Canadian Journal of Health Technologies
June 2024 Volume 4 Issue 6

CADTH Reimbursement Recommendation

Bimekizumab (Bimzelx)

Indication: For the treatment of adult patients with active psoriatic arthritis. Bimekizumab can be used alone or in combination with a conventional non-biologic disease-modifying antirheumatic drug (e.g., methotrexate).

Sponsor: UCB Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Bimzelx?

CADTH recommends that Bimzelx be reimbursed by public drug plans for the treatment of active psoriatic arthritis (PsA) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Bimzelx should only be covered to treat adult patients with active PsA according to the reimbursement criteria used for other biologic disease-modifying antirheumatic drugs (bDMARDs) that are currently reimbursed by public drug plans.

What Are the Conditions for Reimbursement?

Bimzelx should only be reimbursed if it is prescribed by a rheumatologist or a clinician who has experience treating adult patients with active PsA and if it does not cost more than the least expensive bDMARD reimbursed for the treatment of active PsA. Bimzelx should not be reimbursed when used together with other biologic or targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) for active PsA.

Why Did CADTH Make This Recommendation?

- Evidence from 2 clinical trials demonstrated that Bimzelx improves PsA symptoms compared to treatment with placebo.
- Bimzelx may meet some of the needs that are important to patients, including reducing symptoms such as joint pain, clearing psoriasis, and improving health-related quality of life.
- Based on CADTH's assessment of the health economic evidence, Bimzelx does not represent good value to the health care system at the public list price. The committee determined that there is insufficient evidence to justify a cost premium for Bimzelx over the least expensive bDMARD reimbursed for PsA.
- Based on public list prices, Bimzelx is estimated to cost the public drug plans approximately $5.7 million over the next 3 years. The estimated budget impact is sensitive to the number of patients who are expected to receive Bimzelx and the source of Bimzelx market share.

Additional Information

What Is PsA?

Arthritis is the chronic swelling and tenderness of 1 or more joints. There are different types of arthritis, 1 of which is PsA. People with PsA often

Summary

have skin lesions associated with psoriasis and inflamed joints, including the joints of the arms, legs, fingers, toes, and spine. Pain and stiffness of the affected joints are the most common symptoms, and many patients also experience fatigue. The prevalence of PsA in Canada is estimated to be 1.5 per 1,000 people.

Unmet Needs in PsA

Although many treatments for active PsA are reimbursed in Canada, some patients may have active disease that does not respond to these treatments. Other treatment options are needed for these patients.

How Much Does Bimzelx Cost?

Treatment with Bimzelx is expected to cost approximately $21,198 to $27,698 per patient in the first year and $21,198 per patient in subsequent years.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that bimekizumab be reimbursed for the treatment of adult patients with active psoriatic arthritis (PsA) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

In 2 double-blind (DB) randomized clinical trials (RCTs) in adult patients with active PsA who had no prior exposure to biologic therapies (the BE OPTIMAL trial) or who had a history of inadequate response or intolerance to 1 or 2 tumour necrosis factor inhibitors (TNFis) (the BE COMPLETE trial), bimekizumab 160 mg every 4 weeks was associated with statistically significant and clinically meaningful improvements compared with placebo in the proportion of patients with at least a 50% improvement in American College of Rheumatology response criteria (ACR50) at week 16. The difference between the bimekizumab group and the placebo treatment group was 31.2% (95% confidence interval [CI], 25.2% to 37.3%; P < 0.001) in the BE OPTIMAL trial and 29.0% (95% CI, 21.9% to 36.2%; P < 0.001) in the BE COMPLETE trial. Furthermore, bimekizumab 160 mg was associated with statistically significant improvements when compared with placebo for other clinically relevant manifestations of PsA, including function and disability, as measured with the Health Assessment Questionnaire – Disability Index (HAQ-DI); health-related quality of life (HRQoL), as measured by the Physical Component Summary (PCS) component of the Short Form (36) Health Survey (SF-36); skin disease, as measured by the Psoriasis Area and Severity Index (PASI); and other measures of clinical response or disease control, such as minimal disease activity (MDA).

Patient input received for this review indicated that there is a need for new PsA treatment alternatives that are effective in reducing PsA symptoms, including joint pain, clearing psoriasis, and improving HRQoL. Based on the results from the BE OPTIMAL and BE COMPLETE trials, bimekizumab appears to address some of these important outcomes valued by patients.

At the sponsor-submitted price for bimekizumab and publicly listed price for all relevant comparators, bimekizumab was more costly than some relevant comparators used in the treatment of adults with active PsA who are treatment-naive or treatment-experienced. Given the limitations and uncertainty associated with the sponsor-submitted network meta-analysis (NMA), there is insufficient evidence to justify a cost premium over the least expensive biologic disease-modifying antirheumatic drugs (bDMARDs) reimbursed for the treatment of active PsA.

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	There is no direct evidence that bimekizumab is clinically superior or inferior to other biologic treatments currently reimbursed for the treatment of active PsA.	–

Reimbursement condition	Reason	Implementation guidance
bDMARDs for the treatment of adult patients with active PsA.		
Renewal		
2. Bimekizumab should be renewed in a similar manner to other bDMARDs currently reimbursed for the treatment of adult patients with active PsA.	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 PsA.	There is no evidence that bimekizumab should be held to a different standard than other reimbursed options when considering discontinuation.	—
Prescribing		
4. Patients should be under the care of a rheumatologist or a clinician who has experience treating adult patients with active PsA.	Accurate diagnosis and follow-up of patients with active PsA 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 PsA.	There is no evidence to determine the effects of bimekizumab when used in combination with bDMARDs or tsDMARDs in adult patients with active PsA.	—
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 PsA.	There is insufficient evidence to justify a cost premium for bimekizumab over the least expensive bDMARD reimbursed for PsA.	—

bDMARD = biologic disease-modifying antirheumatic drug; DMARD = disease-modifying antirheumatic drug; PsA = psoriatic arthritis; tsDMARD = targeted synthetic disease-modifying antirheumatic drug.

Discussion Points

- Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment of selected outcomes from the BE OPTIMAL and BE COMPLETE trials concluded with high certainty that treatment with bimekizumab results in an increase in the proportion of patients who experience at least a 20%, 50%, and 70% improvement in American College of Rheumatology response criteria (ACR20, ACR50, and ACR70), and MDA when compared with placebo in patients with no prior exposure to biologics and patients with a history of inadequate response or intolerance to 1 or 2

TNFis. In addition, based on the evidence from the 2 trials, adults with PsA who receive bimekizumab 160 mg every 4 weeks were more likely to demonstrate clinically meaningful improvements in dermatological manifestations (i.e., psoriasis), physical function, HRQoL, and pain at week 16. Results were generally consistent whether patients were biologic-naive or TNFi-experienced. Evidence that bimekizumab reduces the number of musculoskeletal manifestations (e.g., enthesitis, dactylitis, or swollen joints) was less certain as per the GRADE assessment, but demonstrated a consistent direction of effect.

- CDEC noted that there was no adequate direct evidence available to assess the safety and efficacy of bimekizumab versus other bDMARDs or targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) for the treatment of PsA. Indirect evidence was available from 2 indirect treatment comparisons (ITCs) (1 sponsor-submitted NMA and 1 matching-adjusted indirect comparison [MAIC]) that examined the comparative short-term efficacy and safety of bimekizumab versus other bDMARDs or tsDMARDs. The ITCs were limited by the heterogeneity in the study designs and patient populations across the included studies and by the uncertainty in the indirect estimates of effect. Given these limitations, there remains uncertainty in the comparative efficacy and safety of bimekizumab compared to other available bDMARD and tsDMARD therapies.
- CDEC noted that bimekizumab is an additional treatment option for adult patients with active PsA. However, with the lack of direct evidence with relevant comparators and the uncertainty in the results from the sponsor-submitted ITCs, it is uncertain whether bimekizumab has any particular advantages over existing bDMARD or tsDMARD treatment options for active PsA.
- CDEC discussed the place in therapy of bimekizumab. According to the clinical expert, bimekizumab may be used as first-line or second-line biologic therapy. The clinical expert indicated that bimekizumab may be a preferred first-line treatment for patients with severe psoriasis in addition to musculoskeletal disease.
- CDEC noted that there is no direct, long-term evidence comparing bimekizumab to other bDMARDs or tsDMARDs available in Canada. In addition, the sponsor-submitted ITCs used study results collected over a relatively short duration. Because PsA is a chronic condition that requires lifelong treatment, there is uncertainty regarding the long-term effectiveness and safety of bimekizumab over other currently available bDMARDs or tsDMARDs for the treatment of active PsA.
- CDEC noted that the MAIC, which assessed ACR20, ACR50, ACR70, and MDA at week 52, had several limitations that preclude conclusions from being made with certainty.
- Patient groups indicated the need for a treatment that would improve HRQoL with minimal adverse effects. The sponsor-submitted ITC did not assess comparative HRQoL or safety. Hence, there is no evidence that bimekizumab would improve HRQoL or have a lower rate of adverse events (AEs) compared with other currently available bDMARDs or tsDMARDs for the treatment of active PsA.

Background

PsA is chronic inflammatory, immune-mediated disease with heterogeneous presentation and disease course in which patients commonly present with peripheral arthritis and psoriasis. Joint inflammation associated with PsA is known to worsen over time and, if left untreated, can lead to permanent joint damage and long-term disability. Global prevalence estimates for PsA vary and are estimated to be 1 to 2 per 1,000 people in the general population. A population-based Canadian study, conducted in Ontario, estimated the age- and sex-standardized cumulative prevalence of PsA to range from 0.9 per 1,000 people in 2008 to 1.5 per 1,000 people in 2015.

The goals of treatment for managing PsA include attaining the lowest level of disease activity (with a target of disease remission), maximizing functional status and HRQoL, preventing further disease progression, controlling symptoms, and avoiding complications. First-line pharmacological treatment typically includes disease-modifying antirheumatic drugs (DMARDs), such as conventional DMARDs (cDMARDs) (e.g., methotrexate, sulfasalazine, leflunomide, or cyclosporine). Later-line targeted treatments are usually reserved for patients who have an inadequate response to cDMARDs, and include bDMARDs (e.g., TNFis, interleukin-17 inhibitors [IL-17is], interleukin-12 and interleukin−23 inhibitors [IL-12/23is], and interleukin-23 inhibitors [IL-23is]) and tsDMARDs (e.g., Janus kinase inhibitors [JAKis] and phosphodiesterase type 4 inhibitors [PDE4is]). Continuation of cDMARDs may be necessary until effectiveness of the targeted therapies is confirmed.

Bimekizumab has been approved by Health Canada for the treatment of adult patients with active PsA and can be used alone or in combination with a cDMARD (e.g., methotrexate). Bimekizumab is a humanized immunoglobulin G1 kappa monoclonal antibody. It is available as a 160 mg/mL solution for subcutaneous (SC) injection, and the dosage recommended in the product monograph is 160 mg (given as 1 SC injection of 160 mg) every 4 weeks.

Sources of Information Used by the Committee

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

- a review of 2 double-blind RCTs in adults with active PsA
- patients' perspectives gathered by 7 patient groups, including Arthritis Consumer Experts, the Canadian Psoriasis Network, Arthritis Society Canada, the Canadian Arthritis Patient Alliance, the Canadian Association of Psoriasis Patients, the Canadian Spondyloarthritis Association, and CreakyJoints
- input from public drug plans that participate in the CADTH review process
- 1 clinical specialist with expertise in diagnosing and treating patients with PsA
- input from 1 clinician group, including the Canadian Rheumatology Association
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Input submitted for this review noted that joint stiffness, fatigue, and pain were the most challenging symptoms to manage. According to the respondents, PsA interfered with their physical activity, sleep, work, social life, mental health, intimacy, and self-esteem. It was also noted that caregivers had to take on additional tasks or daily chores due to patients' reduced mobility and the impact the disease has on patients' mental and social health.

Survey results showed that 32% of respondents found nonsteroidal anti-inflammatory drugs (NSAIDs) effective, 39% found DMARDs effective, 40% found biologic therapies effective (with 24% rating them as very effective), and 44% found steroids effective. Respondents indicated that efficacious treatments are costly and accessing them was challenging, and adverse effects can be very difficult to manage. Among the 3 respondents who had experience with bimekizumab for PsA, 1 respondent noted that treatment was easy to use and effective in improving HRQoL without adverse effects.

Patients seek treatments that improve disease symptoms, improve HRQoL, have fewer adverse effects, are easier to administer, accessible, and affordable.

Clinician Input

Input From the Clinical Expert Consulted by CADTH

Despite there being various treatment options for managing PsA, the clinical expert stated that not all patients' symptoms respond to available therapies and that treatments tend to improve disease in some domains but have variable or suboptimal efficacy in others. There is also concern over safety with all DMARDs, including increased risk of infection and new onset or worsening of comorbidities. According to the expert, few patients experience a state of low disease activity, and it is important to have safe, well-tolerated treatments that are effective in all domains.

The clinical expert indicated that bimekizumab would be used after failure of cDMARDs and, in accordance with its Health Canada indication, with or without a cDMARD. Additionally, it was noted that without good quality evidence to support combination therapy, bimekizumab would not likely be used concomitantly with other bDMARDs or tsDMARDs at this time.

The expert was of the opinion that any patient with active PsA could receive bimekizumab, particularly those with coexisting severe psoriasis, but that the drug would be avoided in those with inflammatory bowel disease (IBD), severe uveitis, or active infection. It was also noted that patients with an inadequate response to targeted DMARDs are most in need of new treatments.

According to the clinical expert, treatment response is typically assessed at 3 months based on improvements in the number of tender and swollen joints, enthesitis, dactylitis, skin psoriasis, and sometimes using composite indices (e.g., MDA or Disease Activity in Psoriatic Arthritis [DAPSA]). Improvements in physical function, pain, fatigue, and lack of radiographic progression (the last of which

is not typically used in clinical practice) may take longer than 3 months in patients with longstanding PsA. Moreover, due to the heterogeneity of the disease, response can differ across patients, although the clinical expert suggested that assessments are not likely to vary among rheumatologists.

The clinical expert stated that lack of response in musculoskeletal or skin domains, disease relapse, intolerance, and patient choice are the most important factors when considering discontinuation of bimekizumab. It was explained that some amount of disease activity can be considered acceptable, but that recurrent infections and IBD would require discontinuation.

The expert noted that a PsA diagnosis should be made by a rheumatologist trained in identifying inflammatory arthritis. Patients are typically treated in an outpatient setting, though severe disease may require hospital admission, and treatment of PsA involves a rheumatologist as well as a dermatologist to manage the associated psoriasis.

Clinician Group Input

According to the Canadian Rheumatology Association, the treatment goals, unmet needs, patient population, and reasons for discontinuation described by the clinician group largely aligned with those noted by the clinical expert consulted by CADTH. The group suggested that measures of treatment response also include improvement in axial disease, patient global impression, PASI, and body surface area (BSA) affected by psoriasis. They also noted that composite measures such as Composite Psoriatic Disease Activity Index, DAPSA, and Psoriatic Arthritis Disease Activity Score can be used, but they are not practical for everyday use in clinics. For axial disease, the most frequently used measure for disease activity in Canada is the Bath Ankylosing Spondylitis Disease Activity Index. The group indicated that a specialist would be required to prescribe bimekizumab and monitor for AEs, but because the drug is administered as an SC injection, a patient could self-administer it.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for bimekizumab:

- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy.

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

Implementation issues	Response
Considerations for initiation of therapy	
The most recent recommendation for a bDMARD for the treatment of PsA (guselkumab) has the following initiation criterion: Eligibility for this drug 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 PsA. Should the initiation of therapy criteria for PsA biologic drugs and JAKis be applied to bimekizumab?	CDEC agreed with the clinical expert consulted by CADTH that the same initiation criteria can be applied to bimekizumab.
Is there a potential indication for bimekizumab to treat juvenile PsA?	The expert expects that, with adequate evidence from good quality trials in a younger population, bimekizumab could be a treatment for juvenile PsA. CDEC noted that patients with juvenile PsA are outside this recommendation scope.
What is an adequate trial for other DMARDs before accessing bimekizumab (or other advanced PsA treatments)?	The clinical expert noted to CDEC that, in general, an adequate trial of 3 months at the recommended therapeutic dose is necessary to see if a patient is responding to a cDMARD, bDMARD, or tsDMARD before switching to or adding another therapy.
Considerations for continuation or renewal of therapy	
The most recent recommendation for a bDMARD for the treatment of PsA (guselkumab) has the following renewal criterion: This drug should be renewed in a similar manner to other bDMARDs currently reimbursed for the treatment of adult patients with active PsA. Should the continuation of therapy criteria for PsA biologic drugs and JAKis be applied to bimekizumab?	CDEC agreed with the clinical expert consulted by CADTH that the same renewal criteria can be applied to bimekizumab.
Considerations for discontinuation of therapy	
The most recent recommendation for a bDMARD for the treatment of PsA (guselkumab) has the following discontinuation criterion: This drug should be discontinued in a similar manner to other bDMARDs currently reimbursed for the treatment of adult patients with active PsA. Should the discontinuation of therapy criteria for PsA biologic drugs and JAKis be applied to bimekizumab?	CDEC agreed with the clinical expert consulted by CADTH that the same discontinuation criteria can be applied to bimekizumab.
Considerations for prescribing of therapy	
The most recent recommendation for a bDMARD for the treatment of PsA (guselkumab) has the following prescribing criterion: Patients should be under the care of a rheumatologist or a clinician who has experience treating adult patients with active PsA. Should the same prescribing criteria for PsA biologic drugs and JAKis be applied to bimekizumab? If a rheumatologist is not accessible (e.g., in remote areas),	CDEC agreed with the clinical expert consulted by CADTH that the same prescribing criteria can be applied to bimekizumab. The expert indicated that a patient should be diagnosed, treated, and managed by a rheumatologist. In situations where a rheumatologist cannot be accessed, the expert suggested that acceptable specialists can include internists or dermatologists.

Implementation issues	Response
which health care providers should be able to prescribe bimekizumab and manage patients receiving the drug?	
The most recent recommendation for a bDMARD for the treatment of PsA (guselkumab) has the following combination criterion: This drug should not be reimbursed when used in combination with bDMARDs or tsDMARDs for active PsA. Should the same criteria for PsA biologic drugs and JAKis be applied to bimekizumab? Can bimekizumab be used concomitantly with other DMARDs (e.g., cDMARDs, bDMARDs, tsDMARDs)?	CDEC agreed with the clinical expert consulted by CADTH that the same criteria can be applied to bimekizumab. The Health Canada indication for adults with active PsA states that bimekizumab can be used alone or in combination with a cDMARD (e.g., methotrexate). However, there is currently limited evidence supporting concomitant use of bimekizumab with bDMARDs or tsDMARDs for the treatment of PsA.
If treatment with bimekizumab fails and a patient is switched to another treatment, would a patient ever be re-treated with bimekizumab?	The clinical expert noted to CDEC that, from a clinical practice standpoint, it would be possible to return to a drug that was previously used.

bDMARD = biologic disease-modifying antirheumatic drug; cDMARD = conventional disease-modifying antirheumatic drug; DMARD = disease-modifying antirheumatic drug; JAKi = Janus kinase inhibitor; IL = interleukin; PsA = psoriatic arthritis; TNFi = tumour necrosis factor inhibitor; tsDMARD = targeted synthetic disease-modifying antirheumatic drug.

Clinical Evidence

Pivotal Studies and RCT Evidence

Description of Studies

Two double-blind RCTs of adults with active PsA who had no prior exposure to biologic therapies (the BE OPTIMAL trial, N = 852) or who had a history of inadequate response or intolerance to 1 or 2 TNFis (the BE COMPLETE trial, N = 400) assessed whether bimekizumab 160 mg for SC injection every 4 weeks increased the proportion of patients with an ACR50 response compared to placebo at 16 weeks. ACR50 response is defined as an improvement of at least 50% in both swollen and tender joint counts, and at least 3 of 5 additional disease criteria. Other clinically relevant outcomes included measurement of MDA, musculoskeletal response, skin response, and changes in function and symptom scores. Patients received either bimekizumab or placebo during the 16-week DB phase of each trial. After 16 weeks in the BE OPTIMAL trial, patients randomized to placebo were reallocated to bimekizumab for the 36-week active treatment-blind phase.

In the BE OPTIMAL trial, the mean age of patients ranged from 48.5 years (standard deviation [SD] = 12.6 years) to 48.7 years (SD = 11.7 years), and demographic characteristics were generally similar between the bimekizumab and placebo groups. The mean time since diagnosis of PsA was approximately 6 years and mean time since diagnosis of psoriasis was approximately 15 years. Baseline clinical characteristics were generally balanced between the 2 treatment groups, except for the presence of enthesitis being higher in the bimekizumab group (33.2%) compared to the placebo group (24.9%). In the BE COMPLETE trial, the mean age of patients ranged from 50.1 years (SD = 12.4 years) to 51.3 years (SD = 12.9 years) and demographic characteristics were generally similar between the bimekizumab and placebo groups. The mean time since

diagnosis of PsA was more than 9 years and mean time since diagnosis of psoriasis was more than 17 years across the treatment groups. More than 76% of patients had an inadequate response to at least 1 TNFi and more than 11% of patients to at least 2 TNFis, and approximately 12% had an intolerance to TNFis. Baseline clinical characteristics were imbalanced between the 2 treatment groups for the presence of enthesitis (higher in the bimekizumab group), NSAID therapy (lower in the bimekizumab group), and methotrexate use (higher in the bimekizumab group).

Efficacy Results

Signs and symptoms of disease activity were measured by American College of Rheumatology (ACR) response, MDA, Patient's Assessment of Arthritis Pain (PtAAP), and swollen joint count (SJC).

ACR Response

In the BE OPTIMAL trial, a greater proportion of patients in the bimekizumab treatment group reached the primary end point of ACR50 at week 16 than in the placebo group; the difference between treatment groups was 31.2% (95% CI, 25.2% to 37.3%; P < 0.001) for ACR50. Similarly, a greater proportion of patients in the bimekizumab treatment group experienced an ACR20 response and an ACR70 response (corresponding to improvements of at least 20% and 70%, respectively, in both swollen and tender joint counts and at least 3 of 5 additional disease criteria) at week 16 than in the placebo group. The difference between treatment groups was 37.2% (95% CI, 30.5% to 44.0%) for ACR20, and 19.3% (95% CI, 14.1% to 24.5%) for ACR70. Week 52 ACR results during the active treatment-blind period for all 3 ACR thresholds indicated that response rates increased in both groups and that there was a similar response between patients who crossed over from placebo to bimekizumab and those originally randomized to bimekizumab.

In the BE COMPLETE trial, a greater proportion of patients in the bimekizumab treatment group reached the primary end point of ACR50 at week 16 than in the placebo group; the difference between treatment groups was 29.0% (95% CI, 21.9% to 36.2%; P < 0.001) for ACR50. Similarly, a greater proportion of patients in the bimekizumab treatment group reached the ACR20 and ACR70 at week 16 than in the placebo group, the difference between treatment groups was 52.8% (95% CI, 43.6% to 61.9%) for ACR20 and 17.2% (95% CI, 12.2% to 22.2%) for ACR70. A larger proportion of patients in the bimekizumab group compared to the placebo group had an ACR50 response for each of the subgroup categories of inadequate response to 1 TNFi (47.8% versus 6.8%), inadequate response to 2 TNFis (20.0% versus 0%), and intolerance to TNFis (38.2% versus 13.3%) in the bimekizumab and placebo treatment groups, respectively.

Minimal Disease Activity

Signs and symptoms of disease activity were also measured by MDA, where MDA is a composite end point and is considered to be experienced if at least 5 of the 7 criteria are reached: tender joint count (TJC) of 0 or 1, SJC of 0 or 1, PASI of 1 or lower or affected BSA of 3% or less, pain visual analogue scale score of 15 or lower, Patient's Global Assessment of Psoriatic Arthritis visual analogue scale score of 20 or lower, HAQ-DI of 0.5 or lower, and tender entheseal points of 0 or 1.

In the BE OPTIMAL trial, for clinical responses measured with the MDA criteria, patients treated with bimekizumab had higher response rates compared with placebo at week 16. The difference between

treatment groups was 31.0% (95% CI, 24.5% to 37.5%; P < 0.001). MDA results at week 52 of the active treatment-blind period indicated that response rates increased in both groups and that there was a similar response between placebo-bimekizumab crossover patients and patients originally randomized to bimekizumab.

In the BE COMPLETE trial, patients treated with bimekizumab had higher response rates compared with placebo at week 16. The difference between treatment groups was 34.2% (95% CI, 26.1% to 42.2%; P < 0.001).

Patient's Assessment of Arthritis Pain

PtAAP is a 100-point visual analogue scale for patients to record their arthritis pain from 0 (no pain) to 100 (most severe pain). The minimally important difference (MID) from the literature is estimated to be a 10-point decrease from baseline.

In the BE OPTIMAL trial, the bimekizumab group had a greater mean decrease from baseline (i.e., improvement) in PtAAP compared with the placebo group at week 16. The mean difference between treatment groups was −19.1 (95% CI, −22.7 to −15.5). PtAAP results at week 52 indicated that the response was maintained in the bimekizumab group and that there was a similar response between patients who crossed over from placebo to bimekizumab and patients originally randomized to bimekizumab during the active treatment-blind period.

In the BE COMPLETE trial, the mean difference between treatment groups was −25.0 (95% CI, −30.0 to −20.0).

Swollen Joint Count

SJC evaluation includes 6 joints of the upper body, 34 joints of the upper extremities, and 26 joints of the lower extremities for a total of 66 joints. Each joint is assessed using a 2-point scale: 0 for no swelling and 1 for swollen joints.

In the BE OPTIMAL trial, at week 16, the mean reduction at week 16 was greater in the bimekizumab group compared to the placebo group, with the mean difference between treatment groups was −4.0 joints (95% CI, −4.8 to −3.1). SJC results at week 52 indicated that response was maintained in the bimekizumab group and that there was a similar response between placebo-bimekizumab crossover patients and patients originally randomized to bimekizumab during the active treatment-blind period.

In the BE COMPLETE trial, at week 16, the mean reduction at week 16 was greater in the bimekizumab group compared to the placebo group; the mean difference between treatment groups was −5.3 joints (95% CI, −6.5 to −4.2).

Measurement of Other Musculoskeletal Disease

The impact of treatment on musculoskeletal disease was assessed by measuring resolution of enthesitis (with the Leeds Enthesitis Index [LEI]), and resolution of dactylitis (with the Leeds Dactylitis Index [LDI]).

Enthesitis-Free State Based on Leeds Enthesitis Index

For the pooled population of patients with enthesitis at baseline in the BE OPTIMAL and BE COMPLETE trials, a greater proportion of patients in the bimekizumab treatment group had resolution of enthesitis (LEI = 0) at week 16 than in the placebo group; the difference between treatment groups was 14.9% (95% CI, 4.0% to 25.9%; P = 0.008).

Dactylitis-Free State Based on Leeds Dactylitis Index

For the pooled population of patients with dactylitis at baseline in the BE OPTIMAL and BE COMPLETE trials, a greater proportion of patients in the bimekizumab treatment group had resolution of dactylitis (LDI = 0) at week 16 than in the placebo group; the difference between treatment groups was 29.4% (95% CI, 11.7% to 47.1%; P = 0.002).

Measurement of Skin Disease

The extent and severity of skin disease was measured in both studies using the PASI and Investigator's Global Assessment (IGA). PASI grades the extent and severity of psoriatic lesions and combines an assessment of the BSA affected with the severity of desquamation, erythema, and plaque induration or infiltration. It is scored from 0 to 72, with higher scores representing more severe disease. PASI90 is a dichotomous (yes or no) scale indicating whether a patient experienced at least a 90% improvement from baseline PASI score. In both trials, only patients who had psoriasis involving at least 3% BSA at baseline were assessed for PASI90 at week 16.

The IGA is a 5-point composite physician assessment of the overall severity of a patient's psoriatic lesions, where 0 is clear, 1 is almost clear, 2 is mild, 3 is moderate, and 4 is severe. In both trials, only patients who had an IGA score of at least 2 and psoriasis involving at least 3% BSA at baseline were evaluated for the outcome of at least a 2-grade reduction in IGA score at week 16.

PASI Score Improvement of 90%

In the BE OPTIMAL trial, for PASI90, patients treated with bimekizumab had higher response rates compared with placebo at week 16. The difference between treatment groups was 56.5% (95% CI, 48.6% to 64.3%; P < 0.001). PASI90 results at week 52 indicated that response rates increased in both groups and that there was a similar response between placebo-bimekizumab crossover patients and patients originally randomized to bimekizumab during the active treatment-blind period.

In the BE COMPLETE trial, for PASI90, patients treated with bimekizumab had higher response rates compared with placebo at week 16. The difference between treatment groups was 57.6% (95% CI, 47.6% to 67.6%; P < 0.001). A larger proportion of patients in the bimekizumab group compared to the placebo group had a PASI90 response for each of the subgroup categories of inadequate response to 1 TNFi (difference versus placebo, 64.4%; 95% CI, 53.6% to 75.3%), inadequate response to 2 TNFis (difference versus placebo, 25.0%; 95% CI, –16.2% to 66.1%), and intolerance to TNFis (difference versus placebo, 49.7%; 95% CI, 18.5% to 80.9%).

IGA Score of 0 or 1 and at Least a 2-Grade Reduction From Baseline

In the BE OPTIMAL trial, a larger proportion of patients in the bimekizumab group compared to the placebo group had at least a 2-grade reduction from baseline in IGA score at week 16. The difference between treatment groups was 46.0% (95% CI, 37.1% to 55.0%). IGA results at week 52 indicated that the response was maintained in the bimekizumab group and that there was a similar response between patients who crossed over from placebo to bimekizumab and patients originally randomized to bimekizumab during the active treatment-blind period.

In the BE COMPLETE trial, a larger proportion of patients in the bimekizumab group compared to the placebo group experienced at least at least a 2-grade reduction from baseline in IGA score at week 16. The difference between treatment groups was 58.2% (95% CI, 46.7% to 69.8%).

Physical Function

Improvement in physical function at week 16 was assessed using the HAQ-DI and SF-36 PCS. The HAQ-DI is a self-assessment questionnaire of 8 domains (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities); patients' difficulty in performing these activities is scored from 0 (without any difficulty) to 3 (unable to do). The SF-36 PCS is a 36-item general health status instrument consisting of 8 health domains: physical functioning, pain, vitality, social functioning, psychological functioning, general health perceptions, role limitations due to physical challenges, and role limitations due to emotional challenges. It ranges from 0 to 100, with higher scores indicating better health status.

Health Assessment Questionnaire – Disability Index

In the BE OPTIMAL trial, the bimekizumab group had a greater mean decrease from baseline (i.e., improvement) in HAQ-DI score than the placebo group at week 16; the least squares mean (LSM) difference between treatment groups was −0.19 (95% CI, −0.25 to −0.13; P < 0.001). HAQ-DI results at week 52 indicated that the response was maintained in the bimekizumab group and that there was a similar response between patients who crossed over from placebo to bimekizumab and patients originally randomized to bimekizumab during the active treatment-blind period.

In the BE COMPLETE trial, the bimekizumab group had a greater mean decrease from baseline (i.e., improvement) in HAQ-DI score compared to the placebo group at week 16; the LSM difference between treatment groups was −0.33 (95% CI, −0.42 to −0.23; P < 0.001). A larger proportion of patients in the bimekizumab group than in the placebo group achieved a HAQ-DI score decrease of at least 0.35 for each of the subgroup categories of inadequate response to 1 TNFi (difference versus placebo, 40.8%; 95% CI, 28.6% to 53.1%), inadequate response to 2 TNFis (difference versus placebo, 11.5%; 95% CI, −19.9% to 42.9%), and intolerance to TNFis (difference versus placebo, 24.7%; 95% CI, −6.0% to 55.5%).

SF-36 Physical Component Summary

In the BE OPTIMAL trial, the bimekizumab group had a greater mean increase from baseline (i.e., improvement) on the SF-36 PCS than the placebo group at week 16; the LSM difference between treatment groups was 4.3 (95% CI, 3.2 to 5.4; P < 0.001). SF-36 PCS results at week 52 indicated that the response was maintained in the bimekizumab group and that there was a similar response between patients who crossed

over from placebo to bimekizumab and patients originally randomized to bimekizumab during the active treatment-blind period.

In the BE COMPLETE trial, the bimekizumab group had a greater mean increase from baseline (i.e., improvement) on the SF-36 PCS than the placebo group at week 16; the LSM difference between treatment groups was 6.0 (95% CI, 4.4 to 7.7; P < 0.001).

Harms Results

Patients reporting at least 1 AE during the DB treatment periods of the BE OPTIMAL and BE COMPLETE trials ranged from 40.4% to 59.6% of patients in the bimekizumab groups and from 33.3% to 49.5% of patients in the placebo groups. Nasopharyngitis was the most common AE (3.7% to 9.3% in the bimekizumab groups versus 0.8% to 4.6% in the placebo groups), followed by upper respiratory tract infection (2.2% to 5.1% in the bimekizumab groups versus 1.5% to 6.4% in the placebo groups). During the BE OPTIMAL trial's active treatment-blind period, 72.0% of patients in the bimekizumab group and 70.5% of patients in the placebo-bimekizumab crossover group reported at least 1 AE, with the most common being nasopharyngitis (7.0% and 8.5% in the bimekizumab and crossover groups, respectively).

The frequency of serious adverse events (SAEs) was 1.9% in the bimekizumab groups and ranged from 0 to 1.1% in the placebo groups during the DB period of both trials. During the BE OPTIMAL trial's active treatment-blind period, 5.6% of patients in the bimekizumab group and 5.9% of patients in the placebo-bimekizumab crossover group reported at least 1 SAE.

Withdrawals from treatment due to AEs ranged from 0.7% to 1.9% of patients in the bimekizumab groups and ranged from 0 to 1.1% of patients in the placebo groups during the DB period of both trials. During the BE OPTIMAL trial's active treatment-blind period, 2.7% of patients in the bimekizumab group and 1.8% of patients in the placebo-bimekizumab crossover group reported an AE leading to drug discontinuation.

There were no deaths during the DB periods of the trials and 1 death in the placebo-bimekizumab crossover group (due to traumatic shock from a motorcycle accident) during the BE OPTIMAL trial's active treatment-blind period.

During the DB period of both trials, few notable harms were reported among either the bimekizumab or placebo groups (i.e., 0 or 1 patient per treatment group) for liver dysfunction based on Hy's law, opportunistic infection, major cardiovascular event, malignancy, anaphylaxis, and IBD. In the trials, approximately 4.5% of patients in the bimekizumab groups and 1% of patients in the placebo groups reported any fungal infection. Of these, 2.6% of patients in the bimekizumab groups and less than 1% of patients in the placebo groups reported a candida infection; approximately 2% of patients in the bimekizumab groups and less than 1% of patients in the placebo groups reported a fungal infection not elsewhere classified (NEC); and less than 1% of patients in the bimekizumab groups and no patients in the placebo groups reported a tinea infection.

During the BE OPTIMAL trial's active treatment-blind period, there were few reports (< 5 patients in the treatment groups) of liver dysfunction based on Hy's law, opportunistic infection, major cardiovascular event, malignancy, anaphylaxis, and IBD. Of the 11.4% of patients who reported any fungal infection in the bimekizumab group, 6.8% reported a candida infection, 4.6% reported a fungal infection NEC, and

1.2% reported a tinea infection. Of the 9.2% of patients who reported any fungal infection in the placebo-bimekizumab crossover group, 7.0% reported a candida infection, 2.6% reported a fungal infection NEC, and 0.7% reported a tinea infection.

Liver toxicity, reactivation of tuberculosis infection, and serious injection-related AEs were not reported in either of the trials.

Critical Appraisal

There were some imbalances in baseline characteristics between the bimekizumab and placebo groups for presence of enthesitis (both trials), proportion of patients with 10% or greater BSA affected by psoriasis, PASI, and methotrexate use (the BE COMPLETE trial), which may have biased the results in favour of patients who start out with low disease activity at baseline, although the direction of bias for the overall treatment groups is less certain. Results during the active treatment-blind period of the BE OPTIMAL trial may have been confounded by the lack of a placebo comparison group (patients randomized to placebo were reallocated to bimekizumab) and any rescue therapies used (permitted after the 16-week DB period and use ranged from 4.8% to 7.0% of patients). Moreover, it is possible that permitted concomitant therapies (particularly cDMARDs) may not have reached full effect during the minimum 8 weeks that defined a stable dose, making it difficult to attribute treatment effects and harms to either bimekizumab or a concomitant drug. Four outcomes relevant to the CADTH review (PASI90, IGA, LEI, and LDI) used subsets of the randomized set and it is uncertain if the known and unknown treatment effect modifiers were still balanced between the groups.

In general, both trials had limited racial diversity, which is not necessarily reflective of patients with PsA across Canada. Patients with other bDMARD or tsDMARD experience (other than TNFis) were not included, and it is uncertain if the trial results are generalizable to these patients. However, based on the reported baseline characteristics, the clinical expert consulted by CADTH indicated that the patients in the trials were generally similar to those who are treated in clinical practice and could receive bimekizumab in Canada. Also, of the permitted concomitant medications, it was noted that hydroxychloroquine is rarely used in Canadian practice and apremilast is a targeted therapy accessed after cDMARDs. It was noted that ACR response and some patient-reported outcomes are not typically used in clinical practice, although they may still provide important information to patients and clinicians.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (i.e., internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

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 an important effect based on thresholds identified in the literature for HAQ-DI, SF-36 PCS, and PtAAP. The target of the certainty of evidence assessment was the presence or absence of an important effect based on thresholds informed by the clinical expert consulted for this review for ACR response, MDA, LEI, LDI, SJC, PASI90, and IGA.

For the GRADE assessments, findings from the BE OPTIMAL and BE COMPLETE trials were assessed together per outcome because these studies were similar in population, intervention, design, and outcome measures.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with the clinical expert, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members: composite measures of disease activity (ACR50, ACR20, ACR70, and MDA), musculoskeletal-related outcomes (LEI, LDI, and SJC), skin-related outcomes (PASI90 and IGA), and patient-reported outcomes for physical functioning and symptoms (HAQ-DI, SF-36 PCS, and PtAAP).

Results of GRADE Assessments

Table 3 presents the GRADE summary of findings for bimekizumab versus placebo for patients with PsA.

Table 3: Summary of Findings for Bimekizumab Versus Placebo for Patients With PsA

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Bimekizumab	Difference		
Composite measures of disease activity							
ACR50 response – patients with no prior exposure to biologics Follow-up: 16 weeks	712 (1 RCT)	OR = 7.1 (4.6 to 10.9)	85 per 1,000	397 (339 to 459) per 1,000	312 (252 to 373) more per 1,000	High[a]	Bimekizumab results in an increase in the proportion of patients who experience ACR50 when compared with placebo.
ACR50 response – patients with a history of inadequate response or intolerance to 1 or 2 TNFis Follow-up: 16 weeks	400 (1 RCT)	OR = 11.1 (5.4 to 23.0)	43 per 1,000	333 (248 to 431) per 1,000	290 (219 to 362) more per 1,000	High[a]	Bimekizumab results in an increase in the proportion of patients who experience ACR50 when compared with placebo.
ACR20 response – patients with no prior exposure to biologics[b] Follow-up: 16 weeks	712 (1 RCT)	OR = 5.4 (3.8 to 7.5)	200 per 1,000	572 (512 to 631) per 1,000	372 (305 to 440) more per 1,000	High[c]	Bimekizumab results in an increase in the proportion of patients who experience ACR20 when compared with placebo.
ACR20 response – patients with a history of inadequate response or intolerance to 1 or 2 TNFis[b] Follow-up: 16 weeks	400 (1 RCT)	OR = 12.2 (7.0 to 21.1)	144 per 1,000	672 (579 to 753) per 1,000	528 (436 to 619) more per 1,000	High[c]	Bimekizumab results in an increase in the proportion of patients who experience ACR20 when compared with placebo.
ACR70 response – patients with no prior exposure to biologics[b] Follow-up: 16 weeks	712 (1 RCT)	OR = 7.2 (3.9 to 13.4)	40 per 1,000	233 (185 to 289) per 1,000	193 (141 to 245) more per 1,000	High[d]	Bimekizumab results in an increase in the proportion of patients who experience ACR70 when compared with placebo.
ACR70 response – patients with a history of inadequate response or intolerance to 1 or 2 TNFis[b] Follow-up: 16 weeks	400 (1 RCT)	OR = 50.6 (6.9 to 370.0)	4 per 1,000	176 (111 to 269) per 1,000	172 (122 to 222) more per 1,000	High[d]	Bimekizumab results in an increase in the proportion of patients who experience ACR70 when compared with placebo.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Bimekizumab	Difference		
MDA response – patients with no prior exposure to biologics Follow-up: 16 weeks	712 (1 RCT)	OR = 5.4 (3.7 to 8.1)	123 per 1,000	433 (374 to 494) per 1,000	310 (245 to 375) more per 1,000	High[e]	Bimekizumab results in an increase in the proportion of patients who experience MDA when compared with placebo.
MDA response – patients with a history of inadequate response or intolerance to 1 or 2 TNFis Follow-up: 16 weeks	400 (1 RCT)	OR = 13.1 (6.1 to 28.0)	46 per 1,000	388 (296 to 488) per 1,000	342 (261 to 422) more per 1,000	High[e]	Bimekizumab results in an increase in the proportion of patients who experience MDA when compared with placebo.
Musculoskeletal-related outcomes							
Enthesitis-free state based on the LEI in patients with enthesitis at baseline – pooled population of patients with no prior exposure to biologics and patients with a history of inadequate response or intolerance to 1 or 2 TNFis Follow-up: 16 weeks	355 (1 RCT)	OR = 1.9 (1.2 to 3.1)	300 per 1,000	450 (379 to 522) per 1,000	149 (40 to 259) more per 1,000	Low[f,g]	Bimekizumab may result in an increase in the proportion of patients who experience an enthesitis-free state when compared with placebo.
Dactylitis-free state based on the LDI in patients with dactylitis at baseline – pooled population of patients with no prior exposure to biologics and patients with a history of inadequate response or intolerance to 1 or 2 TNFis Follow-up: 16 weeks	137 (1 RCT)	OR = 3.4 (1.6 to 7.6)	415 per 1,000	710 (590 to 806) per 1,000	294 (117 to 471) more per 1,000	Low[f,h]	Bimekizumab may result in an increase in the proportion of patients who experience a dactylitis-free state when compared with placebo.
SJC (0 [best] to 66 [worst]) LSM change from baseline, joints – patients with no prior exposure to biologics[b] Follow-up: 16 weeks	712 (1 RCT)	NA	−2.3	−6.3 (SE = 0.3)	−4.0 (−4.8 to −3.1)	Low[i]	Bimekizumab may result in a decrease in the number of swollen joints when compared with placebo.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Bimekizumab	Difference		
SJC (0 [best] to 66 [worst]), LSM change from baseline, joints – patients with a history of inadequate response or intolerance to 1 or 2 TNFis[b] Follow-up: 16 weeks	400 (1 RCT)	NA	−1.7	−7.1 (SE = 0.5)	−5.3 (−6.5 to −4.2)	Moderate[j]	Bimekizumab likely results in a decrease in the number of swollen joints when compared with placebo.
Skin-related outcomes							
PASI90 response in patients with psoriasis involving ≥ 3% BSA at baseline – patients with no prior exposure to biologics Follow-up: 16 weeks	357 (1 RCT)	OR = 63.0 (22.2 to 178.9)	22 per 1,000	587 (487 to 679) per 1,000	565 (486 to 643) more per 1,000	Moderate[f,k]	Bimekizumab likely results in an increase in the proportion of patients who experience PASI90 when compared with placebo.
PASI90 response in patients with psoriasis involving ≥ 3% BSA at baseline – patients with a history of inadequate response or intolerance to 1 or 2 TNFis Follow-up: 16 weeks	264 (1 RCT)	OR = 30.2 (12.4 to 73.9)	53 per 1,000	629 (495 to 746) per 1,000	576 (476 to 676) more per 1,000	Low[f,k,l]	Bimekizumab may result in an increase in the proportion of patients who experience PASI90 when compared with placebo.
IGA score of 0 or 1 and ≥ 2-grade reduction from baseline in patients with psoriasis involving ≥ 3% BSA at baseline – patients with no prior exposure to biologics[b] Follow-up: 16 weeks	333 (1 RCT)	OR = 27.1 (10.6 to 69.5)	35 per 1,000	495 (394 to 597) per 1,000	460 (371 to 550) more per 1,000	Low[f,m]	Bimekizumab may result in an increase in the proportion of patients who experience an IGA score of 0 or 1 when compared with placebo.
IGA score of 0 or 1 and ≥ 2-grade reduction from baseline in patients with psoriasis involving ≥ 3% BSA at baseline – patients with a history of inadequate response or intolerance to 1 or 2 TNFis[b] Follow-up: 16 weeks	245 (1 RCT)	OR = 40.9 (12.3 to 135.6)	39 per 1,000	621 (483 to 742) per 1,000	582 (467 to 698) more per 1,000	Low[f,m]	Bimekizumab may result in an increase in the proportion of patients who experience an IGA score of 0 or 1 when compared with placebo.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Bimekizumab	Difference		
Patient-reported outcomes for physical functioning and symptoms							
HAQ-DI score (0 [best] to 3 [worst]) LSM change from baseline, points – patients with no prior exposure to biologics Follow-up: 16 weeks	712 (1 RCT)	NA	−0.07	−0.26 (SE = 0.03)	−0.19 (−0.25 to −0.13)	High[n]	Bimekizumab results in a reduction in HAQ-DI score when compared with placebo.
HAQ-DI score (0 [best] to 3 [worst]) LSM change from baseline, points – patients with a history of inadequate response or intolerance to 1 or 2 TNFis Follow-up: 16 weeks	400 (1 RCT)	NA	0.02	−0.31 (SE = 0.04)	−0.33 (−0.42 to −0.23)	High[n]	Bimekizumab results in a reduction in HAQ-DI score when compared with placebo.
SF-36 PCS score LSM change from baseline, points – patients with no prior exposure to biologics Follow-up: 16 weeks	712 (1 RCT)	NA	1.9	6.3 (SE = 0.5)	4.3 (3.2 to 5.4)	High[o]	Bimekizumab results in an increase in SF-36 PCS score when compared with placebo.
SF-36 PCS score LSM change from baseline, points – patients with a history of inadequate response or intolerance to 1 or 2 TNFis Follow-up: 16 weeks	400 (1 RCT)	NA	0.1	6.2 (SE = 0.7)	6.0 (4.4 to 7.7)	High[o]	Bimekizumab results in an increase in SF-36 PCS score when compared with placebo.
PtAAP (0 [best] to 100 [worst]) LSM change from baseline, points – patients with no prior exposure to biologics[b] Follow-up: 16 weeks	712 (1 RCT)	NA	−4.6	−23.8 (SE = 1.4)	−19.1 (−22.7 to −15.5)	High[p]	Bimekizumab results in a reduction in PtAAP score when compared with placebo.
PtAAP (0 [best] to 100 [worst]) LSM change from baseline, points – patients with a history of inadequate response or intolerance to 1 or 2	400 (1 RCT)	NA	−1.6	−26.6 (SE = 2.1)	−25.0 (−30.0 to −20.0)	High[p]	Bimekizumab results in a reduction in PtAAP score when compared with placebo.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Bimekizumab	Difference		
TNFis[b] Follow-up: 16 weeks							

ACR20 = at least a 20% improvement in American College of Rheumatology response criteria; ACR50 = at least a 50% improvement in American College of Rheumatology response criteria; ACR70 = at least a 70% improvement in American College of Rheumatology response criteria; BSA = body surface area; CI = confidence interval; HAQ-DI = Health Assessment Questionnaire – Disability Index; IGA = Investigator's Global Assessment; LDI = Leeds Dactylitis Index; LEI = Leeds Enthesitis Index; LSM = least squares mean; MDA = Minimal Disease Activity; MID = minimally important difference; NA = not available; OR = odds ratio; PASI90 = 90% improvement in Psoriasis Area Severity Index score; PCS = Physical Component Summary; PtAAP = Patient's Assessment of Arthritis Pain; RCT = randomized controlled trial; SE = standard error; SF-36 = Short-Form 36-item Health Survey; SJC = swollen joint count; TNFi = tumour necrosis factor inhibitor.

[a]A difference of 20% between groups was identified by the clinical expert consulted by CADTH as a threshold of clinical importance for this outcome.

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

[c]A difference of 30% to 40% between groups was identified by the clinical expert consulted by CADTH as a threshold of clinical importance for this outcome.

[d]A difference of 10% to 15% between groups was identified by the clinical expert consulted by CADTH as a threshold of clinical importance for this outcome.

[e]A difference of 15% to 20% between groups was identified by the clinical expert consulted by CADTH as a threshold of clinical importance for this outcome.

[f]Rated down 1 level for study limitations due to the loss of randomization in the population used for outcome analysis and the results being at a higher risk of bias.

[g]Rated down 1 level for serious imprecision. The 95% CI for difference between groups includes the possibility of no benefit compared to the threshold of clinical importance that the clinical expert suggested for experiencing an enthesitis-free state (150 more per 1,000 patients).

[h]Rated down 1 level for serious imprecision. The 95% CI for difference between groups includes the possibility of no benefit compared to the lower threshold of clinical importance that the clinical expert suggested for experiencing a dactylitis-free state (150 to 200 more per 1,000 patients).

[i]Rated down 2 levels for very serious imprecision. Both boundaries of the 95% CI for difference between groups exclude the threshold of clinical importance that the clinical expert suggested for improvement in SJC (5 fewer swollen joints).

[j]Rated down 1 level for serious imprecision. The 95% CI for difference between groups includes the possibility of no benefit compared to the threshold of clinical importance that the clinical expert suggested for improvement in SJC (5 fewer swollen joints).

[k]Did not rate down for serious imprecision. The 95% CI for difference between groups includes the possibility of no benefit compared to the threshold of clinical importance that the clinical expert suggested for PASI90 (500 more per 1,000 patients); however, the lower bound of the 95% CI was close to the threshold and bimekizumab has previously been reviewed and approved for the treatment of patients with moderate to severe plaque psoriasis.

[l]Rated down 1 level for study limitations. The increased risk of bias is due to an imbalance in baseline characteristics between treatment groups (higher proportion of patients with larger percent BSA affected by psoriasis and higher PASI scores in the bimekizumab group).

[m]Rated down 1 level for serious imprecision. The 95% CI for difference between groups includes the possibility of no benefit compared to the threshold of clinical importance that the clinical expert suggested for IGA (500 more per 1,000 patients).

[n]A difference of −0.35 to −0.13 points between groups was identified from the literature as a MID for this outcome.

[o]A difference of 3.74 points between groups was identified from the literature as a MID for this outcome.

[p]A difference of –10 points between groups was identified from the literature as a MID for this outcome.

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.

Sources: BE OPTIMAL Clinical Study Report, BE COMPLETE Clinical Study Report, and Sponsor's Summary of Clinical Evidence. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

Description of Studies

Two long-term extension studies were submitted by the sponsor that evaluated bimekizumab 160 mg every 4 weeks SC for the treatment of adult patients with PsA. The BE ACTIVE 2 study was a 104-week, phase II, open-label extension (OLE) study that aimed to assess the long-term safety, tolerability, and efficacy of bimekizumab in 184 adult patients with PsA who completed the preceding phase IIb BE ACTIVE study. The BE VITAL study is an ongoing (estimated completion date: May 25, 2026) phase III, OLE study of the BE COMPLETE and BE OPTIMAL trials that is evaluating the long-term efficacy (up to week 140) and long-term safety (up to week 212) of bimekizumab in 1,131 patients with PsA who received bimekizumab 160 mg every 4 weeks.

The eligibility criteria for the BE ACTIVE 2 and BE VITAL studies were consistent with those of the parent trials. All data from the extension studies were analyzed descriptively using summary statistics.

Efficacy Results

In the BE ACTIVE 2 study, rates of ACR20, ACR50, and ACR70 response were similar at baseline and at week 104 with continued bimekizumab treatment. At week 104 of the BE ACTIVE 2 study, 58.6% of patients experienced an MDA response. For a 75% improvement in Psoriasis Area Severity Index (PASI75), PASI90, and 100% improvement in Psoriasis Area Severity Index (PASI100), data were limited at several visits due to an error in the original study protocol, which was later amended. For visits with a meaningful sample size of data collected (according to the sponsor), the proportions of patients who experienced PASI75, PASI90, and PASI100 at week 104 were 79.2%, 73.3%, and 65.8%, respectively. The SF-36 PCS score in the BE ACTIVE 2 study was sustained with continued bimekizumab treatment up to week 104, with a mean PCS change of 9.5 (standard error [SE] = 0.8).

In the BE VITAL study, sustained efficacy was observed with bimekizumab from week 16 to week 52 across clinical and patient-reported outcomes. At week 52, 51.7% of patients originally randomized to bimekizumab and 40.6% of patients randomized to placebo who crossed over to bimekizumab had an ACR50 response. ACR20 and ACR70 similarly improved over time for these groups.

MDA was experienced by 47.2% of patients receiving bimekizumab and 33.1% of patients who crossed over from placebo to bimekizumab at week 52. The proportions of patients experiencing PASI75, PASI90, and PASI100 increased up to week 52 in both treatment groups of patients with psoriasis affecting at least 3% BSA at baseline. Data for the SF-36 PCS were only reported up to week 40. At week 40, the mean SF-36 PCS change from baseline was 8.4 (SE = 0.6) for those who were originally randomized to bimekizumab and 7.3 (SE = 0.9) for patients who switched from placebo to bimekizumab.

Harms Results

The total time at risk was 392.3 patient-years during the BE ACTIVE 2 study. Most patients (80.9%) reported treatment emergent adverse events (TEAEs), which were most commonly infections and infestations (55.2%). Overall, 7.7% of patients reported an SAE, 4.9% of patients discontinued bimekizumab due to TEAEs, and there were no deaths reported.

In the BE VITAL study, at least 1 TEAE was reported by 243 of 388 patients (62.6%) while receiving bimekizumab up to week 52. The most frequently reported TEAEs were hypersensitivity (4.9%), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections (7.2%), fungal infections (9.5%), nasopharyngitis (5.9%), and urinary tract infection (5.9%). Serious infections occurred among 1.8% of patients, and 1.3% of patients had neutropenia. The proportion of patients who reported SAEs was 5.9%. Discontinuation of bimekizumab treatment due to TEAEs occurred in 4.1% of patients. One death was reported, which the sponsor deemed was unrelated to study treatment.

Critical Appraisal

The open-label design of the BE ACTIVE 2 and BE VITAL studies could bias the magnitude of the treatment effect due to unblinded exposure to the study medication during the treatment period, although the direction of bias is uncertain. In addition, the absence of control arms in both studies and the lack of data beyond week 52 in the BE VITAL study make interpretation of the findings challenging. Only those who successfully completed the BE ACTIVE, BE OPTIMAL, and BE COMPLETE studies moved on to the BE ACTIVE 2 and BE VITAL studies, and there may have been selection bias involved.

As the BE ACTIVE 2 and BE VITAL studies consisted of patients who took part in the pivotal studies (the BE ACTIVE, BE OPTIMAL, and BE COMPLETE studies), it is reasonable to expect that the same strengths and limitations related to generalizability apply. The patient population of those studies may not be reflective of the more heterogeneous clinical population in terms of demographic and clinical characteristics; therefore, the results presented may differ from those observed in a real-world clinical setting.

Indirect Comparisons

Description of Studies

The sponsor submitted an NMA and a MAIC for the ITC. The NMA assessed ACR20, ACR50, ACR70, MDA, PASI90, and safety outcomes at weeks 12 to 24, while the MAIC assessed ACR20, ACR50, ACR70, and MDA at week 52. Included trials were phase II to IV RCTs conducted with patients with adult-onset PsA treated with 1 drug from a set of specified interventions and dosing regimens that included IL-17is, IL-23is, and IL-12/23is (NMA and MAIC), as well as specific TNFis, cytotoxic T-lymphocyte protein 4 immunoglobulin (CTLAIg), JAKis, and PDE4is (NMA only).

Efficacy Results

The NMA for the population that was naive to bDMARDs or tsDMARDs indicated that bimekizumab was more efficacious than most IL-12/23is and IL-23is, and abatacept for ACR outcomes, but that it may be similar to IL-17is, TNFis, or JAKis, with a few exceptions. The results for the TNFi-experienced population indicated that bimekizumab was favoured over IL-17 comparators for ACR20 response, but favourability varied relative to comparators for both ACR50 and ACR70 outcomes, and wide credible intervals (CrIs) suggest high imprecision in this subpopulation. The results for PASI90 indicated that bimekizumab was favoured over most TNFi comparators and may be similar to other classes, but fewer comparisons were made in patients who were TNFi-experienced. Results for MDA indicated that bimekizumab was favoured for the IL-12/23 and IL-23 comparisons made in patients who were naive to bDMARDs or tsDMARDs,

but favourability varied in patients who were TNFi-experienced patients, and overall there were fewer comparisons made for this outcome. Golimumab was favoured over bimekizumab for ACR20 and ACR50. The MAIC was subject to important limitations, which preclude drawing firm conclusions about efficacy.

Harms Results

Comparison of specific harms was not possible due to a lack of specific information from the trials. Overall, bimekizumab was not favoured, nor was it less favoured than most comparators for AEs, SAEs, or discontinuations due to AEs. One exception was that bimekizumab was favoured over ustekinumab for discontinuations due to AEs.

Critical Appraisal

While methods to mitigate sources of uncertainty were implemented, the results of the NMA were subject to some uncertainty due to the unmeasurable limitations of baseline risk adjustment and uncertainty over the extent to which it accounted for patient heterogeneity, as well as differences in study design and model selection that affected the comparability of the studies across the network. The results from the MAIC were highly uncertain, at risk of unmeasured bias, and were also of limited applicability to the clinical context due to the inclusion of only some of the treatment options available in the Canadian context.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target populations	Adult patients with active PsA; biologic-naive and biologic-experienced subpopulations explored separately
Treatment	Bimekizumab
Dose regimen	160 mg (given as 1 subcutaneous injection) every 4 weeks
Submitted price	Bimekizumab: $1,625 per 1 ml of 160 mg bimekizumab syringe or autoinjector
Submitted treatment cost	$22,042 for patients who are biologic-naive or $22,563 for patients who are biologic-experienced in year 1. The maintenance annual cost is $21,198 per patient.
Comparators	• Adalimumab, apremilast, certolizumab, etanercept, golimumab, guselkumab, infliximab, ixekizumab, risankizumab, secukinumab, tofacitinib, upadacitinib, ustekinumab and BSC (defined as a mix of methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine, and supportive or palliative care)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (50 years)

Component	Description
Key data source	Comparative clinical efficacy was derived from a sponsor-submitted NMA based on data obtained from the BE OPTIMAL, BE COMPLETE, and respective comparator treatment trials to inform the probability of ACR50 and PASI response at 12 weeks to 16 weeks.
Submitted results	**Biologic-naive** • Bimekizumab was not on the cost-effectiveness frontier as it was ruled out by extended dominance by adalimumab and infliximab. Optimal treatments included BSC, tofacitinib, adalimumab, and infliximab. • The ICER for bimekizumab compared to BSC was $56,130 per QALY gained (incremental costs = $45,199; incremental QALYs = 0.76). **Biologic-experienced** • Compared to tofacitinib, bimekizumab was associated with an ICER of $69,876 per QALY gained (incremental costs = $49,923; incremental QALYs = 0.71). BSC, tofacitinib, and bimekizumab were on the cost-effectiveness frontier.
Key limitations	• Due to the lack of direct clinical evidence and limitations with the sponsor-submitted NMA, the relative treatment effects of bimekizumab to other biologic or targeted DMARDs is uncertain. • While longer-term efficacy and safety of bimekizumab was provided via the BE ACTIVE 2 trial and the ongoing BE VITAL study, only data up to 2 years are available. Thus, the long-term treatment efficacy of bimekizumab is uncertain. • Disease-related resource use is uncertain and likely double counts resource use, such as health care provider visits and labs tests, in some instances.
CADTH reanalysis results	• Given the clinical limitations identified with the sponsor's economic submission (including uncertainty related to comparative treatment effect and long-term efficacy of bimekizumab), CADTH was unable derive a more reliable estimate of the cost-effectiveness of bimekizumab. • While the sponsor's base case suggests differences in treatment benefits between advanced therapies for the treatment of adult PsA, the probability that bimekizumab is cost-effective at a willingness to pay threshold of $50,000 QALY gained was 0% and 4.3% for the populations of patients who were biologic-naive and biologic-experienced, respectively. A price reduction of approximately 52% for those who are biologic-naive and 24% for those who are biologic-experienced is required for bimekizumab to be considered cost-effective at a willingness to pay threshold of $50,000 per QALY gained.

ACR = American College of Rheumatology; BSC = best supportive care; DMARD = disease-modifying antirheumatic drug; ICER = incremental cost-effectiveness ratio; LY = life-year; NMA = network meta-analysis; PASI = psoriasis area and severity index; PsA = psoriatic arthritis; QALY = quality-adjusted life-year.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the total number of eligible patients was inaccurately estimated, the Non-Insured Health Benefits (NIHB) population was inappropriately calculated, and there is uncertainty in the market uptake and displacement for bimekizumab. Based on the CADTH reanalysis, the 3-year budget impact to public drug plans associated with introducing bimekizumab for the treatment of adult patients with PsA is expected to be $5,742,058 ($1,062,138 in year 1; $1,800,715 in year 2; and $2,879,205 in year 3). The estimated budget impact is sensitive to the number of patients who are expected to receive bimekizumab and the source of the bimekizumab market share.

CDEC Information

Members of the Committee

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

Meeting date: March 28, 2024

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

ISSN: 2563-6596

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