted that a SALT score of 20 or less after approximately 6 months of treatment is considered a clinically meaningful response to treatment, with at least 50% scalp hair regrowth and complete eyebrow or eyelash regrowth also viewed as meaningful responses to treatment. In patients who have complete hair loss at baseline, 50% hair regrowth after 2 years is considered a meaningful response to treatment. According to the clinical experts, response to treatment should be assessed over time, with early signs of effectiveness expected within the first 3 months (e.g., facial hair regrowth and initial scalp regrowth), further improvement possible up to 6 to 12 months, and more substantial hair regrowth typically observed by 24 to 32 months. The clinical experts noted that based on their clinical experience, adolescents respond faster to treatment compared to adult patients.

Discontinuing Treatment

According to the clinical experts consulted for this review, treatment with ritlecitinib should be discontinued if a patient experiences significant adverse events (AEs), if the disease does not respond adequately after more than 1 year of treatment, or if treatment is discontinued due to personal reasons.

Prescribing Considerations

The clinical experts noted that ritlecitinib should be prescribed and monitored by physicians (dermatologists) who have experience in the management of AA. The sponsor proposed that ritlecitinib should not be used in combination with other JAK inhibitors, biologic immunomodulators, or systemic immunosuppressants. Although the clinical experts generally agreed with this prescribing approach, they also highlighted that

AA may coexist with other immune-mediated conditions, such as atopic dermatitis or inflammatory bowel disease, which may require treatment with biologic or systemic immunosuppressive therapies. In such cases, the clinical experts emphasized that concomitant use of ritlecitinib with other immunomodulatory treatments may be considered on a case-by-case basis, provided there are no safety concerns or clinically relevant drug interactions.

Additional Considerations

The clinical experts noted that access to specialty care for AA is not equitable across Canada, leading to delayed diagnosis and treatment among equity-deserving groups, and a higher likelihood of presenting with more advanced disease. The clinical experts noted that access to specialty care could be improved through virtual consultations with dermatologists (teledermatology). The 2 clinical experts also emphasized that inequities in drug coverage exacerbate these disparities, as patients without adequate private insurance often lack access to safe and effective treatments.

Clinical Review

Methods

The review team considered studies in the sponsor's systematic review (pivotal studies and randomized controlled trials [RCTs]), sponsor-submitted long-term extensions (LTEs), and indirect treatment comparisons (ITCs). Eligible studies for the systematic review included published and unpublished pivotal studies and phase IIb to III RCTs. Relevant patients and interventions were defined by the indication or reimbursement request and the recommended dosage in the product monograph. Relevant comparators were drugs used in clinical practice in Canada to treat patients described in the indication under review. LTEs of included pivotal studies and RCTs were included, regardless of whether there was a comparison group. ITCs and studies addressing gaps submitted by the sponsor were included when they filled an identified gap in the systematic review evidence (e.g., a missing comparator or a longer follow-up time). The sponsor submitted an LTE of the included pivotal trial, an ITC, and studies addressing gaps for inclusion.

The review team selected outcomes (and follow-up times) for review considering the sponsor's Summary of Clinical Evidence, clinical expert input, and patient and clinician group input. Included outcomes are those considered relevant to expert committee deliberations, and they were selected in consultation with committee members. Evidence from the systematic review for the most important outcomes was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Considerations that informed the selection of efficacy and harms outcomes to be summarized and assessed using GRADE include the following:

- Full and sustained scalp hair regrowth was identified by patient input and clinical experts as a key treatment goal in AA. The SALT score is widely used as a quantitative measure of scalp hair loss and regrowth in AA trials. A SALT score of 20 or less is recognized as a threshold for clinically meaningful hair regrowth in patients with severe AA.³⁰ SALT-based thresholds (a SALT score of 20 or less and a

SALT score of 10 or less) were selected for GRADE to assess treatment response at 24 weeks (the end of the placebo-controlled treatment period of the ALLEGRO-2b/3 study). Given that the SALT score only assesses scalp and not body hair loss, the proportion of patients with at least a 2-grade improvement or a score of 3 in eyebrow assessment (EBA) response and eyelash assessment (ELA) scores at week 24 was also included in the GRADE assessment.

- The ability to maintain HRQoL while receiving treatment was identified by patients as an important outcome. The patient group input and clinical experts consulted for this review emphasized the emotional, psychological, and social effects of AA, with patients reporting depression and anxiety as key concerns. Given that no HRQoL instruments specific to AA were used in the trial, the Patient Global Impression of Change (PGI-C) score and the depression and anxiety subscale scores based on the Hospital Anxiety and Depression Scale (HADS) were included in the GRADE assessment as validated tools because they are informative and assess overall patient perception of treatment efficacy.
- Patient and clinical expert input highlighted safety as an important outcome, with clinical experts identifying serious AEs (SAEs) as a key measure for evaluating the safety of systemic treatments for severe AA, given the immunomodulatory mechanism of action and the need to monitor for harms. In addition, the clinical experts noted that SAEs have a direct effect on patients and are relevant for health resource use. Methods for data extraction, risk-of-bias appraisal, and certainty of evidence assessment are provided in Appendix 2 in the Supplemental Material document.

Clinical Evidence

In this report, the following sources of evidence submitted by the sponsor are reviewed and appraised:

- 1 pivotal study included in the systematic review (the ALLEGRO-2b/3 study)
- 1 LTE study (ALLEGRO-LT)
- 1 ITC using a network meta-analysis (NMA) as the base case for the RCT data and unanchored population-adjusted indirect comparisons (using a matching-adjusted indirect comparison [MAIC]) for the single-arm extension data.

Systematic Review

Description of Studies

Study Characteristics

Characteristics of the included study are summarized in [Table 2](#). Details pertaining to the eligibility criteria, interventions and comparators, and relevant outcome measures are in Appendix 3 in the Supplemental Material document.

The ALLEGRO-2b/3 study was a phase IIb to III, randomized, double-blinded, placebo-controlled study conducted to evaluate the efficacy and safety of ritlecitinib compared to placebo in scalp hair regrowth in adults and adolescents aged 12 years or older with AA who have 50% or more scalp hair loss.³¹ The study took place in 18 countries across Asia, Australia, Europe, and North and South America, with 12 sites in Canada. The study included a screening period of up to 5 weeks, a 48-week treatment period, and a

4-week follow-up period. Patients were randomized (2:2:2:2:1:1:1) to 1 of the following 7 treatment groups: ritlecitinib 200 mg loading dose for 4 weeks followed by ritlecitinib 50 mg; ritlecitinib 200 mg loading dose for 4 weeks followed by ritlecitinib 30 mg; ritlecitinib 50 mg; ritlecitinib 30 mg; ritlecitinib 10 mg; placebo for 24 weeks followed by ritlecitinib 200 mg loading dose for 4 weeks then ritlecitinib 50 mg; or placebo for 24 weeks followed by ritlecitinib 50 mg. A stratified randomization scheme was used to achieve a target global composition for alopecia totalis (AT) or alopecia universalis (AU) and adolescents in the enrolled population. Global enrolment targets were approximately 40% of patients with AT or AU and 15% adolescents.

The assessment of the ALLEGRO-2b/3 study focuses on results for the placebo-controlled period (up to week 24) to inform comparative evidence, and specifically on the ritlecitinib 50 mg once daily (up to week 24) group, to align with the dosage regimen that received approval from Health Canada.²

Intervention and Comparator

- **Ritlecitinib 50 mg group (N = 130):**

- Patients received a 50 mg loading dose once daily for 4 weeks followed by a ritlecitinib 50 mg maintenance dose for 20 weeks during the placebo-controlled period.

- **Placebo (N = 131):**

- Patients received matched placebo (loading dose for 4 weeks followed by maintenance dosing for 20 weeks) during the placebo-controlled period.

To achieve the proper dosage and maintain the blind throughout the study, ritlecitinib or matched placebo tablets were dispensed in a blinded fashion to all patients, regardless of treatment assignment, and patients took the same number of tablets per day. In the ALLEGRO-2b/3 study, there was restricted use of systemic corticosteroids, immunosuppressants, biologics, and prior JAK inhibitors before randomization, with prespecified washout periods. Initiation of new systemic therapies during the placebo-controlled period was not permitted. Stable background topical therapies, such as topical corticosteroids or minoxidil, were allowed if initiated before study entry and remained unchanged.

Table 2: Characteristics of Studies Included in the Systematic Review

Study name, design, and sample size	Key inclusion criteria	Key exclusion criteria	Intervention and comparator	Relevant end points
The ALLEGRO study, phase IIb and III, randomized, double-blinded, multicentre, global study Total N = 718	• Clinical diagnosis of AA in patients aged 12 years or older • Scalp hair loss of 50% or greater, as measured by SALT, including cases of AT and AU • No evidence of terminal hair regrowth within 6	• Severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiovascular, psychiatric, immunologic or rheumatologic, or neurologic disorders if the condition could increase study risk • Current or past malignancies,	Intervention: ritlecitinib 50 mg for 24 weeks Comparator: matched placebo for 24 weeks	Primary end points: • SALT score ≤ 20 at week 24 Key secondary end point: • SALT score ≤ 10 at week 24 Secondary end points: • SALT score ≤ 20 at week 48 • SALT score ≤ 10 at week 48 • Improvement of 75% from

Study name, design, and sample size	Key inclusion criteria	Key exclusion criteria	Intervention and comparator	Relevant end points
	months before the baseline visits Current episode of scalp hair loss of 10 years or less in duration	lymphoproliferative disorders, lymphoma, leukemia, or signs of lymphatic disease - Adolescents without VZV vaccination or IgG antibodies - History of systemic infection requiring hospitalization or antimicrobial therapy within 6 months - Active systemic diseases that could cause hair loss - Previous use of any JAK inhibitor for use in any disease indication or any non-B-cell selective lymphocyte-depleting drug - Active acute or chronic infection - Known immunodeficiency disorder		baseline in SALT score at weeks 24 and 48 - CFB in SALT scores at weeks 24 and 48 - EBA score at weeks 24 and 48 - ELA score at weeks 24 and 48 - CFB in AAPPO scales at weeks 24 and 48 - Proportion of patients with a PGI-C response at weeks 24 and 48 - CFB in the depression and anxiety subscales of the HADS - Incidence of AEs, TEAEs, SAEs, AESI, and WDAEs

AA = alopecia areata; AE = adverse event; AESI = adverse events of special interest; AT = alopecia totalis; AU = alopecia universalis; AAPPO = Alopecia Areata Patient Priority Outcomes; CFB = change from baseline; EBA = eyebrow assessment; ELA = eyelash assessment; HADS = Hospital Anxiety and Depression Scale; SAE = serious adverse event; SALT = Severity of Alopecia Tool; TEAE = treatment-emergent adverse event; VZV = varicella zoster virus; WDAE = withdrawal due to adverse event.

Sources: The ALLEGRO-2b/3 trial Clinical Study Report.³¹ Details included in the table are from the sponsor's Summary of Clinical Evidence.

Statistical Testing and Analysis Populations

The ALLEGRO-2b/3 study was powered to detect differences in the primary end point: response based on an absolute SALT score of 20 or less at week 24 compared to placebo. A sample size of 120 patients per group (for the groups receiving ritlecitinib 200 mg followed by ritlecitinib 50 mg once daily, ritlecitinib 200 mg followed by ritlecitinib 30 mg once daily, ritlecitinib 50 mg followed by ritlecitinib 50 mg once daily, or ritlecitinib 30 mg followed by ritlecitinib 30 mg once daily) provided more than 90% power to demonstrate that at least the group receiving ritlecitinib 200 mg followed by ritlecitinib 50 mg group was superior to placebo by a difference of 24% in the proportion of subjects who achieved the primary end point, assuming a placebo response rate of no more than 5% and a 2-sided significance level.³² The sample size was estimated to maintain the desired statistical power for each comparison after applying the closed testing procedure's alpha adjustments. This sample size also provided more than 90% power for a SALT score of 10 or less at the week 24 end point, assuming that the ritlecitinib 200 mg followed by ritlecitinib 50 mg once daily group was superior to placebo by a difference of 20% in the proportion of patients achieving a SALT score of 10 or less, assuming a placebo response rate of no more than 5% and an alpha level of 0.05 (2-sided significance level). The assumption of the placebo response rate for both a SALT score of 20 or less and a SALT score of 10 or less, as well as the treatment difference, was informed by the week 24 results from a phase IIa study.³²

The primary analysis for the primary end point was analyzed with the Miettinen and Nurminen method for the calculation of 95% confidence intervals (CIs) and P values.³³ The hypotheses tested were that each of the active treatment groups was superior to placebo as measured by the proportion of patients achieving the primary and the key secondary end points. The family-wise type I error was controlled using a gatekeeping approach.

Subgroup analyses for a SALT score of 20 or less at week 24 and a SALT score of 10 or less at week 24 were prespecified based on baseline characteristics, including age, body mass index (BMI), weight, sex, race, region, AA severity (AT or AU versus without AT or AU), duration since AA diagnosis, duration of the current AA episode, and prior pharmacological treatment for AA. The exploratory analyses of response based on a SALT score of 20 or less through week 48 for the subgroup of participants with AT or AU and for the subgroup of participants without AT or AU were conducted post hoc.^{31,34} The primary goal of the subgroup analyses was to check for consistency of results across subgroups. Estimates of the response rates for ritlecitinib 50 mg compared to the placebo group and their 95% CIs based on the MN method were presented for each defined category of each subgroup; no P values were presented. Efficacy end points were analyzed in the full analysis set (FAS). Participants were analyzed in the treatment groups as randomized. Safety was evaluated in the safety analysis set and included all participants who received at least 1 dose of study treatment.

Patient Disposition

Patient disposition for the included study is summarized in Appendix 4 in the Supplemental Material document.

A total of 1,097 patients were screened, and 379 patients did not meet the screening criteria. The treatment group of interest that is reported in this review is the ritlecitinib 50 mg group, aligning with the Health Canada–approved dosage. The comparator group of interest includes the pooled placebo group during the placebo-controlled period (up to 24 weeks). In the ritlecitinib 50 mg group, 130 patients were randomized; of these, 9 patients (6.9%) and 17 patients (13.1%) discontinued treatment up to weeks 24 and 48, respectively. In the placebo group, of the 131 patients who were randomized, 7 patients (5.3%) and 14 patients (10.7%) discontinued treatment up to weeks 24 and 48, respectively.

During the placebo-controlled period, the most common reasons for treatment discontinuation were withdrawal by patients, AEs, and physician decision (which included discontinuation due to COVID-19-related reasons). The incidence of important protocol deviations increased at the onset of the COVID-19 pandemic, but the increase was generally similar across treatment groups.

Baseline Characteristics

Baseline characteristics of patients in the ALLEGRO-2b/3 trial are summarized in [Table 3](#).

Table 3: Summary of Baseline Characteristics From the ALLEGRO-2b/3 Study

Characteristic	Ritlecitinib 50 mg (N = 130)	Placebo (N = 131)
Age (years)		
Mean (SD)	32.4 (13.36)	34.0 (14.96)
Adolescents (aged 12 years to younger than 18 years), n (%)	18 (13.8)	19 (14.5)
Adults (aged ≥ 18 years), n (%)	112 (86.2)	112 (85.5)
Sex, n (%)		
Female	71 (54.6)	86 (65.6)
Male	59 (45.4)	45 (34.4)
Race, n (%)		
American Indian or Alaska Native	0 (0.0)	0 (0.0)
Asian	43 (33.1)	31 (23.7)
Black or of African descent	5 (3.8)	4 (3.1)
Multiracial	1 (0.8)	2 (1.5)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)
White	79 (60.8)	94 (71.8)
Unknown	2 (1.5)	0 (0.0)
Type of AA, n (%)		
AT	30 (23.1)	24 (18.3)
AT or AU	60 (46.2)	60 (45.8)
AU	24 (18.5)	34 (26.0)
Not specified	6 (4.6)	2 (1.5)
Baseline SALT score, mean (SD)	90.3 (14.69)	93.0 (11.50)
Duration of AA since diagnosis (years), mean (SD)	8.7 (8.67)	11.0 (11.77)
Duration of current AA episode (years), mean (SD)	3.2 (2.67)	3.2 (2.65)
Participants with any prior medication for AA, n (%)	100 (76.9)	95 (72.5)

AA = alopecia areata; AT = alopecia totalis; AU = alopecia universalis; SALT = Severity of Alopecia Tool; SD = standard deviation.

Note: Racial categories used in the table are as reported in the source and may not align with Canada's Drug Agency inclusive language guidelines.

Sources: The ALLEGRO-2b/3 trial Clinical Study Report.³¹ Details included in the table are from the sponsor's Summary of Clinical Evidence.

Treatment Exposure and Concomitant Medications

Details of treatment exposure and use of concomitant medications in the ALLEGRO-2b/3 study are in Appendix 4 in the Supplemental Material document.

Exposure to Ritlecitinib

The mean duration of treatment in the ritlecitinib 50 mg treatment group was 306.2 days (standard deviation [SD] = 72.12 days). At 24 weeks of treatment, 98.5% of patients in the ritlecitinib 50 mg group had adherence

rates of 80% to 120%. The rate of adherence was similar during the extension period (at week 48), when 99.2% of patients had between 80% and 120% adherence rates.

Concomitant Medications

During the placebo-controlled period, 95 patients (73.1%) in the ritlecitinib 50 mg group received concomitant medication, and paracetamol was the most frequently used medication (12.3%). The second most common concomitant medication differed by group: ibuprofen in the ritlecitinib group (9.2%) and levothyroxine sodium in the placebo group (12.2%). A similar pattern was observed during the extension period, where 104 patients (80.0%) in the ritlecitinib group and 54 patients (81.8%) in the placebo to ritlecitinib 50 mg group used at least 1 concomitant medication. Paracetamol remained the most common medication in the ritlecitinib 50 mg group (16.9%), while ibuprofen was most frequently used in the placebo to ritlecitinib group (15.2%). No patients in the ritlecitinib 50 mg group or placebo group received concomitant medication for the treatment of AA (e.g., minoxidil) over 24 or 48 weeks.

Critical Appraisal

Internal Validity

The ALLEGRO-2b/3 study used centralized interactive response technology for treatment allocation and a matched dosing schedule across treatment arms to minimize the risk of selection bias during the placebo-controlled period. There were between-group imbalances in baseline demographic and disease characteristics, including sex, race, AT or AU status, mean baseline SALT score, and mean disease duration. Given the relatively small sample size per arm (130 patients in the ritlecitinib 50 mg group and 131 patients in the placebo group), such imbalances are not unusual despite randomization. Some differences, such as the 11% difference in the percentage of female patients (54.6% in the ritlecitinib group versus 65.6% in the placebo group), were notable. Females tend to experience lower psychological well-being than males with AA.³⁵ The differential proportion of female patients might have influenced HRQoL and HADS scores at baseline and at 24 weeks; however, it is not expected to influence biological response to ritlecitinib and is therefore unlikely to confound or modify treatment effects on hair regrowth. The clinical experts consulted for this review agreed with this assessment. The observed treatment effect with ritlecitinib 50 mg was consistent in females and males up to 24 weeks, indicating that no treatment effect modification occurred, although no tests for interaction were reported.

Stratification by AT and AU status was appropriate (both have a worse prognosis than AA) and maintained overall balance in that stratum (46% in each arm). However, within this stratum, the ritlecitinib arm had relatively more patients with AT than the placebo arm (23% versus 18%), whereas the placebo arm had relatively more patients with AU than the ritlecitinib arm (26% versus 19%), which may introduce baseline prognostic imbalance favouring ritlecitinib because AU may be less responsive to treatment.^{36,37} The clinical experts indicated that they did not expect these differences to have a clinically significant influence on results. Subgroup analyses of the primary end point showed smaller differences between the ritlecitinib and placebo treatment groups in the combined AT or AU subgroup (approximately 7%) versus the subgroup without AT or AU (approximately 33%), which is consistent with AT or AU having a poorer prognosis. Thus, there is no clear evidence that the numerical differences in AT and AU status influenced the results. Overall,

baseline differences were likely due to chance and not a failure of randomization, and were therefore not expected to materially influence study results. The risk of bias from the randomization process was determined to be low.

In the primary efficacy analyses at week 24, the 2 placebo groups (the 1 paired with ritlecitinib 50 mg plus the 1 paired with ritlecitinib 200 mg to 50 mg) were pooled as the comparator. Pooling of the placebo groups up to week 24 was prespecified in the protocol and formed part of the primary efficacy analysis plan. The sponsor assumed that the placebo groups were comparable with respect to study procedures, visit schedules, pill burden, adherence, and patterns of missing data. While pooling was prespecified, there is limited information regarding formal assessment of comparability between the placebo subgroups. Sensitivity analyses restricting comparisons to dose-matched placebo groups were not reported. Given that blinding was maintained during the placebo-controlled period and study procedures were consistent across placebo arms as specified in the Clinical Study Report (CSR), the potential risk of bias arising from placebo pooling is likely low, consistent with the opinion of the clinical experts consulted for this review.

Concomitant therapies that were used, including topical corticosteroids and minoxidil, were recorded. According to the clinical experts consulted for this review, these treatments reflect adjunctive therapies with variable clinical effectiveness that would likely not influence the treatment effects of ritlecitinib. None of the patients in the ritlecitinib 50 mg group or the placebo group received concomitant medications that could affect hair regrowth. Rescue therapy, including systemic corticosteroids, other systemic immunosuppressants, or alternative JAK inhibitors, was not permitted during the placebo-controlled period. The absence of rescue therapy reduces bias related to differential treatment modification before week 24; however, other potential sources of bias, such as differential discontinuation or adherence, can influence treatment effects.

During the placebo-controlled period, study treatment discontinuation occurred in 6.9% of patients in the ritlecitinib 50 mg group compared with 5.3% in the placebo group. Treatment discontinuations in the ritlecitinib 50 mg group were primarily due to participant withdrawal (3.1% versus 2.3% with placebo) or AEs (1.5% versus 0.8% with placebo), while treatment discontinuation due to a lack of efficacy occurred in no patients in the ritlecitinib 50 mg group and 1 patient in the placebo group. As such, differences in discontinuation are less likely to have influenced treatment effects during the placebo-controlled period.

The primary analyses were conducted in the FAS using the intention-to-treat approach. Missing data for SALT scores due to reasons related to COVID-19 were imputed using nonresponder imputation (NRI) in the primary analysis. At week 24, 6 patients (4.6%) in the ritlecitinib 50 mg group had missing data for SALT scores compared to 1 patient (0.8%) in the placebo group, indicating a relatively low level of missing data in the primary efficacy end point. The NRI represents a potentially conservative approach; given the higher missingness in the ritlecitinib arm, the bias would likely shift toward the null rather than inflate the treatment effect because more missing assessments in the ritlecitinib group were coded as “nonresponders.” Therefore, the absolute difference in missingness between the ritlecitinib and placebo groups is unlikely to introduce meaningful bias in the week 24 SALT score results. In contrast, these missing data were more substantial for the secondary end points, affecting up to 41.0% of patients (N = 53) in the ritlecitinib 50 mg

group and 35.8% of patients (N = 47) in the placebo group. The sponsor noted that COVID-19–related disruptions required additional missing-data rules that differed from the non-COVID approach and may have been applied differentially across patients depending on the timing and reason for missing assessments. This introduces additional complexity because treatment effect estimates may reflect a mixture of missing-data handling strategies (COVID versus non-COVID), potentially reducing comparability across patients and time points. The implications are most relevant for the extension period and for outcomes more prone to missing data, such as patient-reported outcomes. Missing patient-reported outcome data may bias results if related to treatment response. Different assumptions about missingness can either overestimate or underestimate treatment effects. According to the clinical experts consulted for this review, COVID-19–related disruptions and missing assessments are unlikely to meaningfully influence the treatment effects during the placebo-controlled period, given the low level of missingness for the primary SALT score end point. Alternative missing-data assumptions were explored using missing at random, missing not at random (MNAR), and tipping-point analyses. Results were broadly consistent with the primary analysis, supporting robustness of the week 24 findings. However, the plausibility of extreme MNAR assumptions cannot be empirically verified, and the long-term robustness cannot be assessed due to the absence of a placebo-controlled comparator beyond week 24.

The primary and key secondary efficacy outcomes were assessed using prespecified SALT-based responder thresholds (a SALT score ≤ 20 and a SALT score ≤ 10). The SALT is a validated and widely accepted measure of the severity of scalp hair loss in AA, and it is commonly used in clinical trials and practice, supporting its validity and relevance. However, detailed information on assessor training, calibration, interrater reliability, and site-level consistency of SALT scoring was not reported in the submission. The absence of reported interrater reliability characteristics (e.g., intraclass correlation coefficients) introduces some uncertainty regarding measurement consistency across sites and geographic regions. The clinical experts consulted for this review emphasized that this is not a serious concern because SALT scoring is based on the objective estimation of the percentage of scalp hair loss rather than subjective symptom interpretation and is unlikely to bias the treatment effect, given that SALT thresholds are validated. In addition, there are no published between-group minimal important differences (MIDs) for the prespecified SALT thresholds (a SALT score of 20 or less and a SALT score of 10 or less); therefore, the clinical experts consulted by CDA-AMC indicated that a difference of 100 patients per 1,000 patients could be considered a clinically important treatment effect. The EBA and ELA outcomes were assessed only among patients with baseline eyebrow or eyelash involvement, representing a nonrandom subset of the randomized population and potentially compromising randomization. Given the well-established AE profile of JAK inhibitors, there is a potential for functional unblinding due to AEs. However, no clear differences between the groups in AEs were identified, including for infections. Thus, unblinding from AE signals was unlikely to be a source of bias in the trial up to 24 weeks.

Multiplicity was controlled in the ALLEGRO-2b/3 study using a prespecified hierarchical gatekeeping strategy that included 8 hypotheses and controlled the family-wise type I error rate across the primary and selected key secondary end points. The primary end point (a SALT score ≤ 20 at week 24) was tested first, followed sequentially by key secondary end points, including a SALT score of 10 or less, according to the predefined

testing sequence. Statistical significance for the end points within this hierarchy was contingent upon the success of the preceding hypotheses. Outcomes analyzed outside the hierarchical testing structure, including a 75% improvement in the SALT score, a change from baseline (CFB) in the SALT score, at least a 2-grade improvement or a score of 3 in EBA or ELA scores, and patient-reported outcomes, were not adjusted for multiplicity and should therefore be considered supportive. This prespecified gatekeeping approach strengthens confidence in the statistically significant findings within the formal testing hierarchy, while limiting the interpretability of results outside the controlled sequence. Prespecified subgroup analyses, including the comparison between adolescents and adults, were exploratory and were not powered to formally assess treatment-by-subgroup interactions. As such, treatment effects within subgroups, including adolescents, are subject to greater uncertainty.

External Validity

The study population in the ALLEGRO-2b/3 study is broadly representative of patients with severe AA seen in the treatment landscape in Canada, including both adults and adolescents aged 12 years or older with 50% or more scalp hair loss. This was consistent with the input from the clinical experts consulted for this review; however, they also noted that there is no universally accepted definition of “severe” AA in clinical practice. In the ALLEGRO-2b/3 study, severe disease was defined as greater than or equal to 50% scalp hair loss based on the SALT score at baseline. The clinical experts consulted for this review indicated that although a SALT score greater than or equal to 50% is commonly used in clinical trials, severity in routine practice may also incorporate additional factors, such as disease duration, the rate of progression, eyebrow and eyelash involvement, psychosocial burden, and prior treatment history. Based on this, the trial eligibility criteria may not capture all patients considered to have severe disease in clinical practice in Canada. The exclusion of patients with significant uncontrolled comorbidities, recent use (weeks for conventional immunosuppressants and months for biologic therapies and JAK inhibitors) of certain systemic immunosuppressants within protocol-specified washout periods before randomization, or other autoimmune conditions requiring ongoing systemic therapy may limit the generalizability of the findings to these patients. In particular, the exclusion of patients with depression and suicidal ideation is notable, considering the psychological effect of AA emphasized by patient and clinician group input to CDA-AMC. It is anticipated that this exclusion criterion was intended to ensure a homogeneous patient population enrolled and to reduce the potential for harm to these patients. The proportion of patients who were excluded from the study during screening for psychological comorbidity was not reported in the CSR. Therefore, the study may not have been representative of the population with AA overall.

The study was conducted across multiple international sites, supporting generalizability across health care systems. However, differences in access to dermatology specialists and supportive services across jurisdictions in Canada may influence real-world generalizability, including who is assessed, how quickly patients start therapy, and how outcomes are monitored relative to the trial setting. The clinical experts noted that real-world effectiveness in Canada may differ from the trial environment depending on the availability of and access to specialists.

According to the clinical experts consulted for this review, the placebo group in the ALLEGRO-2b/3 study generally reflects supportive care rather than active standard of care treatment for severe AA in Canada. In routine clinical practice, patients with severe AA may receive off-label topical or intralesional corticosteroids, topical immunotherapy, or other adjunctive therapies, which were prohibited during the placebo-controlled period of the study. While this restriction was applied equally across treatment groups, it may limit external validity by underestimating outcomes in the placebo group compared with real-world practice in Canada. As a result, the observed treatment effects may represent the effect of ritlecitinib relative to minimal active treatment rather than the full range of therapies commonly used in practice.

Adolescents were included in the ALLEGRO-2b/3 study; however, inclusion alone does not ensure generalizability to the broader adolescent or pediatric population. Subgroup analyses were not powered to detect differences between adolescents and adults. The total number of adolescents (aged 12 years to younger than 18 years) included in the study was only 37 patients (14.2%). Country-level distribution data provided by the sponsor indicate that most adolescents were enrolled in the US, with limited representation from other regions. While clinical management of AA may be broadly similar across jurisdictions, differences in access to dermatologists, referral pathways, and treatment availability may influence the generalizability of findings to adolescents in Canada. The consulted clinical experts noted that there are no significant disparities regarding the presentation of AA across different ethnicities in Canada. However, it is reported that compared to populations of patients who are white, AA is more common among patients who are Black or African American but less common among patients who are Asian.³⁸ Limited representation of these groups in the ALLEGRO-2b/3 study introduces uncertainty regarding the generalizability of the findings across diverse patient populations.

According to the clinical experts, the placebo-controlled follow-up period of 24 weeks was appropriate for assessing the initial treatment response in AA. This duration provides the most reliable comparative evidence because it retains the randomized, blinded control group. The treatment response beyond 24 weeks was informed primarily by noncomparative data. Among patients who continued treatment beyond week 24, improvements in efficacy outcomes and low discontinuation rates were observed. However, these findings were based on an open-label extension design that lacks a concurrent control group and may be subject to selection and attrition biases (e.g., patients who continue may be those who benefit from or tolerate the therapy). As such, the long-term effectiveness and safety beyond 24 weeks remain uncertain, and longer-term outcomes should be interpreted as supportive.

Results

The key efficacy and harms results and findings from the GRADE assessment are presented in this section. Detailed efficacy and harms results can be found in Appendix 4 in the Supplemental Material document.

Efficacy

Key results are summarized in the following outcome categories.

Proportion of Patients With a Response Based on a SALT Score of 20 or Less

- At week 24, 29 of 124 patients (23.39%) randomized to ritlecitinib 50 mg achieved a response based on a SALT score of 20 or less, compared to 2 of 130 patients (1.54%) in the placebo group. The difference in the proportion of patients who achieved a response based on a SALT score of 20 or less at week 24 versus placebo was 21.85% (95% CI, 14.65% to 30.23%; $P < 0.000001$) in favour of ritlecitinib.
- In a subgroup analysis, the proportion of patients who achieved a SALT score of 20 or less at week 24 was higher in the ritlecitinib 50 mg group compared to the placebo group in both adolescents (25% versus 0%) and adults (23.15% versus 1.8%). The difference in the proportion of patients with a SALT score of 20 or less versus placebo was 25% (95% CI, 5.50% to 49.86%) in the adolescents and 21.35% (95% CI, 13.57% to 30.39%) in adults.
- At week 48, the proportion of patients who achieved SALT 20 in the ritlecitinib 50 mg group was 43.2% ($N = 54/125$) compared to 18.75% ($N = 12/64$) of patients in the placebo to ritlecitinib 50 mg group.

Proportion of Patients With a Response Based on a SALT Score of 10 or Less

- At week 24, 17 of 124 patients (13.71%) in the ritlecitinib 50 mg group achieved a response based on a SALT score of 10 or less compared to 2 of 130 patients (1.54%) in the placebo group. The difference in the proportion of patients with a SALT score of 10 or less versus placebo was 12.17% (95% CI, 6.27% to 19.53%; $P < 0.000228$) in favour of ritlecitinib.
- In a subgroup analysis, the difference in the proportion of patients with a response based on a SALT score of 10 or less at week 24 between the ritlecitinib 50 mg group and placebo was 12.50% (95% CI, -5.93% to 36.42%) in adolescents and 12.09% (95% CI, 5.57% to 20.11%) in adults.
- At week 48, the proportion of patients who achieved a SALT score of 10 or less in the ritlecitinib 50 mg group was 39 of 125 patients (31.20%) compared to 9 of 64 participants (14.06%) in the placebo to ritlecitinib 50 mg group.

Proportion of Patients With a 75% Improvement in SALT Score

- In the ritlecitinib 50 mg group, 22.58% of patients achieved a 75% improvement in SALT score at week 24, compared to 2.31% of patients in the placebo group. The difference in the proportion of patients with a 75% improvement in SALT score versus placebo was 20.27% [redacted] in favour of ritlecitinib.
- At week 48, the proportion of patients who achieved a 75% improvement in SALT score in the ritlecitinib 50 mg group was 46.4% compared to 21.88% of patients in the placebo to ritlecitinib 50 mg group.

CFB in SALT Score

- The least squares (LS) mean CFB in SALT score at week 24 in the ritlecitinib 50 mg group was -33.2 (2.58) compared to -5.1 (standard error [SE] = 2.52) in the placebo group. The LS mean difference

versus placebo was -28.2 [REDACTED] in favour of ritlecitinib.

- At week 48, the LS mean CFB in SALT score was -48.6 (SE = 3.23) in the ritlecitinib 50 mg group compared to -31.2 (SE = 4.49) in the placebo to ritlecitinib 50 mg group.

Proportion of Patients With at Least a 2-Grade Improvement or a Score of 3 on the EBA

- At week 24, among patients without a 2-grade improvement in the EBA score at baseline in the FAS, 29 of 100 patients (29.00%) in the ritlecitinib 50 mg group achieved at least a 2-grade improvement or a score of 3 in the EBA score, compared to 5 of 107 patients (4.67%) in the placebo group. The difference in the proportion of patients with at least a 2-grade improvement or a score of 3 in the EBA score was 24.33% [REDACTED] in favour of ritlecitinib.
- At week 48, the proportion of patients with at least a 2-grade improvement or a score of 3 in the EBA score remained higher in the ritlecitinib 50 mg group compared to the placebo to ritlecitinib 50 mg group (43.58% versus 31.37%).

Proportion of Patients With at Least a 2-Grade Improvement or a Score of 3 on the ELA

- Among patients without a 2-grade improvement in ELA at baseline in the FAS, 26 of 90 participants (28.89%) in the ritlecitinib 50 mg group achieved at least a 2-grade improvement or a score of 3 in the ELA score at week 24, compared to 5 of 97 participants (5.15%) in the placebo group. The difference in the proportion of patients with at least a 2-grade improvement or a score of 3 in the ELA score versus placebo was 23.73% [REDACTED].
- The proportion of patients with at least a 2-grade improvement or a score of 3 in the ELA score at week 48 remained higher in the ritlecitinib 50 mg group compared to the placebo group (40% versus 35.56%).

PGI-C Response

- At week 24, 49.60% of patients in the ritlecitinib 50 mg group achieved a PGI-C score of “moderately improved” or “greatly improved.” The difference in the proportion of patients with PGI-C response versus placebo was 40.37% [REDACTED].
- In a subgroup analysis, the difference in the proportion of patients who achieved a PGI-C score of “moderately improved” or “greatly improved” at week 24 between ritlecitinib 50 mg and placebo was 43.03% (95% CI, 11.49% to 67.32%) for adolescents and 40.04% (95% CI, 29.05% to 50.43%) for adults.
- At week 48, 56% of patients in the ritlecitinib 50 mg group achieved PGI-C score of “moderately improved” or “greatly improved” compared to 43.75% of patients in the placebo to ritlecitinib 50 mg group.

Proportion of Patients With Improvement in Alopecia Areata Patient Priority Outcomes Scales

- At week 24, the proportion of patients who reported improvement from baseline in current hair loss on the scalp, evaluated using the Alopecia Areata Patient Priority Outcomes (AAPPO) scales, was

higher in the ritlecitinib 50 mg group compared to the placebo (26.27% versus 8.59%). The difference versus placebo was 17.68% (95% CI, 8.45% to 27.27%; [REDACTED]).

- At week 24, the proportion of patients with hair loss on the eyebrows was higher in the ritlecitinib 50 mg group compared to the placebo (30.43% versus 11.46%). The difference versus placebo was 18.98% (95% CI, 7.54% to 30.46%; [REDACTED]).
- At week 24, more patients in the ritlecitinib 50 mg group reported improvement in hair loss on the eyelashes compared to the placebo group (31.17% versus 8.33%); the difference in the proportion of patients with improvement in hair loss on the eyelashes versus placebo was 22.84% (95% CI, 10.96% to 35.01%; [REDACTED]).
- At week 24, 20.43% of patients in the ritlecitinib 50 mg group had improvement in hair loss on the body compared to 13.98% in the placebo group. The difference in the proportion of patients with improvement in current hair loss on the body was 6.45% (95% CI, -4.54% to 17.52%; $P = 0.243751$).
- At week 48, the proportion of patients with improvements in current hair loss on the scalp (42.37% versus 20.97%), hair loss on the eyebrows (43.96% versus 33.33%), hair loss on the eyelashes (38.16% versus 28.95%) and hair loss on the body (36.56% versus 20.45%) remained higher in the ritlecitinib group compared to the placebo to ritlecitinib 50 mg group.

CFB in Emotional Symptoms and Activity Limitations of AAPPO

- At week 24, the LS mean in the CFB in emotional symptoms was -0.69 (SE = 0.07) in the ritlecitinib 50 mg group and -0.47 (SE = 0.07) in the placebo group. The LS mean difference versus placebo was -0.22 [REDACTED].
- At week 48, the LS mean in emotional symptoms was -0.85 (SE = 0.08) in the ritlecitinib 50 mg group compared to -0.58 (SE = 0.11) in the placebo to ritlecitinib 50 mg group.
- At week 24, the LS mean in the CFB in activity limitation was -0.31 (SE = 0.05) in the ritlecitinib 50 mg group and -0.29 (SE = 0.05) in the placebo group. The LS mean difference versus placebo was -0.02 [REDACTED].
- At week 48, the LS mean CFB in activity limitations was -0.32 (SE = 0.05) in the ritlecitinib 50 mg group compared to -0.24 (SE = 0.07) in the placebo to ritlecitinib group.

CFB in Depression Subscale Score of the HADS

- At week 24, the LS mean CFB in the HADS depression subscale score was -0.8 in the ritlecitinib 50 mg group (n = 120) and 0.0 in the placebo group (n = 124) with an LS mean difference versus placebo of -0.5 [REDACTED].
- At week 48, the mean CFB in the HADS depression subscale score was -0.3 (SD = 3.09) in the ritlecitinib group (n = 117) and -0.2 (SD = 4.53) in the placebo to ritlecitinib 50 mg group (n = 60).

CFB in Anxiety Subscale Score of the HADS

- At week 24, the LS mean CFB in the HADS anxiety subscale was -0.8 in the ritlecitinib 50 mg group (n = 120) and -0.6 in the placebo group, with an LS mean difference versus placebo of -0.2 [REDACTED].

- At week 48, the mean CFB in the HADS anxiety subscale score was -0.7 in the ritlecitinib group ($n = 117$) and -0.3 in the placebo to ritlecitinib 50 mg group ($n = 60$).

Harms

The detailed summary of harm results reported in the ALLEGRO-2b/3 study is in Appendix 4 in the Supplemental Material document. Key results are summarized by event type.

Adverse Events

- At the end of the placebo-controlled period (week 24), 75.4% of patients in the ritlecitinib 50 mg group and 71.0% of patients in the placebo group reported AEs. The most commonly reported treatment-emergent adverse events (TEAEs) in the ritlecitinib and placebo groups at week 24 were nasopharyngitis (13 patients [10.0%] and 8 patients [6.1%]), headache (12 patients [9.2%] and 11 patients [8.4%]) and diarrhea (12 patients [9.2%] and 5 patients [3.8%]).
- At week 48, 84.6% of patients in the ritlecitinib 50 mg group compared to 86.4% in the placebo to ritlecitinib 50 mg group experienced AEs. The most commonly reported TEAEs (affecting $\geq 5\%$ of patients) in the ritlecitinib 50 mg and placebo to ritlecitinib 50 mg groups were nasopharyngitis (18 patients [13.8%] and 4 patients [6.1%]), headache (16 patients [12.3%] and 8 patients [12.1%]), and acne (12 patients [9.2%] and 8 patients [12.1%]).

Serious Adverse Events

- At week 24, 3 patients (2.3%) in the placebo group and no patients in the ritlecitinib 50 mg group reported at least 1 SAE. The reported SAEs in the placebo group were conversion disorder, spontaneous abortion, and heavy menstrual bleeding.
- At week 48, 2 patients (1.5%) in the ritlecitinib 50 mg group experienced at least 1 SAE compared to 3 patients (4.5%) in the placebo to ritlecitinib 50 mg group. The reported SAEs in the ritlecitinib 50 mg group were breast cancer, pulmonary embolism while spontaneous abortion, conversion disorder, and heavy menstrual bleeding were reported in the placebo to ritlecitinib 50 mg group.

Patients Who Stopped Treatment Due to Adverse Events

- At week 24, no patients in the ritlecitinib 50 mg and placebo group stopped treatment due to AEs.
- At week 48, no patients in the ritlecitinib 50 mg and placebo to ritlecitinib 50 mg group stopped treatment due to AEs.

Adverse Events of Special Interest

The experts consulted by CDA-AMC did not identify any notable harms. Information about protocol-defined adverse events of special interest (AESIs) was limited; however, the sponsor's statistical plan indicated that "adverse events of special interest will be summarized based on a list of preferred terms that will be provided by safety risk lead to the programming team before database lock." In the CSR, certain neurological and audiological events, as well as dermatological events, were reported as AESIs. These have been reported briefly here, and further details are in Appendix 4 in the Supplemental Material document.

Neurological and Audiological Events

- At week 24, 20 patients (15.4%) experienced nervous system disorders in the ritlecitinib 50 mg group compared to 15 patients (11.5%) in the placebo group. Regarding ear and labyrinth disorders, 2 patients (1.5%) in each treatment group reported AEs.
- At week 48, the proportion of patients who experienced nervous system disorders was higher in the ritlecitinib 50 mg group compared to the placebo to ritlecitinib 50 mg group (26 patients [20%] and 13 patients [18.2%], respectively). Regarding ear and labyrinth disorders, 3 patients (2.3%) in the ritlecitinib 50 mg group, and 1 patient (1.5%) in the placebo to ritlecitinib 50 mg group reported AEs.
- With the exception of headache, none of the specific neurologic and audiological AESIs were reported in more than 4 patients in any treatment group.

Dermatological Events

- Regarding infections, 8 patients (6.2%) in the ritlecitinib 50 mg group and 5 patients (3.8%) in the placebo group reported events related to infections and infestations.
- At week 48, 14 patients (10.8%) in the ritlecitinib 50 mg group and 7 patients (10.6%) in the placebo to ritlecitinib 50 mg group reported events related to infections and infestations.
- Folliculitis was the most commonly reported infection, reported by 8 patients (6.2%) in the ritlecitinib 50 mg group and 4 patients (6.1%) in the placebo to ritlecitinib 50 mg group. All other infections were reported in 3 or fewer patients per treatment group.
- At week 24, a total of 28 patients (21.5%) had skin and subcutaneous tissue disorders, compared to 24 patients (18.3%) in the placebo group.
- At week 48, 38 patients (29.2%) in the ritlecitinib 50 mg group experienced skin and subcutaneous disorders, compared to 16 patients (24.2%) in the placebo to ritlecitinib group.
- With the exception of acne at week 48, reported in 12 patients (9.2%) in the ritlecitinib 50 mg group and 8 patients (12.1%) in the placebo to ritlecitinib 50 mg group, all other specific events related to skin and subcutaneous disorders were reported in 6% or fewer patients.

Summary of Findings and Certainty of the Evidence

In the absence of literature-based MID estimates, thresholds suggested by the clinical experts were used for the following outcomes: a SALT score of 20 or less (threshold of $\geq 10\%$), a SALT score of 10 or less (threshold of $\geq 10\%$), the proportion of patients with at least a 2-grade improvement or a score of 3 in the EBA score (threshold of $\geq 10\%$), the proportion of patients with at least a 2-grade improvement or a score of 3 in the ELA score (threshold of $\geq 10\%$), the proportion of patients with a PGI-C response (threshold of $\geq 20\%$), the CFB in the depression subscale score of the HADS (threshold of ≥ 1.5 points), the CFB in the anxiety subscale score of the HADS (threshold of ≥ 1.5 point), and the proportion of patients with SAEs (threshold of $\geq 2\%$).

Table 4: Summary of Findings for Ritlecitinib vs. Placebo for Patients With Alopecia Areata During the Placebo-Controlled Period (Week 24)

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Ritlecitinib	Difference		
Proportion of patients with a SALT score ≤ 20							
SALT score (0 [no scalp hair loss] to 100 [complete scalp hair loss]), proportion of patients who achieve a SALT score of ≤ 20 Follow-up: 24 weeks	261 (1 RCT)	NR	15 per 1,000	234 per 1,000 (159 to 308 per 1,000)	218 more per 1,000 (146 to 302 more per 1,000)	High ^a	Ritlecitinib 50 mg results in a clinically important increase in the proportion of patients who achieve a SALT score ≤ 20 when compared with placebo.
Proportion of patients with a SALT score ≤ 10							
SALT score (0 [no scalp hair loss] to 100 [complete scalp hair loss]), proportion of patients who achieve a SALT score of ≤ 10 Follow-up: 24 weeks	261 (1 RCT)	NR	15 per 1,000	137 per 1,000 (76 to 197 per 1,000)	122 more per 1,000 (63 to 195 more per 1,000)	Moderate ^{a,b}	Ritlecitinib 50 mg likely results in a clinically important increase in the proportion of patients who achieve a SALT score of ≤ 10 when compared with placebo.
Proportion of patients with at least a 2-grade improvement or a score of 3 on the EBA							
Proportion of patients with an improvement in the EBA score (0 [no eyebrow hair] to 3 [normal eyebrow hair]) Follow-up: 24 weeks	261 (1 RCT)	NR	47 per 1,000	290 per 1,000 (201 to 379 per 1,000)	243 more per 1,000 (148 to 345 more per 1,000)	Moderate ^{a,c}	Ritlecitinib 50 mg likely results in a clinically important increase in the proportion of patients with an improvement in the EBA score (at least a 2-grade improvement or a score of 3 in the EBA score) when compared with placebo.
Proportion of patients with at least a 2-grade improvement or a score of 3 on the ELA							
Proportion of patients with an improvement in the ELA score (0 [no eyelash]	261 (1 RCT)	NR	52 per 1,000	289 per 1,000 (195 to 382 per 1,000)	237 more per 1,000 (136 to 345 more per 1,000)	Moderate ^{a,c}	Ritlecitinib 50 mg likely results in a clinically important increase in the proportion

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Ritlecitinib	Difference		
to 3 [normal eyelashes]) Follow-up: 24 weeks							of patients with an improvement in the ELA score (at least a 2-grade improvement or a score of 3 in the ELA score) when compared with placebo.
Proportion of patients with a “moderately improved” or “greatly improved” PGI-C response							
Proportion of patients with an improved PGI-C response (1 [greatly improved] to 7 [greatly worsened]) Follow-up: 24 weeks	261 (1 RCT)	NR	92 per 1,000	496 per 1,000 (408 to 584 per 1,000)	400 more per 1,000 (300 to 501 more per 1,000)	High ^d	Ritlecitinib 50 mg results in a clinically important increase in the proportion of patients who achieve a “moderately improved” or “greatly improved” PGI-C response when compared with placebo.
CFB in the depression subscale score of the HADS							
HADS depression domain score (0 [least depression] to 21 [greatest depression]), LSM CFB in score Follow-up: 24 weeks	261 (1 RCT)	NR	0.0 (−0.46 to 0.39)	−0.3 (−0.70 to 0.16)	−0.2 (−0.84 to 0.37)	Moderate ^e	Ritlecitinib 50 mg likely results in little to no clinically important difference in depression when compared with placebo.
CFB in the anxiety subscale score of the HADS							
HADS anxiety domain score (0 [least anxiety] to 21 [greatest anxiety]), LSM CFB in score Follow-up: 24 weeks	261 (1 RCT)	NR	−0.6 (−1.06 to −0.07)	−0.8 (−1.28 to −0.27)	−0.2 (−0.92 to 0.50)	Moderate ^e	Ritlecitinib 50 mg likely results in little to no clinically important difference in anxiety when compared with placebo.
Harms							
Proportion of patients with at least 1 SAE	261 (1 RCT)	NR	23 per 1,000	0 per 1,000 (95% CI, NR)	23 less per 1,000 (95% CI, NR)	Low ^f	Ritlecitinib 50 mg may result in little to no difference in serious adverse

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Ritlecitinib	Difference		
Follow-up: 24 weeks							events compared with placebo.

AA = alopecia areata; CFB = change from baseline; CI = confidence interval; EBA = eyebrow assessment; ELA = eyelash assessment; HADS = Hospital Anxiety and Depression Scale; LSM = least squares mean; MID = minimal important difference; NR = not reported; PGI-C = Patient Global Impression of Change; RCT = randomized controlled trial; SAE = serious adverse event; SALT = Severity of Alopecia Tool; vs. = versus.

Notes: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes. The 95% CIs are reported for absolute effects unless otherwise noted.

^aNo published between-group MID was identified to inform the target threshold. The clinical experts consulted by CDA-AMC indicated that a difference of 100 patients per 1,000 patients could be considered a clinically important treatment effect.

^bRated down 1 level for imprecision. The 95% CI crossed the target threshold and included effects ranging from no important difference to clinically important benefit.

^cRated down 1 level for risk of bias. This outcome was assessed only among patients with baseline eyebrow (EBA score) or eyelash (ELA score) involvement, representing a nonrandom subset of the randomized population and potentially compromising randomization. In addition, this outcome was not adjusted for multiplicity, increasing the risk of false-positive findings.

^dThe clinical experts consulted by CDA-AMC indicated that a difference of 200 patients per 1,000 patients could be considered clinically important.

^eRated down 1 level for imprecision. No published between-group MID was identified. A within-group MID specific to AA was not identified in the literature; an MID of 1.5 points was identified from published evidence across various indications and confirmed by clinical experts consulted by CDA-AMC to be appropriate for AA. The 95% CIs for both the HADS depression and HADS anxiety subscale scores were entirely within this threshold; therefore, they excluded any clinically important benefit or harm. In addition, the sample size of 261 participants did not meet the optimal information size, supporting downgrading for imprecision.

^fRated down 2 levels for very serious imprecision. No published between-group MID was identified to inform the target threshold. The clinical experts consulted by CDA-AMC indicated that a difference of 20 per 1,000 patients could represent a clinically important difference in SAEs. SAEs occurred at low event rates (0 of 130 in the ritlecitinib group and 3 of 131 in the placebo group), and the confidence interval for the absolute difference between groups was not reported, resulting in substantial uncertainty around the true difference in SAEs.

Sources: ALLEGRO-2b/3 Clinical Study Report.³¹ Details included in the table are from the sponsor's Summary of Clinical Evidence.

LTE Studies

Description of Studies

One LTE study (ALLEGRO-LT) has been summarized to provide evidence regarding safety and long-term efficacy of ritlecitinib in adults and adolescents with AA. The ALLEGRO-LT study is an ongoing, open-label, phase III trial that included patients who completed the ALLEGRO 2a and 2b/3 studies (referred to as rollover patients herein) (n = 603), as well as those who were not previously treated with ritlecitinib (referred to as de novo patients herein) (n = 447). Only the results of the ALLEGRO-LT study pertaining to the rollover patients will be further discussed in this report, as the inclusion criteria for these patients (reported in the following subsection), were aligned with the indicated population listed in the product monograph. Moreover, de novo patients received a dosage that was not of interest to the review (i.e., a loading dose of 200 mg once daily for 4 weeks, followed by 50 mg once daily).

The ALLEGRO-LT study consisted of up to a 5-week screening period, a 36-month open-label treatment period, and a 4-week follow-up period after completion of the study intervention at month 36 or study discontinuation. The ALLEGRO-LT study enrolled patients aged 12 years or older who had a diagnosis of AA. Full details of the eligibility criteria for the ALLEGRO-LT study are presented in Appendix 5 in the Supplementary Material document. In the ALLEGRO-LT study, rollover patients from the parent studies received 50 mg of oral ritlecitinib once daily. Patients were required to discontinue any treatments that could affect AA or had the potential for drug-drug interactions. Unless prohibited, patients were permitted to receive

any other medications necessary for the treatment of concomitant medical disorders as deemed necessary by the treating physician.

The primary objective of the ALLEGRO-LT study was to evaluate the long-term safety of ritlecitinib in patients with AA, which was measured by the incidences of TEAEs, SAEs, and AEs leading to discontinuation. The secondary objective of the study was to evaluate the long-term efficacy of ritlecitinib up to month 36. At the time of this report, the ALLEGRO-LT study was ongoing, and the results discussed in this report are from an interim analysis (data cut-off date of June 25, 2024).

Patient Disposition

Patient disposition for the ALLEGRO-LT study is summarized in Appendix 5 in the Supplemental Material document. Overall, 603 patients were assigned to receive ritlecitinib 50 mg once daily. These patients comprised of 590 patients (97.8%) rolled over from ALLEGRO-2b/3 (B7981015); of the 590 patients, only 107 patients received ritlecitinib 50 mg once daily in the parent study, and 18 of these 107 patients were adolescents. Additionally, 13 patients (2.2%) rolled over from the ALLEGRO 2a study (B7931005), but the treatment received in the parent study has not been reported. At the time of the data cut-off (June 25, 2024), 234 of 603 patients (38.8%) discontinued treatment in the study. The most common reasons for treatment discontinuation in the LTE study were lack of efficacy (13.1%), withdrawal by the patient (9.5%), and AEs (6.0%).

Baseline Characteristics

A summary of baseline patient and disease characteristics of the ALLEGRO-LT study is presented in Appendix 5 in the Supplemental Material document.

Exposure to Study Treatments and Concomitant Medications

Details of patients' treatment exposure, adherence, and the use of concomitant medications in the ALLEGRO-LT study are presented in Appendix 5 in the Supplemental Material document.

- The mean duration of treatment with ritlecitinib 50 mg once a day among patients in the rollover cohort was 908.9 days (SD = 458.08 days). At month 36, the mean adherence rate among these patients was 98.2% (SD = 4.09%).
- The most frequent ($\geq 5\%$) preferred terms of prior medications for AA included ciclosporin (5.5%), clobetasol (8.7%), clobetasol propionate (10.5%), diphenylcyclopropanone (11.6%), methotrexate (6.1%), minoxidil (22.7%), prednisolone (6.2%), prednisone (8.4%), and triamcinolone acetonide (18.6%).
- In the rollover cohort, 10.1% of patients received concomitant medications for AA, such as biotin; calcium pantothenate, cysteine, methionine, and zinc (1.2%); minoxidil (0.8%); biotin (0.7%); baricitinib (0.3%); triamcinolone acetonide (0.3%); and vitamin D not otherwise specified (0.3%). In addition, 9.4% of patients received concomitant medications for AA, with a frequency of less than 5% for all concomitant medications.

- Moreover, 94.9% of patients received concomitant medications for a condition other than AA. The most common medications used for conditions other than AA were tozinameran (41.5%), paracetamol (28.2%), and ibuprofen (24.7%).

Critical Appraisal

Internal Validity

The noncomparative, open-label structure of the LTE study limits the ability to attribute observed outcomes directly to ritlecitinib. Internal validity is further weakened by substantial selection bias, because only patients who had completed the parent trials were eligible to enter the LTE study; this means the sample likely overrepresents individuals who tolerated or responded well to treatment.

Additionally, patients were required to discontinue any treatments that could affect AA or had the potential for drug-drug interactions, whereas in the real world, patients may receive other medications concomitantly; therefore. As such, this could potentially affect internal validity.

No issues with the characteristics of patients enrolled in the LTE study were identified, as only the rollover group was considered and their characteristics were similar to those of patients in the ALLEGRO-2b/3 study. Regarding missing data, the potential effect remains a concern. There was a high rate of drop-off over time (approximately 50%), and whether the patients who discontinued the study were those who were not experiencing clinical benefit (consistent with a MNAR mechanism) is unknown. However, a slight decrease in the number of patients with a SALT score of 10 or less or 20 or less after week 24 was observed, which may also have been caused by the dropout rate. The results were analyzed appropriately for the available data (descriptive summary); however, the data have limitations because there was no comparison group for the treatment, and conclusions could not be drawn regarding whether the treatment is more effective than placebo during long-term treatment.

Only 13 patients rolled over from the ALLEGRO 2a study, and their treatment assignment in the parent study remains unclear.

External Validity

External validity is constrained by the narrow and selected study population. From the ALLEGRO-2b/3 study, 590 patients rolled over, yet only 107 received the dosage of interest (ritlecitinib 50 mg once daily), further narrowing the evaluable population and representativeness. As with the ALLEGRO-2b/3 trial, generalizability is limited by the exclusion of individuals with psychiatric conditions, which are important comorbidities with AA.

Results

Efficacy

Detailed results for outcomes relevant to this review are in Appendix 5 in the Supplemental Material document.

Proportion of patients with a response based on a SALT score of 20 or less: At month 36, the proportion of rollover patients with a response based on a SALT score of 20 or less was 69.9% (95% CI, 65.23% to 74.55%).

Proportion of patients with a response based on a SALT score of 10 or less: At month 36, the proportion of rollover patients with a response based on a SALT score of 10 or less was 62.1% (95% CI, 57.17% to 67.03%).

Change in SALT score from baseline: At baseline, the mean SALT score among rollover patients was 90.5 points (SD = 14.54 points). At month 36, the mean SALT score among these patients decreased to 21.2 points (SD = 31.66 points) (mean CFB = -68.2 points [SD = 32.18 points]).

Proportion of patients with a 75% improvement in SALT score: At month 36, the proportion of patients who achieved at least a 75% improvement in SALT score from baseline was 70.9% [REDACTED].

Proportion of patients with at least a 2-grade improvement or a score of 3 on the EBA: At month 36, the proportion of patients who achieved at least a 2-grade improvement from baseline or a score of 3 on the EBA was 69.9 (95% CI, 64.79% to 75.02%).

Proportion of patients with at least a 2-grade improvement or a score of 3 on the ELA: At month 36, the proportion of patients who achieved at least a 2-grade improvement from baseline or a score of 3 on the ELA was 70.5% (95% CI, 65.14% to 75.86%).

PGI-C response: At month 36, the proportion of patients who achieved a PGI-C score of at least “moderately improved” or “greatly improved” from baseline was 79.0% (95% CI, 74.90% to 83.17%).

Proportion of patients with improvement in current hair loss on the scalp based on the AAPPO scales: At month 36, the proportion of patients with a score of 0 (“no hair loss”) or 1 (“a little hair loss”) was 58% [REDACTED].

Proportion of patients with improvement in AAPPO current hair loss on the eyebrows based on the AAPPO scales: At month 36, the proportion of patients with a score of 0 (“no hair loss”) or 1 (“a little hair loss”) was 64.7% [REDACTED].

Proportion of patients with improvement in current hair loss on the eyelashes based on the AAPPO scales: At month 36, the proportion of patients with a score of 0 (“no hair loss”) or 1 (“a little hair loss”) was 67.5% [REDACTED].

CFB in emotional symptoms of AAPPO: The CFB to month 36 in the emotional symptoms score of the AAPPO was [REDACTED].

CFB in activity limitations of AAPPO: The CFB to month 36 in the activity limitations score of the AAPPO was [REDACTED].

CFB in anxiety subscale score of the HADS: The CFB to month 36 in the anxiety subscale score of the HADS was [REDACTED].

CFB in depression subscale score of the HADS: The CFB to month 36 in the depression subscale score of the HADS was [REDACTED].

Harms

Detailed results for harms are presented in Appendix 5 in the Supplemental Material document. Key results include the following:

- Among patients in the rollover cohort, 85.6% experienced at least 1 AE. The most common AEs reported by at least 10% of patients were severe acute respiratory syndrome coronavirus 2 positive test result (21.1%), COVID-19 (16.6%), headache (15.4%), cough (12.3%), upper respiratory tract infection (12.1%), nasopharyngitis (10.8), and pyrexia (10.6%).
- SAEs occurred in 7.1% of patients in the rollover cohort. None of the specific SAEs were reported by more than 1% of patients.
- AEs leading to treatment discontinuation occurred in 8.0% of patients in the rollover cohort. The most common reasons for discontinuation were pregnancy (1.5%); all other withdrawals due to adverse events (WDAEs) were reported in less than 1% of patients.
- Only 1 death was reported in the rollover cohort; this death was attributed to acute respiratory failure and cardiorespiratory arrest.

Aligning with the AESIs reported in the pivotal trial, neurologic and audiological events, as well as dermatological events, were reported as AESIs. Briefly, neurologic and audiological events were reported by 28.9% of patients, and dermatological events were reported by 28.9% during the LTE study. Additional details of the AESIs are reported in Appendix 5 in the Supplemental Material document.

Indirect Evidence

In the absence of head-to-head RCTs comparing ritlecitinib with relevant comparators, the sponsor submitted indirect evidence to inform comparative efficacy and safety. Furthermore, an appraisal of the indirect evidence was needed because evidence from the NMA was incorporated into the sponsor's pharmacoeconomic model.

Description of ITCs

The primary objective of the ITC was to provide comparative efficacy and safety of ritlecitinib (30 mg or 50 mg) versus baricitinib (2 mg and 4 mg) in the treatment of adult patients (aged 18 years and older) with AA. The ITC included an NMA and a MAIC. The NMA was used to compare outcomes at week 24, whereas the unanchored MAIC was used to compare outcomes at week 48 or 52.

Study Selection and Review Methods

A systematic literature review (SLR) of clinical trials in AA was conducted to compile an evidence base for the ITC. Electronic searches were performed in major biomedical databases, including Embase, MEDLINE, and Cochrane Central, from database inception to October 24, 2021. Searches were supplemented with

grey literature sources, clinical trial registries, and conference proceedings. Studies that did not include ritlecitinib as an intervention or baricitinib as a comparator were excluded. The eligible population consisted of patients with severe AA, AT, AU, alopecia ophioides, or alopecia circumscripta. The full study selection and eligibility criteria are described in Appendix 6 in the Supplemental Material document. The coprimary end points were the proportion of patients with a SALT score of 20 or less and a SALT score of 10 or less at week 24. The safety outcomes included the proportion of patients with AEs of any grade, grade 3 or grade 4 AEs, treatment-related AEs, discontinuation due to AEs, and discontinuation rates due to any cause. The database and grey literature searches identified RCTs that met the PICOS (population, intervention, comparator, outcomes, and study design) criteria. These trials formed the evidence base for the NMA and population-adjusted indirect comparisons.

Feasibility Assessment

The sponsor conducted an ITC feasibility assessment by comparing the design, duration, dosing schedules, population characteristics, outcome definitions, and time points of retrieved trials. Network connectivity and the presence of a suitable common comparator were also evaluated to identify the most appropriate ITC methods. Potential treatment effect modifiers considered in the feasibility assessment included age, sex, race or ethnicity, geographic region, baseline SALT score, proportion of patients with AT or AU, duration of disease, duration of the current AA episode, prior treatments, and baseline psychosocial measures, based on both published literature and clinical expert ranking of prognostic factors. The evidence base for the feasibility assessment consisted of phase II and phase III RCTs of systemic therapies for severe AA that included ritlecitinib (the ALLEGRO 2a and ALLEGRO-2b/3 studies), and baricitinib (the BRAVE-AA1 and BRAVE-AA2 studies). Other systemic therapies used in clinical practice (methotrexate, cyclosporine, oral corticosteroids) were not eligible due to the absence of trials with comparable design, patient populations, and outcomes. As a result, baricitinib (2 mg and 4 mg) was identified as the only relevant comparator for inclusion in the network.

The sponsor's feasibility assessment identified several challenges for conducting ITCs, including differences in baseline disease severity, disease duration, age distribution (notably the inclusion of adolescents in the ALLEGRO studies but not in the BRAVE studies), geographic distribution, and the proportion of patients with AT or AU across the ritlecitinib and baricitinib programs. Additional challenges included heterogeneity in follow-up durations, nonaligned assessment time points, and the absence of placebo control beyond week 24 in the ALLEGRO studies, which precluded anchored comparisons at longer time points. The network was also sparse, with only 2 trials available for each treatment. For longer-term outcomes at week 48 or 52, where placebo was not available, the sponsor determined that unanchored MAICs and simulated treatment comparison (STC) were required.

ITC Analysis Methods

For additional information on the analysis methods for the ITC, refer to Appendix 6 in the Supplemental Material document.

For outcomes assessed at week 24, the sponsor conducted anchored Bayesian NMAs based on a connected placebo network (primarily the ALLEGRO-2b/3 and the BRAVE-AA1 or the BRAVE-AA2 studies),

with the ALLEGRO 2a study contributing for some outcomes or via individual patient data (IPD)-derived calculations. Because the network consisted of only 2 trials per treatment node and between-trial variability could not be reliably estimated, the sponsor employed fixed-effect models for all NMAs; random-effect models were explored but did not converge due to the sparsity of the network. Binary efficacy outcomes, including a SALT score of 10 or less and a SALT score of 20 or less, and composite safety outcomes such as any AE ($\geq 2\%$ or $\geq 5\%$), SAEs, and discontinuations due to AEs, were analyzed using a binomial likelihood with a logit link, hazard rate methods, and/or Poisson count models. Separate NMA nodes were maintained for each dose of ritlecitinib (50 mg once daily) and baricitinib (2 mg and 4 mg), and placebo groups were kept distinct by trial. The sponsor explored the potential treatment effect modification using multilevel network meta-regression (ML-NMR).

Given that the placebo arms in the ALLEGRO and BRAVE studies did not extend to later time points (to assess week 48 or 52 outcomes), the sponsor conducted an unanchored MAIC and STC to estimate the long-term relative effects between ritlecitinib and baricitinib. The MAIC and STC adjusted IPD from the ALLEGRO studies to the aggregate baseline characteristics reported in BRAVE for variables identified as prognostic or potential effect modifiers, including age, sex, race, weight, BMI, baseline SALT score, very severe disease status, duration of disease, duration of the current episode, HADS, geographical region, and the percentage of patients with AU. The MAIC weights were estimated using a propensity score approach, and the effective sample size (ESS) was reported. For the STC, a regression model was fitted to ALLEGRO data using covariates selected through Akaike Information Criterion and clinical relevance, after which predicted outcomes were generated for the BRAVE population using available aggregate characteristics. Although balance diagnostics were reported, no formal statistical assessment of residual confounding was performed. Sensitivity analyses were conducted on the primary end points exploring alternative imputation methods and expanding the network to include the ALLEGRO 2a study.

Summary of Included Studies

A total of 4 phase II to III RCTs formed the evidence base for the indirect comparisons. These included ALLEGRO 2a and ALLEGRO-2b/3 studies for ritlecitinib, and the BRAVE-AA1 and BRAVE-AA2 studies for baricitinib. All 4 studies enrolled patients with severe AA, with the ALLEGRO 2a study restricted to adults and the ALLEGRO-2b/3 study including adults and adolescents aged 12 years or older, whereas the BRAVE trials enrolled adults only. Sample sizes ranged from 95 patients in the ALLEGRO 2a study to 718 in the ALLEGRO-2b/3 study, with the BRAVE-AA1 and BRAVE-AA2 studies including 654 and 546 patients, respectively. The sponsor's risk-of-bias assessment using the Cochrane Risk of Bias 2.0 tool and the National Institute for Health and Care Excellence quality appraisal checklist concluded that all 4 trials were considered to be low risk in most domains, with "some concerns" for missing primary outcome data across trials. According to the sponsor, this was mitigated by prespecified multiple imputation and NRI strategies.

The trials were comparable in design and inclusion criteria, except that the ALLEGRO-2b/3 study also included adolescents (aged 12 years to younger than 18 years old) in the study. Concomitant treatments permitted in the included studies were generally similar. All 4 studies used SALT-based end points but differed in specific definitions and time points, and they applied different missing-data assumptions and

imputation approaches, which are important sources of heterogeneity. Regarding the baseline characteristics of patients included in the ALLEGRO-2b/3 and BRAVE-11A studies, the ALLEGRO-2b/3 study had a higher proportion of treatment-naïve patients (23% to 40%) than the BRAVE-AA1 and BRAVE-AA2 studies (4% to 12%). Patients in the BRAVE-AA1 and BRAVE-AA2 studies had higher mean body weight and BMI, longer disease duration, and a longer duration of the current episode compared with patients in the ALLEGRO studies. These differences may reflect variations in study populations, including the inclusion of adolescents in the ALLEGRO studies and differences in how disease severity was defined (e.g., AT or AU classification versus SALT-based thresholds), and they limit direct cross-trial comparisons.

For the week 24 anchored NMA, the 4 trials formed a single small network with 1 RCT per active comparator and dosage (ritlecitinib 50 mg; baricitinib 2 mg and 4 mg), using placebo as the common anchor. No closed loops were available to assess inconsistency. At later time points (week 48 in the ALLEGRO studies and week 52 in the BRAVE studies), placebo arms were no longer present; therefore, no connected network existed. As a result, longer-term comparative evidence relied on the MAIC and STC methods based on weighted IPD from the ALLEGRO studies to match aggregate baseline characteristics from the BRAVE studies across key prognostic and potential effect-modifying variables.

Critical Appraisal of ITCs

The sponsor conducted a prespecified SLR using standard databases (MEDLINE, Embase, and the Cochrane Library), conference proceedings, and trial registries to identify relevant evidence for AA treatments. The SLR methods and reporting (the Population, Intervention, Comparator, Outcomes, and Study framework and a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram) were appropriate; however, the resulting evidence base for the ITC was very limited. The SLR search was conducted up to October 2021, and it is unclear whether any relevant studies, longer-term analyses, or updated trial results published after this date were captured. As such, the evidence base informing the ITC may be incomplete, and the potential effect of any omitted evidence on the comparative estimates is unknown. Only the ALLEGRO-2a and ALLEGRO-2b/3 studies contributed evidence for ritlecitinib, whereas baricitinib was informed solely by the BRAVE-AA1 and BRAVE-AA2 studies. As a result, the evidence network was sparse and star-shaped, with at most 1 trial informing each treatment node, limiting the robustness of any indirect comparisons.

Risk-of-bias assessments were conducted using the Cochrane Risk of Bias 2.0 tool; however, in the ITC report, risk-of-bias judgments were reported at the trial level rather than at the outcome- and time point-specific level. Contemporary guidance recommends assessing the risk of bias for each specific result, as the magnitude and direction of bias may differ across end points and time points.³⁹ This limitation is particularly relevant given differences in outcome definitions, imputation strategies, and duration of placebo control across trials. In addition, longer-term analyses relied on data beyond the placebo-controlled period in the ALLEGRO studies, increasing the reliance on modelling assumptions rather than randomized evidence. As such, differences in estimands may further limit the comparability of treatment effects across trials, even when outcomes and nominal time points appear aligned.

A key limitation of the ITC is the clinically important cross-trial heterogeneity between the ALLEGRO and BRAVE-AA studies, including differences in baseline disease severity, the duration of disease, the proportion of patients with AT or AU, and prior treatment exposure. These factors are clinically relevant and may act as prognostic factors and/or treatment effect modifiers (e.g., refer to Appendix 6 in the Supplemental Material document). Because placebo served as the common comparator for the week 24 analyses, cross-trial differences in placebo response potentially driven by these baseline imbalances raise concerns regarding whether the transitivity assumption required for valid indirect comparisons was met. Although meta-regression and population-adjusted methods explored adjustments for baseline age, sex, ethnicity, SALT score, weight, BMI, duration since diagnosis, and the duration of the current episode, adjustment was restricted to covariates reported in both trials. Important characteristics, such as prior systemic treatment exposure and certain severity subgroups, were inconsistently reported or did not overlap across the studies; therefore, the limited number of trials and the lack of overlap in reported covariates restrict the ability to adequately adjust for these imbalances.

For outcomes at week 24, the placebo-anchored Bayesian NMA was methodologically appropriate; however, the star-shaped and sparse network prevented a formal assessment of consistency and limited the reliable estimation of between-study homogeneity. Fixed-effect models were selected due to the limited number of trials; however, in the presence of clear clinical heterogeneity, this modelling choice may have underestimated true uncertainty, resulting in artificially narrow credible intervals (CrIs). The absence of robust random-effects sensitivity analyses with informative priors further limits assessment of how heterogeneity might influence the magnitude and precision of estimated effects. Beyond week 24, the sponsor used unanchored population-adjusted methods (STC and MAIC), which do not preserve randomization, are highly vulnerable to residual confounding, and require all relevant effect modifiers and prognostic factors to be included and adjusted to produce estimates of comparative effects. The sponsor's ITC report acknowledges that only covariates available in both the ALLEGRO and BRAVE studies could be included, increasing the risk of unmeasured or inadequately adjusted confounding. In addition, the MAIC analyses resulted in substantial reductions in ESS, with reductions exceeding 50% in several models, indicating a loss of precision and increasing the likelihood that estimates are driven by a small subset of weighted patients rather than the full trial population. In addition, the STC estimates are conditional on the BRAVE study population, which may not align with the target population for ritlecitinib, further limiting interpretability. Multiple outcomes (e.g., a SALT score of 10 or less, a SALT score of 20 or less, the anxiety subscale HADS score, and the depression subscale HADS score), comparator doses, time points, and analytical approaches (anchored NMA, STC, MAIC, and ML-NMR) were explored without a formal adjustment for multiplicity.

Comparative safety analyses are limited by a short placebo-controlled follow-up, low event rates, and heterogeneity in AE reporting across trials, restricting the ability to draw conclusions about relative safety. Long-term comparative efficacy and safety estimates are based on limited or unanchored evidence and should be considered exploratory and highly uncertain.

Efficacy Results of ITCs

Key results of the ITCs are provided in [Table 5](#) through [Table 8](#). Additional details are reported in Appendix 6 in the Supplemental Material document.

NMA Results

Response Based on a SALT Score of 10 or Less at Week 24

The results showed no difference between ritlecitinib 50 mg and baricitinib 4 mg in response based on a SALT score of 10 or less at week 24; however, the point estimate favoured baricitinib 4 mg (odds ratio [OR] = 0.96; 95% CrI, 0.18 to 7.21). There was also no difference between ritlecitinib 50 mg and baricitinib 2 mg (OR = 2.48; 95% CrI, 0.46 to 19.94); however, the point estimate favoured ritlecitinib. In sensitivity analyses using NRI for the ALLEGRO studies and the BRAVE base case, there were no differences between treatment arms; however, the point estimates appeared to favour baricitinib 4 mg and ritlecitinib 50 mg.

Response Based on a SALT Score of 20 or Less at Week 24

There was no difference between the treatment arms in response based on a SALT score of 20 or less; however, the point estimate appeared to favour ritlecitinib 50 mg (OR = 2.16; 95% CrI, 0.48 to 16.46). In a sensitivity analyses using NRI for the ALLEGRO studies and the BRAVE base case, the results shifted in favour of baricitinib.

Table 5: Summary of NMA Results for Ritlecitinib vs. Baricitinib (Base Case SALT Score ≤ 10 and SALT Score ≤ 20 at Week 24, Fixed-Effect Model)

Comparison	Proportion of patients with a response based on a SALT score ≤ 10, median OR (95% CrI)	Proportion of patients with a response based on a SALT score ≤ 20, median OR (95% CrI)
Ritlecitinib 50 mg vs. baricitinib 4 mg	0.96 (0.18 to 7.21)	2.16 (0.48 to 16.46)
Ritlecitinib 50 mg vs. baricitinib 2 mg	2.48 (0.46 to 19.94)	6.07 (1.35 to 46.55)

CrI = credible interval; NMA = network meta-analysis; OR = odds ratio; SALT = Severity of Alopecia Tool; vs. = versus.

Note: Values greater than 1 favour ritlecitinib.

Sources: The ALLEGRO-2b/3 trial Clinical Study Report.³¹ Details included in the table are from the sponsor's Summary of Clinical Evidence.

Anxiety and Depression Outcomes Based on HADS Subscale Scores at Week 24

There was no evidence of a difference between ritlecitinib 50 mg and baricitinib 4 mg or 2 mg; however, the point estimates numerically favoured ritlecitinib 50 mg for the HADS depression subscale and baricitinib 4 mg for the HADS anxiety subscale.

Table 6: Summary of NMA Results, Ritlecitinib vs. Baricitinib (Base Case of HADS Anxiety and Depression, Fixed-Effect Model)

Comparison	Change from baseline in HADS anxiety subscale, mean differences (95% CrI)	Change from baseline in HADS depression subscale, mean difference (95% CrI)
Ritlecitinib 50 mg vs. baricitinib 4 mg	0.23 (−0.61 to 1.12)	−0.07 (−0.89 to 0.75)
Ritlecitinib 50 mg vs. baricitinib 2 mg	0.18 (−0.67 to 1.05)	−0.11 (−0.93 to 0.67)

CrI = credible interval; HADS = Hospital Anxiety and Depression Scale; NMA = network meta-analysis; vs. = versus.

Note: Mean differences less than 0 favour ritlecitinib.

Sources: The ALLEGRO-2b/3 trial Clinical Study Report.³¹ Details included in the table are from the sponsor's Summary of Clinical Evidence.

ML-NMR Results

Separate ML-NMR models were fitted for a SALT score of 10 or less and a SALT score of 20 or less at week 24. For a SALT score of 10 or less, the base-case model was adjusted for sex, baseline SALT score, episode duration, and disease duration. For a SALT score of 20 or less, the base-case model was adjusted for sex, baseline SALT score, and previous episodes. Additional models explored adjustments for the most influential covariate (baseline SALT score), the second most influential covariate (sex), and all covariates combined. The detailed results of the ML-NMR are presented in Appendix 6 in the Supplemental Material document.

Response Based on a SALT Score of 10 or Less at Week 24

In the base case, there was no difference between ritlecitinib 50 mg and baricitinib 4 mg (OR = 1.93; 95% CrI, 0.36 to 15.43). Results from the other ML-NMR models were aligned with the base-case results.

Comparisons with baricitinib 2 mg favoured ritlecitinib 50 mg (OR = 7.15; 95% CrI, 1.25 to 60.02). With the exception of model 5 (all covariates), which was aligned with the base-case results, the point estimates for results from the other ML-NMR models were smaller, with 95% CrI crossing 1.

Response Based on a SALT Score of 20 or Less at Week 24

In the base case, there was no difference between ritlecitinib 50 mg and baricitinib 4 mg (OR = 0.78; 95% CrI, 0.11 to 6.66). Results from the other ML-NMR models were aligned with the base-case analysis; however, the point estimates varied between favouring ritlecitinib 50 mg and baricitinib 4 mg.

Comparisons with baricitinib 2 mg did not demonstrate a difference between treatments either (OR = 5.84; 95% CrI: 0.42 to 27.38). Results from the alternative ML-NMR models were generally aligned with the base-case analysis, except for model 3, which included sex as a covariate (OR = 6.48; 95% CrI, 1.55 to 44.41).

Anxiety and Depression Outcomes Based on HADS Subscale Scores at Week 24

For CFB in the HADS anxiety subscale, the estimated mean differences in the base-case ML-NMR model for ritlecitinib were 0.13 (95% CrI, −0.76 to 0.98) versus baricitinib 4 mg and 0.08 (95% CrI, −0.76 to 0.92) versus baricitinib 2 mg. Results from the alternative ML-NMR models adjusting for sex or all covariates were generally similar.

For the CFB in the HADS depression subscale at week 24, the estimated mean differences in the base-case model for ritlecitinib were -0.59 (95% CrI, -1.37 to 0.20) versus baricitinib 4 mg and -0.67 (95% CrI, -1.46 to 0.13) versus baricitinib 2 mg. Results from the alternative ML-NMR models were generally aligned with the base-case findings.

MAIC Results

The results of the MAIC for outcomes assessed at week 48 or 52 are summarized in this section. The sponsor also submitted an STC assessing outcomes based on a SALT score of 10 or less and a SALT score of 20 or less at week 48 or 52. The STC results are provided in Appendix 6 in the Supplemental Material document.

Response Based on a SALT Score of 10 or Less and a SALT Score of 20 or Less at Week 48 or 52
In the base-case analysis, there was no difference between ritlecitinib 50 mg and baricitinib 4 mg in response based on a SALT score of 10 or less at week 48 or 52 (OR = 1.169; 95% CI, 0.672 to 2.033; ESS = 64.4). In contrast, results favoured ritlecitinib 50 mg when compared with baricitinib 2 mg (OR = 2.414; 95% CI, 1.462 to 3.984; ESS = 70.9).

There was also no difference between ritlecitinib 50 mg and baricitinib 4 mg in response based on a SALT score of 20 or less (OR = 1.313; 95% CI, 0.789 to 2.185; ESS = 64.4). The results favoured ritlecitinib 50 mg when compared with baricitinib 2 mg (OR = 2.713; 95% CI, 1.675 to 4.396; ESS = 70.9).

Results from the alternative MAIC models, including the baseline SALT score-only adjustment, the AIC-selected covariate model, the all-covariate model, and the naive comparison, were generally aligned with the base-case results. Across these models, comparisons with baricitinib 4 mg did not show a difference between treatments, whereas comparisons with baricitinib 2 mg generally favoured ritlecitinib 50 mg, although the ESS values were reduced.

The sponsor-submitted STC results were generally consistent with the MAIC findings, with no clear differences observed between ritlecitinib and baricitinib across the evaluated outcomes.

Table 7: MAIC Results Comparing Ritlecitinib 50 mg With Baricitinib 4 mg and 2 mg on SALT Score of 10 or Less and a SALT Score of 20 or Less at Week 48 or 52

Outcome	Comparator	Naive model, OR (95% CI)	Base-case model, OR (95% CI)	Baseline SALT score model, OR (95% CI)	AIC-selected model, OR (95% CI)	All-covariate model, OR (95% CI)
SALT score ≤ 10	Baricitinib 4 mg	1.19 (1.05 to 1.36)	1.169 (0.672 to 2.033) (ESS = 64.396)	1.382 (0.895 to 2.135) (ESS = 94.908)	1.202 (0.776 to 1.862) (ESS = 90.783)	1.205 (0.529 to 2.745) (ESS = 28.684)
	Baricitinib 2 mg	2.69 (2.34 to 3.09)	2.414 (1.462 to 3.984) (ESS = 70.886)	2.975 (1.934 to 4.575) (ESS = 98.037)	2.470 (1.586 to 3.848) (ESS = 88.282)	2.530 (1.232 to 5.195) (ESS = 34.407)
SALT score ≤ 20	Baricitinib 4 mg	1.26 (1.12 to 1.42)	1.313 (0.789 to 2.185) (ESS = 64.396)	1.459 (0.969 to 2.197) (ESS = 94.908)	0.997 (0.645 to 1.541) (ESS = 82.655)	1.169 (0.541 to 2.527) (ESS = 28.684)
	Baricitinib 2 mg	2.75 (2.43 to 3.12)	2.713 (1.675 to 4.396) (ESS = 70.886)	3.053 (2.037 to 4.575) (ESS = 98.037)	2.106 (1.345 to 3.297) (ESS = 78.043)	2.495 (1.255 to 4.960) (ESS = 34.407)

AIC = Akaike Information Criterion; CrI = credible interval; ESS = effective sample size; MAIC = matching-adjusted indirect comparison; OR = odds ratio; SALT = Severity of Alopecia Tool.

Note: Values greater than 1 favour ritlecitinib.

Sources: The ALLEGRO-2b/3 trial Clinical Study Report.³¹ Details included in the table are from the sponsor's Summary of Clinical Evidence.

Harms Results of ITCs

The harm results reported here are based on the sponsor-submitted NMAs.

Adverse Events

The NMA results showed that there was no difference between ritlecitinib 50 mg and baricitinib 2 mg on the rate of AEs occurring in at least 5% of patients (hazard ratio [HR] = 0.94; 95% CrI, 0.56 to 1.48); however, the point estimate favoured ritlecitinib 50 mg. When compared with baricitinib 4 mg, the results were also in favour of ritlecitinib 50 mg (HR = 0.49; 95% CrI, 0.30 to 0.75).

When ritlecitinib 50 mg was compared with baricitinib 2 mg, there was no difference in AEs occurring in at least 2% of patients (HR = 0.96; 95% CrI, 0.59 to 1.49). In comparison with baricitinib 4 mg, the results favoured ritlecitinib 50 mg (HR = 0.39; 95% CrI, 0.24 to 0.57).

Serious Adverse Events

For SAEs, the results did not indicate a difference between ritlecitinib 50 mg and baricitinib 2 mg (HR = 0.31; 95% CrI, 0.03 to 2.54). Similarly, no difference was observed between ritlecitinib 50 mg and baricitinib 4 mg (HR = 0.27; 95% CrI, 0.02 to 1.89).

Withdrawals Due to Adverse Events

For WDAEs, there was no difference between ritlecitinib 50 mg and baricitinib 2 mg (HR = 0.33; 95% CrI, 0.01 to 6.41). A similar finding was observed when ritlecitinib 50 mg was compared with baricitinib 4 mg (HR = 0.31; 95% CrI, 0.01 to 5.82).

Table 8: Results for Fixed-Effect Bayesian NMA of Harms for Ritlecitinib vs. Baricitinib

Comparison	AEs in ≥ 5% of patients, median HR (95% CrI)	AEs in ≥ 2% of patients, median HR (95% CrI)	SAEs, median HR (95% CrI)	WDAEs, median HR (95% CrI)
Ritlecitinib 50 mg vs. baricitinib 2 mg	0.94 (0.56 to 1.48)	0.96 (0.59 to 1.49)	0.31 (0.03 to 2.54)	0.33 (0.01 to 6.41)
Ritlecitinib 50 mg vs. baricitinib 4 mg	0.49 (0.30 to 0.75)	0.39 (0.24 to 0.57)	0.27 (0.02 to 1.89)	0.31 (0.01 to 5.82)

AE = adverse event; CrI = credible interval; HR = hazard ratio; NMA = network meta-analysis; SAE = serious adverse event; WDAE = withdrawal due to adverse event; vs. = versus.

Note: Values less than 1 favour ritlecitinib.

Sources: The ALLEGRO-2b/3 trial Clinical Study Report.³¹ Details included in the table are from the sponsor's Summary of Clinical Evidence.

Studies Addressing Gaps in the Systematic Review Evidence

No relevant studies addressing gaps in the systematic review were included.

Discussion

This review summarizes the evidence on the efficacy and safety of ritlecitinib for the treatment of severe AA in adults and adolescents aged 12 years or older. One RCT, the ALLEGRO-2b/3 study (N = 261), was included in the sponsor-conducted SLR. The ALLEGRO-2b/3 study enrolled patients with severe AA (≥ 50% scalp hair loss) and included a 24-week placebo-controlled period, followed by an open-label extension to week 48. Outcomes of key interest included the proportion of patients who achieved a SALT score of 20 or less or a SALT score of 10 or less (representing scalp hair regrowth); the proportion of patients with at least a 2-grade improvement or a score of 3 in the EBA and ELA (representing eyebrow and eyelash hair regrowth improvement); the proportion of patients who achieved a PGI-C response of “moderately improved” or “greatly improved”; and the CFB in the depression and anxiety subscale scores of the HADS.

Evidence from the ongoing 36-month, open-label extension study, the ALLEGRO-LT study, was also summarized. The ALLEGRO-LT study enrolled patients who completed the ALLEGRO 2a and ALLEGRO-2b/3 studies (referred to as rollover patients; N = 603) and patients without prior exposure to ritlecitinib (referred to as de novo patients; N = 477). Only results from the rollover patients were appraised in this review, as their eligibility aligned with the Health Canada–approved indication. The primary objective of the ALLEGRO-LT study was to evaluate long-term safety, including TEAEs, SAEs, and AEs leading to discontinuation.

To address the gap in comparative efficacy and safety for ritlecitinib relative to baricitinib, the sponsor submitted 1 ITC, which included placebo-anchored Bayesian NMAs at week 24, with additional unanchored population-adjusted analyses (STC and MAIC) for later time points.

Efficacy

According to the clinical experts, response to systemic therapy in AA is primarily assessed based on scalp hair regrowth using SALT-based thresholds. Evidence from the ALLEGRO-2b/3 study showed that, compared with placebo, treatment with ritlecitinib 50 mg once daily for 24 weeks resulted in a higher proportion of patients who achieved hair regrowth based on a SALT score of 20 or less and a SALT score of 10 or less. Achieving a SALT score of 20 or less or a SALT score of 10 or less is considered a clinically

meaningful treatment target, consistent with the published literature and clinical expert input.⁴⁰ An absolute difference of 10% (100 patients per 1,000 patients) was applied as a threshold for clinical importance based on the input from the clinical experts. The certainty of the evidence was assessed to be high for a SALT score of 20 or less and moderate for a SALT score of 10 or less using GRADE assessments. The moderate certainty for a SALT score of 10 or less reflected the uncertainty around the precision of the effect estimate; that is, the 95% CI crossed the target threshold and included effects ranging from no important difference to clinically important benefit. Results from other SALT-based outcomes, including a 75% improvement in SALT score and CFB in SALT score, were consistent with the primary SALT outcomes. Although the study was not powered for prespecified subgroup analyses, results for subgroup analyses, including age (adolescents versus adults), were generally consistent with the primary findings. For a SALT score of 20 or less, the difference in treatment effects for the AT or AU subgroup was smaller (approximately 7%) compared with the overall population (approximately 30%), suggesting potential heterogeneity of treatment effect in patients with more severe disease. However, the effect remained in the same direction and excluded the null, and the upper CI included the 10% decision threshold. Given the poorer prognosis and lower expected response in AT or AU, this magnitude was considered clinically plausible and the certainty was therefore not rated down for indirectness. Results in adolescents and adults showed similar point estimates, suggesting no age-related heterogeneity. However, the adolescent subgroup was small and not powered for statistical inference.

The clinical experts noted that eyebrow and eyelash hair regrowth are important for patients due to their visibility and the effect on HRQoL, especially for adolescents who experience bullying and social withdrawal due to visible hair loss. In addition, eyelashes have important physiological functions, such as maintaining a protective barrier to prevent harmful foreign substances from entering the eye. Based on the proportion of patients who achieved at least a 2-grade improvement or a score of 3 on the EBA and ELA at week 24, treatment with ritlecitinib led to an increase in eyebrow and eyelash hair compared with placebo. In the absence of published between-group MIDs, the clinical experts consulted by CDA-AMC indicated that an absolute difference of 10% (100 patients per 1,000 patients) would be clinically meaningful. The observed absolute differences for at least a 2-grade improvement or a score of 3 on the EBA and ELA exceeded this threshold, supporting a clinically important treatment effect. The certainty of the evidence for improvement in the EBA and ELA scores was rated as moderate because these outcomes were only assessed among patients with baseline eyebrow or eyelash involvement, representing a nonrandom subset of the randomized population, which may compromise the balance achieved by randomization. In addition, this outcome was not adjusted for multiplicity, increasing the risk of false-positive findings. Despite these limitations, the magnitude and consistency of the observed effects support a clinically meaningful benefit, consistent with the input from the clinical experts.

Both patients and clinical experts highlighted that AA is associated with a substantial emotional and psychosocial burden, including distress and anxiety, making improvements in these domains important treatment goals. The evidence showed that changes in the HADS depression and anxiety scores were minimal and similar between treatment groups, suggesting that ritlecitinib likely has little to no clinically important effect on anxiety and depression associated with AA when compared with placebo at week 24. The certainty of this evidence was rated as moderate because the effect estimates for both the HADS

depression and HADS anxiety subscales were entirely within the MID of 1.5 points identified from published evidence across various indications and confirmed as appropriate for AA by the clinical experts consulted by CDA-AMC. This finding should be interpreted in the context of the study population, which excluded patients with pre-existing psychiatric conditions at baseline, resulting in generally low baseline scores and minimal changes observed over 24 weeks of treatment. In addition, the sample size of 261 participants did not meet the optimal information size, supporting downgrading for imprecision. Emotional and social well-being was assessed using the AAPPO instrument, a disease-specific instrument that reflects patient priorities. At week 24, a higher proportion of patients treated with ritlecitinib reported improvement in AAPPO items, including current hair loss on the scalp, eyebrows, and eyelashes, compared with placebo. In contrast, improvement in current body hair loss did not differ between treatment groups, and measures related to activity limitations were similar between groups. Although AAPPO is an AA-specific patient-reported outcome, its thresholds for clinically meaningful change and GRADE certainty assessment are less established and were therefore considered as supportive evidence. The PGI-C reflects a global assessment that integrates scalp hair regrowth, eyebrow and eyelash hair changes, and broader psychosocial effect. At 24 weeks, the proportion of patients with a PGI-C response of “moderately improved” or “greatly improved” was higher in patients treated with ritlecitinib compared with placebo. The difference in the proportion of patients was considered clinically meaningful, and the certainty of the evidence was assessed to be high. Taken together, the evidence indicates that ritlecitinib provides meaningful improvements more than placebo in patient-perceived hair regrowth and global well-being, but there was little measurable effect on anxiety and depression over 24 weeks.

Evidence beyond week 24 is informed by the open-label extension of the ALLEGRO-2b/3 and the ALLEGRO-LT studies. At week 48, patients in the ALLEGRO-2b/3 study who continued treatment with ritlecitinib 50 mg generally showed further improvements across scalp, eyebrow, and eyelash hair outcomes, as well as patient-reported improvements in global disease burden; however, changes in anxiety and depression symptoms remained minimal. In the ALLEGRO-LT study, the proportion of patients with an improvement in scalp hair regrowth, an EBA or ELA response, and a PGI-C response increased over time through month 36. However, the absence of a concurrent control group, combined with potential selection and attrition biases, limits the interpretation of these longer-term efficacy data.

The sponsor-submitted ITC evaluated the comparative efficacy of ritlecitinib versus baricitinib primarily for scalp hair regrowth, as measured by SALT scores less than or equal to 10 and less than or equal to 20 at week 24, using placebo-anchored Bayesian NMAs, with additional unanchored MAIC analyses for week 48 or 52 time points. The NMA results suggest that the efficacy of ritlecitinib relative to baricitinib on SALT scores of 10 or less or 20 or less at week 24 was broadly similar, with no consistent differences observed between the treatment groups. The CrIs were wide and included a null effect, indicating substantial uncertainty around the magnitude of any potential differences. The ITCs showed no meaningful differences between ritlecitinib and baricitinib for changes in anxiety or depression symptoms at week 24. Across all NMA and anchored ML-NMR analyses, the CrIs crossed the null, providing no evidence of a difference between ritlecitinib and baricitinib for either outcome. The ITC findings are limited by important cross-trial heterogeneity between the ALLEGRO and BRAVE-AA studies, including differences in baseline disease

severity, the duration of AA, the proportions of patients with AU or AT, prior treatment exposure, and placebo response rates. These differences challenge the transitivity assumptions. In addition, the sparse, star-shaped network, with only a single trial informing each comparison, precluded a formal assessment of inconsistency and the reliable estimation of between-study heterogeneity. As a result, the fixed-effect models used in the base-case analyses likely underestimate the uncertainty. Beyond week 24, comparative analyses relied on unanchored MAIC and STC methods due to the absence of a connected placebo network. These methods do not preserve randomization and are highly sensitive to model assumptions, covariate adjustment, and ESS, leading to greater uncertainty in longer-term comparative estimates.

In the current treatment landscape, baricitinib represents an alternative targeted JAK inhibitor therapy indicated for adult patients. The sponsor-submitted ITC suggested broadly similar efficacy between ritlecitinib and baricitinib for scalp hair regrowth outcomes at week 24; however, these estimates were associated with uncertainty due to the methodological limitations and cross-trial differences already described. Compared to baricitinib, ritlecitinib is indicated for patients aged 12 years or older. As such, ritlecitinib may address an unmet need in adolescents for whom targeted treatment options are currently limited.

Harms

Evidence from the ALLEGRO-2b/3 study showed that TEAEs were common in both treatment groups (> 70% in each), and frequencies were similar between the groups at week 24. The most frequently reported TEAEs in patients treated with ritlecitinib included acne, headache, nasopharyngitis, nausea, and upper respiratory tract infection, consistent with the known safety profile of oral JAK inhibitors. During the placebo-controlled period, 2.3% of patients in the placebo group and no patients in the ritlecitinib 50 mg group reported at least 1 SAE. The clinical experts consulted by CDA-AMC noted that the 24-week duration of placebo-controlled follow-up was insufficient to fully characterize rare AEs. Findings at week 48 were generally consistent with those observed at week 24. However, beyond week 24, the study no longer included a concurrent placebo control, limiting the ability to make comparative safety inferences.

Results from the ALLEGRO-LT study indicated that no new safety signals were identified during the 36-month treatment period, and the overall pattern and types of AEs were generally consistent with those observed during the placebo-controlled period. Rare SAEs were uncommon during extended follow-up. However, interpretation of long-term safety findings is limited by the open-label design, lack of a concurrent control group, and potential for selection and attrition bias, as patients who tolerated and responded to treatment were more likely to remain in the extension study.

Results from the sponsor-submitted ITC suggest that ritlecitinib 50 mg may be associated with numerically lower rates of AEs compared with baricitinib 4 mg, while rates appear similar when compared with baricitinib 2 mg. For SAEs and WDAEs, the ITC did not identify differences between treatments, although point estimates numerically favoured ritlecitinib, with baricitinib 4 mg showing the highest rates of SAEs and WDAEs. Interpretation of these findings is limited by the low frequency of SAEs and WDAEs, which resulted in wide CrIs of effect estimates. As such, the comparative safety of ritlecitinib relative to baricitinib remains uncertain.

Ethics and Equity Considerations

Input from the patient group and the clinical experts consulted for the review highlighted substantial psychological and social effects of AA, particularly among individuals with severe disease. Adolescents with severe AA experience disproportionate psychosocial consequences, including bullying, social isolation, school absenteeism, and impaired self-esteem during a critical period of identity development. According to the clinical experts, limited access to effective treatment options for adolescents represents an equity concern, as delayed or inadequate disease control may lead to long-term mental health and social consequences. Given that ritlecitinib is indicated for patients aged 12 years or older, it may help address this gap by providing a targeted treatment option for adolescents with severe AA. Access to dermatologists for the treatment of AA is not equitable across Canada, as patients living in rural, remote, or underserved communities often face delays in diagnosis and treatment due to limited specialist availability. The clinical experts noted that teledermatology can improve access and continuity of care; however, its availability and integration vary across Canada.

The financial burden was identified as a further equity consideration according to the patient group input. Patients and caregivers reported significant out-of-pocket costs related to wigs, cosmetic adaptations, and supportive care. Variability in public and private drug coverage may further restrict access to systemic therapies, disproportionately affecting patients without comprehensive insurance coverage. Although access to ritlecitinib may expand treatment options, access to this therapy may remain influenced by coverage across jurisdictions. Persistent hair loss is associated with anxiety and depression. Caregivers of pediatric and adolescent patients also experience emotional strain and challenges navigating educational and social systems.

Conclusion

Evidence from the ALLEGRO-2b/3 study demonstrated that treatment with ritlecitinib for 24 weeks results in a clinically meaningful increase in the proportion of patients with improvement in scalp hair regrowth, as measured by a SALT score of 20 or less, and in a higher proportion of patients with a PGI-C response of “moderately improved” or “greatly improved” in adults and adolescents aged 12 years or older with severe AA when compared with placebo. Ritlecitinib also likely results in a clinically meaningful increase in the proportion of patients who achieved a SALT score of 10 or less and patients with at least a 2-grade improvement or a score of 3 on the EBA or ELA at week 24. In contrast, ritlecitinib resulted in little to no clinically important difference in anxiety and depression based on the HADS when compared with placebo. Improvements observed across other outcomes, such as the CFB in SALT score, a 75% improvement in SALT score, and current hair loss on the scalp, eyebrows, and eyelashes as measured by the AAPPO scale, were consistent with the primary findings. No new safety signals were reported during the 24-week placebo-controlled period, with the safety profile consistent with that of the oral JAK inhibitor class. Evidence showed that ritlecitinib may result in little to no difference in the proportion of patients with SAEs compared with placebo; however, the 24-week placebo-controlled observation period was likely too short to fully capture the comparative harms profile.

At week 48, patients who continued ritlecitinib 50 mg generally showed improvements across scalp, eyebrow, and eyelash hair outcomes, as well as patient-perceived hair regrowth and global well-being; however, changes in anxiety and depression symptoms remained minimal. Evidence beyond the placebo-controlled period is informed by the ALLEGRO-LT open-label extension study, which suggests that treatment with ritlecitinib for 36 months was associated with the improvements or maintenance of scalp, hair regrowth, eyebrow, and eyelash hair regrowth, and an acceptable safety profile. However, the open-label, noncomparative design of the ALLEGRO-LT study limits the interpretation of this evidence.

Results from the ITC suggest that the efficacy of ritlecitinib relative to baricitinib for scalp hair regrowth (as measured by a SALT score ≤ 20 or a SALT score ≤ 10) at week 24 was broadly similar; however, there were no clear differences in point estimates between treatments, and the CrIs were wide, indicating imprecision and uncertainty in the magnitude of any potential differences. Comparative evidence for patient-reported anxiety and depression outcomes based on the HADS and safety outcomes was uncertain, as the CrIs crossed the null, providing no evidence of a between-treatment difference. Interpretation of the ITC is limited by important cross-trial heterogeneity, a sparse network structure, and methodological limitations associated with analyses that relied on unanchored population-adjusted methods.

Based on the evidence available for this review, ritlecitinib represents another treatment option for adult patients with severe AA. There was also supportive evidence of the efficacy and safety of ritlecitinib compared to placebo in adolescent patients with severe AA, a population for whom targeted treatment options are currently limited.

Economic Review

Methods

The review team appraised the pharmacoeconomic evidence submitted by the sponsor on the cost-effectiveness and budget impact of ritlecitinib compared to best supportive care (BSC) and baricitinib for the treatment of adults and adolescents 12 years and older with severe AA.

Summary of the Submitted Economic Evaluation

The sponsor submitted a cost-utility analysis to estimate the cost-effectiveness of ritlecitinib from the perspective of a public health care payer in Canada over a lifetime horizon (100 years).⁴¹ The modelled population comprised patients aged 12 years and older with AA and a baseline SALT score of 50 or greater, which is aligned with the Health Canada indication and was based on the participants in the ALLEGRO trial.³¹ The sponsor's base-case analysis included costs related to drug acquisition, resource use, and psychological burden.

In the sponsor's base case, ritlecitinib was associated with incremental costs of \$768,644 and 0.65 incremental quality-adjusted life-years (QALYs) relative to BSC. This resulted in an incremental cost-effectiveness ratio of \$1,184,918 per QALY gained.⁴¹ Of the incremental benefit compared to BSC (0.65 incremental QALYs), approximately 89% of the benefit was predicted to be accrued after the observation

period of the ALLEGRO-2b/3 trial. Additional information about the sponsor's submission is summarized in Appendix 9 in the Supplemental Material document. CDA-AMC identified several key issues with the sponsor's analysis (e.g., refer to [Table 9](#); full details are provided in Appendix 10 in the Supplemental Material document).

Table 9: Key Issues With the Sponsor's Economic Submission

Issue	What evidence is there to inform this issue?	How was this issue addressed by CDA-AMC?	Did CDA-AMC explore uncertainty in a scenario analysis?
The comparative efficacy of ritlecitinib vs. baricitinib is uncertain.	There is no head-to-head evidence comparing ritlecitinib vs. baricitinib. Evidence is limited to a sponsor-submitted ITC suggesting broadly similar efficacy at week 24; however, credible intervals were wide and interpretation was limited by cross-trial heterogeneity, sparse network structure, and unanchored population-adjusted methods.	CDA-AMC could not address this issue in the base case due to a lack of robust comparative evidence.	No scenario analysis was conducted.
BSC costs incorrectly calculated and inconsistently applied.	The sponsor's inputs incorrectly used package-level costs and did not incorporate the dose of the drug. Application of BSC costs differed across arms without justification and did not align with clinical expectations. Finally, BSC costs in the BSC arm were independent of health state occupancy.	CDA-AMC notified the sponsor of concerns regarding BSC costs during the review period and these were not fully resolved by the sponsor.	No scenario analysis was conducted.
The sponsor's modelling approach was uncertain and could not be fully resolved by CDA-AMC.	Transitions in each cycle were partially conditioned on state distributions within the same cycle, creating circular dependencies inconsistent with cohort Markov principles. As well, spontaneous remission and disease progression were both inconsistently applied across strategies.	CDA-AMC could not address the issue in a reliable way as the sponsor's modelling approach does not fully reflect the natural history of AA.	No scenario analysis was conducted. CDA-AMC notes that the sponsor's model and CDA-AMC reanalysis are unlikely to capture the waxing and waning natural history or alopecia.
The long-term comparative efficacy of ritlecitinib vs. best supportive care is uncertain.	The sponsor assumed no changes in health state distribution after the trial evidence, unless someone discontinued treatment or died. This is uncertain because placebo-controlled evidence from the ALLEGRO-2b/3	CDA-AMC could not address this issue in the base case due to a lack of long-term evidence and limitations in the sponsor's modelling approach.	No scenario analysis was conducted.

Issue	What evidence is there to inform this issue?	How was this issue addressed by CDA-AMC?	Did CDA-AMC explore uncertainty in a scenario analysis?
	study is limited to 24 weeks. Longer-term data are from an open-label extension study without comparator.		
The valuation of health-related quality of life is uncertain.	The base-case utilities imply substantial decrements between AA severity levels, which is uncertain given the currently available clinical evidence.	CDA-AMC could not address this.	No scenario analysis was conducted.
The stopping rule incorporated in the sponsor's base-case analysis was not aligned with trial follow-up.	The sponsor applied a 48-week stopping rule despite controlled comparative evidence from the ALLEGRO-2b/3 study being limited to 24 weeks and despite the sponsor's proposed reimbursement criteria indicating a maximum initial authorization of 24 weeks.	CDA-AMC could not address this issue because of other model limitations rendering the model uninformative for decision-making.	No scenario analysis was conducted.

AA = alopecia areata; BSC = best supportive care; CDA-AMC = Canada's Drug Agency; ITC = indirect treatment comparison; vs. = versus.

Note: Full details of the issues identified by CDA-AMC are provided in Appendix 10 in the Supplemental Material document.

CDA-AMC Assessment of Cost-Effectiveness

Based on the CDA-AMC Clinical Review of the sponsor's submitted ITC comparing ritlecitinib with baricitinib, the results for scalp hair regrowth (as measured by a SALT score of 20 or less and a SALT score of 10 or less) at week 24 are broadly similar, with no clear differences in point estimates between treatments. However, the CIs were wide and included the null effect, indicating imprecision and uncertainty in the magnitude of any potential differences. Comparative evidence for patient-reported anxiety and depression outcomes based on HADS and safety outcomes was uncertain; the CIs crossed the null, providing no evidence of a between-treatment difference. The interpretation of the ITC was limited by important cross-trial heterogeneity, a sparse network structure, and methodological limitations associated with analyses that relied on unanchored population-adjusted methods. Therefore, the ITC does not support a greater health benefit associated with ritlecitinib versus baricitinib in adult patients (refer to [Table 9](#)). If there are no differences in health outcomes between ritlecitinib and baricitinib, then the total cost of ritlecitinib to the health system should not exceed that of baricitinib for the treatment of AA.

Additional limitations in the economic analysis were identified (refer to [Table 9](#)). These limitations were extensive and could not reliably be addressed by CDA-AMC; as such, it was deemed that the sponsor's submission is not informative for decision-making.

Summary of the Budget Impact

The sponsor submitted a budget impact analysis to estimate the 3-year (2027 to 2029) budget impact of reimbursing ritlecitinib for use in the Health Canada–indicated population.⁴² The sponsor assumed that the payer would be CDA-AMC—participating public drug plans and derived the size of the eligible population using an epidemiologic approach. The price of ritlecitinib was aligned with the price included in the sponsor’s economic evaluation, while the prices of comparators were based on the publicly available list prices. Additional information pertaining to the sponsor’s submission is provided in Appendix 11 in the Supplemental Material document.

CDA-AMC identified a number of issues with the sponsor’s estimated budget impact and made changes to model parameters and assumptions in consultation with clinical experts to derive the CDA-AMC base case (e.g., refer to Appendix 11 in the Supplemental Material document). CDA-AMC estimated that by year 3 of reimbursement, 9,528 patients would be eligible for ritlecitinib; of these, 2,558 patients are expected to receive ritlecitinib. The estimated incremental budget savings of reimbursing ritlecitinib is predicted to be approximately \$11 million over the first 3 years, with an expected expenditure of \$85 million on ritlecitinib. The actual budget impact will depend on the eligible patient population size, the market uptake of ritlecitinib, and the displacement of the comparators, all of which are uncertain.

Conclusion

Based on the CDA-AMC Clinical Review of the sponsor-submitted ITC, the comparative efficacy of ritlecitinib relative to baricitinib in terms of scalp hair regrowth of may be broadly similar; however, this conclusion is uncertain due to several limitations, including imprecision, cross-trial heterogeneity, and methodological limitations. The results for safety and patient-reported anxiety and depression were uncertain. Given these findings, there is insufficient evidence to suggest that ritlecitinib provides a greater health benefit than baricitinib for the treatment of adult patients with severe AA. If there are no differences in health outcomes between ritlecitinib and baricitinib, then the total cost of ritlecitinib to the health system should not exceed that of baricitinib for the treatment of AA. Baricitinib is not available for adolescents (patients aged 12 years to younger than 18 years) in Canada. Cost-effectiveness could not be determined in this population due to limitations associated with the sponsor’s submitted analysis.

The budget savings of reimbursing ritlecitinib to the public drug plans in the first 3 years is estimated to be approximately \$11 million. The 3-year expenditure on ritlecitinib (i.e., not accounting for current expenditure on comparators) is estimated to be \$85 million. The estimated budget impact is uncertain due to uncertainty in the eligible patient population size, market uptake, and comparator market displacement.

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