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CADTH Reimbursement Recommendation

Baricitinib (Olumiant)

Indication: For the treatment of adult patients with severe alopecia areata
Sponsor: Eli Lilly Canada Inc.
Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Olumiant?

CADTH recommends that Olumiant be reimbursed by public drug plans for the treatment of adults with severe alopecia areata (AA) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Olumiant should only be covered to treat adults who have severe AA with at least 50% loss in scalp hair. The current AA episode should have already lasted for more than 6 months and less than 8 years.

What Are the Conditions for Reimbursement?

Olumiant should only be reimbursed if prescribed by a dermatologist with expertise managing patients with severe AA and if the cost is reduced. Olumiant should not be used in combination with other Janus kinase (JAK) inhibitors, biologic immunomodulators, or systemic immunosuppressants. Olumiant should only be reimbursed for 36 weeks when first prescribed. If a patient continues to experience improvements, reimbursement of Olumiant can be extended every 12 months.

Why Did CADTH Make This Recommendation?

- Evidence from 2 clinical trials demonstrated that Olumiant improved hair regrowth on the scalp, eyebrows, and eyelashes compared to placebo.
- Olumiant may meet a need that is important to patients in terms of improving scalp hair regrowth.
- Based on our assessment of the health economic evidence, Olumiant does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Olumiant is estimated to cost the public drug plans $227 million over the next 3 years. However, the actual budget impact is uncertain.

Additional Information

What Is AA?

AA is a condition that causes hair loss, typically on the scalp, but could also occur in other areas, such as eyebrows and eyelashes. Some patients have extensive hair loss, which could cause significant emotional distress and reduce their quality of life. The prevalence of AA in Canada is estimated to be between 0.1% and 0.58%.

Summary

Unmet Needs in AA

There is a need for effective and safe treatments for severe AA as currently available treatments (conventional immunosuppressants) are not effective and are associated with serious adverse events (SAE) when used long term.

How Much Does Olumiant Cost?

Treatment with Olumiant is expected to cost approximately $20,894 per patient annually when used daily at the 2 mg dose and $41,789 per patient annually when used daily at the 4 mg dose.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that baricitinib be reimbursed for the treatment of adult patients with severe 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 adults who had severe AA with at least 50% scalp involvement. The difference in proportion of patients achieving a Severity of Alopecia Tool (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 the BRAVE-AA1 trial and 14.7% (95% CI, 8.3% to 21.6%; P < 0.001) in the BRAVE-AA2 trial. The between-group difference comparing baricitinib 4 mg with placebo was 29.9% (95% CI, 23.2% to 36.2%; P < 0.001) in the BRAVE-AA1 trial and 29.9% (95% CI, 23.1% to 36.3%; P < 0.001) in the BRAVE-AA2 trial. There was also a 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, and improve quality of life, as well as 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 when compared with no active treatment. The weighted ICER for baricitinib is $6,748,810 per QALY gained when compared to no active treatment. At this ICER, baricitinib is not cost-effective at a $50,000 per QALY gained willingness-to-pay threshold for the treatment of adults with severe AA. The cost-effectiveness of baricitinib is sensitive to assumptions concerning response threshold, which determine treatment discontinuation. In a scenario that adopted at least a 75% reduction in SALT score from baseline ($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 willingness-to-pay 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 of 20 or less at 36 weeks.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Patients must be adults with severe AA who meet the following criteria: 1.1. have a SALT score of 50 or above 1.2. have a duration of the current episode of AA of 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 adults (males aged 18 to 60 years and females aged 18 to 70 years) with AA who had at least 50% scalp hair loss and a current episode of AA of no more than 6 months and less than 8 years in duration.	The pivotal trials excluded males aged older than 60 years and females aged older 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 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 a 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 end point 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 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. CADTH 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	—

Reimbursement condition	Reason	Implementation guidance
	dose, the weighted ICER for baricitinib is $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 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.	—

AA = alopecia areata; CDEC = Canadian Drug Expert Committee; ICER = incremental cost-effectiveness ratio; JAK = Janus kinase; QALY = quality-adjusted life-year; SALT = Severity of Alopecia Tool; $SALT_{75}$ = 75% reduction in Severity of Alopecia Tool score from baseline; 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 (i.e., conventional immunosuppressants) for severe AA are associated with poor efficacy and a risk of relapse with dose 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 with no notable safety concerns identified. However, analyses beyond week 36 were noncomparative, 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, per Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) assessments. This was because of 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 as 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 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 aged older than 12 years; however, this treatment was not considered a relevant comparator for this submission as it had not undergone a reimbursement review by CADTH and was not reimbursed by the public drug plans at the time of this review.
- Males over the age of 60 and females over the age of 70 were excluded from the BRAVE-AA1 and BRAVE-AA2 trials. CDEC considered clinical expert input that older adults 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 older and noted that no definitive conclusions could be drawn regarding the benefits of baricitinib in older adults because of 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 end point in the BRAVE trials (a SALT score of 20 or less), which represents an absolute measure of response. CDEC considered a 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 end point observed in the BRAVE trials, where patients with severe AA (i.e., baseline SALT scores ranging from 50 to 100) who achieved 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 nonscarring 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 its 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 HRQoL. It is estimated that the prevalence of AA in Canada

is between 0.1% and 0.58%. 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 (i.e., cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil), and 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; as well as 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 dose 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 JAK 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; 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, prescribers should consider starting with 4 mg once daily. Once patients achieve an adequate response to treatment with 4 mg, prescribers should 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 adults 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 the 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 CANAAF, which was registered as a charitable organization in 2010 and is described as the voice for all patients and families affected by AA in Canada. 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, which is supported by data gathered from a CANAAF community alopecia patient focus group conducted in 2023. The most significant cost item for patients in the group was a wig purchase and maintenance, which can cost more than $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 (i.e., limited effectiveness, only effective for patients with very limited AA, difficult product application, scalp irritation), intralesional corticosteroids (i.e., painful injections, limited drug coverage by drug plans), oral corticosteroids (i.e., variable success rates, high relapse rate, limited drug coverage, unfavourable side effects), topical minoxidil (i.e., nondurable 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 (i.e., systemic adverse events [AEs] relating to its antihypertensive property, limited drug coverage), and systemic immunosuppressants (i.e., 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 noted 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 than existing treatments. Finally, the patient input indicated that baricitinib is a much easier treatment option for patients as it only requires that they take 1 pill once a day. This is in comparison with 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 dose 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, according to clinical expert input. The clinical experts noted that, because of 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 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., aged older than 60 years for males or older than 70 years for females, who were excluded from the pivotal trials) to be reasonable, while the other clinical expert suggested to restrict the use of baricitinib per the age restrictions in the pivotal trials because of 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 a 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 do not experience cosmetically acceptable hair regrowth at 36 weeks, who have further loss of hair at 36 weeks, who experience severe AEs deemed to be related to the use of a JAK inhibitor, or who develop intercurrent condition(s) that make discontinuation of a JAK inhibitor advisable (e.g., malignancy). In the clinical expert's opinion, baricitinib treatment should be prescribed by dermatologists with experience 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 (an 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 (i.e., 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

Implementation issues	Response
	consider oral minoxidil as a relevant comparator of baricitinib as it is not used as monotherapy in the treatment of severe AA. The clinical expert did not consider systemic corticosteroids as relevant comparators as they are used for short-term treatment. CDEC considered input from the clinical experts and noted that the 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. Have the clinical experts encountered any barriers in access to medications for patients within the jurisdictions?	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 offered by the drug manufacturer at the request of their dermatologist. One clinical expert further noted that access to a dermatologist could be difficult in their province as 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 previously noted severity definition 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 as 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 as 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 include treatment with bimatoprost ophthalmic solution for eyelashes may be continued if the patient has been on a stable dose for 8 weeks before 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	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 younger than 18 years old. One clinical expert noted that older adults (above the 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 because of 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 as older adults tend to have other concurrent causes of hair loss that are not expected be responsive to baricitinib treatment.

Implementation issues	Response
population (< 18 years; off-label use) and the older adult population (> 60 years in males and > 70 years for females)? 2. In practice, how often is baricitinib used in combination with other medications such as bimatoprost ophthalmic solution, finasteride, or minoxidil (oral or topical)? Most of these medications may be listed as general or open benefit in the jurisdictions and it may be challenging to know the reason for their use. Some jurisdictions may have minoxidil topical as a formulary exclusion.	CDEC considered input from both clinical experts and the submitted clinical evidence (Tang et al.) 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. They noted that it would be reasonable to use baricitinib in combination with bimatoprost ophthalmic solution, finasteride, or minoxidil (oral or topical).
Should patients receive prior systemic therapies, including corticosteroids, methotrexate, and cyclosporine before 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's condition relapsed, would they 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, 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, per the 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 has 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 a 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 time frame?	1. The clinical experts anticipated that baricitinib would be a lifelong treatment for many patients. 2. The clinical experts noted that in those who have complete response, a 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.

Implementation issues	Response
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 should be made for what medications not to use in combination with baricitinib. Per the product monograph, the use of baricitinib in combination with other JAK inhibitors, biologic immunomodulators, or 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, per the 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 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 or 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, as more data accumulates over time, it is likely that baricitinib would have a role in therapy in patients with a 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 health care system: assessing patients with viral hepatitis, latent tuberculosis, renal insufficiency, and pregnancy before the start of therapy; baseline and periodic monitoring of CBC with differential platelets, liver enzymes, and lipid levels; and periodic assessments of signs and symptoms of infection, skin examination (in patients with increased risk of skin cancer), and 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 ($1,716.17 for 30 tablets for baricitinib 2 mg, $3,432.34 for 30 tablets for baricitinib 4 mg, which amounts to approximately $20,400 to $40,800 per year) relative to other off-label systemic therapy × 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.

AA = alopecia areata; CBC = complete blood count; CDEC = Canadian Drug Expert Committee; EL = eyelash; LOI = letter of intent; JAK = Janus kinase; SALT = Severity of Alopecia Tool; vs. = versus.

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 adults who had severe or very severe AA with at least 50% scalp involvement (i.e., a 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 reassigned a new intervention (i.e., 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) per the protocol-defined criteria. This was followed by a 96-week bridging extension in which patients continued to receive the same intervention until the end of the study. The long-term extension period is ongoing in both trials.

The efficacy end points of interest to this review included the proportion of patients achieving a SALT score of 20 or less (primary end point), at least a 50% reduction in SALT score from baseline ($SALT_{50}$), Clinician-Reported Outcome (ClinRO) Measures for Eyebrow (EB) and Eyelash (EL) Hair Loss score of 0 or 1 with at least a 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 the BRAVE-AA1 and BRAVE-AA2 trials, respectively. Approximately 90% of patients had received a 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 a SALT Score of 20 or Less

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 the BRAVE-AA1 trial and 14.7% (95% CI, 8.3% to 21.6%; P < 0.001) in the BRAVE-AA2 trial. The between-group difference comparing baricitinib 4 mg and placebo was 29.9% (95% CI, 23.2% to 36.2%; P < 0.001) in the BRAVE-AA1 trial and 29.9% (95% CI, 23.1% to 36.3%; P < 0.001) in the BRAVE-AA2 trial. The 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 (the BRAVE-AA1 trial, −23.1%; 95% CI, −30.6% to −15.6%; P < 0.001; the BRAVE-AA2 trial, −25.3%; 95% CI, −32.8% to −17.7%) and 4 mg (the BRAVE-AA1 trial, −37.7%; 95% CI, −44.4% to −30.9%; P < 0.001); the BRAVE-AA2 trial, 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 the BRAVE-AA1 trial and 23.1% (95% CI, 15.1% to 31.0%; P < 0.001) in the BRAVE-AA2 trial. The between-group difference comparing baricitinib 4 mg with placebo was 33.6% (95% CI, 25.6% to 40.7%; P < 0.001) in the BRAVE-AA1 trial and 41.9% (95% CI, 34.0% to 48.7%; P < 0.001) in the BRAVE-AA2 trial. The 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 a 2-Point or Greater Improvement From Baseline Among Patients With ClinRO Measure for EB Hair Loss Score of 2 or Greater 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 with a ClinRO Measure for EB Hair Loss score of 0 or 1 with at least a 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 the BRAVE-AA1 trial and 7.1% (95% CI, −0.3% to 15.0%; P = 0.08) in the BRAVE-AA2 trial. In BRAVE-AA2, no formal testing was conducted for subsequent end points in the statistical hierarchy because of failure of this end point in the study. The between-group difference was in favour of baricitinib 4 mg over placebo in both trials (the BRAVE-AA1 trial, 28.2%; 95% CI, 20.3% to 35.4%; P < 0.001; the BRAVE-AA2 trial, 30.3%; 95% CI, 21.4% to 38.4%; P < 0.001). The results of the Patient-Reported Outcome (PRO) Measure were consistent.

Proportion of Patients Achieving ClinRO Measure for EL Hair Loss Score of 0 or 1 With a 2-Point or Greater Improvement From Baseline Among Patients With ClinRO Measure for EL Hair Loss Score of 2-Point or Greater 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 with a ClinRO Measure for EL Hair Loss score of 0 or 1 with at least a 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 the BRAVE-AA1 trial and 4.6% (95% CI, −3.7% to 13.2%) in the BRAVE-AA2 trial, both of which were not formally tested for statistical significance because of a prior failure of an outcome in the statistical hierarchy.

The between-group difference favoured baricitinib 4 mg treatment over placebo in both trials (the BRAVE-AA1 trial, 30.4%; 95% CI, 21.6% to 38.1%; P < 0.001; the BRAVE-AA2 trial, 28.7%; 95% CI, 18.7% to 37.5%; P < 0.001). The results of the PRO Measure were consistent.

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 the BRAVE-AA1 trial (−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 the BRAVE-AA2 trial. The between-group difference comparing baricitinib 4 mg and placebo favoured baricitinib 4 mg in both trials (the BRAVE-AA1 trial, −0.5; 95% CI, −1.1 to 0.0; P = 0.04; the BRAVE-AA2 trial, −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 the BRAVE-AA1 trial and −0.5 (95% CI, −1.1 to 0.1; P = 0.08) in the BRAVE-AA2 trial. The between-group difference comparing baricitinib 4 mg and placebo favoured baricitinib 4 mg in the BRAVE-AA2 trial (−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 the BRAVE-AA1 trial. 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 the BRAVE-AA1 trial ([redacted]) and [redacted]) in the BRAVE-AA2 trial. The difference between baricitinib 4 mg and placebo favoured baricitinib 4 mg in the BRAVE-AA2 trial was ([redacted]) and ([redacted]) in the BRAVE-AA1 trial. This was an exploratory end point in the BRAVE-AA1 trial and secondary end point in the BRAVE-AA2 trial. 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 for the Skindex-16 AA emotions domain score at week 36 was in favour of baricitinib over placebo in both trials for both the baricitinib 2 mg (BRAVE-AA1, [redacted]; BRAVE-AA2: [redacted]) and baricitinib 4 mg (the BRAVE-AA1 trial, [redacted]; the BRAVE-AA2 trial, [redacted]) regimens. This was an exploratory end point in the BRAVE-AA1 trial and secondary end point in the BRAVE-AA2 trial. 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 for the Skindex-16 AA Functioning domain score at week 36 was [redacted]) in the BRAVE-AA1 trial and [redacted]) in the BRAVE-AA2 trial. The difference between baricitinib 4 mg and placebo favoured baricitinib 4 mg in both trials (the BRAVE-AA1 trial, [redacted]; the BRAVE-AA2 trial, [redacted]).

This was an exploratory end point in the BRAVE-AA1 trial and secondary end point in the BRAVE-AA2 trial. It was not adjusted for multiplicity.

Harms Results

Treatment-Emergent AEs, SAEs, Withdrawal Due to AEs, and Mortality

Treatment-emergent AEs (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 group) were upper respiratory tract infection, headache, urinary tract infection, nasopharyngitis, acne, and increased blood creatine phosphokinase. SAEs (1.6% to 3.4%) and withdrawal due to AEs (1.1% to 2.6%) were uncommon in the studies. No deaths were reported in either trial.

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 the BRAVE-AA2 trial, the frequency of infection was higher in the baricitinib 2 mg group (37.4%) than the placebo group (29.2%), but this was not observed in the BRAVE-AA1 trial. In the BRAVE-AA1 trial, none of the infections were reported to be serious or lead to treatment discontinuation. In the BRAVE-AA2 trial, serious infection was reported in 2 patients (1.3%) and 1 patient (0.4%) in the baricitinib 2 mg and 4 mg groups, respectively, and infection leading to treatment discontinuation was reported in 1 patient (0.6%) in the baricitinib 2 mg group. Infection leading to treatment interruption was reported in [redacted] to [redacted] of patients across the trials.

In the BRAVE-AA1 trial, myocardial infarction and coronary revascularization was reported in 1 patient (0.5%) in the baricitinib 2 mg group. Serious arrhythmia was reported in 1 patient (0.5%) 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 nonmelanoma skin cancers in either trial. 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 the 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 judgment 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 I error (i.e., 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 to change from baseline in HADS and Skindex-16

AA domain scores given the differential discontinuation rate between the baricitinib and placebo groups (i.e., a higher proportion of dropouts in the placebo group) and the use of last observation carried forward or modified last observation carried forward 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 minimal important difference 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 was generally reflective of the patient population eligible for baricitinib treatment in Canada, although patients with a primarily diffuse type of AA would not necessarily be excluded from treatment in clinical practice. As well, older adults (i.e., males aged older than 60 years and females aged older than 70 years) 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, per clinical expert input, which could impact the generalizability of the 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 AEs, as 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 aged older than 60 years and females aged older than 70 years), 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 Group. Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from 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 at least a 2-point improvement from baseline, among patients with a baseline score of at least 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)	The BRAVE-AA1 trial: • 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) The BRAVE-AA2 trial: • 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 a 50% reduction in score from baseline) (95% CI) Follow-up: 36 weeks	685 (2 RCTs)	The BRAVE-AA1 trial: • 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] The BRAVE-AA2 trial: • 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	476 (2 RCTs)	The BRAVE-AA1 trial: • 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	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
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		per 1,000) The BRAVE-AA2 trial: • 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)		
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)	The BRAVE-AA1 trial: • 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] The BRAVE-AA2 trial: • 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)	The BRAVE-AA1 trial: • Baricitinib 2 mg: −1.2 (SE = 0.2) • Placebo: −0.4 (SE = 0.2) • Difference: −0.8 (−1.4 to −0.3)[b] The BRAVE-AA2 trial: • Baricitinib 2 mg: −0.7 (SE = 0.2)	Very low[g,h]	The evidence is very uncertain about the effect of baricitinib 2 mg on anxiety when compared with placebo.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		• Placebo: −0.5 (SE = 0.2) • Difference: −0.2 (−0.8 to 0.4)[b]		
HADS Depression score (0 [least depression] to 21 [highest depression]), change from baseline in score (95% CI) Follow-up: 36 weeks	580 (2 RCTs)	The BRAVE-AA1 trial: • Baricitinib 2 mg: −0.4 (SE = 0.2) • Placebo: 0.0 (SE = 0.2) • Difference: −0.4 (−0.9 to 0.1)[b] The BRAVE-AA2 trial: • Baricitinib 2 mg: −0.2 (SE = 0.2) • Placebo: 0.3 (SE = 0.2) • Difference: −0.5 (−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)	The BRAVE-AA1 trial: • Baricitinib 2 mg: [redacted] • Placebo: [redacted] • Difference: [redacted][b] The BRAVE-AA2 trial: • Baricitinib 2 mg: [redacted] • Placebo: [redacted] • Difference: −3.02 (−6.91 to 0.88)[b]	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.
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)	The BRAVE-AA1 trial: • Baricitinib 2 mg: [redacted] • Placebo: [redacted] • Difference: [redacted][b] The BRAVE-AA2 trial: • 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.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
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)	The BRAVE-AA1 trial: • Baricitinib 2 mg: [redacted] • Placebo: [redacted] • Difference: [redacted][b] The BRAVE-AA2 trial: • 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)	The BRAVE-AA1 trial: • Baricitinib 2 mg: 22 per 1,000 (NR) • Placebo: 16 per 1,000 (NR) • Difference: 6 more per 1,000 (NR)[b] The BRAVE-AA2 trial: • 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 Tool; $SALT_{50}$ = at least a 50% reduction in Severity of Alopecia Tool score from baseline; 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 following 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 the BRAVE-AA1 trial is 95 more per 1,000, this was not considered to be a source of serious imprecision because of its proximity to the threshold of 100 more per 1,000, per the clinical expert input.

[d]Rated down 1 level for serious study limitations. Randomization could potentially be impacted because of 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, per the clinical expert input. This is because of 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 because of 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 than the baricitinib 2 mg group in both trials. The differential discontinuation rate, along with the use of modified last observation carried forward or last observation carried forward as the data imputation method could potentially lead to attrition bias in favour of the baricitinib 2 mg group. In addition, evidence for the validity of this outcome measure in the patient population under review (i.e., patients with AA) 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, per the clinical expert input.

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

[j]There is no concern with imprecision using the null as a threshold. Although the upper boundary of the 95% CI is [redacted] and [redacted] in the BRAVE-AA1 and BRAVE-AA2 trials, respectively, this was not considered to be a source of serious imprecision because of 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, per the clinical expert input. Rated down 1 level for serious imprecision as the results were based on a small number of events across the trials.

Sources: 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)	The BRAVE-AA1 trial: • 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) The BRAVE-AA2 trial: • 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 a 50% reduction in score from baseline) (95% CI) Follow-up: 36 weeks	860 (2 RCTs)	The BRAVE-AA1 trial: • 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] The BRAVE-AA2 trial: • 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	585 (2 RCTs)	The BRAVE-AA1 trial: • 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	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
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		per 1,000) The BRAVE-AA2 trial: • 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)	The BRAVE-AA1 trial: • 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) The BRAVE-AA2 trial: • 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)	The BRAVE-AA1 trial: • Baricitinib 4 mg: −0.9 (SE = 0.2) • Placebo: −0.4 (SE = 0.2) • Difference: −0.5 (−1.1 to −0.0)[a] The BRAVE-AA2 trial: • Baricitinib 4 mg: −1.2 (SE = 0.2)	Very low[c,d]	The evidence is very uncertain about the effect of baricitinib 4 mg on anxiety when compared with placebo.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		• Placebo: −0.5 (SE = 0.2) • Difference: −0.7 (−1.3 to −0.2)[a]		
HADS Depression score (0 [least depression] to 21 [highest depression]), change from baseline in score (95% CI) Follow-up: 36 weeks	740 (2 RCTs)	The BRAVE-AA1 trial: • Baricitinib 4 mg: −0.3 (SE = 0.2) • Placebo: 0.0 (SE = 0.2) • Difference: −0.3 (−0.8 to 0.1) The BRAVE-AA2 trial: • Baricitinib 4 mg: −0.4 (SE = 0.2) • Placebo: 0.3 (SE = 0.2) • Difference: −0.7 (−1.2 to −0.2)[a]	Very low[c,d]	The evidence is very uncertain about the effect of baricitinib 4 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)	The BRAVE-AA1 trial: • Baricitinib 4 mg: [redacted] • Placebo: [redacted] • Difference: [redacted][a] The BRAVE-AA2 trial: • 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)	The BRAVE-AA1 trial: • Baricitinib 4 mg: [redacted] • Placebo: [redacted] • Difference: [redacted][a] The BRAVE-AA2 trial: • 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.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
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)	The BRAVE-AA1 trial: • Baricitinib 4 mg: [redacted] • Placebo: [redacted] • Difference: [redacted] The BRAVE-AA2 trial: • 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)	The BRAVE-AA1 trial: • Baricitinib 4 mg: 21 per 1,000 (NR) • Placebo: 16 per 1,000 (NR) • Difference: 6 more per 1,000 (NR)[a] The BRAVE-AA2 trial: • 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 Tool; $SALT_{50}$ = at least a 50% reduction in Severity of Alopecia Tool score from baseline; 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 following 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 because of 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 than the baricitinib 4 mg group in both trials. The differential discontinuation rate, along with the use of modified last observation carried forward or last observation carried forward as the data imputation method could potentially lead to attrition bias in favour of the baricitinib 4 mg group. In addition, evidence for the validity of this outcome measure in the patient population under review (i.e., patients with AA) 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, per the clinical expert input.

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

Sources: 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

The BRAVE-AA1 Trial

This study is a long-term extension (week 36 onward) 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 the product labelling of baricitinib.

At week 52, patients initially randomized to baricitinib whose disease responded to treatment (i.e., those with a SALT score of 20 or less) were rerandomized at a 3:1 ratio to stay on their current dose of baricitinib or transition to placebo (randomized withdrawal). Those whose disease responses to treatment who had been rerandomized to placebo and experienced a loss of treatment benefit at any time after week 52 (i.e., more than a 20 point worsening in SALT score from week 52) were retreated with their original baricitinib dose and the efficacy of re-treatment was analyzed as part of the other secondary end points of the BRAVE-AA1 study.

This extension study included week 0 to 52 and week 52 to 76 efficacy and safety for patients whose dose was titrated up at week 52. The uptitration cohort included [redacted] patients randomized to baricitinib 2 mg at week 0 who did not achieve a SALT score of 20 or less at week 52. All [redacted] patients had their dose titrated up to baricitinib 4 mg.

The BRAVE-AA2 Trial

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 labelling.

At week 52, patients were divided into 2 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 have their dose titrated down to baricitinib 2 mg. The uptitration cohort included [redacted] patients randomized to baricitinib 2 mg at week 0 who did not achieve a SALT score of 20 or less at week 52. All [redacted] patients were had their dose titrated up to baricitinib 4 mg.

Efficacy Results

Proportion of Patients Achieving a SALT Score of 20 or Less

In both trials, the proportion of patients achieving a SALT score of 20 or less 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 a SALT score of 20 or less in the BRAVE-AA1 study. Similarly, 36.8% and 24.4% of patients receiving baricitinib 4 mg and 2 mg, respectively, achieved a SALT score of 20 or less at week 52 in the BRAVE-AA2 trial.

The BRAVE-AA1 Trial Uptitration Cohort

At week 52, [redacted] patients who were originally randomized to baricitinib 2 mg were considered nonresponders and were eligible for inclusion in the uptitration cohort had their dose titrated up to baricitinib 4 mg. At week

76, following 24 weeks of treatment on baricitinib 4 mg, [redacted] in the uptitration cohort achieved a SALT score of 20 or less.

The BRAVE-AA2 Trial Randomized Downtitration Cohort

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 a SALT score 20 or less. [redacted].

Among patients receiving baricitinib 4 mg who achieved a SALT score of 20 or less at week 52, this response was retained up to week 76 in [redacted] of patients who had their dose titrated down to baricitinib 2 mg, and [redacted] of patients who remained on baricitinib 4 mg.

The BRAVE-AA2 Trial Uptitration Cohort

At week 52, 84 patients who were originally randomized to baricitinib 2 mg were considered nonresponders and were eligible for inclusion in the cohort which had their dose titrated up to baricitinib 4 mg. At week 76, after 24 weeks of uptitration treatment on baricitinib 4 mg, [redacted] achieved a SALT score of 20 or less.

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 a ClinRO Measure for EB Hair Loss score of 0 or 1 (with at least a 2-point improvement from baseline through week 52 among patients with a score of at least 2 at baseline) in the BRAVE-AA1 trial. Similarly, 49.7% and 16.3% of patients receiving baricitinib 4 mg and 2 mg, respectively, achieved a ClinRO Measure for EB Hair Loss score of 0 or 1 (with at least a 2-point improvement from baseline through week 52 among patients with a score of at least 2 at baseline) at week 52 in the BRAVE-AA2 trial.

At week 52, 40.7% and 21.6% of patients receiving baricitinib 4 mg and 2 mg, respectively, achieved a ClinRO Measure for EL Hair Loss score of 0 or 1 (with at least a 2-point improvement from baseline through week 52 among patients with a score of at least 2 at baseline) in the BRAVE-AA1 trial. Similarly, 50.7% and 30.3% of patients receiving baricitinib 4 mg and 2 mg, respectively, achieved ClinRO Measure for EL Hair Loss score of 0 or 1 (with at least a 2-point improvement from baseline through week 52 among patients with a score of at least 2 at baseline) at week 52 in the BRAVE-AA2 trial.

Harms Results

The BRAVE-AA1 Trial Uptitration Cohort

TEAEs were reported for [redacted].

The BRAVE-AA2 Trial Randomized Downtitration Cohort

For both treatment groups, [redacted].

The BRAVE-AA2 Trial Uptitration Cohort

TEAEs were reported for [redacted].

Critical Appraisal

Both the 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 because of 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 judgment 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, given that 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. As both the BRAVE-AA1 and BRAVE-AA2 trials 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. Furthermore, 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 because of discontinuation of the placebo in nonresponders. 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 had their dose titrated up or down). 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 before the regulatory approval of baricitinib for severe AA in Canada, the standard of care included off-label therapies and nonpharmacological 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 aged older than 60 years and females aged older than 70 years who 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 duration of 18.5 (SD = 11.9) months, a 72.0% reduction in the mean SALT score from baseline was observed. Moreover, 11 of 14 patients (SD = 78.6%) achieved a SALT score of 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 (a SALT score of 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 because of grade 2 neutropenia. No cases of venous thromboembolism, major adverse cardiac events, or malignancy were reported.

Numata et al. (2024)

Infectious complications occurred in 6 patients during the initial 12 weeks. Herpes simplex and COVID-19 (severe acute respiratory syndrome coronavirus 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, AEs were mild. Three patients were discontinued because of inadequate treatment response: 2 at week 52 and 1 at week 76. Additionally, 1 patient had temporary lymphopenia with methotrexate treatment.

Critical Appraisal

Limitations of the 3 studies included their retrospective designs and small sample sizes. Moreover, most 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. (2024) were not reported. Both Tang et al. (2024) and Numata et al. (2024) 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. (2024) included patients exclusively from Japan, whereas the study by Moreno-Vilchez et al. (2024) 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 patients in Canada, 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 to 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 a patient achieves an adequate response to treatment with 4 mg, the dose 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 $SALT_{50}$) 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 clinical practice in Canada. 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, patients treated with baricitinib continued treatment regardless of response at week 36. The clinical experts indicated that both clinician and patient assessments of clinically significant hair regrowth are expected to take precedence over the percentage improvement in SALT score. Alternatively, some clinicians may adopt the primary response outcome from the trials to determine treatment response and discontinuation (SALT ≤ 20; i.e., greater than or equal to 20% scalp

Component	Description
	hair coverage). • In the economic model, patients whose disease does not respond to no active treatment incur an annual costs of $2,382 for BSC drug acquisition, drug monitoring, and disease management for the duration of their lives, whereas patients whose disease does not respond to baricitinib do not incur these costs. All patients enrolled in the BRAVE-AA1 and BRAVE-AA2 trials were BSC experienced and the clinical experts agreed that the indicated population is likely to have prior experience with BSC therapies. Hence, if response is not achieved with baricitinib or no active treatment, patients who have exhausted all BSC therapy options would not receive further treatment in the "BSC" health state. In contrast, patients who do not respond to baricitinib or no active treatment and are naive 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 the BRAVE-AA1 and BRAVE-AA2 trials. 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 or 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; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year; SALT = Severity of Alopecia Tool; $SALT_{30}$ = at least a 30% improvement from baseline in the Severity of Alopecia Tool score; $SALT_{50}$ = at least a 50% improvement from baseline in the Severity of Alopecia Tool score; $SALT_{75}$ = at least a 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 best supportive care basket is highly uncertain.

CADTH conducted reanalyses of the budget impact analysis by adjusting the proportion of patients who 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 best supportive care 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 3-year budget 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 3-year budget 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

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