Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

baricitinib (Olumiant)

Indication: For the treatment of adult patients with severe alopecia areata

Sponsor: Eli Lilly Canada Inc.

Recommendation: Reimburse with Conditions

Version: 1.0
Publication Date: August 2024
Report Length: 29 Pages

Single Technology

Redactions: Confidential information in this document may be redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that baricitinib be reimbursed for the treatment of adult patients with severe alopecia areata (AA) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 2 double-blind, randomized, placebo-controlled trials (BRAVE-AA1, N = 654; BRAVE-AA2, N = 546) demonstrated that treatment with baricitinib resulted in statistically significant and clinically meaningful regrowth of scalp hair compared with placebo at 36 weeks in adult patients who had severe AA with at least 50% scalp involvement. The difference in proportion of patients achieving a Severity of Alopecia Tools (SALT) score of 20 or less at 36 weeks between the baricitinib 2 mg and placebo groups was 16.4% (95% confidence interval [CI], 9.7% to 23.4%; p<0.001) in BRAVE-AA1 and 14.7% (95% CI, 8.3% to 21.6%; p<0.001) in BRAVE-AA2. The between-group difference comparing baricitinib 4 mg with placebo was 29.9% (95% CI, 23.2% to 36.2%; p<0.001) in BRAVE-AA1 and 29.9% (95% CI, 23.1% to 36.3%; p<0.001) in BRAVE-AA2. There was also statistically significant and clinically meaningful increase in eyebrow and eyelash hair regrowth in patients who received baricitinib 4 mg compared with those who received placebo in both trials.

Patients identified a need for an effective treatment that could result in full and sustained hair regrowth, reduce the psychosocial burden associated with AA, improve quality of life, and has a tolerable safety profile. Although there was insufficient evidence to draw a definitive conclusion on the effects of baricitinib on anxiety, depression, or health-related quality of life (HRQoL), CDEC concluded that baricitinib may meet some of the needs identified by patients by resulting in clinically important regrowth of scalp hair.

Using the sponsor submitted price for baricitinib and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for baricitinib was $5,465,503 per quality-adjusted life-year (QALY) gained at the 2 mg dose and $6,803,200 per QALY gained at the 4 mg dose, compared with no active treatment. The weighted ICER for baricitinib is $6,748,810 per QALY gained compared to no active treatment. At this ICER, baricitinib is not cost-effective at a $50,000 per QALY gained willingness to pay (WTP) threshold for the treatment of adult patients with severe AA. The cost-effectiveness of baricitinib is sensitive to assumptions concerning response threshold, which determine treatment discontinuation. In a scenario that adopted $SALT_{75}$ (i.e., at least 75% reduction in SALT score from baseline) as the response threshold, a price reduction of 88% for the 2 mg dose and 91% for the 4 mg dose would be necessary for baricitinib to be cost-effective compared to no active treatment at a WTP threshold of $50,000 per QALY gained. In this scenario, the weighted price reduction for baricitinib is 91%. As the economic model was built based on SALT scores change from baseline (instead of absolute SALT scores), the $SALT_{75}$ is the response threshold that most closely aligns with an absolute SALT score 20 or less at 36 weeks.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with baricitinib should be initiated in adult patients with severe AA who meet the following criteria: 1.1. SALT score of 50 or above 1.2. Duration of the current episode of AA more than 6 months and less than 8 years	Evidence from the BRAVE-AA1 and BRAVE-AA2 trials demonstrated that treatment with baricitinib resulted in clinically important regrowth of scalp hair in adult patients (males aged 18 to 60 years and females aged 18 to 70 years) with AA who had at least 50% scalp hair loss, a current episode of AA of no more than 6 months and less than 8 years in duration.	The pivotal trials excluded male patients aged more than 60 years and female patients aged more than 70 years. While there was insufficient robust evidence to support the use of baricitinib in older adults, CDEC considered it appropriate to leave the determination of the eligibility for baricitinib treatment in this patient population to the clinical judgment of the treating physician.
2. The maximum duration of initial authorization is 36 weeks	Response to treatment in the pivotal trials was assessed at 36 weeks.	—
Renewal		
3. The physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement, defined as a SALT score of 20 or less at 36 weeks after treatment initiation, and every 12 months thereafter. Maintenance of SALT score of 20 or less is required at renewal for continuation of therapy.	The proportion of patients with a SALT score of 20 or less at Week 36 was the primary endpoint of the BRAVE-AA1 and BRAVE-AA2 trials. The clinical experts noted to CDEC that in clinical practice, the response to treatment is assessed at 36 weeks after initiating baricitinib, then every 12 months thereafter.	—
Prescribing		
4. Baricitinib should be prescribed by dermatologists with expertise in managing patients with severe AA.	This condition is meant to ensure that baricitinib is prescribed for appropriate patients and that adverse effects are managed in an optimized manner.	—
5. Baricitinib treatment should not be used in combination with other JAK inhibitors, biologic immunomodulators, or systemic immunosuppressants.	The use of other JAK inhibitors, biologic immunomodulators, or systemic immunosuppressants was prohibited in the BRAVE-AA1 and BRAVE-AA2 trials. CDA-AMC reviewed no clinical trial evidence to demonstrate the safety and potential benefits of using baricitinib in combination with the medications listed in this condition.	—
Pricing		
6. A reduction in price	The ICER for baricitinib is $5,465,503 per QALY gained at the 2 mg dose and $6,803,200 per QALY gained at the 4 mg dose, when compared with no active treatment. Based on clinical expert opinion that 90% of patients would receive the 4 mg dose and 10% would receive the 2 mg dose, the weighted ICER for baricitinib is	—

Reimbursement condition	Reason	Implementation guidance
	$6,748,810 per QALY gained compared to no active treatment. The cost-effectiveness of baricitinib is sensitive to assumptions concerning response threshold, which determine treatment discontinuation In a scenario that adopted $SALT_{75}$ as the response threshold, a price reduction of 88% for the 2 mg dose and 91% for the 4 mg dose would be necessary for baricitinib to be cost-effective compared to no active treatment at a WTP threshold of $50,000 per QALY gained. Assuming that 90% of patients are likely to receive the 4 mg dose while 10% receive the 2 mg dose, the weighted price reduction for baricitinib is 91%.	
Feasibility of adoption		
7. The economic feasibility of adoption of baricitinib must be addressed	At the submitted price, the incremental budget impact of baricitinib is expected to be greater than $40 million in year 2 and year 3.	—
8. The economic feasibility of adoption of baricitinib must be addressed	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate.	—

HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; WTP = willingness to pay.

Discussion Points

- Patients expressed a need for an effective treatment that sustains hair regrowth, reduces psychological burden, and has a tolerable safety profile. The clinical experts noted that currently reimbursed systemic therapies (conventional immunosuppressants) for severe AA are associated with poor efficacy and a risk of relapse with dosage reduction and/or discontinuation.
- CDEC discussed the long-term extension results of the BRAVE-AA1 and BRAVE-AA2 trials, which suggested that baricitinib treatment could potentially sustain hair growth through 104 weeks and no notable safety concerns were identified. However, analyses beyond week 36 were non-comparative, which precluded firm conclusions. Evidence for the effect of baricitinib on anxiety and depression, and HRQoL at 36 weeks was of very low and low certainty, as per GRADE assessments. This was due to study limitations including differential dropouts between treatment groups and absence of evidence for validity of outcome measures in patients with AA. Additionally, the generalizability of anxiety and depression outcomes may have been limited since the trials excluded patients with uncontrolled neuropsychiatric disorders.
- CDEC discussed that the comparative effects of baricitinib versus systemic treatments currently reimbursed by the public drug plans (i.e., off-label conventional immunosuppressants) for the treatment of severe AA were unknown since no direct or indirect comparative evidence was submitted. CDEC considered clinical expert input that conventional immunosuppressants are in general associated with poor efficacy and potential serious adverse events (SAEs) when used long-term. CDEC noted that baricitinib treatment could potentially meet the need for a safe and effective systemic treatment currently not met by conventional immunosuppressants. CDEC also discussed that another systemic JAK inhibitor, ritlecitinib, was approved by Health Canada for the treatment of severe AA in adults and adolescents over 12 years of age; however, this treatment was not considered a relevant comparator for this submission since it had not undergone a reimbursement review by CDA-AMC, and was not reimbursed by the public drug plans at the time of this review.

- Male patients over the age of 60 and female patients over the age of 70 were excluded from the BRAVE-AA1 and BRAVE-AA2 trials. CDEC considered clinical expert input that older adult patients tend to have other concurrent causes of hair loss that are not expected to be responsive to baricitinib treatment. In addition, the committee discussed the evidence from a sponsor-submitted single-arm, retrospective observational study in patients aged 65 or above and noted that no definitive conclusions could be drawn regarding the benefits of baricitinib in older adults due to a small sample size, lack of a control group, and a heterogeneous patient population (patients with moderate-to-severe AA). Ultimately, CDEC agreed that the decision for the treatment of older adults with baricitinib should be left to the clinical judgment of the treating physician.
- CDEC emphasized the importance of differentiating between the relative response outcome used in the economic model ($SALT_{75}$) and the primary endpoint in the BRAVE trials (SALT score of 20 or less), which represents an absolute measure of response. CDEC considered SALT score of 20 or less to be a meaningful response outcome for patients with severe AA given that it signified patients would achieve at least 80% hair coverage on the scalp. As such, CDEC adopted the weighted price reduction associated with the use of $SALT_{75}$ as the response outcome to capture the quality of life benefit akin to achieving the primary endpoint observed in the BRAVE trials, where patients with severe AA (i.e., baseline SALT scores ranging from 50 to 100) achieving a 75% improvement would attain SALT scores between 13 and 25, thus aligning with the pivotal trials' SALT score of 20 or less primary end point.

Background

AA is a chronic autoimmune disease characterized by non-scarring hair loss at the scalp as well as eyebrows, eyelashes, beard, pubic, or axillary hair. The onset of hair loss in AA is typically rapid and the progression is unpredictable, with the majority of patients experiencing disease onset by 40 years of age. AA is associated with psychological impacts and impairment in health-related quality of life (HRQoL). It is estimated that the prevalence of AA in Canada is between 0.1% and 0.58%. As per input from the clinical experts consulted by CADTH, clinicians in Canada consider systemic drugs for the treatment of adults with severe AA, including off-label conventional immunosuppressants (cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil), and Janus kinase (JAK) inhibitors (i.e., ritlecitinib is recently approved by Health Canada for the treatment of adults and adolescents 12 years and older with severe AA; tofacitinib, upadacitinib, and abrocitinib, which are off-label treatments for severe AA). Conventional immunosuppressants are currently reimbursed by the public drug plans in Canada. The clinical experts noted that conventional immunosuppressants are associated with poor efficacy, a risk of relapse with dosage reduction and/or discontinuation, as well as potential SAEs when used long-term.

Baricitinib has been approved by Health Canada for the treatment of adult patients with severe AA. Baricitinib is a Janus kinase inhibitor. It is available as 2 mg and 4 mg oral tablets and the dosage recommended in the product monograph is 2 mg once daily and, if the response to treatment is not adequate, the dose may be increased to 4 mg once daily. For patients with nearly complete or complete scalp hair loss, and/or substantial eyelash or eyebrow hair loss, consider starting with 4 mg once daily. Once patients achieve an adequate response to treatment with 4 mg, consider decreasing the dosage to 2 mg once daily. When clinically advisable, the lowest effective dose should be used to minimize adverse effects. Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit after 36 weeks of treatment.

Sources of Information Used by the Committee

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

- A review of 2 pivotal randomized controlled trials (RCTs) in adult patients with severe AA and their long-term extension phase; and 3 observational studies
- Patients' perspectives gathered by 1 patient group, the Canadian Alopecia Areata Foundation (CANAAF)
- Input from public drug plans that participate in the CADTH review process
- Input from 2 clinical specialists with expertise diagnosing and treating patients with AA
- A review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Patient Input

CADTH received 1 patient group submission from the CANAAF. CANAAF was registered as a charitable organization in 2010 and is described as the voice for all Canadian patients and families affected by AA. CANAAF collected data on the psychosocial and emotional impact of AA from peer-reviewed literature, as well as patient perspectives on AA from patient reports and support sessions.

CANAAF commented that AA is incredibly burdensome on a patient's mental health and quality of life, and the disease causes disfiguring hair loss that occurs unexpectedly and can progress rapidly. Based on a patient report, CANAAF further stated that anxiety, depression, and other resultant psychological conditions are not minor in nature; therefore, the loss of hair can create layers of stigma and misunderstandings. Short hair or baldness may be associated with a preference for an 'edgy' look or having a certain sexuality, which may not be accurate. Those with this disease may feel less feminine or less masculine without hair. Children and teenagers may experience bullying. In addition, CANAAF revealed that there is also a significant financial burden associated with AA, supported by a CANAAF community alopecia patient focus group conducted in 2023. The most significant cost item was a wig purchase and maintenance, which can cost over $2,500 a year. Some patients experienced significant impacts on their ability to work.

Based on the literature, CANAFF identified limitations of the currently available treatments for AA, including topical corticosteroids (limited effectiveness, only effective for patients with very limited AA, difficult product application, scalp irritation), intralesional corticosteroids (painful injections, limited drug coverage by drug plans), oral corticosteroids (variable success rates, high relapse rate, limited drug coverage, unfavourable side effects), topical minoxidil (non-durable benefits for very mild AA, AEs such as excessive hair growth on body parts other than the site of application, irritation, allergic contact dermatitis), oral minoxidil (systemic AEs relating to its antihypertensive property, limited drug coverage), and systemic immunosuppressants (variable effectiveness, risk of organ toxicity, infection, and malignancy, requires concomitant administration of oral corticosteroids for some agents, limited drug coverage).

CANAAF identified a need for an effective treatment option that could result in full and sustained hair growth and alleviate anxiety and depression associated with AA. CANAAF believed that baricitinib may fulfill this need by serving as an effective treatment that has a favourable side effect profile and is easy to administer. The group noted that most patients regrew all of their hair with baricitinib treatment. CANAAF also noted that the side effect profile of baricitinib is much more favourable compared to existing treatments. Finally, the patient input indicated that baricitinib is a much easier treatment option for patients as it only requires that they take one pill, once a day. This is in comparison to other treatments that must be applied topically, injected (often by a health care professional), or taken orally more than once a day.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts consulted by CADTH noted that currently reimbursed off-label systemic treatments for severe AA are associated with poor efficacy, a risk of relapse with dosage reduction and/or discontinuation, and potential SAEs when used long-term (especially with conventional immunosuppressants). As well, access to emerging therapies, such as ritlecitinib, is currently limited, as per clinical expert input. The clinical experts noted that, due to the limited efficacy of the conventional systemic immunomodulators, it is rational to use baricitinib (and JAK inhibitors in general) as a first-line systemic therapy in severe AA, rather than the last line of treatment after failure of conventional systemic immunomodulators. The clinical experts noted that it would be appropriate to use baricitinib in combination with topical treatments and/or intralesional corticosteroids but not in combination with other immunomodulators, except for prednisone where concomitant use with baricitinib may be appropriate.

In the clinical experts' opinion, patients who have severe AA with scalp involvement as reflected by a Severity of Alopecia Tool (SALT) score of 50 or above and have a current episode of AA of greater than 1 year but less than 10 years are potential candidates for baricitinib treatment, though they noted that adhering to the inclusion criterion on duration of current episode used in the pivotal trials (i.e., more than 6 months and less than 8 years in duration) would also be reasonable. One clinical expert considered the use

of baricitinib in older adults (i.e., above 60 years of age for males or above 70 years of age for females, who were excluded from the pivotal trials) to be reasonable, while the other clinical expert suggested to restrict the use of baricitinib as per age restriction in the pivotal trials due to a lack of clinical trial data and unknown clinical treatment benefits.

The clinical experts felt that it is reasonable to define meaningful response to treatment as achievement of SALT score of 20 or less after 36 weeks of baricitinib treatment, consistent with the pivotal trials. The clinical experts noted that it would be reasonable to consider discontinuation of baricitinib treatment in patients who fail to achieve cosmetically acceptable hair regrowth at 36 weeks, further loss of hair at 36 weeks, experience severe AEs deemed to be related to the use of a JAK inhibitor, or development of intercurrent condition(s) making discontinuation of a JAK inhibitor advisable (e.g., malignancy). In the clinical expert's opinion, baricitinib treatment should be prescribed by dermatologists with experience in diagnosing, treating, and monitoring patients with severe AA.

Clinician Group Input

No clinician group input was received by CADTH for the drug under review.

Drug Program Input

Table 2: Responses to Questions from the Drug Programs

Implementation issues	Response
Relevant comparators	
There is currently no approved standard of care treatment for severe AA. Off-label treatments include intralesional corticosteroids, potent topical corticosteroids, systemic corticosteroids, conventional immunosuppressants, and minoxidil. Baricitinib treatment was compared with placebo in patients with severe AA in the phase II/III BRAVE-AA1 and phase III BRAVE-AA2 trials, which were multicenter, randomized, double-blind, placebo-controlled trials with primary efficacy analysis at 36 weeks and extension phases up to a total of 200 weeks (about 4 years). What is the appropriate comparator for patients with severe AA?	The clinical experts noted that systemic treatments are relevant comparators of baricitinib. They noted that from a clinical perspective, oral JAK inhibitors, including ritlecitinib (a JAK inhibitor recently approved by Health Canada for the treatment of severe AA) and tofacitinib (off-label treatment for severe AA) are the most appropriate comparators for baricitinib. As well, upadacitinib and abrocitinib may be used off-label for the treatment of severe AA in patients with coexisting atopic dermatitis. However, these treatments are not currently reimbursed by the public drug plans for the treatment of severe AA in Canada. Conventional immunosuppressants (methotrexate, azathioprine, mycophenolate, cyclosporine) are currently used by clinicians as off-label treatments for severe AA and are currently reimbursed by public drug plans. The clinical experts did not consider oral minoxidil as a relevant comparator of baricitinib since it is not used as monotherapy in the treatment of severe AA. The clinical expert did not consider systemic corticosteroids as relevant comparators since they are used for short-term treatment. CDEC considered input from the clinical experts and noted that systemic treatments currently reimbursed by public drug plans (i.e., immunosuppressants including cyclosporine, methotrexate, azathioprine, mycophenolate mofetil) are relevant comparators of baricitinib for the purpose of this review. These systemic drugs may be used with or without topical corticosteroids, intralesional corticosteroids, and/or oral minoxidil, as adjunctive treatments.
This is the first reimbursement review for a medication indicated for severe AA. Some jurisdictions may have formulary exclusions for cosmetic drugs and/or hair growth stimulants.	The clinical experts consulted for this review noted that, in their practice, patients have not encountered significant barriers to access to medications used to treat AA. According to the clinical experts, access to ritlecitinib is currently limited to patients who participate in clinical trials or are eligible for a support program

Implementation issues	Response
Have the clinical experts encountered any barriers in access to medications for patients within the jurisdictions?	offered by the drug manufacturer at the request of their dermatologists. One clinical expert further noted that access to a dermatologist could be difficult in their province since many practices are closed to all patients with hair disorders.
Considerations for initiation of therapy	
Severe AA is defined as ≥ 50% scalp hair loss and the trials included patients with a current episode of severe AA of more than 6 month in duration as measured by the SALT scale. Severity of disorders ranges from small patches of alopecia on any hair-bearing area to the complete loss of scalp, eyebrow, eyelash and body hair. 1. Is the severity definition, provided above, the standard for eligibility for initiation of baricitinib in clinical practice? 2. Would the clinical experts be able to comment on ≥ 50% scalp hair loss vs. ≥ 50% hair loss as eligibility requirement for patients?	1. According to the clinical experts, it is the standard to require ≥ 50% scalp hair loss for initiation of a systemic treatment (e.g., baricitinib) in clinical practice. 2. CDEC agreed with the clinical experts that the use of ≥ 50% scalp hair loss as a reimbursement criterion for treatment initiation was appropriate. The clinical experts noted that focusing on scalp hair loss would capture the vast majority of patients who would be treated with baricitinib since scalp hair is generally the treatment target. The clinical experts did not favour the use of ≥ 50% hair loss (without regard to site of hair loss) as a reimbursement criterion since it would include a lot of patients who would not be offered systemic treatment routinely in clinical practice (e.g., patients with eyebrow and/or eyelash involvement whose SALT score is less than 50, or patients in whom the hair loss is restricted to the body or beard).
Inclusion criteria of the pivotal trials included: - 18 years and ≤ 60 years for males (≤ 70 years of age for females) - Agree not to use any AA treatments during the study, exceptions: treatment with bimatoprost ophthalmic solution for eyelashes may be continued if the patient has been on a stable dose for 8 weeks prior to randomization. Treatment with finasteride (or other 5-alpha reductase inhibitors) or oral or topical minoxidil may be continued if the patient has been on a stable dose for 12 months and is expected to continue until Week 36. 1. Is this a medication that can be used in the pediatric population (<18 years; off-label use) and the older adults (> 60 years in males and >70 years for females)? 2. In practice, how often do the clinical experts see baricitinib used in combination with other medications such as bimatoprost ophthalmic solution, finasteride, or minoxidil (oral, topical)? Most of these medications may be listed as general/open benefit in the jurisdictions, challenging to know reason for use. Some jurisdictions may have minoxidil topical as formulary exclusion.	1. CDEC was unable to comment on the pediatric population, as the committee did not review any evidence to support treatment with baricitinib in patients under 18 years of age. One clinical expert noted that older adults (above age limit specified in the trial inclusion criterion) are reasonable candidates for baricitinib treatment. The other clinical expert suggested restricting the use of baricitinib as per age restriction in the pivotal trials due to a lack of clinical trial data and unknown clinical treatment benefits. In addition, this clinical expert anticipated that older adults would not benefit from baricitinib treatment as much as younger patients since older adults tend to have other concurrent causes of hair loss that are not expected be responsive to baricitinib treatment. CDEC considered input from both clinical experts and the submitted clinical evidence (Tang et al., 2014) and noted that there is insufficient evidence to support the use of baricitinib treatment in older adults. CDEC noted that treating older adults with baricitinib should be left to the discretion of the treating physician. 2. The clinical experts noted that baricitinib was approved for the treatment of AA in Canada recently and that they had not prescribed baricitinib in clinical practice yet. The clinical experts noted that it would be reasonable to use baricitinib in

Implementation issues	Response
	combination with bimatoprost ophthalmic solution, finasteride, or minoxidil (oral, topical).
Should patients receive prior systemic therapies including corticosteroids, methotrexate, and cyclosporine prior to accessing baricitinib?	CDEC agreed with the clinical experts that JAK inhibitors may be positioned as a first-line systemic therapy in patients with severe AA. The clinical experts' opinion was based on their clinical experience in the effectiveness of JAK inhibitors relative to conventional immunosuppressants, and the paucity of published data of immunosuppressants in patients with severe AA.
If the treatment is interrupted and the patient relapsed, would the patient restart treatment immediately with effect?	The clinical experts noted that relapse of condition following dose reduction or interruption of treatment is a significant risk with all systemic treatments. In case of relapse, patients and clinicians would be motivated to restart treatment immediately; however, recapture of clinical benefit is not guaranteed, as per the clinical experts.
Considerations for continuation or renewal of therapy	
1. What is the definition of refractory disease (based on what parameters?) 2. What is the definition of absence of clinical benefit (based on what parameters?). Note, as per product monograph, consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit after 36 weeks (about 8 and a half months) of treatment. *3.* What is the definition of disease progression (based on what parameters)?	1. and 2. The clinical experts noted that refractory disease and absence of clinical benefit are established when the patient shows no evidence of cosmetically acceptable hair regrowth at 36 weeks or progression of hair loss at 36 weeks. For the purpose of drug reimbursement, CDEC agreed with the clinical experts that it would be reasonable to define response to treatment as achievement of SALT score of 20 or less at Week 36, consistent with the pivotal trials of baricitinib. 3. The clinical experts noted that it would be reasonable to define disease progression as any increase in SALT score and/or development of new sites of hair loss, particularly with eyebrow and eyelash involvement.
Considerations for discontinuation of therapy	
1. For patients with severe AA, is the treatment with baricitinib lifelong? 2. If there is progression during a "drug holiday", can treatment be resumed? According to what timeframe?	1. The clinical experts anticipated that baricitinib would be a lifelong treatment for many patients. 2. The clinical experts noted that in complete responders, dose reduction of baricitinib would take place rather than complete cessation of treatment (e.g., drug holiday), an approach that is consistent with the use of conventional systemic immunosuppressants.
Considerations for prescribing of therapy	
Which prescriber specialty would initiate medication for severe AA?	CDEC agreed with the clinical experts that it would be appropriate for dermatologists with experience in diagnosing, treating and monitoring patients with severe AA to prescribe baricitinib treatment.
Consideration of what medications not to be used in combination with baricitinib. As per product monograph, the use of baricitinib in combination with other JAK inhibitors, biologic immunomodulators, or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.	CDEC agreed with the clinical experts that baricitinib treatment may not be used in combination with other JAK inhibitors, biologic immunomodulators, or systemic immunosuppressants, as per pivotal trial design. The use of corticosteroids (systemic, intralesional, or topical) was also prohibited in the trials, although CDEC considered clinical expert input and noted that the use of

Implementation issues	Response
	corticosteroids concomitantly with baricitinib is reasonable from a clinical perspective.
Generalizability	
If the disease severity is <50% scalp hair loss or <50% hair loss, would baricitinib have a role/place in therapy? At what point, would the clinical experts consider patients with this disease severity be eligible for baricitinib therapy?	The clinical experts anticipated that over time, as more data accumulates, it is likely that baricitinib would have a role in therapy in patients with SALT score of less than 50%; however, it is likely not a consideration at this time.
Care provision issues	
Baricitinib is associated with potential costs to the healthcare system: assessing patient with viral hepatitis, latent tuberculosis, renal insufficiency, pregnancy prior to the start of therapy; baseline and periodic monitoring of CBC with differential, platelets, liver enzymes, lipid levels; periodic assessments of signs and symptoms of infection, skin examination (in patients with increased risk of skin cancer), abdominal symptoms (for patients at risk of gastrointestinal perforation).	This is a comment from the drug programs to inform CDEC deliberations.
System and economic issues	
Provision of this drug in the first line setting may translate into an increased budget impact ($1716.17/30 tablets for baricitinb 2 mg, $3432.34/30 tablets for baricitiinib 4 mg, ~$20,400 to $40,800/year) relative to other off-label systemic therapy x number of patients.	This is a comment from the drug programs to inform CDEC deliberations.
Baricitinib concluded with a successful LOI for Rheumatoid Arthritis.	This is a comment from the drug programs to inform CDEC deliberations.

CBC = complete blood count; Canadian Drug Expert Committee; EL = eyelash; LOI = letter of intent; JAK = Janus kinase inhibitor; SALT = Severity of Alopecia Tools.

Clinical Evidence

Systematic Review

Description of Studies

The sponsor-conducted systematic literature review identified 2 pivotal double-blind, randomized, placebo-controlled trials (RCTs; BRAVE-AA1, N = 654; BRAVE-AA2, N = 546) that assessed the efficacy and safety of baricitinib relative to placebo in adult patients who had severe or very severe AA with at least 50% scalp involvement (i.e., SALT score of at least 50) and had a current AA episode of over 6 months and less than 8 years. In the double-blind, placebo-controlled treatment period, patients were randomized in a 2:2:3 ratio to receive placebo, baricitinib 2 mg, and baricitinib 4 mg once daily for 36 weeks, at which time the primary analysis of efficacy and safety was conducted. In the 68-week long-term extension period, patients continued the existing intervention or were re-assigned a new intervention (placebo, baricitinib 2 mg, or baricitinib 4 mg) depending on response to treatment at Week 36 (patients initially assigned to placebo) or Week 52 (patients initially assigned to baricitinib 2 mg or 4 mg) as per protocol-defined criteria. This was followed by a 96-week bridging extension where patients continued to receive the same intervention until the end of the study. The long-term extension period is ongoing in both trials.

Efficacy end points of interest to this review included the proportion of patients achieving a SALT score of 20 or less (primary end point), $SALT_{50}$ (i.e., at least 50% reduction in SALT score from baseline), Clinician-reported Outcome (ClinRO) Measures for Eyebrow (EB) and Eyelash (EL) Hair Loss score of 0 or 1 with at least 2-point reduction from baseline (key secondary end points), change from baseline in Hospital Anxiety and Depression Scale (HADS) Anxiety and Depression scores, and Skindex-16 Adapted for Alopecia Areata (Skindex-16 AA) Symptoms, Emotions, and Functioning scores (secondary or exploratory outcomes); all of which were assessed at Week 36.

In both trials, at baseline, there was about an equal proportion of patients with severe AA and very severe AA. The mean duration of the current AA episode of 3.6 (standard deviation [SD] = 3.9) years and 4.3 (SD = 4.9) years in BRAVE-AA1 and BRAVE-AA2, respectively. Approximately 90% of patients received prior AA treatment, with the most common ones (reported in at least 40% of patients) being topical therapies, intralesional therapy, and systemic immunosuppressants and immunomodulators.

Efficacy Results

Proportion of Patients Achieving SALT ≤20

The proportion of patients achieving a SALT score of 20 or less at Week 36 was the primary end point in both trials. At week 36, the between-group difference comparing baricitinib 2 mg versus placebo was 16.4% (95% CI, 9.7% to 23.4%; p<0.001) in BRAVE-AA1 and 14.7% (95% confidence interval [CI], 8.3% to 21.6%; p<0.001) in BRAVE-AA2. The between-group difference comparing baricitinib 4 mg and placebo was 29.9% (95% CI, 23.2% to 36.2%; p<0.001) in BRAVE-AA1 and 29.9% (95% CI, 23.1% to 36.3%; p<0.001) in BRAVE-AA2. Results were in favour of both regimens of baricitinib treatment. In both trials, subgroup analyses by baseline disease severity and duration of current episode of AA were consistent with the primary analysis.

Percent change from baseline in SALT score was assessed at Week 36 (key secondary end point) in both trials. In both trials, the between-group difference comparing baricitinib and placebo was in favour of baricitinib for both 2 mg (BRAVE-AA1, -23.1% [95% CI, -30.6% to -15.6%; p<0.001]; BRAVE-AA2, -25.3% [95% CI, -32.8% to -17.7%]) and 4 mg (BRAVE-AA1, -37.7% [95% CI, -44.4% to -30.9%; p<0.001); BRAVE-AA2, 44.5% [95% CI, -51.3% to -37.7%; p<0.001]) regimens.

Proportion of Patients Achieving $SALT_{50}$

The between-group difference in the proportion of patients achieving $SALT_{50}$ at Week 36 (secondary end point) comparing baricitinib 2 mg versus placebo was 17.7% (95% CI, 9.5% to 25.8%; p<0.001) in BRAVE-AA1 and 23.1% (95% CI, 15.1% to 31.0%; p<0.001) in BRAVE-AA2. The between-group difference comparing baricitinib 4 mg with placebo was 33.6% (95% CI, 25.6% to 40.7%; p<0.001) in BRAVE-AA1 and 41.9% (95% CI, 34.0% to 48.7%; p<0.001) in BRAVE-AA2. Results of the $SALT_{75}$ responder analysis were consistent with the $SALT_{50}$ responder analysis. Both end points were not adjusted for multiplicity in the trials.

Proportion of Patients Achieving ClinRO Measure for EB Hair Loss score of 0 or 1 with ≥2-point Improvement from Baseline among Patients with ClinRO Measure for EB Hair Loss Score of ≥2 at Baseline

Between 66.3% and 73.9% of all randomized patients had a ClinRO Measure for EB Hair Loss score of at least 2 at baseline in the trials and contributed to the analysis of the proportion of patients ClinRO Measure for EB Hair Loss score of 0 or 1 with at least 2-point improvement from baseline at Week 36 (key secondary end point).

The between-group difference comparing baricitinib 2 mg versus placebo was 15.9% (95% CI, 8.4% to 23.6%; p<0.001), in favour of baricitinib 2 mg, in BRAVE-AA1; and 7.1% (95% CI, -0.3% to 15.0%; p=0.08) in BRAVE-AA2. In BRAVE-AA2, no formal testing was conducted for subsequent end points in the statistical hierarchy due to failure of this end point in the study. The between-group difference was in favour of baricitinib 4 mg over placebo in both trials (BRAVE-AA1, 28.2% [95% CI, 20.3% to 35.4%; p<0.001]; BRAVE-AA2, 30.3% [95% CI, 21.4% to 38.4%; p<0.001]). Results based on the Patient-Reported Outcome (PRO) Measure showed consistent results.

Proportion of Patients Achieving ClinRO Measure for EL Hair Loss score of 0 or 1 with ≥2-point Improvement from Baseline among Patients with ClinRO Measure for EL Hair Loss Score of ≥2 at Baseline

Between 51.3% and 60.3% of all randomized patients had a ClinRO Measure for EL Hair Loss score of at least 2 at baseline in the trials and contributed to the analysis of the proportion of patients ClinRO Measure for EL Hair Loss score of 0 or 1 with at least 2-point improvement from baseline at Week 36 (key secondary end point).

The between-group difference comparing baricitinib 2 mg and placebo was 10.4% (95% CI, 2.7% to 18.3%) in BRAVE-AA1 and 4.6% (95% CI, -3.7% to 13.2%) in BRAVE-AA2, both of which were not formally tested for statistical significance due to a prior failure of an outcome in the statistical hierarchy. The between-group difference favoured baricitinib 4 mg treatment over placebo in both trials (BRAVE-AA1, 30.4% [95% CI, 21.6% to 38.1%; p<0.001]; BRAVE-AA2, 28.7% [95% CI, 18.7% to 37.5%; p<0.001]). Results based on the PRO Measure showed consistent results.

Change from baseline in HADS-Anxiety score

The between-group difference comparing baricitinib 2 mg and placebo with respect to change from baseline in HADS-Anxiety score at Week 36 (secondary end points) favoured baricitinib 2 mg in BRAVE-AA1 (-0.8; 95% CI, -1.4 to -0.3; p ≤ 0.01) and was -0.2 (95% CI, -0.8 to 0.4; p = 0.5) in BRAVE-AA2. The between-group difference comparing baricitinib 4 mg and placebo favoured baricitinib 4 mg in both trials (BRAVE-AA1, -0.5 [95% CI, -1.1 to 0.0; p = 0.04]; BRAVE-AA2, -0.7 [95% CI, -1.3 to -0.2; p = 0.01]). This end point was not adjusted for multiplicity.

Change from baseline in HADS-Depression score

The between-group difference comparing baricitinib 2 mg and placebo with respect to change from baseline in HADS-Depression score at week 36 (secondary end points) was -0.4 ([95% CI, -0.9 to 0.1; p = 0.1)] in BRAVE-AA1 and; -0.5 ([95% CI, -1.1 to 0.1; p = 0.08]) in BRAVE-AA2. The between-group difference comparing baricitinib 4 mg and placebo favoured baricitinib 4 mg in BRAVE-AA2 (-0.7; 95% CI, -1.2 to -0.2; p = 0.01) and was -0.3 (95% CI, -0.8 to 0.1; p = 0.2) in BRAVE-AA1. This end point was not adjusted for multiplicity.

Change from baseline in Skindex-16 AA Symptoms domain score

The difference between baricitinib 2 mg and placebo with respect to change from baseline in Skindex-16 AA symptoms domain score at week 36 favoured baricitinib 2 mg in BRAVE-AA1 [redacted]) and was [redacted]) in BRAVE-AA2.The difference between baricitinib 4 mg and placebo favoured baricitinib 4 mg in BRAVE-AA2 [redacted]) and was -[redacted]) in BRAVE-AA1. This was an exploratory end point in BRAVE-AA1 and secondary end point in BRAVE-AA2. It was not adjusted for multiplicity.

Change from baseline in Skindex-16 AA Emotions domain score

The between-group difference with respect to change from baseline in Skindex-16 AA emotions domain score at week 36 was in favour of baricitinib over placebo in both trials for both baricitinib 2 mg (BRAVE-AA1, [redacted]; BRAVE-AA2: [redacted]) and baricitinib 4 mg (BRAVE-AA1, [redacted]; BRAVE-AA2, [redacted]) regimens. This was an exploratory end point in BRAVE-AA1 and secondary end point in BRAVE-AA2. It was not adjusted for multiplicity.

Change from baseline in Skindex-16 AA Functioning domain score

The difference between baricitinib 2 mg and placebo with respect to change from baseline in Skindex-16 AA functioning domain score at week 36 was [redacted]) in BRAVE-AA1 and [redacted]) in BRAVE-AA2. The difference between baricitinib 4 mg and placebo favoured baricitinib 4 mg in both trials (BRAVE-AA1, [redacted]; BRAVE-AA2, [redacted]). This was an exploratory end point in BRAVE-AA1 and secondary end point in BRAVE-AA2. It was not adjusted for multiplicity.

Harms Results

Treatment-emergent adverse events, serious adverse events, withdrawal due to adverse events, and mortality

Treatment-emergent adverse events (TEAEs) were reported in 50.8% to 68.4% of patients across the trials and occurred in similar proportions of patients across treatment groups. The most common TEAEs of baricitinib (reported in at least 5% of patients in either baricitinib groups) were upper respiratory tract infection, headache, urinary tract infection, nasopharyngitis, acne, and increased blood creatine phosphokinase. Serious adverse events (SAEs; 1.6% to 3.4%) and withdrawal due to adverse events (WDAE; 1.1% to 2.6%) were uncommon in the studies. No deaths were reported in both trials.

Notable Harms (Infections, cardiovascular and thromboembolic events, gastrointestinal perforations, malignancies)

Treatment-emergent infections were reported in between 25.1% and 37.4% of patients across treatment groups in the trials. In BRAVE-AA2, the frequency of infection was higher in the baricitinib 2 mg group (37.4%) compared with the placebo group (29.2%), but this was not observed in BRAVE-AA1. In BRAVE-AA1, none of the infections were reported to be serious or lead to treatment discontinuation. In BRAVE-AA2, serious infection was reported in 2 (1.3%) and 1 (0.4%) patients in the baricitinib 2 mg and 4 mg

groups, respectively, and infection leading to treatment discontinuation was reported in 1 (0.6%) patient in the baricitinib 2 mg group. Infection leading to treatment interruption was reported in [redacted] to [redacted] of patients across the trials.

In BRAVE-AA1, myocardial infarction and coronary revascularization was reported in 1 (0.5%) patient in the baricitinib 2 mg group. Serious arrhythmia was reported in 1 (0.5%) patient in the baricitinib 4 mg group. There was no report of cardiovascular events in the BRAVE-AA2 trial. There were no reports of venous or pulmonary thromboembolic events, gastrointestinal perforations, and non-melanoma skin cancers in both trials. One patient in each of the placebo group (0.6%) and the baricitinib 4 mg group (0.4%) reported other forms of malignancies.

Critical Appraisal

The trials used adequate methods of randomization and allocation concealment. There were a few small baseline imbalances in patient characteristics that may be compatible with chance and were not believed to substantially impact study results. The trials were adequately blinded; however, there is a potential for bias in measurement of subjective outcomes (i.e., ClinRO Measures, HADS, and Skindex-16 AA) leading to inflated efficacy of baricitinib based on the inferred judgement by patients and investigators regarding treatment assignment based on response to treatment, without being actually unblinded. $SALT_{50}$ responder analysis, HADS, and Skindex-16 AA outcomes were not adjusted for multiplicity, so statistically significant results were at an increased risk of type 1 error (false positive results). Between 31% and 42% were excluded from ClinRO Measures-based outcomes as a result of not having the specified baseline score, which could impact randomization, although the extent and direction of the resulting bias is unclear. There is a risk of attrition bias in favour of baricitinib with respect change from baseline in HADS and Skindex-16 AA domain scores given the differential discontinuation rate between the baricitinib and placebo groups (higher proportion of dropouts in the placebo group) and the use of last observation carried forward (LOCF) or modified last observation carried forward (mLOCF) as the data imputation method. There is a lack of sample size consideration and control for multiplicity for subgroup analyses, which preclude definitive conclusions on subgroup effects. Evidence for the validity and MID estimate of HADS and Skindex-16 AA outcomes in patients with AA was not identified by the sponsor.

The clinical experts consulted by CADTH noted that the inclusion and exclusion criteria of the trials in general were reflective of the patient population eligible for baricitinib treatment in Canada, although patients with primarily diffuse type of AA would not necessarily be excluded from treatment in clinical practice. As well, older adults (i.e., males above 60 years of age and females above 70 years of age) were excluded from the trials. There are differing opinions from the clinical experts suggesting that older adults may or may not be eligible for baricitinib treatment in clinical practice. In addition, the clinical experts noted that compared to clinical practice, the trials appeared to have enrolled a higher proportion of patients with very severe AA. As well, the trial populations had a lower degree of anxiety and depression at baseline as per clinical expert input, which could impact the generalizability of HADS outcomes. The clinical experts noted that a longer duration of follow-up beyond 36 weeks is required to adequately capture the long-term safety of baricitinib, including potential rare adverse events, since baricitinib is expected to be a lifelong treatment for many patients. No head-to-head evidence comparing baricitinib with systemic treatments for severe AA that are currently reimbursed by the public drug plans (conventional immunosuppressants) were submitted. As well, the absence of evidence for baricitinib in older adults (males above 60 years of age and females above 70 years of age), who were excluded from the trials represents another gap in evidence.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working. Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from a patient group and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- Scalp hair regrowth (proportion of patients with a SALT score of 20 or less, $SALT_{50}$)

- EB and EL hair regrowth (proportion of patients achieving an EB [or EL] score of 0 or 1 with ≥2-point improvement from baseline, among patients with a baseline score of ≥2)
- Anxiety and depression (change from baseline in HADS Anxiety and Depression scores)
- HRQoL (change from baseline in Skindex-16 AA Symptoms, Emotions, and Functioning scores)
- Harms (SAEs)

The GRADE summary of findings for baricitinib versus placebo for the treatment of adults with severe or very severe AA is presented in Table 3 (baricitinib 2 mg versus placebo) and Table 4 (baricitinib 4 mg versus placebo).

Table 3: Summary of Findings for Baricitinib 2 mg Versus Placebo for Adults With Severe or Very severe AA

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Scalp Hair Regrowth				
SALT score (0 [no scalp hair loss] to 100 [complete scalp hair loss]), proportion of patients achieving SALT ≤ 20 (95% CI) Follow-up: 36 weeks	685 (2 RCTs)	BRAVE-AA1 • Baricitinib 2 mg: 217 per 1,000 (164 to 282 per 1,000) • Placebo: 53 per 1,000 (29 to 95 per 1,000) • Difference: 164 more per 1,000 (97 more to 234 more per 1,000) BRAVE-AA2 • Baricitinib 2 mg: 173 per 1,000 (122 to 240 per 1,000) • Placebo: 26 per 1,000 (10 to 64 per 1,000) • Difference: 147 more per 1,000 (83 more to 216 more per 1,000)	Moderate[a]	Baricitinib 2 mg likely results in a clinically important increase in the proportion of patients achieving SALT ≤20 when compared with placebo.
Proportion of patients achieving a $SALT_{50}$ (i.e., at least 50% reduction in score from baseline) (95% CI) Follow-up: 36 weeks	685 (2 RCTs)	BRAVE-AA1 • Baricitinib 2 mg: 304 per 1,000 [redacted] • Placebo: 127 per 1,000 [redacted] • Difference: 177 more per 1,000 (95 more to 258 more per 1,000)[b] BRAVE-AA2 • Baricitinib 2 mg: 282 per 1,000 [redacted] • Placebo: 51 per 1,000 [redacted] • Difference: 231 more per 1,000 (151 more to 310 more per 1,000)[b]	High[c]	Baricitinib 2 mg results in a clinically important increase in $SALT_{50}$ response when compared with placebo.
EB Hair Regrowth				
ClinRO Measure for EB Hair Loss (0 [full coverage and no areas of hair loss], to 3 [no notable EB hair, proportion of patients achieving a score of 0 (full coverage and no areas of hair loss) or 1 (minimal gaps in EB hair and even distribution) with ≥2-point improvement from baseline, among patients with a baseline score of ≥2 (95% CI) Follow-up: 36 weeks	476 (2 RCTs)	BRAVE-AA1 • Baricitinib 2 mg: 191 per 1,000 [redacted] • Placebo: 32 per 1,000 [redacted] • Difference: 159 more per 1,000 (84 more to 236 more per 1,000) BRAVE-AA2 • Baricitinib 2 mg: 115 per 1,000 [redacted] • Placebo: 45 per 1,000 [redacted] • Difference: 71 more per 1,000 (3 less to 150 more per 1,000)	Low[d,e]	Baricitinib 2 mg may result in a clinically important increase in EB hair regrowth when compared with placebo.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
EL Hair Regrowth				
ClinRO Measure for EL Hair Loss (0 [continuous line of EL along eyelids] to 3 [no notable EL]), proportion of patients achieving a score of 0 (continuous line of EL along eyelids) or 1 (minimal gaps in EL hair and even distribution) with ≥2-point improvement from baseline, among patients with a baseline score of ≥2 (95% CI) Follow-up: 36 weeks	386 (2 RCTs)	BRAVE-AA1 • Baricitinib 2 mg: 135 per 1,000 [redacted] • Placebo: 31 per 1,000 [redacted] • Difference: 104 more per 1,000 (27 more to 183 more)[f] BRAVE-AA2 • Baricitinib 2 mg: 101 per 1,000 [redacted] • Placebo: 56 per 1,000 [redacted] • Difference: 46 more per 1,000 (37 less to 132 more per 1,000)[f]	Low[d,e]	Baricitinib 2 mg may result in little to no clinically important difference in EL hair regrowth when compared with placebo.
Anxiety and Depression				
HADS Anxiety score (0 [least anxiety] to 21 [highest anxiety]), change from baseline in score (95% CI) Follow-up: 36 weeks	580 (2 RCTs)	BRAVE-AA1 • Baricitinib 2 mg: -1.2 (SE = 0.2) • Placebo: -0.4 (SE = 0.2) • Difference: -0.8 (95% CI, -1.4 to -0.3)[b] BRAVE-AA2 • Baricitinib 2 mg: -0.7 (SE = 0.2) • Placebo: -0.5 (SE = 0.2) • Difference: -0.2 (95% CI, -0.8 to 0.4)[b]	Very low[g,h]	The evidence is very uncertain about the effect of baricitinib 2 mg on anxiety when compared with placebo.
HADS Depression score (0 [least depression] to 21 [highest depression]), change from baseline in score (95% CI) Follow-up: 36 weeks	580 (2 RCTs)	BRAVE-AA1 • Baricitinib 2 mg: -0.4 (SE = 0.2) • Placebo: 0.0 (SE = 0.2) • Difference: -0.4 (95% CI, -0.9 to 0.1)[b] BRAVE-AA2 • Baricitinib 2 mg: -0.2 (SE = 0.2) • Placebo: 0.3 (SE = 0.2) • Difference: -0.5 (95% CI, -1.1 to 0.1)[b]	Very low[g,h]	The evidence is very uncertain about the effect of baricitinib 2 mg on depression when compared with placebo.
HRQoL				
Skindex-16 AA Symptoms score (0 [no effect] to 100 [effect experienced all the time]), change from baseline in score (95% CI) Follow-up: 36 weeks	[redacted] (2 RCTs)	BRAVE-AA1 • Baricitinib 2 mg: [redacted] • Placebo: [redacted] • Difference: [redacted][b] BRAVE-AA2 • Baricitinib 2 mg: [redacted] • Placebo: [redacted]	Low[g,i]	Baricitinib 2 mg may result in an improvement in symptoms when compared with placebo. The clinical importance of the improvement is unclear.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		• Difference: -3.02 (95% CI, -6.91 to 0.88)[b]		
Skindex-16 AA Emotions score (0 [no effect] to 100 [effect experienced all the time]), change from baseline in score (95% CI) Follow-up: 36 weeks	[redacted] (2 RCTs)	BRAVE-AA1 • Baricitinib 2 mg: [redacted] • Placebo: [redacted] • Difference: [redacted][b] BRAVE-AA2 • Baricitinib 2 mg: [redacted] • Placebo: [redacted] • Difference: [redacted][b]	Low[g]	Baricitinib 2 mg may result in an improvement in emotions when compared with placebo. The clinical importance of the improvement is unclear.
Skindex-16 AA Functioning score (0 [no effect] to 100 [effect experienced all the time], change from baseline in score (95% CI) Follow-up: 36 weeks	[redacted] (2 RCTs)	BRAVE-AA1 • Baricitinib 2 mg: [redacted] • Placebo: [redacted] • Difference: [redacted][b] BRAVE-AA2 • Baricitinib: [redacted] • Placebo: [redacted] • Difference: [redacted]	Low[g,j]	Baricitinib 2 mg may result in an improvement in functioning when compared with placebo. The clinical importance of the improvement is unclear.
Harms				
Serious adverse event Follow-up: 36 weeks	681 (2 RCTs)	BRAVE-AA1 • Baricitinib 2 mg: 22 per 1,000 (NR) • Placebo: 16 per 1,000 (NR) • Difference: 6 more per 1,000 (NR)[b] BRAVE-AA2 • Baricitinib 2 mg: 26 per 1,000 (NR) • Placebo: 19 per 1,000 (NR) • Difference: 6 more per 1,000 (NR)[b]	Low[k]	Baricitinib 2 mg may result in little to no difference in serious adverse events compared with placebo.

AA = alopecia areata; ClinRO = Clinician-Reported Outcome; CI = confidence interval; EB = eyebrow; EL = eyelash; HADS = Hospital Anxiety and Depression Scale; HRQoL = health-related quality of life; RCT = randomized controlled trial; SE = standard error; SALT = Severity of Alopecia Tools; Skindex-16 AA = Skindex-16 Adapted for Alopecia Areata; NR = not reported.

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

[a] Rated down 1 level for serious imprecision. The clinical experts consulted by CADTH indicated that a difference of 100 per 1,000 patients could be considered clinically important. The 95% CI included the possibility of benefit and no difference in both trials.

[b] Statistical testing for this outcome was not adjusted for multiplicity. The results are considered as supportive evidence.

[c] Did not rate down for imprecision. Although the lower boundary of the 95% CI in BRAVE-AA1 is 95 more per 1,000, this was not considered to be a source of serious imprecision due to its proximity to the threshold of 100 more per 1,000 as per clinical expert input.

[d] Rated down 1 level for serious study limitations. Randomization could potentially be impacted due to exclusion of patients whose baseline score did not meet the specified value of at least 2, from each treatment group. The extent and direction of the resulting bias is unclear.

[e] Rated down 1 level for serious imprecision. The clinical experts consulted by CADTH indicated that a difference of 100 per 1,000 patients could be considered clinically important. In both trials, the 95% CI included the possibility of benefit and little to no difference. Did not rate down for inconsistency though the point estimates from the trials were in different directions based on the threshold of 100 per 1,000 patients as per clinical expert input. This is due to overlap in the 95% CIs in the trials, including the possibility of benefit and little to no difference for both.

[f] No formal statistical testing was conducted due to a prior failure of an outcome in the statistical hierarchy. The results are considered as supportive evidence.

[g] Rated down 2 levels for very serious study limitations. Study treatment discontinuation was notably higher in the placebo group compared with the baricitinib 2 mg group in both trials. The differential discontinuation rate, along with the use of modified last observation carried forward (mLOCF) or last observation carried forward (LOCF) as the data imputation method, could potentially lead to attrition bias in favour of baricitinib 2 mg group. In addition, evidence for validity of this outcome measure in patient population under review (i.e., patients with alopecia areata) was not identified by the sponsor.

[h] Rated down 1 level for serious indirectness. The trial population had a higher mean baseline score (less severe anxiety or depression) than patients in clinical practice as per clinical expert input.

[i] Did not rate down for imprecision using null as a threshold. Although the upper boundary of the 95% CI in BRAVE-AA2 is [redacted], this was not considered to be a source of serious imprecision due to its proximity to the null.

[j] There is no concerns with imprecision using the null as a threshold. Although the upper boundary of the 95% CI is [redacted] and [redacted] in BRAVE-AA1 and BRAVE-AA2, respectively, this was not considered to be a source of serious imprecision due to its proximity to the null.

[k] Rated down 1 level for serious indirectness. The duration of follow-up of 36 weeks is inadequate for capturing potential rare serious adverse events of baricitinib as per clinical expert input. Rated down 1 level for serious imprecision, since the results were based on a small number of events across the trials.

Source: Source: Clinical Study Reports for BRAVE-AA1 and BRAVE-AA2.[7,8] Details included in the table are from the sponsor's Summary of Clinical Evidence.[9]

Table 4: Summary of Findings for Baricitinib 4 mg Versus Placebo for Adults With Severe or Very severe AA

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Scalp Hair Regrowth				
SALT score (0 [no scalp hair loss] to 100 [complete scalp hair loss]), proportion of patients achieving SALT ≤ 20 (95% CI) Follow-up: 36 weeks	860 (2 RCTs)	BRAVE-AA1 • Baricitinib 4 mg: 352 per 1,000 (299 to 410 per 1,000) • Placebo: 53 per 1,000 (29 to 95 per 1,000) • Difference: 299 more per 1,000 (232 more to 362 more per 1,000) BRAVE-AA2 • Baricitinib 4 mg: 325 per 1,000 (268 to 387 per 1,000) • Placebo: 26 per 1,000 (10 to 64 per 1,000) • Difference: 299 more per 1,000 (231 more to 363 more per 1,000)	High	Baricitinib 4 mg results in a clinically important increase in the proportion of patients achieving SALT ≤20 when compared with placebo.
Proportion of patients achieving a $SALT_{50}$ (i.e., at least 50% reduction in score from baseline) (95% CI) Follow-up: 36 weeks	860 (2 RCTs)	BRAVE-AA1 • Baricitinib 4 mg: 463 per 1,000 [redacted] • Placebo: 127 per 1,000 [redacted] • Difference: 336 more per 1,000 (256 more to 407 more per 1,000)[a] BRAVE-AA2 • Baricitinib 4 mg: 470 per 1,000 [redacted] • Placebo: 51 per 1,000 [redacted] • Difference: 419 more per 1,000 (340 more to 487 more per 1,000)[a]	High	Baricitinib 4 mg results in a clinically important increase in $SALT_{50}$ response when compared with placebo.
EB Hair Regrowth				
ClinRO Measure for EB Hair Loss (0 [full coverage and no areas of hair loss], to 3 [no notable EB hair, proportion of patients achieving a score of 0	585 (2 RCTs)	BRAVE-AA1 • Baricitinib 4 mg: 314 per 1,000 [redacted] • Placebo: 32 per 1,000 [redacted] • Difference: 282 more per 1,000 (203 more to 354 more per 1,000)	Moderate[b]	Baricitinib 4 mg likely results in a clinically important increase in EB hair regrowth when compared with placebo.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
(full coverage and no areas of hair loss) or 1 (minimal gaps in EB hair and even distribution) with ≥2-point improvement from baseline, among patients with a baseline score of ≥2 (95% CI) Follow-up: 36 weeks		BRAVE-AA2 • Baricitinib 4 mg: 348 per 1,000 [redacted] • Placebo: 45 per 1,000 [redacted] • Difference: 303 more per 1,000 (214 more to 384 more per 1,000)		
EL Hair Regrowth				
ClinRO Measure for EL Hair Loss (0 [continuous line of EL along eyelids] to 3 [no notable EL]), proportion of patients achieving a score of 0 (continuous line of EL along eyelids) or 1 (minimal gaps in EL hair and even distribution) with ≥2-point improvement from baseline, among patients with a baseline score of ≥2 (95% CI) Follow-up: 36 weeks	493 (2 RCTs)	BRAVE-AA1 • Baricitinib 4 mg: 335 per 1,000 [redacted] • Placebo: 31 per 1,000 [redacted] • Difference: 304 more per 1,000 (216 more to 381 more) BRAVE-AA2 • Baricitinib 4 mg: 343 per 1,000 [redacted] • Placebo: 56 per 1,000 [redacted] • Difference: 287 more per 1,000 (187 more to 375 more per 1,000)	Moderate[b]	Baricitinib 4 mg likely results in a clinically important increase in EL hair regrowth when compared with placebo.
Anxiety and Depression				
HADS Anxiety score (0 [least anxiety] to 21 [highest anxiety]), change from baseline in score (95% CI) Follow-up: 36 weeks	740 (2 RCTs)	BRAVE-AA1 • Baricitinib 4 mg: -0.9 (SE = 0.2) • Placebo: -0.4 (SE = 0.2) • Difference: -0.5 (95% CI, -1.1 to -0.0)[a] BRAVE-AA2 • Baricitinib 4 mg: -1.2 (SE = 0.2) • Placebo: -0.5 (SE = 0.2) • Difference: -0.7 (95% CI, -1.3 to -0.2)[a]	Very low[c,d]	The evidence is very uncertain about the effect of baricitinib 4 mg on anxiety when compared with placebo.
HADS Depression score (0 [least depression] to 21 [highest depression]), change from baseline in score (95% CI) Follow-up: 36 weeks	740 (2 RCTs)	BRAVE-AA1 • Baricitinib 4 mg: -0.3 (SE = 0.2) • Placebo: 0.0 (SE = 0.2) • Difference: -0.3 (95% CI, -0.8 to 0.1) BRAVE-AA2 • Baricitinib 4 mg: -0.4 (SE = 0.2) • Placebo: 0.3 (SE = 0.2)	Very low[c,d]	The evidence is very uncertain about the effect of baricitinib 4 mg on depression when compared with placebo.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		• Difference: -0.7 (95% CI, -1.2 to -0.2)[a]		
HRQoL				
Skindex-16 AA Symptoms score (0 [no effect] to 100 [effect experienced all the time]), change from baseline in score (95% CI) Follow-up: 36 weeks	[redacted] (2 RCTs)	BRAVE-AA1 • Baricitinib 4 mg: [redacted] • Placebo: [redacted] • Difference: [redacted][a] BRAVE-AA2 • Baricitinib 4 mg: [redacted] • Placebo: [redacted] • Difference: [redacted][a]	Low[c]	Baricitinib 4 mg may result in an improvement in symptoms when compared with placebo. The clinical importance of the improvement is unclear.
Skindex-16 AA Emotions score (0 [no effect] to 100 [effect experienced all the time]), change from baseline in score (95% CI) Follow-up: 36 weeks	[redacted] (2 RCTs)	BRAVE-AA1 • Baricitinib 4 mg: [redacted] • Placebo: [redacted] • Difference: [redacted][a] BRAVE-AA2 • Baricitinib 4 mg: [redacted] • Placebo: [redacted] • Difference: [redacted][a]	Low[c]	Baricitinib 4 mg may result in an improvement in emotions when compared with placebo. The clinical importance of the improvement is unclear.
Skindex-16 AA Functioning score (0 [no effect] to 100 [effect experienced all the time], change from baseline in score (95% CI) Follow-up: 36 weeks	[redacted] (2 RCTs)	BRAVE-AA1 • Baricitinib 4 mg: [redacted] • Placebo: [redacted] • Difference: [redacted] BRAVE-AA2 • Baricitinib: [redacted] • Placebo: [redacted] • Difference: [redacted]	Low[c]	Baricitinib 4 mg may result in an improvement in functioning when compared with placebo. The clinical importance of the improvement is unclear.
Harms				
Serious adverse event (95% CI) Follow-up: 36 weeks	856 (2 RCTs)	BRAVE-AA1 • Baricitinib 4 mg: 21 per 1,000 (NR) • Placebo: 16 per 1,000 (NR) • Difference: 6 more per 1,000 (NR)[a] BRAVE-AA2 • Baricitinib 4 mg: 34 per 1,000 (NR) • Placebo: 19 per 1,000 (NR) • Difference: 15 more per 1,000 (NR)[a]	Low[e]	Baricitinib 4 mg may result in little to no difference in serious adverse events compared with placebo.

AA = alopecia areata; ClinRO = Clinician-Reported Outcome; CI = confidence interval; EB = eyebrow; EL = eyelash; HADS = Hospital Anxiety and Depression Scale; HRQoL = health-related quality of life; RCT = randomized controlled trial; SE = standard error; SALT = Severity of Alopecia Tools; Skindex-16 AA = Skindex-16 Adapted for Alopecia Areata; NR = not reported.

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

[a] Statistical testing for this outcome was not adjusted for multiplicity. The results are considered as supportive evidence.

[b] Rated down 1 level for serious study limitations. Randomization could potentially be impacted due to exclusion of a large proportion of patients, whose baseline score did not meet the specified value of at least 2, from each treatment group. The extent and direction of the resulting bias is unclear.

[c] Rated down 2 levels for serious study limitations. Study treatment discontinuation was notably higher in the placebo group compared with the baricitinib 4 mg group in both trials. The differential discontinuation rate, along with the use of modified last observation carried forward (mLOCF) or last observation carried forward (LOCF) as the data imputation method, could potentially lead to attrition bias in favour of baricitinib 4 mg group. In addition, evidence for validity of this outcome measure in patient population under review (i.e., patients with alopecia areata) was not identified by the sponsor.

[d] Rated down 1 level for serious indirectness. The trial population had a higher mean baseline score (less severe anxiety or depression) than patients in clinical practice as per clinical expert input.

[e] Rated down 1 level for serious indirectness. The duration of follow-up of 36 weeks is inadequate for capturing potential rare serious adverse events of baricitinib as per clinical expert input. Rated down 1 level for serious imprecision, since the results were based on a small number of events across the trials.

Source: Clinical Study Reports for BRAVE-AA1 and BRAVE-AA2.[7,8] Details included in the table are from the sponsor's Summary of Clinical Evidence.[9]

Long-Term Extension Studies

Description of Studies

BRAVE-AA1

This study is a long-term extension (Week 36 onwards) of the BRAVE-AA1 study. The purpose of this study was to provide the safety and efficacy analyses through Week 104 to support dosing recommendations in product labeling of baricitinib.

At Week 52, patients initially randomized to baricitinib who were responders (SALT score 20 or less) were re-randomized at a 3:1 ratio to stay on their current dose of baricitinib or transition to placebo (randomized withdrawal). Responders who had been re-randomized to placebo and experienced a loss of treatment benefit at any time after Week 52 (more than 20-point worsening in SALT score from Week 52) were re-treated with their original baricitinib dose and the efficacy of retreatment was analyzed as part of the other secondary endpoints of the BRAVE-AA1 study.

This extension study included Week 0 to 52 and Week 52 to 76 efficacy and safety for patients who uptitrated at Week 52. The uptitration cohort included [redacted] patients randomized to baricitinib 2 mg at Week 0 who did not achieve SALT ≤20 at Week 52. All [redacted] patients were uptitrated to baricitinib 4 mg.

BRAVE-AA2

This study is a long-term extension (Week 36 onwards) of the BRAVE-AA2 study. The purpose of this study was to provide efficacy and safety analyses to support dosing recommendations in product labeling.

At Week 52, patients were divided into two cohorts. The randomized downtitration cohort included 82 patients who were randomized at Week 0 to baricitinib 4 mg who achieved SALT score 20 or less at Week 52. Of these, 42 patients were randomly assigned to remain on baricitinib 4 mg, and 40 patients were randomly assigned to downtitrate to baricitinib 2 mg. The uptitration cohort included [redacted] patients randomized to baricitinib 2 mg at Week 0 who did not achieve SALT score 20 or less at Week 52. All [redacted] patients were uptitrated to baricitinib 4 mg.

Efficacy Results

Proportion of Patients achieving SALT ≤20

In both trials, the proportion of patients achieving SALT ≤20 continuously increased over the treatment period beyond 36 weeks for baricitinib 4mg cohort. At Week 52, 40.9% and 21.2% of patients receiving baricitinib 4 mg and 2 mg, respectively, achieved SALT ≤20 in BRAVE-AA1. Similarly, 36.8% and 24.4% of patients receiving baricitinib 4 mg and 2 mg, respectively, achieved SALT ≤20 at Week 52 in BRAVE-AA2.

<u>BRAVE-AA1- Uptitration Cohort</u>

At Week 52, [redacted] patients who were originally randomized to baricitinib 2 mg were considered non-responders and were eligible for inclusion in the uptitration cohort uptitrated to baricitinib 4 mg. At Week 76, following 24 weeks of treatment on baricitinib 4 mg, [redacted] in the uptitration cohort achieved SALT≤20.

<u>BRAVE-AA2 – Randomized Downtitration Cohort</u>

At Week 52, 82 patients who were originally randomized to baricitinib 4 mg were eligible for randomized downtitration to baricitinib 2 mg. At Week 52, [redacted] of patients achieved SALT ≤20. [redacted].

Among patients receiving baricitinib 4 mg who achieved SALT ≤20 at Week 52, this response was retained up to Week 76 in [redacted] of patients who were downtitrated to baricitinib 2 mg, and [redacted] of patients who remained on baricitinib 4 mg.

BRAVE-AA2 – Uptitration Cohort

At Week 52, 84 patients who were originally randomized to baricitinib 2 mg were considered non-responders and were eligible for inclusion in the uptitration cohort uptitrated to baricitinib 4 mg. At Week 76, after 24 weeks of uptitration treatment on baricitinib 4 mg, [redacted] achieved SALT≤20.

ClinRO measure for EB and EL hair loss

At Week 52, 39.4% and 27.9% of patients receiving baricitinib 4 mg and 2 mg, respectively, achieved ClinRO measure for EB hair loss (0,1) (with ≥2-point improvement from baseline through Week 52 among patients with a score of ≥2 at baseline) in BRAVE-AA1. Similarly, 49.7% and 16.3% of patients receiving baricitinib 4 mg and 2 mg, respectively, achieved ClinRO measure for EB hair loss (0,1) (with ≥2-point improvement from baseline through Week 52 among patients with a score of ≥2 at baseline) at Week 52 in BRAVE-AA2.

At Week 52, 40.7% and 21.6% of patients receiving baricitinib 4 mg and 2 mg, respectively, achieved ClinRO measure for EL hair loss (0,1) (with ≥2-point improvement from baseline through Week 52 among patients with a score of ≥2 at baseline) in BRAVE-AA1. Similarly, 50.7% and 30.3% of patients receiving baricitinib 4 mg and 2 mg, respectively, achieved ClinRO measure for EL hair loss (0,1) (with ≥2-point improvement from baseline through Week 52 among patients with a score of ≥2 at baseline) at Week 52 in BRAVE-AA2.

Harms Results

BRAVE-AA1- Uptitration cohort

TEAEs were reported for [redacted].

BRAVE-AA2 - Randomized Downtitration Cohort

For both treatment groups, [redacted]

BRAVE-AA2 Uptitration Cohort

TEAEs were reported for [redacted].

Critical Appraisal

Both BRAVE-AA1 and BRAVE-AA2 extension studies were limited by their noncomparative design. At time points after 36 weeks, there remained no randomized comparison to placebo, challenging causal interpretations. Although the patients and investigators remained blinded to the assigned interventions, there remains the possibility that patients may be able to infer treatment assignment due to differences in efficacy (relative to placebo during the double-blind treatment phase). As such, there may be a risk of bias in the reporting of efficacy outcomes that required some level of subjective judgement by the evaluators (e.g., ClinRO), and harms outcomes, although the extent and direction of bias cannot be predicted. It is unlikely that bias would be introduced for the SALT response, since it is measured relatively objectively. Finally, missing information such as pooling strategies constrained a robust critical appraisal; hence, firm conclusion cannot be drawn on the long-term efficacy and safety. Both BRAVE-AA1 and BRAVE-AA2 included rollover patients consistent with their characteristics at entry into the core study, it is reasonable to expect similar limitations to generalizability of the study results are relevant to the long-term extension phase. Further, some outcomes that are important to patients (e.g., HRQoL, anxiety, depression) could not be evaluated against a placebo control beyond the 36-week double-blind treatment phase due to discontinuation of the placebo in non-responders. As such, there is limited evidence for the effect of baricitinib 2 mg or 4 mg on these outcomes for time points after 36 weeks (including for patients who uptitrated or downtitrated). Despite longer follow up for harms, some rare harms (e.g., malignancies) may still not be fully captured.

Indirect Comparisons

No indirect comparative evidence was submitted by the sponsor. The sponsor noted that prior to the regulatory approval of baricitinib for severe AA in Canada, the standard of care included off-label therapies and non-pharmacological options. The sponsor further noted that the pivotal trials of baricitinib were placebo-controlled and given that no approved comparator drugs were available at the time of the Phase III clinical development conduct, there is no indirect comparative efficacy evidence to present in this section.

Studies Addressing Gaps in the Evidence From the Systematic Review

Description of Studies

Additional insights into the effects of baricitinib in patients with AA were sought for males over 60 years and females over 70 years of age that were not included in the pivotal trials. A retrospective chart study (n = 14) by Tang *et al.* (2024) describing baricitinib treatment in patients over the age of 65 years was included. A retrospective chart review of 36 patients conducted by Moreno-Vilchez *et al*. (2024) and a retrospective chart review of 95 patients in Japan by Numata *et al.* (2024) provided additional data about the effects of baricitinib.

Efficacy Results

Tang et al. (2024)

After a mean (SD) duration of 18.5 (11.9) months, a 72.0% reduction in the mean SALT score from baseline was observed. Moreover, 11 of 14 patients (78.6%) achieved SALT less than 10 after a mean duration of 18.6 months where SD is not reported.

Numata et al. (2024)

The percentage of patients in the entire cohort who achieved a SALT score of 20 or less at week 12, 24, and 36 was 6.4% (6 out of 94), 35.4% (28 out of 79), and 46.7% (21 out of 45), respectively.

The complete response rate (SALT 0) at week 24 and 36 was 1.3% (1 out of 79) and 6.7% (3 out of 45), respectively.

Moreno-Vilchez et al. (2024)

In the study, 58.8% of patients achieved a SALT score of 20 or less at week 24. The response continued for 52 weeks, with 66.6% classified as responders. Additionally, the study compared the SALT scores between patients treated with monotherapy and those who received adjuvant treatment.

Harms Results

Tang et al. (2024)

Adverse effects of baricitinib were moderate and included reactivation of herpes zoster (n=1), elevated creatine kinase (n=1) and grade 2 neutropenia (n=1). Only 1 patient required a reduction in the dose of baricitinib due to grade 2 neutropenia. No cases of venous thromboembolism, MACE or malignancy were reported.

Numata et al. (2024)

Infectious complications occurred in 6 patients during the initial 12 weeks. Herpes simplex and COVID-19 (SARS-CoV-2) occurred in 1 and 5 patients, respectively. No severe other complications occurred during the entire 36-week course.

Moreno-Vilchez et al. (2024)

Overall, adverse events were mild. Three patients were discontinued because of inadequate treatment response: 2 at week 52 and 1 at week 76. Additionally, one patient had temporary lymphopenia with methotrexate treatment.

Critical Appraisal

Limitations of the 3 studies included their retrospective designs and small sample sizes. Moreover, most of patients were treated with concomitant treatments, and without a randomized comparison group, it is not possible to attribute the observed effects to baricitinib with certainty. Furthermore, information such as treatment exposure and concomitant treatments in Numata et al were not reported.

Both Tang et al and Numata et al included patients with moderate-to-severe AA; however, patients with moderate AA would not be candidates for baricitinib treatment in Canada. The results of these studies may not be generalizable to patients with severe or very severe AA, which may be more difficult to treat compared with moderate AA. The study by Numata et al. included patients exclusively from Japan, whereas the study by Moreno-Vilchez et al. included patients exclusively from 2 centres in Spain. It is uncertain whether results from small samples of patients treated in these countries would be generalizable to Canadian patients, given the potential for differences in standard of care in these countries.

Economic Evidence

Cost and Cost-Effectiveness

Table 5: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Patients with AA with a SALT score higher or equal to 50 at baseline (i.e., SALT 50-100).
Treatment	Baricitinib
Dose regimen	The recommended dose is 2 mg daily, which may be increased to 4 mg once daily if the response to treatment is not adequate. For patients with nearly complete or complete scalp hair loss, and/or substantial eyelash or eyebrow hair loss the recommended dose is 4 mg once daily. Once patients achieve an adequate response to treatment with 4 mg, dosage may be decreased to 2 mg daily.
Submitted prices	Baricitinib 2 mg: $57.21 per tablet 4 mg: $114.41 per tablet
Submitted treatment cost	2 mg daily: $20,894 per patient annually 4 mg daily: $41,789 per patient annually
Comparator	No active treatment
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (63 years)
Key data source	Pooled data from the BRAVE-AA1 and BRAVE-AA2 trials were used to inform change from baseline in SALT score (defined as at least 50% improvement; $SALT_{50}$) and treatment discontinuation rates.
Key limitations	• The response outcome used in the economic model ($SALT_{50}$ at week 36) is inconsistent with the definition of response and discontinuation rules in the BRAVE trials, and there is likely to be variability in how baricitinib will be used in Canadian clinical practice. Some clinicians are likely to continue prescribing baricitinib even if patients achieve less than a 50% improvement in scalp hair regrowth at 36 weeks. In the BRAVE trials, baricitinib-treated patients continued treatment regardless of response at week 36. Clinical experts indicated that both clinician and patient assessments of clinically significant hair regrowth are expected to take precedence over the percentage improvement in the SALT score. Alternatively, some clinicians may adopt the primary response outcome from the trials to determine treatment response and discontinuation (SALT≤20). • In the economic model, patients who do not respond to no active treatment incur annual costs of $2,382 for BSC drug acquisition, drug monitoring, and disease management for the duration of their lives, whereas patients who do not respond to baricitinib do not incur these costs. All patients enrolled in BRAVE-AA1 and BRAVE-AA2 were BSC-experienced and clinical experts agree that the indicated population is likely to have prior experience with BSC therapies. Hence,

Component	Description
	if response is not achieved with baricitinib or no active treatment, patients who had exhausted all BSC therapy options would not receive further treatment in the 'BSC' health state. In contrast, if patients do not respond to baricitinib or no active treatment and were naïve to certain BSC therapies would have an equal opportunity to access those treatments. • The impact of baricitinib on the HRQoL of patients with severe AA is highly uncertain. No significant difference was observed between baricitinib (4 mg or 2 mg) and no active treatment in the change from baseline in EQ-5D health state index at week 36 in BRAVE-AA1 and BRAVE-AA2. Despite trial evidence, the sponsor derived EQ-5D utility values from an observational study, which does not align with the disease severity of patients from the pivotal trials, or with the relative change from baseline assumed in the economic model. • Clinical experts, participating drug plans, and patient group input highlighted that BSC therapies (including antihypertensives, corticosteroids, and immunosuppressants/immunomodulators) are frequently used off-label for the treatment of severe AA. Therefore, the sponsor's use of no active treatment as the sole comparator in the economic model does not reflect current clinical practice. The cost-effectiveness of baricitinib relative to BSC therapies remains unknown. • The probabilistic sensitivity analysis lacks transparency. The submitted economic model includes a macro that affects the calculation of the probabilistic ICER for baricitinib in certain situations. Specifically, when baricitinib results in lower QALYs compared to no active treatment, the model uses deterministically estimated QALYs instead of probabilistically estimated QALYs for the probabilistic ICER calculation.
CADTH reanalysis results	• The CADTH base case was derived by making changes to the following model parameters: adopting $SALT_{30}$ as the primary response outcome; assuming equal costs associated with drug acquisition, drug monitoring, and disease management for the 'BSC' health state regardless of initial treatment (baricitinib or no active treatment); and using the EQ-5D utility values derived from the BRAVE-AA1 and BRAVE-AA2 trials. • In the CADTH base case, the use of baricitinib at the 2 mg dose was associated with an ICER of $5,465,503 per QALY gained compared to no active treatment (incremental costs: $62,457; incremental QALYs: 0.01). In addition, the use of baricitinib at the 4 mg dose was associated with an ICER of $6,803,200 per QALY gained compared to no active treatment (incremental costs: $203,814; incremental QALYs: 0.03). There is no price reduction upon which baricitinib would be considered cost-effective at a WTP threshold of $50,000 per QALY gained. • The cost-effectiveness of baricitinib is sensitive to assumptions concerning response. When adopting $SALT_{75}$ as the response threshold to continue baricitinib treatment beyond 36 weeks, the ICER of baricitinib decreased to $346,345 per QALY gained for the 2 mg dose, and $497,449 per QALY gained for the 4 mg dose, compared to no active treatment. In this scenario, a price reduction of 88% for the 2 mg dose and 91% for the 4 mg dose would be necessary for baricitinib to be cost-effective compared to no active treatment at a WTP threshold of $50,000 per QALY gained.

AA = alopecia areata; BSC = best supportive care; EQ-5D = European Quality of Life 5 dimensions; ICER = incremental cost-effectiveness ratio; LY = life-year; PSA = probabilistic sensitivity analysis; QALY= quality-adjusted life-year; SALT = Severity of Alopecia Tool; incr. = incremental; SALT≤20 = greater than or equal to 20% scalp hair coverage; $SALT_{30}$ = at least 30% improvement from baseline in the Severity of Alopecia Tool score; $SALT_{50}$ = at least 50% improvement from baseline in the Severity of Alopecia Tool score; $SALT_{75}$ = at least 75% improvement from baseline in the Severity of Alopecia Tool score; WTP = willingness to pay

Budget Impact

CADTH identified the following limitations in the sponsor's base case: the proportion of patients assumed to receive baricitinib 2 mg and 4 mg doses is highly uncertain; assumptions regarding compliance underestimated drug acquisition costs; the projected market share of baricitinib is underestimated; and the distribution of therapies in the BSC basket is highly uncertain.

CADTH conducted reanalyses of the BIA by adjusting the proportion of patients that would receive the 2 mg and 4 mg doses of baricitinib; assuming 100% compliance in alignment with the cost-effectiveness model; modifying the projected market share of baricitinib; and revising the distribution of therapies in the BSC basket.

Based on the CADTH base case, the estimated budget impact associated with the reimbursement of baricitinib for the treatment of severe AA is expected to be $35,487,043 in Year 1, $74,358,125 in Year 2, and $116,749,276 in Year 3, for a three-year budgetary impact of $226,594,445.

CADTH conducted a scenario analysis to address remaining uncertainty. When assuming that the 2 mg and 4 mg doses of baricitinib would be prescribed equally (50% each) within the indicated population, the three-year budgetary impact of reimbursing baricitinib decreased to $178,463,530. This indicates that the budget impact is sensitive to assumptions regarding the proportion of patients likely to receive each dose of baricitinib.

CDEC Information

Members of the Committee:

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Danyaal Raza, Dr. Edward Xie, and Dr. Peter Zed.

Meeting date: July 24, 2024

Regrets:

Three expert committee members did not attend.

Conflicts of interest:

None