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## CADTH Reimbursement Recommendation

# Upadacitinib (Rinvoq)

**Indication:** For the treatment of adults with active ankylosing spondylitis who have had an inadequate response to a biologic disease-modifying antirheumatic drug or when use of those therapies is inadvisable. Upadacitinib may be used as monotherapy or in combination with nonsteroidal anti-inflammatory drugs.

**Sponsor:** AbbVie Corporation

**Final recommendation:** Reimburse with conditions

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

# Summary

## What Is the CADTH Reimbursement Recommendation for Rinvoq?

CADTH recommends that Rinvoq be reimbursed for the treatment of adults with active ankylosing spondylitis (AS) who have had an inadequate response to a biologic disease-modifying antirheumatic drug (bDMARD) or when use of those therapies is inadvisable only if certain conditions are met.

### Which Patients Are Eligible for Coverage?

Eligibility for Rinvoq should be based on the criteria used by each of the public drug plans for reimbursement of bDMARDs for the treatment of adult with active AS who have had an inadequate response to a bDMARD, are intolerant, or who have contraindications to bDMARDs.

### What Are the Conditions for Reimbursement?

Rinvoq should only be reimbursed if it is prescribed by a rheumatologist. For patients with other manifestations, an ophthalmologist, gastroenterologist, or dermatologist may be consulted. Rinvoq should not be reimbursed when used in combination with bDMARDs or other Janus kinase (JAK) inhibitor treatments for active AS. The cost of Rinvoq should not exceed the drug program cost of treatment with the least expensive bDMARD reimbursed for the treatment of AS.

### Why Did CADTH Make This Recommendation?

- Based on evidence from 2 clinical trials in which Rinvoq demonstrated clinically meaningful improvements in clinical response (e.g., Assessment in SpondyloArthritis international Society 40%), AS symptom reduction (e.g., total back pain), function and disability improvement (i.e., Bath Ankylosing Spondylitis Functional Index), and AS disease activity reduction (e.g., Bath Ankylosing Spondylitis Disease Activity Index 50) in adult patients with active AS. Rinvoq also demonstrated clinically meaningful improvements in health-related quality of life (i.e., Ankylosing Spondylitis Quality of Life) in Study 944 and MRI-detected axial inflammation in Study 098.
- Rinvoq addresses some of the unmet needs identified as important by patients, such as reducing AS symptoms, reducing disease activity, and improving health-related quality of life.
- Based on CADTH's assessment of the health economic evidence, Rinvoq does not represent good value to the health care system

# Summary

at the public list price. The committee determined there is not enough evidence to justify a greater cost for Rinvoq compared with bDMARDs.

- Based on public list prices, Rinvoq is estimated to cost the public drug plans approximately $6 million over the next 3 years.

## Additional Information

### What Is Ankylosing Spondylitis?

AS (also referred to as radiographic axial spondyloarthritis) is a chronic inflammatory disease primarily involving the spine and the sacroiliac joints. Patients with AS experience back pain and spinal stiffness that negatively affect their quality of life. In 2019, AS was estimated to affect 300,000 people in Canada. The goals of treatment for patients with AS are to maximize long-term health-related quality of life, control symptoms and inflammation, maintain spinal flexibility and normal posture, reduce functional limitations, maintain work ability, decrease disease complications, and prevent progressive structural damage.

### Unmet Needs in AS

Not all patients with AS respond to currently available treatments. Patients on AS medications experience various adverse effects with current therapies; report that medications become less effective more frequently, which requires a switch to another medication; and experience the persistence of constant spinal pain and active extra-articular manifestations. Finally, the lack of orally administrated treatment options affects compliance and adherence to the treatment plan.

### How Much Does Rinvoq Cost?

Treatment with Rinvoq is expected to cost approximately $17,965 per patient per year.

## Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that upadacitinib be reimbursed for the treatment of adults with active ankylosing spondylitis (AS) who have had an inadequate response to a biologic disease-modifying antirheumatic drug (bDMARD) or when use of those therapies is inadvisable only if the conditions listed in Table 1 are met.

## Rationale for the Recommendation

Two double-blind, randomized controlled trials (Study 944 [N = 420] for patients with AS who inadequately responded or were intolerant to 1 or 2 bDMARDs and Study 098 [N = 187] for patients with AS who inadequately responded or were intolerant to ≥ 2 nonsteroidal anti-inflammatory drugs [NSAIDs] but were bDMARD-naive) demonstrated that, compared with placebo, treatment with upadacitinib 15 mg orally once daily at 14 weeks was associated with statistically significant and clinically meaningful improvements in clinical response as measured by Assessment in SpondyloArthritis international Society 40% (ASAS 40). The difference between upadacitinib 15 mg and placebo groups in ASAS 40 response was 26.4% (95% confidence interval [CI], 17.9% to 34.9%) in Study 944 and 26.1% (95% CI, 12.6% to 39.5%) in Study 098. Treatment with upadacitinib 15 mg orally once daily at 14 weeks was also associated with statistically significant improvements for key secondary outcomes in both Study 944 and Study 098, including AS symptom reduction (e.g., total back pain), function and disability improvement (i.e., Bath Ankylosing Spondylitis Functional Index [BASFI] score), and AS disease activity reduction (e.g., Bath Ankylosing Spondylitis Disease Activity Index [BASDAI 50] score). In patients treated with upadacitinib, health-related quality of life (HRQoL) improved in Study 944, while MRI-detected axial inflammation improved in Study 098. Furthermore, the overall efficacy achieved at week 14 appeared to be maintained at 52 weeks [redacted] and week 104 (for Study 098). Adverse events (AEs) were aligned with the known safety profile of upadacitinib. No new safety signals were identified at weeks 14 and up to week 104. The evidence from 3 indirect treatment comparisons (ITCs) suggested that [redacted]

Based on the evidence reviewed, CDEC concluded that upadacitinib met some of the needs identified as important by patients, such as reducing AS symptoms, reducing disease activity, and improving HRQoL.

At the sponsor-submitted price for upadacitinib and publicly listed prices of all relevant comparators, upadacitinib was more costly than several relevant comparators used in the treatment of adults with active AS who have had an inadequate response to a bDMARD or when use of those therapies is inadvisable. Given the lack of direct comparative evidence and the findings from the ITCs suggesting upadacitinib was no more

effective than available bDMARDs, there is insufficient evidence to justify a cost premium over the least expensive bDMARD reimbursed for the treatment of active AS.

## Table 1: Reimbursement Conditions and Reasons

| Reimbursement condition | Reason | Implementation guidance |
|---|---|---|
| **Initiation** | | |
| 1. Eligibility for upadacitinib should be based on the criteria used by each of the public drug plans for reimbursement of bDMARDs for the treatment of adults with active AS who have had an inadequate response to a bDMARD, are intolerant, or who have contraindications to bDMARDs. | There is no direct evidence that upadacitinib is clinically superior or inferior to biologic treatments currently reimbursed for the treatment of active AS who have had an inadequate response to a bDMARD, are intolerant, or who have contraindications to bDMARDs. | — |
| **Renewal** | | |
| 2. Upadacitinib should be renewed in a similar manner to bDMARDs currently reimbursed for the treatment of adult patients with active AS who have had an inadequate response to a bDMARD, are intolerant, or who have contraindications to bDMARDs. | There is no evidence that upadacitinib should be held to a different standard than other reimbursed options when considering renewal in adult patients with active AS who have had an inadequate response to a bDMARD, are intolerant, or have contraindications to bDMARDs. | Upadacitinib should not be considered a first-line treatment option. |
| **Prescribing** | | |
| 3. Upadacitinib should be prescribed by a rheumatologist or clinicians who have experience treating adult patients with active AS. | Accurate diagnosis and follow-up of patients with active AS are important to ensure that upadacitinib is prescribed to the most appropriate patients. In addition, there are several bDMARD and tsDMARD treatment options that may be considered when selecting the most appropriate therapy for patients, which is best determined by a rheumatologist or clinician who is familiar with this complex treatment paradigm. | In some rural areas of Canada, patients may be followed by a general internist with special interest in rheumatology. |
| 4. Upadacitinib should not be reimbursed when used in combination with bDMARDs or other JAK inhibitor treatments for active AS. | No data were identified to demonstrate a benefit of upadacitinib in combination with bDMARDs. | — |
| **Pricing** | | |
| 5. Upadacitinib should be negotiated so that it does not exceed the drug program cost of treatment with the least costly bDMARD reimbursed for the treatment of AS. | There is insufficient evidence to justify a cost premium for upadacitinib over the least expensive bDMARD reimbursed for AS. | — |

AS = ankylosing spondylitis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; bDMARD = biologic disease-modifying antirheumatic drug; tsDMARD = targeted synthetic disease-modifying antirheumatic drug.

## Discussion Points

- CDEC acknowledged that patients with AS expressed a need for additional effective treatment options. The committee discussed upadacitinib's role in fulfilling such an unmet need. In Canada, numerous bDMARDs are available for treating AS including tumour necrosis factor (TNF) inhibitors and interleukin-17 (IL-17) inhibitors. Upadacitinib, a Janus kinase (JAK) inhibitor, is a new second-line option for the treatment of adults with active AS who have had an inadequate response to a bDMARD or when use of those therapies is inadvisable (i.e., intolerant or who have contraindications to bDMARDs).
- CDEC discussed which patients may be most appropriate for treatment with upadacitinib. Clinical experts indicated that if treatment with a TNF inhibitor or an IL-17 inhibitor does not result in adequate efficacy within 3 months or if their use is contraindicated, a JAK inhibitor should be an option. In patients already on a TNF inhibitor or an IL-17 inhibitor, a response would be expected within 3 to 6 months. Scenarios of patients for whom use of bDMARDs are inadvisable include patients who were intolerant to, or who have contraindications to, bDMARDs for AS.
- CDEC noted the variation in criteria for coverage of TNF and IL-17 inhibitors across Canada with current initiation of bDMARD therapies in most jurisdictions for AS requiring patients to have a BASDAI score of 4 or higher. Other factors are also considered in different jurisdictions, such as visual analogue scale (VAS); Health Assessment Questionnaire (HAQ) or ability to return to work HAQ, or other indicators of disease.

## Background

AS (also referred as radiographic axial spondyloarthritis) is a chronic inflammatory disease primarily involving the spine and the sacroiliac joints. Patients with AS exhibit radiographic abnormalities consistent with sacroiliitis. Patients experience back pain and progressive spinal stiffness and may also suffer from extra-articular manifestations, such as uveitis, skin psoriasis, and inflammatory bowel disease. The AS symptoms and the rate of progression fluctuate with time and can vary substantially between patients. AS negatively impacts patients' HRQoL. A diagnosis of AS can be made based on the clinical features, biological testing, and imaging examinations of the disease. The modified New York classification criteria for AS have often been used as a diagnostic instrument. A Canadian population-based study published by Haroon et al. showed that the prevalence of AS nearly tripled in Ontario from 1995 to 2010, with the 2010 estimate being 0.2%. In the same study, the annual incidence of AS remained relatively stable with a rate of 15 per 100,000 population. In 2019, AS was estimated to affect 300,000 people in Canada. The goals of treatment for patients with AS are to maximize long-term HRQoL, to control symptoms and inflammation, maintain spinal flexibility and normal posture, reduce functional limitations, maintain work ability, decrease disease complications, and prevent progressive structural damage. Several drug classes are used in the pharmacologic therapy of AS.NSAIDs, including nonselective and selective cyclooxygenase-2 inhibitors, are the first choice of treatment for adult patients with active AS. Should NSAIDs fail or if there are contraindications, the next line of treatment is bDMARDs, including TNF inhibitors and IL-17 inhibitors or JAK

inhibitors. Current practice is to start a TNF inhibitor or IL-17 inhibitor. TNF inhibitors marketed in Canada for treatment of AS include adalimumab, certolizumab, etanercept, golimumab, and infliximab. IL-17 inhibitors marketed in Canada for the treatment of AS include ixekizumab and secukinumab.

Upadacitinib has been approved by Health Canada for the treatment of adults with active AS who have had an inadequate response to a bDMARD or when use of those therapies is inadvisable. Upadacitinib may be used as monotherapy or in combination with NSAIDs. Upadacitinib is an oral, selective JAK inhibitor. JAK inhibitors are also classified as targeted synthetic DMARDs (tsDMARDs). It is available as 15 mg and 30 mg extended-release oral tablets. The recommended dose regimen in patients with AS is 15 mg, orally, once daily.

## Sources of Information Used by the Committee

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

- a review of 2 randomized, double-blind, placebo-controlled clinical trials (i.e., Study 944 and Study 098); Study 944 (i.e., Study 1 of Study M19-944; N = 420) was a phase III trial in adult patients with active AS who were bDMARD-inadequate response or intolerant and Study 098 (N = 187) was a phase II/III trial in adult patients with active AS, who had an inadequate response to or intolerance of 2 or more NSAIDS but were bDMARD-naive
- patients' perspectives gathered by patient groups, including the Arthritis Consumer Experts (ACE) and a joint submission from the Canadian Arthritis Patient Alliance (CAPA), Arthritis Society Canada, Canadian Spondylitis Association (CSA), and Creaky Joints Canada
- input from public drug plans that participate in the CADTH review process
- 1 clinical specialist with expertise diagnosing and treating patients with AS
- input from 1 clinician group, the Canadian Rheumatology Association (CRA)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

## Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from the clinical expert consulted by CADTH for the purpose of this review.

### Patient Input

Two responses to CADTH's call for patient input for this review were received from ACE and through a joint submission from CAPA, Arthritis Society Canada, CSA, and Creaky Joints Canada. All these groups serve individuals living with arthritis, including AS, and their caregivers, health care providers, and community members.

Patient perspectives from the joint input were obtained from a survey shared via email, social media, and the 4 organizations' websites from October 12, 2022, to October 30, 2022. Patient perspectives from the ACE input were obtained from an ACE Survey Monkey platform.

Of the total of 264 joint survey participants living with AS, 9 patients had direct experience with upadacitinib. Almost 90% of the survey respondents indicated they live with back pain while 72% have back pain, 86% have joint stiffness, and 51% experience sore heels and feet. Patient respondents also had other symptoms of AS, such as anxiety and depression (52%), bowel inflammation (49%), psoriasis (35%), migraine (32%), uveitis (31%), osteoporosis (23%), and heart problems (11%). Most survey participants rated their disease severity as 59 out of 100. In addition, patients indicated they had trouble managing symptoms, including fatigue, difficulty concentrating, stress, mobility issues, and loss of appetite. Similarly, patient respondents from the ACE patient input indicated that they suffer from fatigue, mobility issues, weight gain, and constant pain, indicating that the disease affects their quality of life, their daily activities, and their mood. In addition, caregivers of patient respondents from the ACE input stated that the disease also impacted their quality of life because they must pay attention to their time management; when patients are in pain, caregivers have to help with house chores and many other aspects of life at home.

The joint patient input stated that during an AS flare (a period of worsening symptoms), patients may have difficulties performing day-to-day activities. Patient respondents with AS reported that the disease severely affects all aspects of their lives, from their physical and mental health to their family life, self-esteem, work, intimacy, and participation in social and leisure activities.

According to the joint patient input, many treatments are available to manage AS, including NSAIDs, corticosteroids, conventional synthetic DMARDs, and bDMARDs. The joint patient input stated that the effectiveness and tolerance of these treatments vary significantly between patients, with more than 40% of 264 patient respondents indicating that they had an inadequate response to currently available treatments. The joint patient input indicated that some patients had to change their medication after a short period of time; others did not respond adequately to the currently available treatments. In addition, the joint patient input indicated that side effects of current AS medications were another major concern for people living with AS. Fatigue, nausea and vomiting, increased risk of infections, liver toxicity, and weight gain affect patients' adherence to medication and their daily activities.

According to the patient respondents from the ACE patient input, currently available treatments are good in managing their disease symptoms. However, concerns were raised regarding the cost of the medications, side effects, and changing medications due to decreased effectiveness within a short period of time.

The joint patient input highlighted that other treatment options, such as medical cannabis and/or nonpharmacological approaches to managing AS symptoms, are challenging to access because they are not reimbursed, not offered, or because these options require lengthy waits. According to the joint patient input, many factors need to be considered by health care providers to determine the most effective treatment, such as side effects, mode of administration, time required for treatment, travel, patient preferences, and cost.

Nine respondents from the joint input reported having experience with upadacitinib. Positive aspects of treatment with upadacitinib reported by patient respondents included the simple route of administration, improved disease symptoms, mobility, and better quality of life with more energy. Few patient respondents experienced more frequent infections and headaches from treatment with upadacitinib.

Patient respondents from the joint patient input stated that managing AS can be improved by having access to affordable treatments that have a simple administration route (e.g., pills), fewer adverse effects and infection rates, and are also able to reduce disease-related symptoms, improve their quality of life, and enable them to pursue their daily activities. The ACE patient input highlighted that patient respondents value additional treatment options with fewer AEs and improved pain control and remission rates.

## Clinician Input

The clinical experts consulted by CADTH for this review indicated that not all patients respond to available treatments. The ASAS40 is a common primary end point in clinical trials, which corresponds to a 40% improvement in 3 of 4 domains (patient global, total back pain, BASFI, and morning stiffness), with an absolute improvement of at least 2 domains and no worsening of the remaining domain. Approximately 40% of patients are able to achieve this response in clinical trials. More stringent measures of response, such as ASAS partial remission or Ankylosing Spondylitis Disease Activity Score (ASDAS) inactive disease, are much lower. Approximately 10% of patients with AS also have inflammatory bowel disease (IBD). Although TNF inhibitors can be effective to treat both, many patients with severe IBD do not respond to TNF inhibitors even at a very high dose (infliximab10 mg/kg every 4 weeks), initially respond but lose efficacy, or have to stop due to side effects (i.e., drug-induced psoriasis, lupus, or multiple sclerosis). IL-17 inhibitors would be contraindicated in these patients which does not leave many further options available to patients. For approximately half of patients, the efficacy of their first biologic is lost within 3 to 5 years. When patients inadequately respond to treatment with a biologic, clinicians often consider switching to a different mechanism of action if there is inadequate efficacy. If they have a secondary loss of effect, clinicians can consider switching within a class. Additionally, some patients may have a contraindication to available therapies. With TNF inhibitors, clinicians are cautious in patients with a personal or family history of multiple sclerosis, lupus, or drug-induced psoriasis. With IL-17 inhibitors, clinicians would try to avoid these agents in patients with a history of IBD. Finally, there are no oral bDMARD options available, and many patients are younger, or have an aversion to needles.

The clinical experts consulted by CADTH for this review indicated that treatment data from the upadacitinib trials in axial spondyloarthritis show treatment response rates that seem comparable to biologic agents, such as TNF and IL-17 inhibitors. JAK inhibitors do not seem to work through a TNF or IL-17 pathway so having an alternative mechanism of action would be ideal for these patients. Upadacitinib has been shown to reduce objective markers of inflammation such as C-reactive protein (CRP) and bone marrow edema in the sacroiliac joints and spine on MRI. Bone marrow edema has been shown to be a strong predictor of future syndesmophyte formation. If a patient requires an escalation in therapy, clinicians will decide whether a TNF, IL17, or JAK inhibitor would be the most appropriate and initiate therapy. Currently, the approved Health Canada label is to use these agents if a previous biologic has failed or if biologics are unsuitable; most

rheumatologists were disappointed with that decision and were hoping to use this drug as a first-line DMARD drug in the appropriate patient. Upadacitinib was recently shown to be effective for non-radiographic axial spondyloarthritis with a sufficient sample size; therefore, the expectation is that the sponsor will want Health Canada approval for use as a first-line drug for this indication. The drug under review would provide further options to treat patients either due to contraindications to TNF and IL-17 inhibitors, previous failures to these drugs, convenience to patients by giving them an oral option, and efficacy in patients with both IBD and axial spondyloarthritis. Patients should try 2 NSAIDs for 2 to 4 weeks first unless there is a contraindication. If they still have high disease activity, DMARDs are expected to be a first-line option available to patients along with a TNF and IL-17 inhibitor. With the current Health Canada indication as a second-line drug, upadacitinib could be used if patients have previously failed a biologic or have a contraindication. Because upadacitinib has been approved to treat rheumatoid arthritis, most rheumatologists are comfortable with using it as a first-line biologic drug from a safety perspective.

The clinical experts consulted by CADTH for this review indicated that any patient with active AS would likely benefit from treatment with upadacitinib. Patients who also have active IBD prefer an oral option; and patients who had treatment with a TNF/ or IL-17 inhibitor that has failed or who have a contraindication to a TNF or IL-17 inhibitor may also benefit. Patients with high disease activity are in most need of an intervention. Elevated CRP levels and bone marrow edema on MRI may predict a higher response, but many patients with neither of these will also respond very well. The diagnosis of AS involves characteristic clinical findings in conjunction with identifying sacroiliitis in a pelvic X-ray. There can be considerable inter-reader reliability issues, especially with early disease. Many rheumatologists typically confirm a diagnosis with a sacroiliac joint MRI before proceeding with a bDMARD. The probability of under- or over-diagnosis is largely related to the experience of the clinician. Most cases are quite straightforward; convincing imaging, clinical features, and possibly a positive HLA-B27 can help the rheumatologist make the correct diagnosis. Additionally, the experience of the radiologist reading the X-ray, CT, or MRI is also important. Predictors of treatment response would be early onset of symptoms, male sex, CRP elevation, and the degree of bone marrow edema seen on MRI.

The clinical experts consulted by CADTH for this review indicated that clinicians typically follow up with a patient after 3 months of therapy. If there is absolutely no response, clinicians would consider switching to a different drug. If there is partial response, clinicians may wait up to 6 months to determine benefit. In daily practice, treatment response is measured by improvement in BASDAI or ASDAS. Typically, for BASDAI score, a decrease by at least 2 units or a 50% reduction from baseline score is a reasonable response. Clinicians would see patients every 3 to 6 months to ensure stability of their disease. In clinical trials, clinicians want to see an ASAS response of approximately 40% and statistically significant improvement in other measures, such as ASDAS change from baseline, CRP levels, MRI, ASAS Health Index, Ankylosing Spondylitis Quality of Life (ASQoL), and BASFI. The clinical experts consulted by CADTH for this review indicated that clinicians would discontinue the medication if patients developed side effects such as infections. If a patient's symptoms were to recur, clinicians may consider switching to another medication if they were convinced that this was due to active disease The clinical experts consulted by CADTH for this review indicated a rheumatologist would be needed to confirm a diagnosis, treat, and monitor patients with AS. If there are

other manifestations involved, they may also be followed by an ophthalmologist, gastroenterologist, and/or dermatologist.

### Clinician Group Input

CRA provided the clinical group input. Two clinicians, who are members of the Spondyloarthritis Research Consortium of Canada (SPARCC) executive committee and were involved in the 2014 CRA/SPARCC treatment recommendations, contributed to these submissions.

The clinician group indicated that there is an unmet need for the treatment of patients with AS for the following reasons: not all patients respond to currently available treatments; medications become less effective more frequently, which requires a switch to another medication; various adverse effects of the current therapies; persistence of constant spinal pain; and active extraarticular manifestations are common. There is also a lack of orally administered options, which affects compliance and adherence to the treatment plan.

The views of the clinician group were overall consistent with those of the clinical experts consulted by CADTH. The clinician group indicated that the most essential treatment goals are reducing pain and improving function.

The group advocated for NSAIDs as first-line pharmacologic therapy for AS and a biologic (TNF inhibitor or IL-17 inhibitor) as first-line biologic therapies when NSAIDs are insufficient. Other classes of biologic treatments, such as targeted synthetic DMARD (JAK inhibitor), could be used if initial treatments fail.

Clinician input suggested that patients would benefit more from upadacitinib, a selective JAK inhibitor for axial spondyloarthritis, given its unique mechanism of action and oral administration, which are considered ideal options for many patients, especially those who have failed treatment with continuous NSAIDs and continue to have high measures of disease activity. However, people with severe active infections, either acute or chronic, and people with severe hepatic disorders might not be suitable for upadacitinib use.

## Drug Program Input

The drug programs provide input on each drug reviewed through CADTH's Reimbursement Review processes by identifying issues that may affect their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in Table 2.

## Table 2: Responses to Questions From the Drug Programs

| Drug program implementation questions | Clinical expert response |
|---|---|
| **Relevant comparators** | |
| The clinical trials were multicentre, randomized, double blind, and placebo controlled. Is placebo an appropriate comparator given the number of treatment options available?<br>There are a variety of treatment options available, and if | The clinical expert stated the importance of demonstrating efficacy compared with placebo, although including an active comparator (e.g., adalimumab) would have been helpful. The treatment response rates were what would be expected with either a TNF or IL-17 inhibitor. CDEC acknowledged that an active comparator would |

| Drug program implementation questions | Clinical expert response |
|---|---|
| there is failure with 1 bDMARD, patients would likely be able to trial 1 with an alternate mechanism of action. | have more helpful than placebo due to the uncertainty with the comparative efficacy from the submitted ITCs. |
| The criteria for access to bDMARDs for treatment of AS varies greatly across jurisdictions.<br>TNF inhibitors and IL-17 inhibitors are the classes of currently available bDMARDs available for treatment of AS.<br>Secukinumab (Cosentyx) was reviewed by CDEC for the indication of AS in 2016, and successfully completed pCPA negotiations and therefore is a benefit in most jurisdictions.<br>Ixekizumab (Taltz) was reviewed by CDEC for the indication of AS in 2020 and given a positive recommendation with criteria/conditions, 1 condition being a reduction in price.<br>pCPA negotiations for ixekizumab for AS concluded without an agreement. | Comment from the drug programs to inform CDEC deliberations. |
| **Considerations for initiation of therapy** | |
| There is significant variation in criteria for coverage of secukinumab (Cosentyx) and TNF inhibitors across Canada.<br>Current initiation of bDMARD therapies in most jurisdictions for AS require patients to have a score of ≥ 4 on the BASDAI.<br>A number of other factors are also considered in different jurisdictions, such as visual analogue scale, HAQ, or ability to return to work HAQ, or other indicators of disease.<br>Renewal of coverage of bDMARDs in most jurisdictions requires at least a 50% reduction from baseline BASDAI or a reduction by ≥ 2 units to demonstrate response to therapy.<br>Generally, it is noted that these improvements in scores must be maintained for continuation of coverage. | Comment from the drug programs to inform CDEC deliberations. |
| The indication for upadacitinib for AS is for patients who have had inadequate response to bDMARDs or for whom use of those therapies is inadvisable.<br>Is it possible to define for which patients bDMARDs are inadvisable?<br>Drug plans may receive requests for upadacitinib in situations in which bDMARDs are inadvisable. If these patients have inadequate response or intolerance to upadacitinib, they may then want access to bDMARDs. | CDEC heard from the clinical expert that patients must be comfortable with therapy and that the absolute serious infection risk is quite small with bDMARDs; however, a patient must be comfortable with that risk.<br>Circumstances in which 1 drug would be preferrable might include:<br>• pregnancy or lactation: TNF inhibitor<br>• active malignancy: IL-17 inhibitor<br>• active IBD: TNFi or JAK inhibitor<br>• previous CVD: TNFi or IL-17 inhibitors<br>• CHF: IL-17 inhibitor<br>• severe psoriasis: IL-17 inhibitor<br>• paradoxical psoriasis: IL-17 or JAK inhibitors<br>• recurrent or severe uveitis: TNF inhibitor |

| Drug program implementation questions | Clinical expert response |
|---|---|
| | • preference for oral option: JAK inhibitor<br>• personal or family history of multiple sclerosis: IL-17 inhibitor and possibly JAK inhibitor |
| The indication places upadacitinib as either third- or fourth-line therapy, behind NSAIDs and/or DMARDs, and bDMARDs<br>Currently, to access bDMARDs for treatment of AS, patients must fail NSAIDs at maximally tolerated dosages. Many NSAIDs are available OTC.<br>Some jurisdictions also require a trial of conventional DMARDs to meet criteria for bDMARDs.<br>There is variability across jurisdictions. | Comment from the drug programs to inform CDEC deliberations. |
| Is there evidence to suggest Rinvoq is efficacious in patients who have failed TNF inhibitors or IL-17 inhibitors or both? What is the optimal sequencing of these products? | The clinical expert stated that the SELECT-AXIS 2 trial (Study 944) showed impressive efficacy in patients who inadequately responded to either TNF or IL-17 inhibitors. The trial did not include patients who had failed both TNF and IL-17 inhibitors. If axial symptoms are the only issue, there is no optimal sequencing. |
| Are patients with axial disease treated similarly to those with peripheral disease? | The clinical expert noted that peripheral disease may respond to cortisone injections or csDMARDs, such as methotrexate, sulfasalazine, or leflunomide. If these are ineffective (typically a 3-month trial of 2 csDMARDs is recommended), a biologic would be a reasonable option. |
| Is there a need to progress to more advance treatments sooner in patients with axial disease? | The clinical expert noted some patients with axial spondyloarthritis have very severe and debilitating disease. In these patients, the clinical expert would try to escalate sooner to help maintain the patient's function. In the INFAST trial, approximately 30% of patients with AS and activity on MRI were able to achieve remission with naproxen alone. RCTs have shown no benefit with axial disease using csDMARDs, such as methotrexate, sulfasalazine, or leflunomide. |
| Do patients with peripheral disease respond to treatment similarly to those with axial disease? | The clinical expert noted that peripheral and axial disease tend to respond quite well to bDMARD treatment although approximately 40% of patients are able to achieve an ACR50 (approximately 50% improvement in peripheral joint disease) in the psoriatic arthritis trials. Psoriatic arthritis is considered to be within the spectrum of spondyloarthritis. |
| **Consistency with initiation criteria associated with other drugs reviewed by CADTH in the same therapeutic space** | |
| How should failure of bDMARD be defined for the purpose of reimbursement?<br>(It would be helpful if this was consistent with the current listing criteria for bDMARDs relating to BASDAI.) | The clinical expert believes the clinician should be allowed to decide when a JAK inhibitor might be most appropriate. If treatment with TNF or IL-17 inhibitors does not result in adequate efficacy within 3 months, or if their use is not advisable, a JAK inhibitor should be an option.<br>In patients already on a TNF or IL-17 inhibitor, we would expect some response within 3 months and definitely by 6 months. |
| Is a washout period required when stopping a bDMARD and initiating Rinvoq? | The clinical expert noted that there is not much data regarding the need for a washout period; the clinical expert stated they never used a washout period when using a TNF, IL-17, or JAK inhibitor. |

| Drug program implementation questions | Clinical expert response |
|---|---|
| If a patient has had a partial response to a bDMARD and moves onto Rinvoq, how should further response to Rinvoq be assessed? Clinical trials assessed ASAS 40. | The clinical expert confirmed that the BASDAI would be measured in clinical practice. A standard expected treatment response would be an improvement by 2 or a 50% reduction from baseline BASDAI score. ASDAS could be used; however, this requires a calculator to determine and clinicians often do not have a point-of-care CRP testing available. Most trials use an ASAS 40, but this is not something clinicians would use in clinical practice (similar to the way ACR50 is not measured regularly in patients with RA except in clinical trials). |
| If the patient had demonstrated partial response to a bDMARD before upadacitinib, their disease activity scores may be lower at baseline than those who had not been treated with a bDMARD. How should response to therapy with upadacitinib be assessed in these patients, and what is an appropriate response for continued reimbursement? | CDEC heard from the clinical expert that switching would depend on the reason: If patients had a side effect or another extramusculoskeletal manifestation, such as IBD, clinicians would just want to see stability in their scores.<br>If patients are changing due to lack of efficacy, measuring by an improvement in BASDAI by 2 or 50% improvement compared with baseline would still work. Usually, clinicians would not consider switching unless the BASDAI score was at least 4. |
| What measure of response should be used with patients with peripheral disease? | The clinical expert stated to CDEC that improvement in the swollen joint count, tenosynovitis, or enthesitis should be captured. |
| **Considerations for continuation or renewal of therapy** | |
| Current criteria for bDMARDs varies across jurisdictions with respect to assessment of response.<br>Some measures that are used are:<br>• BASDAI – reduction of 50% or 2 points (most consistent)<br>• VAS<br>• HAQ or ability to return to work HAQ.<br>• symptoms<br>• reductions in pain medications.<br>In the SELECT-AXIS 1 and SELECT-AXIS 2 trials, the primary end point was examined at week 14 and week 52. The primary outcome measure was ASAS 40.<br>(TNF inhibitors are assessed for initial response after 12 weeks, and IL-17 inhibitors after 16 weeks.)<br>The clinical trials for Taltz looked at the ASAS 40 response at 16 weeks.<br>Clinical trials considered during the Cosentyx reimbursement review looked at the ASAS 20 response at week 16 as the primary outcome.<br>How do ASAS 40 and ASAS 20 relate to the BASDAI score? | The clinical expert responded to CDEC that the ASAS 20 and 40 responses reflect a change (i.e., approximately 20% or 40% improvement), whereas the BASDAI is a state (i.e., 4 out of 10 for pain). ASAS scores are common primary or secondary end points in clinical trials but are not used in clinical practice in the same way clinicians often use ACR20 or 50 as end points for RA but never calculate it in clinical practice. |
| What is the appropriate outcome measure for response in AS? | The clinical expert noted that the most common would be BASDAI 50% improvement or 2 point absolute decrease . Another option would be ASDAS decrease by 1.1. ASDAS is not as commonly used because you need an app to calculate it as well as a same-day CRP test. The expert noted that the CRA treatment recommendations are |

| Drug program implementation questions | Clinical expert response |
|---|---|
| | currently being drafted and these suggest BASDAI because it is the most common one in clinical use. |
| There is variation in renewal criteria across the country (refer to previous comments). | CDEC discussed this input from public drug plans and agreed that renewal criteria should be consistent, with bDMARDs currently reimbursed for the treatment of adult patients with active AS who have had an inadequate response to a bDMARD, are intolerant, or who have contraindications to bDMARDs. |
| **Considerations for prescribing of therapy** | |
| 15 mg extended-release oral tablet, administered once daily, with or without food. | Comment from the drug programs to inform CDEC deliberations. |
| Rinvoq will be the first oral targeted DMARD treatment for the treatment of AS. | Comment from the drug programs to inform CDEC deliberations. |
| Access to rheumatologists may be limited in some jurisdictions. Some jurisdictions allow internists to prescribe in their criteria.<br>Time frames for assessment of response for the bDMARDs vary from 12 (TNF inhibitors) to 16 weeks (Cosentyx) | Comment from the drug programs to inform CDEC deliberations. |
| Can CDEC provide a comment on the potential for combination use of Rinvoq with:<br>• bDMARDs<br>• conventional DMARDs? | CDEC heard from the clinical expert about the publication of a case series on the use of tofacitinib with either an IL-17 or -23 inhibitor for treatment of severe refractory psoriatic arthritis and that these patients still have very active disease despite having failed multiple biologics often at supertherapeutic doses. The clinical expert confirmed there are no data on the use of upadacitinib in combination with bDMARDs in which many clinicians may also consider combining upadacitinib with vedolizumab if there is severe bowel disease in conjunction with joint disease.<br>The clinical expert added that methotrexate may be added if there is ongoing peripheral arthritis, psoriasis, or uveitis because there are plenty of data on the safety of this combination from the rheumatoid arthritis trials since that is a common combination in that condition. |
| The indication places Rinvoq after bDMARDs; therefore, it may be difficult to have alignment within the criteria. | Comment from the drug programs to inform CDEC deliberations. |
| **Generalizability** | |
| Were patients with peripheral disease adequately represented in clinical trials? | CDEC heard from the clinical expert that most clinical trials for AS do not have many patients with peripheral arthritis. Clinicians typically extrapolate from the psoriatic arthritis trials because it is believed there is a strong overlap of these 2 diseases, and they likely represent manifestations of the spectrum of the same condition (or a highly similar condition). This is still a matter of debate in the spondyloarthritis community at large. |
| SELECT-AXIS 1 included a population of bDMARD-naive adults who had an inadequate response to NSAIDs.<br>This population is not consistent with the reimbursement request but may be of interest to clinicians and patients.<br>Upadacitinib has also been studied in IBD, and there may | Comment from the drug programs to inform CDEC deliberations. |

| Drug program implementation questions | Clinical expert response |
|---|---|
| be interest in upadacitinib in patients with concurrent IBD and AS because there is frequent overlap in the 2 conditions. The CDEC review for upadacitinib for UC has been placed on hold pending NOC for this indication. A positive recommendation and listing of upadacitinib for AS may mean patients with UC and AS may be able to access therapy with upadacitinib, whereas patients with UC alone will not be able to access therapy with upadacitinib. | |
| **Care provision issues** | |
| **Management of adverse effects**<br>On October 31, 2022, Health Canada issued a Professional Risk Communication regarding the risk of major adverse cardiovascular events, thrombosis (including fatal events), and malignancy associated with JAK inhibitors (Cibinqo, Inrebic, Jakavi, Olumiant, and Rinvoq). | **Sponsor's comment:** Health Canada initiated a safety review in light of the emerging safety findings of tofacitinib (in ORAL Surveillance) and baricitinib, specifically related to major adverse cardiovascular events, venous thrombotic events, malignancies, and all-cause mortality. The safety review aimed to determine whether risks are associated with all JAK inhibitors authorized in Canada (upadacitinib, baricitinib, tofacitinib, abrocitinib, fedratinib, and ruxolitinib) and whether regulatory action is warranted. During this review, Health Canada did not find any new information on these identified risks specifically for upadacitinib, and this safety review was not based on any new safety data for upadacitinib. There were no changes to the approved indications of Rinvoq following this review. |
| **System and economic issues** | |
| JAK inhibitors such as Rinvoq have the potential for generics in the future. | Comment from the drug programs to inform CDEC deliberations. |
| There are several biosimilar TNF inhibitors available for the treatment of AS.<br>• Cosentyx has successfully completed pCPA negotiations for AS. Biosimilars are on the horizon, but there is no availability date at this time.<br>• Taltz for AS did not complete successful pCPA negotiations.<br>• Rinvoq has completed successful pCPA negotiations for psoriatic arthritis and rheumatoid arthritis.<br>• For Rinvoq for RA and psoriatic arthritis: CDEC recommended a price point that drug plan cost should not exceed that of treatment with least costly bDMARD or tsDMARD reimbursed for these conditions.<br>• Rinvoq is currently under consideration for negotiation at pCPA for atopic dermatitis. | Comment from the drug programs to inform CDEC deliberations. |
| An oral therapy may provide greater access to treatment for patients with AS. | Comment from the drug programs to inform CDEC deliberations. |

AS = ankylosing spondylitis; ASAS = Assessment of Spondyloarthritis International Society; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; bDMARD = biologic disease-modifying antirheumatic drug; CDEC = CADTH Canadian Drug Expert Committee; CRP = C-reactive protein; IBD = inflammatory bowel disease; HAQ = Health Assessment Questionnaire; IL-17 = interleukin-17; JAK = Janus kinase; NOC = Notice of Compliance; NSAID = nonsteroidal anti-inflammatory drug; OTC = over the counter; pCPA = pan-Canadian Pharmaceutical Alliance; QALY = quality-adjusted life-year; RA = rheumatoid arthritis; TNF = tumour necrosis factor; tsDMARD = targeted synthetic disease-modifying antirheumatic drug; UC = ulcerative colitis.

# Clinical Evidence

## Pivotal Studies and Protocol-Selected Studies

### Description of Studies

Two manufacturer-sponsored, double-blind, randomized controlled trials (14 weeks), Study 944 (N = 420) and Study 098 (N = 187), are included in this review. The 2 trials evaluated the efficacy and safety of upadacitinib 15 mg orally once daily compared with placebo in patients with active AS. Study 944 was conducted in patients with AS who inadequately responded or were intolerant to 1 or 2 bDMARDs. Study 098 was conducted in patients with AS who inadequately responded or were intolerant to at least 2 NSAIDs but bDMARD-naive. The primary outcome in both trials was the proportion of patients meeting the ASAS 40 response criteria at week 14. The key secondary outcomes (multiplicity controlled) included change from baseline in ASDAS; change from baseline in MRI SPARCC (spine) score; BASDAI 50 response; ASAS 20 response; ASDAS inactive disease (ASDAS < 1.3); change from baseline in patient's assessment of total back pain (total back pain); change from baseline in patient's assessment of nocturnal back pain (nocturnal back pain); ASDAS low disease activity (ASDAS < 2.1); change from baseline in BASFI score; ASAS partial remission; change from baseline in ASQoL score; change from baseline in ASAS Health Index score; change from baseline in linear Bath Ankylosing Spondylitis Metrology Index (BASMIlin) score; and change from baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES).

Both Study 944 and Study 098 included 4 periods: screen period, double-blinded treatment period (for 14 weeks), extended treatment period (up to week 104), and posttreatment follow-up period (30 days after last visit). Both Study 944 and Study 098 were conducted in multiple countries, including Canada, the US, Europe, Australia, New Zealand, and Asian countries. Study 944 also included Mexico and countries from South America. Results of an extension phase at week 52 of both studies (Study 944 and Study 098) as well as week 104 for Study 098 are also presented in this report. Study 944 is still ongoing. The long-term efficacy and safety outcome at week 104 in Study 944 is not available at the time of this review. Study 098 was complete.

### Efficacy Results

**Clinical response (e.g., ASAS 40) at week 14:** In Study 944, The proportion of patients who achieved ASAS 40 was reported as 44.5% and 18.2% in the upadacitinib 15 mg, orally, once daily (upadacitinib) group and the placebo group, respectively. The mean between-group difference (upadacitinib – placebo) was 26.4% (95% CI, 17.9% to 34.9%; P < 0.0001). In Study 098, the proportion of patients who achieved ASAS 40 was reported as 51.6% and 25.5% in the upadacitinib and placebo groups, respectively. The mean between-group difference (upadacitinib – placebo) was 26.1% (95% CI, 12.6% to 39.5%; P < 0.001). According to the clinical expert CADTH consulted for this review, ASAS 20 at week 12 has been considered an acceptable clinical response for bDMARDs trials in AS. Therefore, ASAS 40 at week 14 represents a more substantial clinical improvement, and more recent trials have used this as the primary end point.

**Measures of AS symptoms (e.g., total back pain) at week 14:** In Study 944, the mean changes from baseline for total back pain were −3.00 points (95% CI, −3.30 to −2.70) and −1.47 (95% CI, −1.77 to −1.16) in the

upadacitinib and placebo groups, respectively. The mean between-group difference for change from baseline (upadacitinib – placebo) was −1.53 (95% CI, −1.96 to −1.11; P < 0.0001). In Study 098, the mean (95% CI) of changes from baseline for total back pain were −3.21 [redacted] and −1.68 [redacted] in the upadacitinib and placebo groups, respectively. The mean between-group difference for change from baseline (upadacitinib – placebo) was −1.53 (95% CI, −2.19 to −0.87; P < 0.001). The improvement of total back pain may be considered clinical meaningful (or useful) in both studies.

**Function and disability (i.e., BASFI) at week 14:** In Study 944, the mean changes from baseline for BASFI were −2.26 (95% CI, −2.53 to −2.00) and −1.09 (95% CI, −1.35 to −0.83) in the upadacitinib and placebo groups, respectively. The mean between-group difference for change from baseline (upadacitinib – placebo) was −1.17 (95% CI, −1.55 to −0.80; P < 0.0001). In Study 098, the mean changes from baseline for BASFI were −2.29 (95% CI, −2.73 to −1.85) and −1.30 (95% CI, −1.74 to −0.86) in the upadacitinib and placebo groups, respectively. The mean between-group difference for change from baseline (upadacitinib – placebo) was −1.00 (95% CI, −1.60 to 0.39; P < 0.001). The improvement of BASFI is considered clinical meaningful.

**HRQoL (i.e., ASQoL) at week 14:** In Study 944, the mean of changes from baseline for ASQoL were −5.10 (95% CI, −5.69 to −4.52) and −2.03 (95% CI, −2.62 to −1.44) in the upadacitinib and placebo groups, respectively. The mean between-group difference of change from baseline (upadacitinib – placebo) was −3.07 (95% CI, −3.90 to −2.24; P < 0.0001). In Study 098, the mean changes from baseline for ASQoL were −4.20 (95% CI, −5.12 to −3.29) and −2.67 (95% CI, −3.58 to −1.75) in the upadacitinib and placebo groups, respectively. The mean between-group difference for change from baseline (upadacitinib – placebo) was −1.54 (95% CI, −2.78 to 0.30; P < 0.016). The improvement in ASQoL is considered clinical meaningful in Study 944, but not in Study 098.

**Work productivity (i.e., Work Productivity and Activity Impairment – Ankylosing Spondylitis [WPAI-SpA] Overall Work Impairment) at week 14:** In Study 944, the mean (95% CI) of changes from baseline for WPAI Overall Work Impairment score were [redacted] in the upadacitinib and placebo groups, respectively. The mean between-group difference for change from baseline (upadacitinib – placebo) was [redacted]. In Study 098, the mean changes from baseline for WPAI Overall Work Impairment score were −18.11 (95% CI, −24.73 to −11.50) and −12.60 (95% CI, −19.04 to −6.15) in the upadacitinib and placebo groups, respectively. The mean between-group difference for change from baseline (upadacitinib – placebo) was −5.52 (95% CI, −13.82 to 2.78; P = 0.19), which was not statistically significant.

**Disease activity (e.g., ASDAS, BASDAI 50) at week 14:** In Study 944, the mean changes from baseline for ASDAS (CRP) were −1.52 (95% CI, −1.64 to −1.39) and −0.49 (95% CI, −0.62 to −0.37) in the upadacitinib and placebo groups, respectively. The mean between-group difference for change from baseline (upadacitinib – placebo) was −1.02 (95% CI, −1.20 to −0.85; P < 0.0001). In Study 098, the mean changes from baseline for ASDAS (CRP) were −1.45 (95% CI, −1.62 to −1.28) and −0.54 (95% CI, −0.71 to −0.37) in the upadacitinib and placebo groups, respectively. The mean between-group difference for change from baseline (upadacitinib –

placebo) was −0.91 (95% CI, −1.14 to −0.68; P < 0.001). A cut-off of 1.1 or higher is considered a clinically important improvement, which was seen in Study 944, but not in Study 098. In Study 944, the proportion of patients who achieved BASDAI50 (i.e., 50% decreased) was 43.1% and 16.7% in the upadacitinib and placebo groups, respectively. The mean between-group difference (upadacitinib – placebo) was 26.4% (95% CI, 18.0% to 34.8%; P < 0.0001). In Study 098, the proportion of patients who achieved BASDAI 50 at week 14 was 45.2% and 23.4% in the upadacitinib and placebo groups, respectively. The mean between-group difference (upadacitinib – placebo) was 21.8% (95% CI, 8.5% to 35.0%; P = 0.002). The response of BASDI 50 was considered clinical meaningful in both studies.

**MRI SPARCC Index (spine) at week 14:** In Study 944, the mean of changes from baseline for MRI SPARCC Index (spine) were −3.95 (95% CI, −5.06 to −2.83) and −0.04 (95% CI, −1.14 to 1.06) in the upadacitinib and placebo groups, respectively. The mean between-group difference for change from baseline (upadacitinib – placebo) was −3.90 (95% CI, −5.47 to −2.33; P < 0.0001). In Study 098, the mean of changes from baseline for MRI SPARCC Index (spine) were −6.93 (95% CI, −8.58 to −5.28) and −0.22 (95% CI, −2.01 to 1.57) in the upadacitinib and placebo groups, respectively. The mean between-group difference for change from baseline (upadacitinib – placebo) was −6.71 (95% CI, −9.01 to −4.41; P < 0.001). The improvement of MRI SPARCC Index (spine) was considered clinical meaningful in Study 098, but not in Study 944.

**MASES at week 14:** In Study 944, the mean changes from baseline for MASES were −2.6 (95% CI, −3.0 to −2.2) and −1.1 (95% CI, −1.5 to −0.8) in the upadacitinib and placebo groups, respectively. The mean between-group difference of change from baseline (upadacitinib – placebo) was −1.50 (95% CI, −2.00 to −0.90; P < 0.0001). But, whether the improvement of the MASES in Study 944 is clinical meaningful remains unclear. In Study 098, at week 14, the mean of changes from baseline for MASES were −2.25 (95% CI, −2.86 to −1.64) and −1.41 (95% CI, −2.02 to −0.80) in the upadacitinib and placebo group, respectively. The mean between-group difference for change from baseline (upadacitinib – placebo) was −0.84 (95% CI, −1.68 to 0.00; P < 0.049), which was considered not significant.

**BASMI at week 14:** In Study 944, the mean of changes from baseline for BASMI were −0.48 (95% CI, −0.58 to −0.38) and −0.16 (95% CI, −0.26 to −0.06) in the upadacitinib and placebo groups, respectively. The mean between-group difference of change from baseline (upadacitinib – placebo) was −0.32, 95% CI, −0.46 to −0.18. P < 0.0001. But, whether the improvement of BASMI in Study 944 is clinical meaningful remains unclear. In Study 098, the mean of changes from baseline for BASMI were −0.37 (95% CI, −0.52 to −0.21) and −0.14 (95% CI, −0.29 to 0.01) in the upadacitinib and placebo groups, respectively. The mean between-group difference for change from baseline (upadacitinib – placebo) was −0.22 (95% CI, −0.43 to −0.02; P < 0.03), which was considered not significant.

**Efficacy reported in extension phase:** The efficacy achieved at week 14 appeared to be maintained at 52 weeks [redacted] and week 104 (for Study 098).

### Harms Results

By week 14, the overall proportion of patients in the upadacitinib group with treatment emergent AEs (TEAEs) appeared low but was higher compared with the proportion in the placebo group in both Study

944 (40.8% versus 36.8%, respectively) and Study 098 (62.4% versus 55.3%, respectively). In Study 944, no TEAEs occurred in 5% or more of patients in either of the arms. In Study 098, the most common TEAEs (> 5% patients in either of the treatment groups) were increased blood creatine phosphokinase, diarrhea, nasopharyngitis, headache, and nausea. The overall frequency of patients with serious AEs (SAEs) seemed very low (< 3%) in both studies by week 14. No patients withdrew due to AEs in the upadacitinib group in Study 944. In Study 098, the proportion of patients that withdrew due to AEs was also very low (< 3%). No deaths were reported in either of the studies by week 14. The incidence of notable harms identified in this review was also low (including serious infection; anemia; neutropenia; lymphopenia; thrombocytopenia; malignancies; thrombosis, including increased platelets; elevation of creatine phosphokinase; other gastrointestinal SAEs; hypersensitivity; acne; and folliculitis). No major adverse cardiovascular events; gastrointestinal perforations; hepatotoxicity; dyslipidemia; opportunistic infection, excluding tuberculosis and herpes zoster; and active tuberculosis were reported. In either of the studies. Based on the clinical expert CADTH consulted for this review, the TEAE reported in both Study 944 and Study 098 were common TEAE as observed in other upadacitinib clinical trials for RA, psoriatic arthritis, and atopic dermatitis. Notable harms were nothing unexpected.

For the extension phase, the proportion of patients with TEAE were not reported in either of the 2 studies. Instead, the number of TEAEs and the number of TEAE person-years were provided. The clinical expert CADTH consulted for the review indicated that the safety profile of upadacitinib for AS over [redacted] over week 104 was consistent with that observed by week 14, with no new safety signals reported. The overall observed AEs were aligned with the known safety profile of upadacitinib. No new safety signals were identified in weeks 14 to week 104.

### Critical Appraisal

Randomization appeared sufficient and blinding appeared to be maintained throughout the study. Missing data were minimal and unlikely to affect study results. The multiplicity adjustment was done for the primary and main secondary outcomes at week 14; however, in Study 944, no multiplicity adjustment was performed for other secondary outcomes or exploratory outcomes, such as ASAS 5/6 (The ASAS5/6 includes assessments of all 6 individual ASAS domains and represents improvement above or equal to 20% in at least 5 domains), HRQoL (5-Level EQ-5D [EQ-5D-5L], Short Form [36] Health Survey [SF-36]), Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F), WPAI-SpA, MRI SPARCC score (SI joints). In Study 098, no multiplicity adjustment was performed for symptom measurement scale (total back pain and nocturnal back pain), ASDAS Inactive Disease (ASDAS < 1.3), ASDAS low disease activity (ASDAS < 2.1); HRQoL (EQ-5D-5L,SF-36), FACIT-F, and MRI SPARCC score (SI joints). Given the large number of comparisons in the study, a statistically significant finding (P < 0.05) for the comparisons between upadacitinib and placebo for these outcomes without multiplicity adjustment may be a high risk of bias due to an inflated type I error rate. Therefore, the statistical significance (P value) reported for those outcomes without multiplicity adjustment remains uncertain. One limitation was that both Study 944 and Study 098 were not designed for assessing the comparative efficacy and safety between upadacitinib and the existing bDMARDs marketed in Canada (i.e., TNF inhibitors and IL-17 inhibitors) in the treatment of AS. Therefore, the direct comparative efficacy and safety evidence comparing upadacitinib with bDMARDs remains unknown. In addition, in both

studies, the extra-articular manifestations were not assessed as an efficacy outcome in either of the studies. Therefore, the efficacy of upadacitinib on the extra-articular manifestations in the patients with AS remains to be investigated.

**Limitations for long-term period:** The findings at week 52 for both studies and at 104 weeks for Study 098 in the extension phase were limited by the lack of any control group and the nature of open label. Efficacy data beyond week 52 was not provided for the ongoing Study M19-944. The clinical experts CADTH consulted in this review indicated that, in clinical trials, it is common seen that the efficacy magnitude (especially, for those patient self-reported outcomes) often overestimated due to the nature of the open-label and no control group. Moreover, patients who enter into long-term extension are patients that are generally responding to the medication, or are aware they will now receive the medication, and are relatively free of AEs, which further increases biases observed around efficacy and safety. Therefore, the long-term outcome efficacy should be interpreted with the consideration of this limitation, although this would apply to all long-term extension studies. Finally, for the extension phase, the proportion of patients with TEAE were not reported in either of the 2 studies. Instead, the number of TEAEs and the number of TEAE person-years were provided.

The clinical expert CADTH consulted for this review indicated that exclusion of patients with total ankylosis of the spine and patients who had inadequate response to 2 and more bDMARDs in the trials were a "clinical trial strategy" to exclude patients that were not likely to demonstrate changes in numerous outcome measures. However, this is consistent with previous AS clinical trials (e.g., secukinumab, ixekizumab, anti-TNFs). In real life, it is possible that those patients with total ankylosis and who failed more than 2 bDMARDs may still demonstrate decreases in pain, stiffness, fatigue, and so on, and meaningful improvements in quality of life with the treatment. Overall, according to the clinical expert involved in the review, in both Study 944 and Study 098, the patients included in the trial are similar to those seen in Canadian clinical settings, except those patients with AS with total ankylosis of the spine and who had failed more than 2 bDMARDs would also be considered eligible for therapy would also be treated in clinic. There is little concern about the generalizability in Canada of the findings from both Study 944 and Study 098.

## Indirect Comparisons

### Description of Studies

The sponsor submitted an ITC of upadacitinib in adults with AS and is included in this review. [redacted]

A focused literature search identified 2 published ITCs which are also included in the review.

### Efficacy Results

[redacted]

[redacted]

The published ITCs had similar findings. One used a frequentist approach and did not specify prior bDMARD exposure. The number of included studies was larger than the sponsor-submitted ITC. Fewer efficacy outcomes were assessed, but the ITC also included an assessment of SAEs. Upadacitinib was superior to placebo and no different than relevant comparators for efficacy outcomes. The other published ITC used a Bayesian approach to estimate comparative efficacy of JAK inhibitors and secukinumab in patients with no prior exposure to bDMARDs. Secukinumab was the only relevant comparator for the Canadian context included in this ITC. Upadacitinib was better than placebo and no different than secukinumab for efficacy outcomes.

### Harms Results

[redacted]The 2 published ITCs included comparative estimates for SAEs. In the ITC using a frequentist approach, upadacitinib was no different than placebo or other relevant comparators for SAEs. In the published ITC using a Bayesian approach, upadacitinib was no different than placebo or secukinumab for SAEs.

### Critical Appraisal

A key limitation in the sponsor-submitted ITC is the evidence base for patients who had an inadequate response to a previous bDMARD, which appears to be the primary target population for this drug based on the Health Canada indication. The ITC provides comparative efficacy for only ixekizumab and secukinumab in those with an inadequate response to a prior bDMARD. Although comparative efficacy is available for all relevant comparators in a bDMARD-naive population, it is uncertain if comparative efficacy results in bDMARD-naive patients can be generalized to patients who had an inadequate response to a bDMARD. The clinical expert consulted said that patients who responded inadequately to bDMARD would be expected to have a lower response compared with bDMARD-naive patients.

Another key limitation of the sponsor-submitted study is the presence of heterogeneity in baseline patient characteristics among studies. Additional aspects of study design may also contribute to heterogeneity. Many of the baseline characteristics with heterogeneity have been identified in the literature as treatment effect modifiers in AS. [redacted]Therefore, there is increased uncertainty in the ITC findings.

One of the 2 published ITCs had similar limitations related to heterogeneity of baseline patient characteristics among included studies while heterogeneity in the other study could not be evaluated because no baseline patient characteristics were provided. One study had additional concerns about heterogeneity related to time points used for efficacy assessment. Both ITCs also have limitations related to reporting of methods and results, as well as details about included studies.

### Other Relevant Evidence

No other relevant evidence was identified.

## Conclusions

Two double-blind, randomized controlled trials of patients with active AS were included in this review. One (Study 944) was conducted in patients with inadequate response to or intolerance of 1 or 2 bDMARDs; the other (Study 098) was conducted in patients with an inadequate response to at least 2 NSAIDs, but who were bDMARD naive. The observed evidence indicated that, at week 14, once-daily, oral upadacitinib 15 mg showed a statistically significant and clinically meaningful (or useful) benefit as demonstrated by clinical response (e.g., ASAS 40), AS symptom reduction, function, and disability improvement, HRQoL, AS disease activity reduction, and MRI-detected axial inflammation compared with placebo. The treatment with upadacitinib also demonstrated a statistically significant improvement in terms of ASAS Health Index, MRI spine SPARCC change, enthesitis and spinal mobility compared with placebo at week 14 in study 944. Furthermore, the treatment with upadacitinib also appeared favourable compared with placebo in terms of WPAI and patient global assessment. The magnitude of clinical response (ASAS 40) to upadacitinib appeared similar in bDMARD-experienced patients compared with bDMARD-naive patients, although most clinical trials assessing efficacy in patients with an inadequate response to bDMARDs have demonstrated reduced treatment response. The efficacy achieved at week 14 appeared to be maintained at 52 weeks [redacted] and at week 104 in Study 098. The overall observed AEs were aligned with the known safety profile of upadacitinib. No new safety signals were identified at weeks 14 and up to week 104. The evidence from 3 ITCs suggests that no treatment for AS is favoured over others for most efficacy outcomes in bDMARD-naive patients and patients who had an inadequate response to a bDMARD, although the evidence base is limited in the latter population. No treatment is favoured over others for the outcome of SAEs. The presence of heterogeneity in the included studies increases uncertainty in the findings.

## Economic Evidence

### Table 3: Cost and Cost-Effectiveness

| Component | Description |
|---|---|
| **Type of economic evaluation** | Cost-utility analysis<br>Decision tree combined with a Markov model |

| Component | Description |
|---|---|
| **Target populations** | Adults with AS diagnosed with BASDAI activity and total back pain scores ≥ 4. Two subpopulations were considered:<br>1. bDMARD inadvisable: Biologic-naive patients who have had treatment failure with NSAIDs (due to inadequate response or intolerance) and for whom treatment with a biologic (TNF or IL-17 inhibitors) is inadvisable.<br>2. bDMARD-inadequate response: Patients who have had treatment failures with NSAIDs (due to inadequate response or intolerance) as well as at least 1 biologic therapy. |
| **Treatment** | Upadacitinib |
| **Dose regimen** | 15 mg extended-release oral tablets, taken once daily |
| **Submitted price** | $49.22 per tablet |
| **Treatment cost** | $17,965 per year |
| **Comparators** | Adalimumab<br>Etanercept<br>Golimumab<br>Infliximab<br>Secukinumab<br>Conventional therapy (corticosteroids, NSAIDs, or csDMARDs, such as sulfasalazine, methotrexate, leflunomide). |
| **Perspective** | Canadian publicly funded health care payer |
| **Outcomes** | QALYs, LYs |
| **Time horizon** | Lifetime (60 years, to maximum age of 100 years) |
| **Key data sources** | SELECT-AXIS 1, SELECT-AXIS 2<br>Sponsor-submitted NMA |
| **Key limitations** | • The comparative effect of upadacitinib on key clinical outcomes is uncertain due to a lack of direct comparative evidence to relevant comparators and the high degree of uncertainty in the sponsor's network meta-analysis. The CADTH clinical review concluded there were no differences in efficacy between therapies used to treat AS considered in the sponsor's NMA for both the bDMARD-inadvisable and -inadequate response subpopulations. No comparative safety or discontinuation information was available.<br>• The timing for the initial treatment effect for BASDAI and BASFI, as well as the baseline scores upon which the treatment effects were applied, were incorrectly implemented. This affected the total QALYs estimated for all treatments included in the analyses.<br>• The sponsor assumed that conventional therapy would have no effect on treatment response status or disease progression. This was inconsistent with the submitted NMA and clinical expectations.<br>• Although evidence was available for the 150 mg and 300 mg doses of secukinumab, only the data for the 150 mg dose was used in the sponsor's analysis. However, [redacted] dose split was assumed when calculating costs, thus overestimating costs associated with the 150 mg dose and omitting the efficacy information specific to the 300 mg dose.<br>• Although certolizumab pegol satisfied the criterion for relevant comparators, the absence of subpopulation-specific trial data led to its exclusion from the sponsor's base case. Further, several relevant comparators (i.e., infliximab, golimumab, etanercept, adalimumab) were omitted from the bDMARD-inadequate response subpopulation due to a lack of evidence. |

| Component | Description |
|---|---|
| **CADTH reanalysis results** | • CADTH conducted a reanalysis incorporating changes to the sponsor's economic submission to address key limitations. These changes included more appropriate assumptions regarding the calculation and timing of treatment effects, use of overall instead of response-stratified baseline BASDAI and BASFI, use of consistent dosing for secukinumab to calculate costs, assumption of a treatment effect with conventional therapy, and the inclusion of relevant comparators as permitted by the evidence available for each subpopulation.<br>• In the biologic-inadvisable subpopulation: Upadacitinib was dominated by secukinumab and etanercept (i.e., patients receiving secukinumab or etanercept gained more QALYs at a lower cost).<br>• In the biologic-inadequate response subpopulation (which did not consider all relevant TNF inhibitors): Upadacitinib dominated secukinumab. The ICER for upadacitinib relative to conventional therapy was $52,442 per QALY gained.<br>• The results of these analyses are dependent on estimates of treatment effect from the sponsor's NMA, which are associated with uncertainty, and these differences in treatment effect translate into clinically meaningful improvements in disease status for patients. |

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; bDMARD = biologic disease-modifying antirheumatic drug; TNF = tumour necrosis factor; IL-17: interleukin-17; IR = inadequate response; NMA = network meta-analysis; NSAID = nonsteroidal antirheumatic drug; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year.

### Budget Impact

CADTH identified 2 key limitations to the submitted budget impact analysis. First, market size was estimated using a claims-based approach, which relies on aggregated data summarizing total prescriptions or claims. It was not clear what steps were taken to identify individual patients within these data. Second, market size estimates relied on 2 simplifying assumptions, which could not be verified. These related to the prevalence of adults with AS and the proportion of patients with AS with prior biologic experience. Although both limitations affected the size of the target population, the effect on estimated budget impact was unknown. In the absence of more reliable input values to address these limitations, the sponsor's base case was maintained. The net budget impact of upadacitinib was estimated to be $445,516 in year 1, $2,282,075 in year 2, and $3,632,308 in year 3. The net budget impact over the 3-year time horizon was $6,359,899.

## CDEC Information

### Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

**Meeting date:** March 22, 2023

**Regrets:** One expert committee member did not attend

**Conflicts of interest:** None