CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Bimekizumab (Bimzelx)

Indication: The treatment of adult patients with active ankylosing spondylitis who have responded inadequately or are intolerant to conventional therapy

Sponsor: UCB Canada Inc

Recommendation: Reimburse with Conditions

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CADTH

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

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

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that bimekizumab be reimbursed for the treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately or are intolerant to conventional therapy only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from a double-blind, placebo-controlled, randomized phase III trial (BE MOBILE 2 [N = 332]) demonstrated that treatment with bimekizumab resulted in added clinical benefit for adult patients with active moderate to severe AS who had failed to respond to 2 different NSAIDs or had contraindication/intolerance to NSAID compared to placebo. Specifically, assessment after the 16-week double-blind period showed that the adjusted ASAS40 rate was 41.5% for patients treated with bimekizumab compared with 19.8% for those who received placebo, with a between group difference: 21.8%; (95% CI, 11.4% to 32.1%). The corresponding odds ratio (OR) was 2.88 (95% CI, 1.71 to 4.87; $P < 0.001$) in favour of bimekizumab, indicating that treatment with bimekizumab led to a statistically significant improvement in ASAS40 response rate. Although a minimal clinically important difference (MID) threshold was not identified for ASAS40, CDEC agreed with the clinical expert that the difference is likely to be clinically meaningful. Assessment of other disease activity and symptom outcomes such as Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), nocturnal spinal pain (NSP), Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) also showed least square (LS) mean differences in favour of bimekizumab that were statistically significant and reached the respective MID thresholds for the outcomes.

CDEC noted that the BE MOBILE 2 trial lacked long-term comparative evidence of bimekizumab versus placebo beyond 16 weeks. The sponsor submitted another study (Be AGILE 2 trial, N=255) to address this gap. However, CDEC discussed that it was a single-arm Phase 2 open-label study with potential selection bias and insufficient evidence to conclude any long-term comparative efficacy and safety advantages of bimekizumab over other treatments for AS.

CDEC acknowledged clinicians- and patients-identified unmet needs such as effective and safe treatment that work well for all patients, a limited availability of targeted therapies, waning effectiveness of current therapies over time, and a continuing need for effective treatment options for AS patients who do not respond adequately to currently available treatments. Based on the results from the BE MOBILE 2 trial, bimekizumab may address some of these unmet needs.

At the sponsor submitted price for bimekizumab and publicly listed price for all relevant comparators, bimekizumab was more costly than several relevant comparators used in the treatment of adults with active AS who have responded inadequately or are intolerant to conventional therapy. Given the lack of direct comparative evidence and the findings from the indirect treatment comparisons (ITCs) suggesting bimekizumab was no more effective than available biologic disease-modifying antirheumatic drugs (bDMARDs), there is insufficient evidence to justify a cost premium over the least expensive bDMARDs reimbursed for the treatment of active AS.

Table 1. Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Eligibility for reimbursement of bimekizumab should be based on the criteria used by each of the public drug plans for reimbursement of bDMARDs for the treatment of adult patients with active AS.	There is no evidence that bimekizumab is clinically superior or inferior to other biologic treatments currently reimbursed for the treatment of active AS.	—
Renewal		
2. Bimekizumab should be renewed in a similar manner to other bDMARDs currently reimbursed for the treatment of adult patients with active AS.	There is no evidence that bimekizumab should be held to a different standard than other reimbursed options when considering renewal.	—
Discontinuation		
3. Bimekizumab should be discontinued in a similar manner to other bDMARDs currently reimbursed for the treatment of adult patients with active AS.	There is no evidence that bimekizumab should be held to a different standard than other reimbursed options when considering renewal.	—
Prescribing		
4. Patients should be under the care of a rheumatologist or a clinician who has experience treating adult patients with active AS.	Accurate diagnosis and follow-up of patients with active AS are important to ensure that bimekizumab is prescribed to the most appropriate patients. In addition, there are several DMARD treatment options that may be considered when selecting the most appropriate therapy for patients; these are best determined by a rheumatologist or clinician who is familiar with this complex treatment paradigm.	—
5. Bimekizumab should not be reimbursed when used in combination with bDMARDs or tsDMARDs for active AS.	There is no evidence to determine the effects of bimekizumab when used in combination with bDMARDs or tsDMARDs in adult patients with active AS.	—
Pricing		
6. Bimekizumab 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 bimekizumab over the least expensive bDMARD reimbursed for AS.	—

AS = ankylosing spondylitis. BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; bDMARD = biologic disease disease-modifying antirheumatic drug; IL-17 = interleukin -17; NSAID = nonsteroidal anti-inflammatory drug; NRS = numeric rating scale.

Discussion Points

- Patients identified improvement in quality of life as an important outcome. The BE MOBILE 2 pivotal trials evaluated quality of life outcomes using both the disease-specific Ankylosing Spondylitis Quality of Life (ASQoL) tool and the Work Productivity and Activity Impairment Questionnaire-specific health problem (WPAI-SHP) instrument. For the ASQoL total score, a GRADE assessment of the evidence from the trials rated the certainty of effect estimates for change from baseline at Week 16 as moderate. For the WPAI-SHP, the GRADE assessments found that the certainty of effect estimates for the different domains ranged from high to low. However, the committee observed that WPAI-SHP outcomes were assessed outside the pre-specified statistical testing approach, which increases the risk of type I error. Therefore, CDEC determined that while bimekizumab likely improves HRQoL there was insufficient evidence to conclude on its clinical benefit in improving the work productivity of patients with AS.
- CDEC noted that the BE MOBILE 2 trial lacked direct safety and efficacy evidence for the comparison of bimekizumab versus other available treatments for AS. The committee observed that the sponsor-submitted ITC comparing bimekizumab to TNF inhibitors, interleukin-17 (IL-17) inhibitors or Janus kinase inhibitor (JAK) inhibitors had insufficient evidence to suggest that the clinical efficacy or safety benefit of bimekizumab was superior or inferior to the comparative treatments that were assessed in the ITC.
- CDEC observed that the BE MOBILE 2 trial did not provide any long-term comparative evidence of bimekizumab versus placebo beyond 16 weeks. The sponsor submitted another study (Be AGILE 2 trial, N=255) to address this gap. However, CDEC discussed that it was a single-arm Phase 2 open-label study with potential selection bias and insufficient evidence to conclude any long-term comparative efficacy and safety advantages of bimekizumab over other treatments for AS.
- CDEC discussed the clinical expert's information that patients with AS who experience treatment failure may either switch to another advanced therapy within the same class or in another class. The committee noted that while bimekizumab potentially addresses a current unmet need for a new treatment option, the BE MOBILE 2 trial primarily included bDMARD-naïve patients, except for a limited number of patients (16.3 %) with a prior TNFα inhibitor exposure, but for whom data analysis did not evaluate the statistical power to detect differences in treatment effects or control for type 1 error. Therefore, CDEC determined that there was insufficient evidence for the comparative effectiveness of bimekizumab versus other options after treatment failure with another bDMARD.
- Considerable uncertainty remains in the submitted pharmacoeconomic analyses given the number of limitations that could not be addressed by CADTH, including the short-term nature of the pivotal trial, the lack of direct comparative evidence relative to other approved therapies, and the uncertainty associated with available indirect comparative evidence.

Background

Ankylosing spondylitis (AS) is a chronic, inflammatory, and heterogeneous disease with significant burden to patients driven by pain, fatigue, and stiffness. Axial spondyloarthritis (axSpA) encompasses radiographic axial spondyloarthritis (r-axSpA, also known as AS) and non-radiographic axial spondyloarthritis (nr-axSpA). Although nr-axSpA shares several features with AS, advanced sacroiliac (SI) joint damage and spine ankylosis are absent. Patients with uncontrolled inflammation may progress to irreversible axial structural damage, spinal fractures, and severe spinal cord injury. Patients may also experience extramusculoskeletal manifestations, such as uveitis. A population-based study of the incidence and prevalence of AS in year 2010 using Ontario provincial health administrative databases found an age- and sex-standardised prevalence and incidence rates of 0.213% and 0.015%, respectively. AS was estimated to affect 300,000 patients in Canada in 2019.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first line treatment for adult patients with active AS. After NSAIDs, advanced therapy consists of biologic or targeted disease modifying anti-rheumatologic drugs (bDMARDs or tDMARDs, respectively). There are currently 2 classes of bDMARDs available in Canada for AS: tumour necrosis factor (TNF) inhibitors and interleukin-17A (IL-17A) inhibitors. Janus kinase (JAK) inhibitors are the only class of tDMARD available for the treatment of AS in Canada, and they are indicated after a patient has experienced inadequate response to a bDMARD. Many patients with AS receiving advanced therapy will experience treatment failure. When failure of advanced therapies occurs, it is recommended to switch to another advanced therapy either within the same class or to another class. There is very little evidence to guide switching between advanced therapies. Therefore, guidelines recommend any switch within or between treatment classes when treatment failure occurs.

Bimekizumab has been approved by Health Canada for the treatment of adult patients with active AS. Bimekizumab is a humanized IgG1/κ monoclonal antibody that neutralizes IL-17A, IL-17F and IL-17AF cytokines. It is available as 160 mg/mL, solution for subcutaneous injection and the dosage recommended in the product monograph is 160 mg given as 1 subcutaneous injection every 4 weeks.

Sources of Information Used by the Committee

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

- a review of 1 randomized, double-blind, placebo-controlled, multicenter phase 3 trial (BE MOBILE 2) and single-arm phase 2 trial (BE AGILE) and its open label extension study (BE AGILE 2) in adult patients with active AS
- patients perspectives gathered by 2 inputs from 5 patient groups: 1 submission from Arthritis Consumer Experts (ACE), and the other was a joint submission by 4 patient groups: The Canadian Spondyloarthritis Association (CSA), Canadian Arthritis Patient Alliance (CAPA), Arthritis Society Canada (ASC), and Creaky Joints (CJ).
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 1 of clinical specialist with expertise diagnosing and treating patients with active AS
- no clinician group input was submitted for this review.
- a review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Patient Input

A total of two inputs were submitted for this review. One came from Arthritis Consumer Experts (ACE), and the other was a joint submission by 4 patient groups: The Canadian Spondyloarthritis Association (CSA), Canadian Arthritis Patient Alliance (CAPA), Arthritis Society Canada (ASC), and Creaky Joints (CJ). ACE conducted an online survey between 2019 and 2022 to gather information from patients with AS (n = 4). The joint input by 4 patient groups was prepared based on an online survey conducted from September – October 2023 among patients with AS (n = 109).

According to the joint input by 4 patient groups, the majority of patients with AS experience back pain (90.48%), joint stiffness (79.05%), fatigue (77.14%), and hip pain (71.43%), have difficulties in exercising or being active (80.77%), challenges with sleep (73.08%), as well as impaired ability to work (57.69%) and make social connections (53.85%). Besides, patients living with AS require help with daily activities and emotional support from caregivers. Input by ACE echoes the patient experiences provided by the joint input and added flare-ups, deconditioning, anxiety, and mood changes as the impact of AS on their daily lives. Outcomes of interest to patients mentioned in the joint input were improved symptoms (71%) such as less fatigue, pain, and stiffness, better quality of life (67%) including ability to socialize more and better mental well-being, affordability to manage AS (66%), reduced side effects of medications (48%), and convenience (36%) in terms of drug dosing schedules, route of administration or formulations. The ACE input agrees with these outcomes of interest and added that ease of movement, ability to exercise more, control of back spasms and inflammation, less weight gain are other outcomes of interest.

The joint input emphasized that approximately half of patients become resistant to their treatments within 5 years, therefore, access to new treatment options is essential. Of note, the 4 patient groups pointed out that for Canadians it takes on average 7 – 10 years from the onset of symptoms to be diagnosed with AS. Delayed diagnosis and treatment then lead to irreversible damage and negative impact on mental health. According to the input, patients with AS experience a significantly impacted quality of life and frustration during this time.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical expert consulted by CADTH indicated that the goals of treatment are to control pain and inflammation and prevent radiographic damage and disability related to AS. The clinical expert stated that the treatment of AS is tailored according to current manifestations of the disease (axial, peripheral, entheseal, extraarticular symptoms and signs), level of current symptoms, clinical findings, and prognostic indicators, disease activity, pain, physical function, structural damage (joint especially hip involvement, spinal deformities), comorbidity, concomitant drugs, and the wishes and expectations of the patient. The clinical expert consulted by CADTH indicated that unmet needs in the management of AS included some patients not responding to available treatments once initiated (primary failure), many patients developing active disease after initially responding to treatment (secondary failure), limited access to early diagnosis and treatment; choosing the right drug for the right patient at the right time (precision medicine) due to the availability of relatively few targeted therapies (TNFi, IL17Ai, and JAKi); and safety concerns for most DMARDs as well as NSAIDs. According to the clinical expert, these safety concerns include infections with most drugs, new onset or worsening of associated diseases (uveitis, inflammatory bowel disease [IBD], and psoriasis) and comorbidities, thus, treatments that are safe, effective for all manifestations and well tolerated by most patients are needed. Though the efficacy of various drugs on the musculoskeletal manifestations are similar, no drug is equally effective for all manifestations and their effect on associated diseases may vary as per feedback from the clinical expert.

The clinical expert consulted by CADTH indicated that bimekizumab would fit after failure of NSAIDs either by itself or in combination with NSAIDs in clinical practice. The clinical expert would not reserve bimekizumab for patients with refractory disease or patients who are intolerant to other therapies as there are no other drugs targeting both IL17A and F cytokines. The clinical expert stated that given bimekizumab's efficacy in both musculoskeletal and skin disease, it may be the drug of choice following treatment with NSAIDs in patients with severe skin psoriasis and who do not have IBD.

Patients with a previous personal or family history of IBD may not be candidates for treatment with bimekizumab. This is because, according to the clinical expert consulted by CADTH, the use of IL17 inhibitors would increase the risk of IBD flares based on the experience with using DMARDs targeting IL17A in patients with IBD. The clinical expert consulted by CADTH stated that patients having inadequate response to currently available DMARDs are most in need of an additional treatment option. The clinical expert indicated that patients best suited for treatment with bimekizumab are generally identified by clinician examination and judgement.

According to the clinical expert consulted by CADTH, clinical response is determined by change in severity of back pain as assessed by patient reported questionnaires including total back pain score and the BASDAI. More objective measures, such as the Ankylosing Spondylitis Disease Activity Score (ASDAS), are used in tertiary care centres. Other measures include improvement in enthesitis counts, joint counts (tender and swollen), as well as improvement in skin psoriasis. These measures aligned with the

assessments used in clinical trials. The clinical expert consulted by CADTH indicated that BASDAI score at 3 to 6 months would be used to assess response. At least a 50% reduction in BASDAI score or at least 2 absolute point reduction in BASDAI score is usually required to suggest clinically significant improvement.

According to the clinical expert consulted by CADTH, a lack of response in back pain (given that other causes of back pain are excluded) and secondary failure (relapse) are the most important factors to consider when deciding to discontinue treatment with bimekizumab. The clinical expert indicated that recurrent infections, and the occurrence of IBD would require discontinuation of bimekizumab. The clinical expert indicated that discontinuing the treatment with bimekizumab is determined by clinical evaluation by a rheumatologist, sometimes involving imaging by MRI.

The clinical expert stated that rheumatologists are trained to identify inflammatory sacroiliitis and spondylitis; therefore, the diagnosis should be made by them. According to the clinical expert consulted by CADTH, patients with AS are usually treated in an outpatient setting both in community clinics and clinics attached to community and academic hospitals. In rare instances severe disease including skin, eye and bowel disease may warrant admission to a hospital. A rheumatologist is required to diagnose, treat, and monitor patients with AS. Since uveitis, IBD and skin psoriasis are present with AS, ophthalmologists, gastroenterologists and dermatologists are also relevant to disease management.

The clinical expert consulted by CADTH stressed that the treatment options for patients with active AS are limited and thus bimekizumab provides an additional treatment option for such patients.

Clinician Group Input

No clinician group input was submitted for this review.

Drug Program Input

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2. Responses to Questions from the Drug Programs

Drug program implementation questions	Clinical expert response
Relevant comparators	
Comparator drug is placebo (BE MOBILE 1 – non-radiographic axSpA and BE MOBILE 2 – radiographic axSpA). Biologics that have been reviewed by CDEC for the use in ankylosing spondylitis – golimumab (Mar 17, 2010), ixekizumab (Mar 24, 2020), etanercept (Oct 25, 2016), certolizumab pegol (Apr 17, 2015), secukinumab (Aug 23, 2016), adalimumab (June 27, 2007), infliximab (Dec 19, 2014) and upadacitinib (May 11, 2023). Noted: Bimekizumab is a dual inhibition of IL-17A and IL-17F. According to the 2022 update: ASAS-EULAR recommendations for the management of SpA – medications used for axial SpA are secukinumab, ixekizumab, tofacitinib and TNFi biosimilars. It suggests that NSAIDs and TNF inhibitors remain primary classes of medications for radiographic and non-radiographic axSpA. What is an appropriate comparator for patients with axSpA given the biosimilar/biologic space? E.g., Secukinumab (Cosentyx)	According to the clinical expert consulted by CADTH, an anti-TNF biosimilar monoclonal antibody would be an appropriate comparator to bimekizumab. The clinical expert indicated placebo is not an appropriate comparator, head-to-head studies with an active drug would be ideal but such trials are few and far between. CDEC agreed with the clinical expert.

Drug program implementation questions	Clinical expert response
Would bimekizumab be an option for patients with peripheral symptoms of ankylosing spondylitis (no axial involvement)?	The clinical expert consulted by CADTH indicated that there are no studies for pure peripheral SpA. Extrapolation from PsA studies would indicate that bimekizumab is likely to be effective. CDEC agreed with the clinical expert.
Both trials, enrolled patients who had prior failure of ≥2 NSAIDs or history of intolerance or contraindications to NSAIDs. Patients were excluded if they had received > 1 TNFi, >2 additional biologic response modifiers or any IL-17 response modifier. Should bimekizumab be first line in treating patients with AS as NSAIDs are for symptomatic control of pain and does not modify the disease? Should the CDEC reimbursement criteria align with the enrolment criteria where patients need to have failure of 2 or more NSAIDs? If yes, could you define duration of adequate trial of NSAIDs?	The clinical expert consulted by CADTH indicated that unless there are strong contraindications against the NSAIDs use, the use of DMARDs (i.e., bimekizumab) would be second line after the NSAIDs. The clinical expert confirmed that failure of two or more NSAIDs is fair criterion for reimbursement. Many patients are adequately controlled with NSAIDs and physical therapy and do not need tDMARDs. According to the clinical expert, the duration of adequate trials of NSAIDs would be about one month. This is because NSAIDs are quick-acting, and the clinical expert would not wait as AS is a systemic inflammatory disease. CDEC agreed with the clinical expert that bimekizumab could be considered after 2 adequate trials of NSAID or contraindication to NSAID.
Would patients access this medication at the same level as TNFi and IL-17 modifiers, despite no head-to-head comparison data? How about in relation to JAK inhibitors like upadacitinib?	The clinical expert consulted by CADTH would suggest that unless contraindicated, TNFi biosimilar should be the first biologic of choice for AS followed by other TNFi, the IL17i including bimekizumab and JAKi like upadacitinib. The clinical expert stated that for patients with active AS who have contraindications to NSAIDs, such as advanced cardiovascular disease, renal disease, IBD, and Crohn's disease, tDMARDs (i.e.,JAK inhibitors) therapy would be appropriate. CDEC agreed with the clinical expert but noted that there is no direct evidence to support a CDEC recommendation reflecting the sequencing proposed by the clinical expert.
Can the medication be used as monotherapy? i.e, without methotrexate?	The clinical expert consulted by CADTH confirmed that bimekizumab can be used as monotherapy. CDEC agreed with the clinical expert.
Medications such as secukinumab and ixekizumab are not preferred for patients with extramusculoskeletal manifestations e.g., IBD and uveitis according to the 2022 ASAS-EULAR recommendations for the management of axial spondyloarthritis. What is the place in therapy of bimekizumab regarding use in patients exhibiting these manifestations?	According to the clinical expert consulted by CADTH, until it is adequately proven that bimekizumab improves uveitis and does not lead to de novo IBD or IBD flares, bimekizumab should not be preferred in patients with these manifestations. CDEC agreed with the clinical expert.
Would treatment goals include reducing structural damage progression? Does bimekizumab help in reducing structure damage progression in axial ankylosing spondylitis?	The clinical expert consulted by CADTH indicated that treatment goals should not include reducing structural damage progression as this would require early and prolonged treatment, which is difficult to implement in routine clinical practice. According to the clinical expert consulted by CADTH, currently, there is no evidence to prove that bimekizumab helps in reducing structure damage progression in axial ankylosing spondylitis.

Drug program implementation questions	Clinical expert response
	CDEC agreed with the clinical expert.
What advantages/disadvantages does bimekizumab hold over other medications in this space?	According to the clinical expert consulted by CADTH, the advantage of bimekizumab over other medications in treating patients with active AS was it is an option in patients with severe psoriasis or those failing TNFi or other IL17i (although such patients were excluded from clinical trials) or JAKi. The disadvantages of bimekizumab were the risk of IBD and fungal infections especially mucocutaneous candidiasis but that is easily treated with oral and topical antifungals. CDEC agreed with the clinical expert.
It almost feels like a class review is required to form consistent criteria with all these agents.	Comment from the drug programs to inform CDEC deliberations. CDEC agreed that considering a class of drug as a whole and forming consistent criteria would be helpful.
CADTH has reviewed bimekizumab before for more moderate-severe psoriasis. The medication received a positive reimbursement (March 30, 2022).	Comment from the drug programs to inform CDEC deliberations.
There are other medications in this space – alignment with criteria for biologics in place in the various drug plans for ankylosing spondylitis, instead of being specific to IL-17 inhibitors.	Comment from the drug programs to inform CDEC deliberations.
Considerations for initiation of therapy	
Is there a standardized definition for “active ankylosing spondylitis”? The trials use: BASDAI ≥4 and spinal pain (BASDAI item 2) ≥ 4. Is this definition used in practice? Or is this definition for “active axial ankylosing spondylitis”?	The clinical expert consulted by CADTH confirmed that the definition for “active ankylosing spondylitis” used in the BE MOBILE 2 trial (i.e., BASDAI ≥4 and spinal pain [BASDAI item 2] ≥ 4) is used in practice but includes judgement by rheumatologist and might include CRP and MRI evaluation. CDEC agreed with the clinical expert.
Patients enrolled in BE MOBILE 1 and 2 were 18 years and older. Is this a medication that can be used in the pediatric population? Mostly all patients enrolled in MOBILE 1 and 2 had high or very high disease activity measured by ASDAS-CRP, would you be able to comment on efficacy in patients with mild or moderate activity? Should this medication not be offered to these patients?	The clinical expert consulted by CADTH confirmed that bimekizumab might be used in the paediatric population even though the drug is not approved in the paediatric population. Other IL-17i have been used in related diseases. The clinical expert consulted by CADTH indicated that patients with mild to moderate disease are also likely to respond especially if they have objective measures of inflammation such as elevated CRP and MRI changes. CDEC noted that given the insufficient evidence in the pediatric population and mild activity, treatment with bimekizumab should be limited to adults with moderate to severe AS.
In what situations would a clinician start bimekizumab right away without the requirement of NSAID trial? Would it be possible to include discussion on comorbidities? Would you be able to comment on onset of action and response relative to other comparators? When presented with a patient who may have failed (to define) TNFi or IL-17i, what is the efficacy of the switch to bimekizumab?	According to the clinical expert consulted by CADTH, bimekizumab may be used directly if NSAIDs are contraindicated especially in the presence of bleeding disorders, peptic ulcer disease, renal disease, hypertension and atherosclerotic vascular disease. The clinical expert consulted by CADTH commented that bimekizumab has a relatively quick onset of action and is comparable to TNFi. According to the clinical expert consulted by CADTH, the response rate is likely to be lower in patients who have failed TNFi and may be even lower in those who have failed other IL17i. After NSAIDs these

Drug program implementation questions	Clinical expert response
	drugs could be used as first line tDMARDs. The clinical expert consulted by CADTH indicated that the choice is based on the presence of comorbidities and risk of side effects. After NSAIDs, a TNFi biosimilar may be preferred followed by any of the other DMARDs for AS. CDEC noted that there is insufficient data to support efficacy in patients who failed >2 non-TNFi or IL-17i.
There are other medications in this space – alignment with criteria for biologics in place in the various drug plans for ankylosing spondylitis, instead of being specific to IL-17 inhibitors.	Comment from the drug programs to inform CDEC deliberations.
Considerations for continuation or renewal of therapy	
What is an appropriate tool to monitor disease activity (e.g., ASDAS: high disease activity defined as ≥2.1 vs. ASAS40 vs. BASDAI [which is a tool used as criteria in jurisdictions for to show beneficial effects of treatment for renewal])? Could you comment on subjective vs. objective tools?	According to the clinical expert consulted by CADTH, ASDAS or BASDAI may be used to monitor disease activity, BASDAI is simple to use and is preferred but ASDAS is more objective since it includes CRP, ASAS40 is a response criterion and not a measure of disease state and hence not preferred for long term monitoring. The clinical expert consulted by CADTH indicated that physician judgement should also be considered. The clinical expert consulted by CADTH commented that the tools are inherently subjective since the main manifestation is back pain. ASDAS is more objective than BASDAI. CDEC agreed with the clinical expert.
There are other medications in this space – alignment with criteria for biologics in place in the various drug plans for ankylosing spondylitis, instead of being specific to IL-17 inhibitors.	Comment from the drug programs to inform CDEC deliberations.
Considerations for discontinuation of therapy	
What definition would you use for loss of response, absence of clinical benefit, and disease progression in clinical practice? Based on what parameters?	The clinical expert consulted by CADTH indicated that the lack of response should be based on BASDAI response as stated above or using the ASDAS, worsening back pain as judged by the rheumatologist to be due to ongoing inflammation would define absence of clinical benefit and disease progression. The clinical expert stated that CRP and MRI may help the rheumatologist with their judgement. CDEC agreed with the clinical expert.
For renewal and subsequent renewal for this medication, it would be good to understand tools used, targets for these tools (pretreatment vs. during treatment vs. stabilization) to help jurisdictions for adjudication.	Comment from the drug programs to inform CDEC deliberations. CDEC mentioned that given other medications treating AS are already recommended in many jurisdictions and adjudication, CDEC would likely follow existing precedent.
Considerations for prescribing of therapy	
Current dose is 160 mg/mL s/c every 4 weeks (no loading dose, based on dose-response studies). Is there any evidence to increase/reduce frequency of medication administration for this indication?	According to the clinical expert consulted by CADTH, there is no evidence to increase or reduce the frequency of medication administration for this indication but may be required in patients with severe disease or frequent flares between doses, which the clinical expert expected to be infrequent.

Drug program implementation questions	Clinical expert response
	CDEC noted that available evidence is limited to the 160mg subcutaneously every 4 weeks dosing
Generalizability	
Patients with inflammatory conditions other than nr-axSpA/r-axSpA were excluded. What is the incidence of inflammatory conditions in patients with non-radiographic-axSpA/radiographic-axSpA? Is this generalizable to the axial ankylosing spondylitis population if this population has concomitant inflammatory conditions?	According to the clinical expert consulted by CADTH, peripheral arthritis, psoriasis, uveitis and IBD are often present in patients with AS. The clinical expert commented that these were not exclusion criteria except for active IBD and recent flare of uveitis. The clinical expert consulted by CADTH confirmed that the data presented in the BE MOBILE 2 trial would be generalizable to the patient with active AS and concomitant inflammatory conditions. The clinical expert stated that psoriasis, IBD and peripheral arthritis are inflammatory conditions related to the disease and patients with AS rarely have comorbid inflammatory conditions such as rheumatoid arthritis in their clinical practice. CDEC agreed with the clinical expert.
Care provision issues	
The screening period included LTBI treatment (additional health intervention). What is the incidence/prevalence of fungal infections while using bimekizumab?	The clinical expert stated that inhibition of IL-17 is associated with mucocutaneous candidiasis including oropharyngeal, vaginal and esophageal candidiasis. The clinical expert indicated that the incidence would be higher with higher doses as seen in psoriasis and psoriatic arthritis trials and ranges from 2% to 21%. CDEC agreed with the clinical expert.
Depending on the incidence/prevalence, this may add out-of-pocket costs/costs to patients/healthcare system to acquire antifungal therapy.	Comment from the drug programs to inform CDEC deliberations.
System and economic issues	
Presence of confidential negotiated prices for comparators	Comment from the drug programs to inform CDEC deliberations.

AS = ankylosing spondylitis; ASAS40 = Assessment of SpondyloArthritis International Society 40%; ASAS-EULAR = Assessment of SpondyloArthritis international Society- The European Alliance of Rheumatology Associations; ASDAS = Ankylosing Spondylitis Disease Activity Score; axSpA = axial spondyloarthritis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CRP = C-reactive protein; DMARDs = disease-modifying antirheumatic drugs; IBD = inflammatory bowel disease; IL-17 = Interleukin 17; IL-17i = Interleukin 17 inhibitor; JAK = Janus kinase inhibitor; LTBI = latent tuberculosis infection; MRI = magnetic resonance imaging; NSAIDs = nonsteroidal anti-inflammatory drugs; SpA = axial spondyloarthritis; tDAMRDs = targeted disease-modifying antirheumatic drugs; TNFi = tumor necrosis factor inhibitor.

Clinical Evidence

Systematic Review

Description of Studies

One pivotal trial (BE MOBILE 2) was included in the sponsor's systematic review. The BE MOBILE 2 trial was a phase 3, multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of bimekizumab in patients with active AS compared to placebo. This study enrolled adults who had active AS (i.e., radiographic axial spondyloarthritis [axSpA]) and fulfilled the modified New York (mNY) criteria. Eligible study participants (N = 332) were randomized 2:1 to receive bimekizumab (n=221) 160 mg/mL or placebo (n = 111) subcutaneously every 4 weeks (Q4W). The mean age of all study participants was 40.4 years with a range of 19 to 80 years. Treatment groups were generally well balanced with respect to AS-related and other baseline disease characteristics. At Baseline, the majority of all study participants were using NSAID therapies (79.8%) and prior anti-TNF therapy was used by 16.3% of all study participants. The primary objective of the BE MOBILE 2 trial was to demonstrate the efficacy of bimekizumab administered subcutaneously Q4W compared to placebo in the treatment of patients with active AS. The primary end point of the study was Assessment of SpondyloArthritis International Society 40% (ASAS40) and secondary end points included Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), nocturnal spinal pain (NSP); based on numeric rating scale (NRS), Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), and health-related quality of life (HRQoL) using the Ankylosing Spondylitis Quality of Life [ASQoL] and Work Productivity and Activity Impairment Questionnaire-specific health problem [WPAI-SHP]) scales.

Efficacy Results

Assessment of SpondyloArthritis International Society 40%

At Week 16 of the double-blind treatment period, patients in the bimekizumab group reported a higher adjusted ASAS40 response rate compared with the placebo group (41.5% vs 19.8% for bimekizumab vs. placebo; between group difference: 21.8%; 95% CI, 11.4% to 32.1%). This corresponded to an OR of 2.88 (95% CI, 1.71 to 4.87; P < 0.001) in favour of bimekizumab. No estimate of a between group minimally important difference (MID) was identified by CADTH, but clinical expert input suggested the absolute difference between groups was clinically important based on a 15% threshold. The ASAS40 response in the bimekizumab group was also observed at Weeks 24, 36, and 52. Pre-specified subgroup analyses of ASAS40 response rate at Week 16 were generally consistent with the primary analysis. At Week 16 of the double-blind treatment period, patients who were TNFα inhibitor-naïve or experienced in the bimekizumab group reported a higher adjusted ASAS40 response rate compared with those in the placebo group (45.7% and 40.5% vs. 23.4% and 17.6% for bimekizumab vs. placebo). The results of sensitivity and supportive analyses, including the tipping point analyses, were in line with the primary efficacy results.

Bath Ankylosing Spondylitis Disease Activity Index

At Week 16, patients in the bimekizumab group had a greater LS mean reduction (reductions reflect improvement) from baseline in BASDAI score compared with patients in the placebo group (LS means, –2.7 vs. –1.7 for bimekizumab vs. placebo). An estimated median MID of 1.4 points (range = 0.9 to 1.8) was identified in the literature. The clinical expert consulted by CADTH indicated that they would consider a 1-point difference between groups as clinically meaningful. The difference in LS means between treatment groups was –1.04 (95% CI, –1.5 to –0.6; P<0.001) in favour of bimekizumab. Generally, the treatment effects of bimekizumab on the BASDAI were observed at Weeks 24, 36, and 52.

Bath Ankylosing Spondylitis Functional Index

At Week 16, patients in the bimekizumab group had a greater LS mean reduction (reductions reflect improvement in physical function) from baseline in BASFI score compared with patients in the placebo group which worsened (LS means, –1.9 vs. –1.0 for bimekizumab vs. placebo). An estimated median MID of 1.1 points (range = 1.0 to 1.4) was identified in the literature. The difference in LS means between treatment groups was –1.1 (95% CI, –1.5 to –0.6; P<0.001) in favour of bimekizumab. The clinical expert consulted by CADTH suggested a MID of 1 point for between group difference. Generally, the treatment effects of bimekizumab on the BASFI were observed at Weeks 24, 36, and 52.

Nocturnal Spinal Pain (based on numeric rating scale)

At Week 16, patients in the bimekizumab group had a greater LS mean reduction (reductions reflect improvement) from baseline in NSP (based on NRS) score compared with patients in the placebo group which worsened (LS means, –3.2 vs. –1.7 for bimekizumab vs. placebo). An estimated median MID of 1.5 points (range = 1.1 to 2.3) was identified in the literature. The difference in LS means between treatment groups was –1.5 (95% CI, –2.0 to –1.0; P<0.001) in favour of bimekizumab. The clinical expert consulted by CADTH identified a MID of 1 point for between group difference. Generally, the treatment effects of bimekizumab on the NSP were observed at Weeks 24, 36, and 52.

Enthesitis-free State Based on The Maastricht Ankylosing Spondylitis Enthesitis Score in Patients with Enthesitis at Baseline

At Week 16 of the double-blind treatment period, patients with enthesitis at baseline in the bimekizumab group reported a higher adjusted enthesitis-free rate compared with those in the placebo group (43.8% vs. 23.9% for bimekizumab vs. placebo; between group difference: 19.8%; 95% CI, 6.3% to 33.4%). This corresponded to an OR of 2.47 (95% CI, 1.30 to 4.68) in favour of bimekizumab. No estimate of a between group MID was identified by CADTH, but clinical expert input suggested a 15% difference would be clinically important, therefore, the absolute difference between groups was clinically important. Generally, the treatment effects of bimekizumab on the enthesitis-free rate were observed at Weeks 24 and 52. The enthesitis-free state outcome was not controlled for type I error rate and thus these data should be interpreted as supportive evidence only.

Ankylosing Spondylitis Quality of Life

At Week 16, patients in the bimekizumab group had a greater LS mean reduction (reductions reflect improvement) from baseline in ASQoL score compared with patients in the placebo group which worsened (LS means, –4.6 vs. –3.1 for bimekizumab vs. placebo). A MID of 1 unit of worsening (i.e.,+ 1) or 2 units improvement (i.e., −2) was identified in the literature. The difference in LS means between treatment groups was –1.5 (95% CI, –2.4 to –0.7; P<0.001) in favour of bimekizumab. The clinical expert consulted by CADTH identified a MID of 2 points for between group difference. Generally, the treatment effects of bimekizumab on the ASQoL were observed at Weeks 24, 36, and 52.

Work Productivity and Activity Impairment Questionnaire-specific health problem

At Week 16, the bimekizumab group compared with the placebo group had a greater mean reduction (improvement) from baseline in WPAI–SHP score for percent time missed due to disease-related problems (–5.5 vs. –1.2; between group difference: –2.9; 95% CI,–6.9 to 1.1), percent impairment while working due to disease-related problems (–20.8 vs. –6.1; between group difference: –12.5; 95% CI,–18.2 to –6.9), percent overall work impairment due to disease-related problems (–22.2 vs.–6.7; between group difference: –12.8; 95% CI,–18.7 to –6.9), and percent activity impairment due to disease-related problems (–23.3 vs. –14.4; between group difference: –9.4; 95% CI,–13.9 to –4.9). No MIDs for WPAI-SHP were identified in the literature. Generally, the treatment effects of bimekizumab on the WPAI-SHP domains were observed at Weeks 24, 36, and 52 except for percent activity impairment due to disease-related problems where patients reported similar results between groups. The WPAI-SHP outcome was not controlled for type I error rate and thus these data should be interpreted as supportive evidence only.

Harms Results

Any adverse event (AE) was reported among 54.3% of patients in the bimekizumab group and 43.2% of patients in the placebo group at Week 16. The most commonly reported adverse events (i.e., reported by ≥ 5% of patients in either group) were: infections and infestations (28.1% vs. 22.5% for bimekizumab vs. placebo), gastrointestinal disorders (13.1% vs. 9.9%), nervous system disorders (8.1% vs. 4.5%), upper respiratory tract infection (2.7% vs. 7.2%), and eye disorders (2.3% vs. 6.3%).

Serious adverse events (SAEs) were reported among 2.3% of patients in the bimekizumab group and 0.9% of patients in the placebo group at Week 16. The following SAEs were commonly reported in the bimekizumab group but no patients in the placebo group: Goitre (0.5%), colitis ulcerative (0.5%), Crohn's disease (0.5%) cholelithiasis (0.5%), and hepatitis A (0.5%).

Discontinuation due to AEs was reported among 2.7% of patients in the bimekizumab group but no patients in the placebo group at Week 16. The commonly reported AEs that led to study discontinuation in the bimekizumab group were psychiatric evaluation

abnormal (0.9%), lymphoid tissue hyperplasia (0.5%), Crohn's disease (0.5%), oral candidiasis (0.5%), and rash (0.5%). No deaths due to AEs were reported during the double-blind treatment period in the BE MOBILE 2 trial.

Serious infections, fungal infections, opportunistic infection, malignancies, major adverse cardiac event, neutropenia, suicidal ideation and behavior, IBD, hypersensitivity reactions, and liver injury or disorders were considered notable harms by the sponsor and/or the clinical expert consulted by CADTH. The commonly reported notable harms were hypersensitivity reactions (7.7% vs. 1.8 for bimekizumab vs. placebo), fungal infections (6.3% vs. 0), liver injury or disorders (4.5% vs. 3.6%), IBD (1.8% vs. 0), neutropenia (0.5% vs. 0), and serious infections (0.5% vs. 0.9).

Critical Appraisal

Internal Validity

The CADTH review team noted that there were no comparative data available beyond Week 16 as patients in the placebo group were reallocated to receive bimekizumab during the 36-week maintenance period after finishing all assessments at the end of the 16-week double-blind treatment period. Therefore, it is uncertain what the direct comparative efficacy and safety of bimekizumab are after Week 16. For the analysis of the primary and key secondary end points, a fixed sequence testing procedure was employed to adjust for multiple comparisons across multiple end points, thereby controlling the type I error. The CADTH review team noted that the analyses of enthesitis-free state based on MASES index was not included in the fixed sequence testing hierarchy and thus the results should be considered as supportive evidence. Although the subgroup analyses were pre-specified, the BE MOBILE 2 trial was not powered to detect any change in the ASAS40 response rate between bimekizumab and placebo in subgroup analyses except for the subgroup of patients who are TNFi-naïve, additionally, no formal statistical tests for interaction between subgroups were conducted. There were 2 protocol amendments regarding eligibility criteria made after the enrollment of the first patient (April 25, 2019). The CADTH review team considered these 2 protocol amendments may increase patient heterogeneity and introduce bias. The direction of the bias is uncertain as there were no data reported on the numbers of patients with psoriatic arthritis and patients who had failed to more than 2 NSAIDs included in the trial. HRQoL is considered a relevant outcome by patients with active AS and the clinical expert consulted by CADTH. However, the assessment of the ability of returning to normal activities and/or functioning using WPAI-SHP was not controlled for multiplicity and thus should be considered as exploratory and supportive.

External Validity

The BE MOBILE 2 trial used placebo as the comparator group. According to the clinical expert consulted by CADTH, an anti-TNF biosimilar monoclonal antibody would be an appropriate comparator to bimekizumab. The clinical expert indicated placebo is not an appropriate comparator, head-to-head studies with an active drug would be ideal. The BE MOBILE 2 trial excluded patients with more than 1 TNFα inhibitor and/or more than 2 additional non-TNFα biological response modifiers, or any IL-17 biological response modifier at any time. The clinical expert indicated that those patients should be considered eligible for bimekizumab, although the response rate might be lower, some patients do respond to bDMARDs after failure to TNF inhibitors and IL17 inhibitors, therefore, the clinical expert would switch treatments within the same class due to relatively limited treatment options. According to the clinical expert, the study results would not be generalizable to those prior mentioned patients as it is expected that the response rates will be lower in this patient population, which tends to have lower response rates with subsequent treatments in clinical practice. In addition, there was no study site in Canada in the BE MOBILE 2 trial, which may compromise the generalizability of the study results to the clinical practice in Canada.

GRADE Summary of Findings and Certainty of the Evidence

For the pivotal BE MOBILE 2 trial identified in the sponsor's systematic review, Grading of Recommendations, Assessment, Development and Evaluation (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 patient and public drug plans. The following list of outcomes was finalized in consultation with expert committee members: ASAS40, BASDAI, BASFI, NSP, MASES, HRQoL (ASQoL and WPAI-SHP), and SAEs.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The target of the certainty of evidence assessment was the presence or absence of a clinically important effect based on thresholds informed by the clinical expert consulted by CADTH for this review for ASAS40, BASDAI, BASFI, NSP, MASES, ASQoL, and SAEs. For WPAI-SHP, there is no established MID and the clinical expert consulted by CADTH could not provide a threshold of important difference so the target of the certainty of evidence assessment was the presence or absence of any (non-null) effect.

Table 3: Summary of Findings for Bimekizumab Versus Placebo for Patients With Active Ankylosing Spondylitis

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Bimekizumab 160 mg/mL	Difference		
Disease activity and symptom							
Adjusted ASAS40 response rate at Week 16 Follow-up: 16 weeks	332 (1 RCT)	OR: 2.88 (1.71 to 4.87)	198 per 1000	415 per 1000 (333 to 503 per 1000)	218 more per 1,000 (114 to 321 more per 1,000)	Moderate[a]	Bimekizumab likely results in a clinically important increase in the adjusted ASAS40 response rate at Week 16 when compared with placebo.
Change from baseline in BASDAI total score at Week 16 Follow-up: 16 weeks	332 (1 RCT)	NR	1.7 fewer	2.7 fewer (NR)	1.0 fewer (1.5 fewer to 0.6 fewer)	Moderate[b]	Bimekizumab likely results in a clinically important difference in the change from baseline in BASDAI total score at Week 16 when compared with placebo.
Change from baseline in BASFI at Week 16 Follow-up: 16 weeks	332 (1 RCT)	NR	1.0 fewer	2.0 fewer (NR)	1.1 fewer (1.5 fewer to 0.6 fewer)	Moderate[c]	Bimekizumab likely results in a clinically important reduction in BASFI at Week 16 when compared with placebo.
Change from baseline in NSP score (based on NRS) at Week 16 Follow-up: 16 weeks	332 (1 RCT)	NR	1.7 fewer	3.2 fewer (NR)	1.5 fewer (2.0 fewer to 1.0 fewer)	High[d]	Bimekizumab results in a clinically important reduction in NSP score (based on NRS) at Week 16 when compared with placebo.
Adjusted enthesitis-free rate based on the MASES Index at Week 16 in study participants with enthesitis at baseline Follow-up: 16 weeks	199 (1 RCT)	OR: 2.47 (1.30 to 4.68)	239 per 1000	438 per 1000(331 to 550 per 1000)	198 more per 1,000 (63 to 334 more per 1,000)	Moderate[a,e]	Bimekizumab likely results in a clinically important increase in the adjusted enthesitis-free rate based on the MASES Index at Week 16 when compared with placebo.
Health-related quality of life							
Change from baseline in ASQoL total score at Week 16 Follow-up: 16 weeks	332 (1 RCT)	NR	3.1 fewer	4.6 fewer (NR)	1.5 fewer (2.4 fewer to 0.7 fewer)	Moderate[f]	Bimekizumab likely results in a clinically important reduction in ASQoL total score at Week 16 when compared with placebo.
Change from baseline in WPAI-SHP at Week 16: Percent time missed due	239 (1 RCT)	NR	1.2 fewer	5.5 fewer (NR)	2.9 fewer (6.9 fewer to 1.1 more)	Low[e,g]	Bimekizumab may result in a reduction in WPAI-SHP: Percent time missed due to disease-related

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Bimekizumab 160 mg/mL	Difference		
to disease-related problems Follow-up: 16 weeks							problems at Week 16 when compared with placebo. The clinical importance of the reduction is unclear.
Change from baseline in WPAI-SHP at Week 16: Percent impairment while working due to disease-related problems Follow-up: 16 weeks	225 (1 RCT)	NR	6.1 fewer	20.8 fewer (NR)	12.5 fewer (18.1 fewer to 6.8 fewer)	High[e,g]	Bimekizumab results in a reduction in WPAI-SHP: Percent impairment while working due to disease-related problems at Week 16 when compared with placebo. The clinical importance of the reduction is unclear.
Change from baseline in WPAI-SHP at Week 16: Percent overall work impairment due to disease-related problems Follow-up: 16 weeks	225 (1 RCT)	NR	6.7 fewer	22.2 fewer (NR)	12.8 fewer (18.7 fewer to 6.9 fewer)	High[e,g]	Bimekizumab results in a reduction in WPAI-SHP: Percent overall work impairment due to disease-related problems at Week 16 when compared with placebo. The clinical importance of the reduction is unclear.
Change from baseline in WPAI-SHP at Week 16: Percent activity impairment due to disease-related problems Follow-up: 16 weeks	318 (1 RCT)	NR	14.4 fewer	23.3 fewer (NR)	9.4 fewer (13.9 fewer to 4.9 fewer)	High[e,g]	Bimekizumab results in a reduction in WPAI-SHP: Percent activity impairment due to disease-related problems. The clinical importance of the reduction is unclear.
Harms							
Proportion of patients who experienced any serious adverse event(s) at Week 16 Follow-up: 16 weeks	332 (1 RCT)	NR	Bimekizumab: 23 per 1000 (NR) Placebo: 9 per 1000 (NR) Difference: 14 more per 1000 (13 fewer to 40 more per 1000)			Low[h]	Bimekizumab may result in an increase in proportion of patients who experienced any serious adverse event(s) at Week 16 when compared with placebo.

ASAS40 = Assessment of SpondyloArthritis International Society 40%; ASQoL = Ankylosing Spondylitis Quality of Life; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; CI = confidence interval; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; NR = not reported; NRS = numeric rating scale; NSP = Nocturnal Spinal Pain; OR = odds ratio; RCT = randomized controlled trial; WPAI-SHP = Work Productivity and Activity Impairment Questionnaire-specific health problem.

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

[a] –1 level for serious imprecision. There is no established MID but the clinical expert consulted by CADTH considered that a 15% difference between groups in the adjusted ASAS40 response rate and the adjusted enthesitis-free rate at Week 16 could be considered a threshold of clinical importance. For both outcomes, the point estimate and the upper bound of the 95% CI for the between-group difference suggested a clinical important difference for bimekizumab versus placebo while the lower bound of the 95% CI suggested no clinically important difference between the two groups.

[b] –1 level for serious imprecision. There is no established between-group MID but the estimated median MID for the change from baseline is 1.4 points (range = 0.9 to 1.8). The clinical expert consulted by CADTH considered that a 1-point difference between groups in the change from baseline in BASDAI total score at Week 16 could be considered a threshold of clinical importance. The point estimate and the upper bound of the 95% CI for the between-group difference suggested a clinical important difference for bimekizumab versus placebo based on a 1-point threshold while the lower bound of the 95% CI suggested no clinical important difference between the two groups.

[c] –1 level for serious imprecision. There is no established MID for between-group difference but the estimated median MID for the change from baseline is 1.1 points (range = 1.0 to 1.4). The clinical expert consulted by CADTH considered that a 1-point difference between groups in the change from baseline in BASFI at Week 16 could be considered a threshold of clinical importance. The point estimate and the upper bound of the 95% CI for the between-group difference suggested a clinical important difference for bimekizumab versus placebo based on a 1-point threshold while the lower bound of the 95% CI suggested no clinically important difference between the two groups.

[d] Imprecision was not rated down. There is no established between-group MID but the estimated median MID for the change from baseline is 1.5 points (range = 1.1 to 2.3). The clinical expert consulted by CADTH considered that a 1-point difference between groups in the change from baseline in NSP score (based on NRS) at Week 16 could be considered a threshold of clinical importance. The point estimate and the 95% CI for the between-group difference suggested a clinical important difference for bimekizumab versus placebo based on a 1-point threshold.

[e] The statistical testing was not adjusted for multiplicity in the trial and should be considered as supportive evidence

[f] –1 level for serious imprecision. There is no established between-group MID but the estimated median MID for the change from baseline is −2 points for improvement. The clinical expert consulted by CADTH considered that a 2.0-point difference between groups in the change from baseline in ASQoL total score at Week 16 could be considered a threshold of clinical importance. The point estimate and the upper bound of the 95% CI for the between-group difference suggested no clinical important difference for bimekizumab versus placebo while the lower bound of the 95% CI suggested a clinically important difference between the two groups based on a 2-point threshold.

[g] There is no established MID and the clinical expert consulted by CADTH could not provide a threshold of important difference so target of certainty appraisal was any effect for the change from baseline in WPAI-SHP at Week 16. For percent time missed due to problems (related to disease), impression was rated down for 2 levels, the CADTH review team judged that the point estimate suggested a possibility of benefit but the 95% CI for the between-group difference included possibility of both benefit and harm (fewer benefits) for bimekizumab versus placebo. For percent impairment while working due to problems, percent overall work impairment due to problems, and percent activity impairment due to problems, impression was not rated down, the CADTH review team judged that the point estimate and the 95% CI for the between-group difference suggested no clinical important difference for bimekizumab versus placebo.

[h] –2 level for very serious imprecision. The CADTH review team considered the 16-week double-blind follow-up period is not long enough to assess comparative long-term harms. The lower bound of the 95% CI for the between-group difference was below zero while the upper bound was above zero suggested no clinically important difference between the two groups. Additionally, the event rate of SAE(s) was relatively low in either treatment group based on a small sample size.

Source: BE MOBILE 2 final clinical study report (data cut-off date: September 09, 2022).[17] Details included in the table are from the sponsor's Summary of Clinical Evidence.[18]

Long-Term Extension Studies

Description of Studies

One single-arm, Phase 2, OLE study, BE AGILE 2, was submitted by the sponsor as supporting evidence. Patients who had been enrolled in and completed BE AGILE trial were rolled over to BE AGILE 2 (N = 255), which was conducted in European countries and the U.S. All patients in BE AGILE 2 received open-label bimekizumab 160 mg every 4 weeks for up to 204 weeks, i.e., a total possible exposure of 252 weeks for those who have taken bimekizumab in the parent trial, BE AGILE.

Efficacy Results

ASAS40 response was sustained up to week 208 in BE AGILE 2 (147/249 [59%] by non-responder imputation (NRI), 147/201 [73.1%] by observed case data). The mean BASDAI score decreased from baseline value and was sustained by week 208 (n = 249, -4.01, standard error [SE] = 0.13 vs. an MID range of 0.9 – 1.8 points). The mean BASFI score decreased from baseline and sustained at week 208 (n = 249, -3.1 [SE = 0.15]). Relative to baseline, the NSP score decreased and maintained at week 208 (n = 249, -4.55 [SE = 0.16] vs. an MID range of 1.1 – 2.3 points). Also, the mean ASQoL score decreased from baseline and was maintained through week 208 (n = 249, -5.9 [SE = 0.3] vs. an MID range of +1 [worsening] to -2 [improvement] units). Among patients with enthesitis at baseline, the mean MASES score decreased and maintained improvement up to week 208 in BE AGILE 2 (n = 164, -0.37 [SE = 0.23]). WPAI-SHP was not assessed in BE AGILE 2 study.

Harms Results

A total of 237 (92.9%) study participants reported any treatment-emergent adverse event (TEAE) during BE AGILE 2. Most commonly reported TEAEs were nasopharyngitis (18%), upper respiratory tract infection and corona virus infection (12.9% each), and bronchitis (8.6%). There were 46 (18.0%) patients who experienced at least 1 SAE, with corona virus infection and pneumonia being the most common (1.2% each). Twenty-one (8.2%) patients discontinued study treatment due to TEAE mostly due to ALT (1.2%) and AST (0.8%) elevation. Two fatal TEAEs were reported during the study: one incident due to road traffic accident and another incident due to cardiorespiratory arrest. Fungal infection (18.4%) and hypersensitivity (11.4%) were the most common adverse events of special interest reported during BE AGILE 2, where vast majority of fungal infections did not lead to treatment discontinuation (a single patient discontinued due to perirectal abscess).

Critical Appraisal

A lack of a control group, open-label design, and selective patient population are the major limitations of BE AGILE 2 extension study. Open-label design without comparator arm could overestimate results for efficacy outcomes, especially the patient-reported outcomes. Moreover, a risk of selection bias was noted for BE AGILE 2 since patients who have responded to bimekizumab and tolerated side effects are more likely to continue the extension period.

Indirect Comparisons

Description of Studies

The network meta-analyses (NMAs) were performed to determine the clinical efficacy and safety of bimekizumab, compared with other relevant interventions at Weeks 12-16, for the treatment of patients with AS. The NMAs were conducted on three different networks: purely naïve (100% bDMARD-naïve, 24 studies, 4,145 patients), predominantly naïve (~90% bDMARD-naïve, 26 studies, 5,271 patients), and purely experienced (100% bDMARD-experienced, 9 studies, 1,048 patients).

The unanchored matching-adjusted indirect comparisons (MAIC) were performed to establish long-term relative clinical efficacy of bimekizumab compared to other IL-17A inhibitors in patients with AS at Week 52.

Efficacy Results

Network meta-analyses

In the *bDMARD pure naïve network*, for most comparisons between bimekizumab versus TNFi's, IL-17i's or JAKi's, there were no clear differences observed. The exceptions to this were two findings in which bimekizumab showed statistically significant improvement in SF-36 PCS results compared to adalimumab and compared to secukinumab but the differences observed were not clinically significant and the credible intervals were wide, indicating uncertainty.

In the *bDMARD predominantly naïve network*, for most comparisons between bimekizumab versus TNFi's, IL-17i's or JAKi's, there were no clear differences observed. There were some exceptions to this general observation which were statistically significant differences, but these were not clinically significant and credible intervals were wide, indicating uncertainty. Bimekizumab showed improvement in SF-36 PCS and Assessment of SpondyloArthritis International Society (ASAS-PR) results compared to secukinumab. Results favoured etanercept compared to bimekizumab for BASDAI50 and BASFI. Results favoured golimumab IV compared to bimekizumab for BASFI and ASQoL. Results favoured adalimumab and certolizumab over bimekizumab for Ankylosing Spondylitis Disease Activity Score – inactive disease (ASDAS-ID). Results favoured tofacitinib over bimekizumab for BASMI. Results favoured upadacitinib over bimekizumab for ASDAS-ID.

In the *bDMARD experienced network,* for most comparisons between bimekizumab versus TNFi's, IL-17i's or JAKi's, there were no clear differences observed. The exceptions to this were two findings in which results favoured certolizumab over bimekizumab for ASQoL and SF-36 PCS. In these two instances, the difference may be clinically significant, but the credible intervals were wide, indicating uncertainty, and these results were not confirmed in the other networks.

Matching-adjusted indirect comparison

MAIC analyses suggested that bimekizumab 160 mg Q4W had statistically significantly better results at Week 52 compared with ixekizumab 80 mg Q4W for ASAS20, ASAS40 and BASDAI-Change from baseline and BASDAI50. Results also favoured bimekizumab over secukinumab 150 mg Q4W for ASAS40 and BASDAI-Change from baseline. However, there were significant limitations to the MAIC that preclude making claims of superiority of bimekizumab over comparators.

Harms Results

Network meta-analyses

The sponsor conducted NMAs of bimekizumab compared to other medications in the context of axial spondyloarthritis for two harms outcomes: discontinuation due to any reason and serious adverse events. The comparators of interest with data available for this NMA were IL-17A inhibitors ixekizumab and secukinumab, Tumour necrosis factor-α inhibitors adalimumab, certolizumab pegol, etanercept, golimumab (SC or IV routes) and infliximab (IV), Janus kinase inhibitors tofacitinib and Upadacitinib.

The network for analysis of discontinuation due to any reason contained 18 studies. Study discontinuation rates were low in all trials (range: 0-14 patients per treatment arm). Time points between 12-16 weeks were used for this analysis. Credible intervals were very wide for most estimates. There were no clear differences seen between bimekizumab and any other treatment. There was one finding in which bimekizumab had a higher risk of study discontinuation compared to tofacitinib, however, the uncertainty around this estimate was high as reflected by a wide credible interval.

The network for analysis of SAE's contained 18 studies. SAE rates were low in all studies (range 0-10 SAE's per treatment arm). Time points between 12-16 weeks were used for this analysis. Credible intervals were very wide for most estimates. There were no clear differences between bimekizumab and any other treatments in the network.

Matching-adjusted indirect comparison

There were no harms outcomes assessed in the MAIC.

Critical Appraisal

Network meta-analyses

The sponsor conducted an NMA using a Bayesian approach. This was a reasonable method to apply given the common comparator of placebo. The sponsor's decision to perform 3 separate NMA analyses based on the potential effect modifier of prior exposure to bDMARDs was appropriate. Some networks had a large number of trials and a large number of patients which were considered a strength of the NMA analyses. The sponsor did not perform sensitivity analyses in the NMA and did not attempt to identify and adjust for effect modifiers despite the availability of a large number of trials for some of the networks. The time point of 12-16 weeks that was selected for outcome analyses was reasonable and clinically relevant for efficacy but not as meaningful for harms since an assessment of long-term harms was lacking.

Confidence intervals and credible intervals were wide for many estimates in the NMA. Despite the large number of trials, the number of patients and events in some analyses were small, precluding the possibility of detecting a difference between treatments. For example, the incidence of harms outcomes was small, resulting in very wide credible intervals around the estimates. For this reason, the results of the harms analyses were not informative and did not serve to illuminate the risk of harms for bimekizumab relative to other treatments.

Matching-adjusted indirect comparison

The sponsor performed an unanchored MAIC because of the lack of a placebo arm beyond week 16 for bimekizumab and comparators. This was an adequate justification for performing a MAIC. The selection of comparators from the same pharmacologic group (IL-17A inhibitors) was a rational approach, but comparisons to other biologics would also have been of interest. The MAIC allowed a comparison of 52 weeks of clinical data. The MAIC analyses suggested there were some differences favouring bimekizumab compared to secukinumab and ixekizumab for ASAS20, ASAS40 BASDAI-Change from baseline and BASDAI50 but several limitations of the MAIC prevent drawing strong conclusions regarding the comparative effectiveness of bimekizumab. For example, there were important differences between the studies included in the MAIC that did not account for several of the prognostic factors that were deemed important by the authors of the MAIC, were not used in the weighting adjustments of the MAIC. There were notable differences in study populations before and after adjustment. In the MAIC analyses, the ESS for the bimekizumab group was reduced to 80% for the comparison to secukinumab 150 mg, 51% for the comparison to secukinumab 300 mg, and 20% for the comparison to ixekizumab. Not all matching variables that were deemed important were used in the weighting adjustments of the MAIC analyses. Regarding the MAIC analyses, the sponsor noted that "the amount of bias in the indirect comparisons are likely to be substantial" and CADTH reviewers agree with this assessment.

Summary

Results of the sponsor's NMA did not show consistent differences between bimekizumab and comparators in the networks for efficacy or harms outcomes. While differences were reported in a small number of comparisons in some populations, these were associated with wide 95% CrIs for many of the comparisons, indicating imprecision of the results.

Results of the sponsor's MAIC favoured bimekizumab for some outcomes but there were significant limitations. The limitations include differences in study design and providing models with partial adjustments of prognostic and effect modifiers rather than fully adjusted. These limitations, in addition to the substantial reduction in effective sample sizes, undermine any claims of superior performance of bimekizumab over comparators in the MAIC.

Neither the NMA nor the MAIC provided clear evidence of a difference in efficacy or harms outcomes for bimekizumab versus comparators.

Studies Addressing Gaps in the Evidence From the Systematic Review

The BE MOBILE 1 trial was a phase 3, multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of bimekizumab in patients with active nr-axSpA. The sponsor identified the BE MOBILE 1 study as the study addressing the gap in efficacy and safety of bimekizumab in patients with active nr-axSpA. The CADTH review team considered the BE MOBILE 1 trial not relevant to this review as patients with active nr-axSpA are different than patients with active AS for whom the indication is

being reviewed. Therefore, the CADTH review team notes that no studies addressing gaps in the systematic review evidence were identified for this review.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Decision tree plus Markov model
Target population	Adult patients with active ankylosing spondylitis (AS)
Treatment	Bimekizumab
Dose regimen	160 mg (given as one subcutaneous injection) every 4 weeks
Submitted price	Bimekizumab, 160 mg/ 1mL, subcutaneous injection: $1,625.00
Submitted treatment cost	$21,198 annually
Comparators	• Adalimumab, etanercept, golimumab, infliximab, secukinumab, certolizumab pegol, ixekizumab, upadacitinib, tofacitinib, and • Conventional care (defined as recommended first-line treatment of AS including non-pharmacological management and non-steroidal anti-inflammatory drugs [NSAIDs])
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (75 years)
Key data sources	Comparative clinical efficacy was derived from a sponsor-submitted network meta-analysis (NMA) based on data from the BE MOBILE 2 and comparator treatment trials to inform the probability of BASDAI50 and difference in mean change from baseline in clinical scores for BASDAI and BASFI response at 12-16 weeks.
Submitted results	• In the sequential analysis, 3 comparators (conventional care, tofacitinib, and etanercept) were on the cost-effectiveness frontier. • Bimekizumab was dominated (more costs and fewer QALYs) by tofacitinib, etanercept, adalimumab, infliximab, upadacitinib, golimumab and certolizumab pegol.
Key limitations	• The efficacy and safety of bimekizumab relative to other biologic DMARDs for the treatment of active AS is uncertain owing to a lack of head-to-head trials and limitations with the sponsor's NMAs. Indirect evidence submitted by the sponsor did not show clear differences in the efficacy or safety of bimekizumab compared to other currently available treatments for active AS. Findings were inconsistent in the NMA and confidence intervals were wide.
CADTH reanalysis results	• There is insufficient clinical evidence to justify a price premium for bimekizumab relative to currently available treatments for active AS.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the total number of eligible patients was inaccurately estimated, the NIHB population was inappropriately calculated, the total population size is uncertain given the trial eligibility criteria, and the proportion of adult patients with AS requiring biologic/advanced therapies is uncertain. Based on the CADTH reanalysis, the three-year budget impact to public drug plans of introducing bimekizumab for the treatment of adult patients with AS is expected to be $1,464,006 (-$533,456 in Year 1, $473,163 in Year 2, and $1,524,299 in Year 3). In a scenario analysis exploring the impact of reimbursing bimekizumab for the treatment of adult patients with moderate-to-severe AS, the three-year budget impact is expected to be $1,601,864.

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, Ms. Alicia McCallum, Dr. Srinivas Murthy, Dr. Danyaal Raza, Dr. Edward Xie, and Dr. Peter Zed.

Meeting date: March 27, 2024

Regrets:

2 of the expert committee members did not attend.

Conflicts of interest:

None